ECMO for severe acute respiratory distress syndrome: systematic review and individual patient data meta-analysis.

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ABSTRACT (248 words)

Purpose:

To assess the effect of venovenous extracorporeal membrane oxygenation (ECMO) compared to conventional management in patients with severe acute respiratory distress syndrome (ARDS).

Methods:

We conducted a systematic review and individual patient data meta-analysis of randomised controlled trials (RCTs) performed after Jan 1, 2000 comparing ECMO to conventional management in patients with severe ARDS. The primary outcome was 90-day mortality. Primary analysis was by intent-to-treat.

Results:

We identified two RCTs (CESAR and EOLIA) and combined data from 429 patients. On day 90, 77 of the 214 (36%) ECMO-group and 103 of the 215 (48%) control group patients had died (relative risk (RR), 0.75, 95% confidence interval (CI), 0.60–0.94; P=0.013; I^2=0%). In the per-protocol and as-treated analyses the RRs were 0.75 (95% CI, 0.60–0.94) and 0.86 (95% CI, 0.68–1.09), respectively. Rescue ECMO was used for 36 (17%) of the 215 control patients (35 in EOLIA and 1 in CESAR). The RR of 90-day treatment failure, defined as death for the ECMO-group and death or crossover to ECMO for the control group was 0.65 (95% CI, 0.52–0.80; I^2=0%). Patients randomised to ECMO had more days alive out of the ICU and without respiratory, cardiovascular, renal and neurological failure. The only significant treatment-covariate interaction in subgroups was lower mortality with ECMO in patients with two or less organs failing at randomization.

Conclusions:

In this meta-analysis of individual patient data in severe ARDS, 90-day mortality was significantly lowered by ECMO compared with conventional management. (PROSPERO registration: CRD42019130034).

Take home message

In this meta-analysis of individual patient data in severe ARDS, 90-day mortality was significantly lowered by ECMO compared with conventional management. Patients randomised to ECMO had more days alive out of the ICU and without respiratory, cardiovascular, renal and neurological failure.

Tweet

ECMO significantly lowered 90-day mortality compared with conventional management in this IPDMA of patient with severe ARDS.

Introduction

Ventilatory management of patients with severe acute respiratory distress syndrome (ARDS) has improved over the last decades with a strategy combining low tidal volume (VT) ventilation,[1] high positive end-expiratory pressure (PEEP),[2, 3] neuromuscular blocking agents[4] and prone positioning.[5] However, ventilator-induced lung injury (VILI) may persist in these patients since a recent and large epidemiological study showed that their hospital mortality was still 46%.[6] Recently, even higher mortality was reported for patients with severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) infection who needed invasive mechanical ventilation.[7-9]

Venovenous extracorporeal membrane oxygenation (ECMO) providing full blood oxygenation, CO_2 elimination and combined with more gentle ventilation has benefited from major technological advances in the last 15 years.[10, 11] In 2009, favourable outcomes were reported in patients who received ECMO during the influenza A (H1N1) pandemic.[12-14] The Conventional Ventilator Support vs Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Failure (CESAR) trial[15, 16] showed that transfer to an ECMO centre was associated with fewer deaths or severe disabilities at 6 months compared with conventional mechanical ventilation (37% vs. 53%; *p* 0 = 0.03), although 6 month mortality was not significantly reduced (37% vs. 45%; $p = 0.07$). The more recent ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial showed a non-statistically significant reduction in 60-day mortality with ECMO (35% vs. 46%; $p = 0.09$).[17] However, neither trial was separately powered to detect a 10-15% survival benefit with ECMO.

We performed a systematic review with an individual patient data meta-analysis of randomised controlled trials comparing ECMO to conventional mechanical ventilation in patients with severe ARDS. The primary objective was to evaluate the effect of ECMO on 90-day mortality. Secondary objectives included the evaluation of ECMO for other clinical outcomes and in pre-specified subgroups for the primary outcome.

Methods

Study Design

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Individual Patient Data (PRISMA-IPD checklist in eTable 1 in the Supplement) and the protocol was registered in PROSPERO (CRD42019130034).

Eligibility criteria

We included all randomised controlled trials (RCTs) evaluating venovenous ECMO in the experimental group and conventional ventilatory management in the control group, that included patients with ARDS fulfilling the American–European Consensus Conference definition[18] or the Berlin definition for ARDS,[19] and that were published or whose primary completion date was after 2000.[10, 20, 21] This choice was justified by the major improvements in intensive care treatments and in ECMO technology that occurred in the last two decades. Additional information on selection criteria is provided in the Supplement.

Search strategy

We searched MEDLINE via PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (Central) from January 1, 2000 to September 30, 2019 using a search algorithm developed for the purpose of this study and adapted to each database (eTable 2 in the Supplement). We also searched trial registries including ClinicalTrials.gov and the International Clinical Trial Registry Platform (ICTRP) for completed and ongoing trials, conference proceedings of major critical care societies and screened reference lists of identified articles as well as systematic or narrative reviews on the topic (see the Supplement).

Selection and data collection

Selection was conducted independently by two reviewers (DA and MS) on titles and abstracts first and then, on the full text. For each included RCT, the corresponding author was contacted to provide fully anonymized individual patient data as well as format, coding and definition of any variables. Risk of bias in each trial was evaluated by two independent reviewers (DH and AD) using the updated version of the risk-of-bias tool developed by Cochrane[22] (see the Supplement).

Study outcomes

The primary endpoint was mortality 90 days after randomisation. Main secondary endpoints comprised time to death up to 90 days after randomisation, treatment failure up to 90 days, defined as crossover to ECMO or death for patients in the control group, and death for patients in the ECMO group, number of days alive and out-of-hospital between randomisation and day 90, number of days alive without mechanical ventilation, renal replacement therapy and vasopressor support between randomisation and day 90. Other preplanned secondary outcomes comprised mortality at 28 and 60 days after randomisation, number of days alive and out of the ICU between randomisation and day 90, number of days alive without respiratory failure, neurological failure, cardiovascular failure, liver failure, renal failure and coagulation failure, defined as the corresponding component sequential organ failure assessment (SOFA) score greater than 2 between randomisation and day 90. Data related to patients' management, causes of death and safety outcomes were also described (see the Supplement).

Statistical Analysis

The statistical analysis was performed for each outcome of interest using individual patient data. An intention-to-treat analysis was used for all outcomes, whereby all patients were analysed in the groups to which they were randomised. The measures of treatment effect were risk ratios for binary outcomes, hazard ratios for time-to-event outcomes and mean differences for quantitative outcomes. The primary endpoint was defined as a binary outcome and analysed using both one-step (as primary analysis) and two-steps (as sensitivity analysis) methods.[23] In the one-step method, we analysed both studies simultaneously to obtain the combined treatment effect with 95% CIs and p-value by using a generalized linear mixed effect model to account for the clustering of data within each trial with a random effect. In the two steps method, we first analysed separately each trial using individual patient data before combining them using a random effects meta-analysis model to account for variability between studies. A two-step method was used for all secondary outcomes. Heterogeneity was evaluated with the Cochran's Q-test, I^2 statistic and between study variance τ^2. Survival curves for the time to death up to 90 days were generated using individual patient data and the Kaplan-Meier method.

We conducted sensitivity analyses for the primary outcome in different populations (per-protocol, as-treated). The per-protocol population included all randomised patients having received the treatment attributed by randomisation (i.e., patients having received ECMO in the ECMO arm and patients not having received ECMO in the control arm). The as-treated population compared patients receiving ECMO to those who did not receive ECMO, whatever the randomisation arm. A sensitivity analysis excluding trials at high risk of bias was also planned.

We explored whether the effect of ECMO on 90-day mortality varied according to baseline patient characteristics (see the Supplement). For each subgroup, the treatment-subgroup interaction was tested in the one-step model. For quantitative baseline characteristics, we used the median values to define the subgroups. All these subgroup analyses were pre-planned (PROSPERO, CRD42019130034).

Alpha risk was set at 5% for the primary outcome. For all secondary outcomes, we did not correct for multiple testing. As such, subgroup and sensitivity analyses should be considered as exploratory. All the analyses were performed with the use of R software version 3.6.1 (R Foundation).

The quality of evidence for the 7 most important outcomes was graded with GRADEpro GDT (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]; McMaster University, 2015 (developed by Evidence Prime, Inc.; Available from gradepro.org).

Results

Selection process and general characteristics

From the 1179 references identified by the search strategy, we included two randomised controlled trials fulfilling our eligibility criteria – CESAR and EOLIA.[15, 17] Reasons for exclusion are reported in eFigure 1 of the Supplement. The two trials provided individual patient data for all randomised patients (429 overall, 180 in CESAR and 249 in EOLIA), and there was no eligible trial not providing individual patient data. Detailed characteristics of the two trials are reported in eTable 3 in the Supplement.

Comparison of patient characteristics at randomisation did not show baseline imbalance between groups (Table 1 and eTable 4 and 5 in the Supplement). The main disorder leading to study entry was severe hypoxia (in 88% of the patients, with a mean (±SD) PaO_2:FIO_2 of 75±34 mm Hg). The main cause of ARDS was pneumonia (>60% of the patients) and 39% had 3 or more organs failing at randomisation. Of the 214 patients randomised to the ECMO groups, 189 (88%) received ECMO (98% and 76% in EOLIA and CESAR, respectively). Rescue extracorporeal gas exchange was used for 36 (17%) of the 215 control patients (35 patients crossed over to ECMO in EOLIA, and 1 to pumpless arteriovenous CO_2 removal in CESAR that was a protocol violation by the conventional management team as rescue extracorporeal gas exchange was not part of the CESAR trial design). Risk of bias was judged low in both trials (eFigure 2 in the Supplement).

Primary Outcome

By day 90, 77 (36%) ECMO-group and 103 (48%) control group patients had died (relative risk, 0.75, 95% confidence interval, 0.60 to 0.94; p = 0.013) (Table 2 and Figure 1). Results were similar in the one-step and two-steps models. There was no evidence of heterogeneity across studies (p = 0.640, I^2=0%, τ^2=0.000).

Secondary Outcomes

The hazard ratio for death within 90 days after randomisation in the ECMO group, as compared with the control group, was 0.65 (95% CI, 0.49 to 0.88) (Fig. 2). The relative risk of treatment failure, defined as death by day 90 for the ECMO-group and death or crossover to ECMO for the control group was 0.65 (0.52 to 0.80) (Table 2 and eFigure 3 in the Supplement). At 90 days, ECMO-group patients had more days alive without ventilation (40 vs 31 days, mean difference, 8 days; 95% CI, 2 to 15) and out of the ICU (36 vs 28 days, mean difference, 8 days; 95% CI, 2 to 14) than those in the control group (Table 2 and eFigure 4 in the Supplement).

At day 60 post-randomisation (90-day follow-up was not available for the following outcomes in EOLIA), patients in the ECMO group had more days alive without vasopressors (35 vs 28 days, mean difference, 8 days; 95% CI, 3 to 13), renal replacement therapy (35 vs 28 days, mean difference, 7 days; 95% CI, 2 to 13) and neurological failure (38 vs 31 days, mean difference, 7 days;

95% CI, 2 to 13) than those in the control group (Table 2 and eFigure 5 in the Supplement). Prone positioning and low-volume low-pressure mechanical ventilation were applied to 71% and 85% of control group patients, respectively (Table 3). Multiorgan failure and respiratory failure were the main causes of death in both groups (Table 3), while a cannulation-related fatal complication occurred in 3 of the 225 patients who received ECMO. Of the 214 patients randomised to ECMO, 7 (3%) died before ECMO could be established. Additional data on secondary outcomes are provided in Tables 2 and 3 and eFigure 6 in the Supplement.

Sensitivity and subgroup analyses

The relative risks of death at day 90 post-randomisation according to the per-protocol and as-treated analyses were 0.75 (95% CI, 0.60 to 0.94) and 0.86 (95% CI, 0.68 to 1.09), respectively (eFigure 7 in the Supplement). The only significant treatment-covariate interaction identified in subgroup analyses was the number of organs failing at randomisation with RR=0.53 (95% CI 0.36-0.78) among patients with 1-2 organ failures and RR=1.00 (95% CI 0.78-1.30) among patients with 3 or more organ failures, $p = 0.006$ for interaction (Figure 3). There was no evidence to suggest a differential treatment effect for any other subgroups.

Quality of Evidence

The Summary Of Findings Table reporting the evaluation of the quality of evidence for the 7 most important outcomes is presented in eTable 6 in the Supplement. The level of evidence was high for mortality at 90 days, time to death and treatment failure.

Discussion

In this individual patient data meta-analysis of patients with severe ARDS included in the CESAR[15] and EOLIA[17] randomised trials, there is strong evidence to suggest that early recourse to ECMO leads to a reduction in 90-day mortality and less treatment failure compared with conventional ventilatory support. Patients randomised to ECMO also had more days alive out of the ICU and without respiratory, cardiovascular, renal and neurological failure.

The benefit of ECMO in severe ARDS patients has long been debated.[24-27] Because of highly challenging design and conduct issues, only four randomised trials of extracorporeal life support for adult patients with acute respiratory failure have been performed in the last 5 decades.[15, 17, 28, 29] Our meta-analysis included only the two most recent trials (CESAR[15] and EOLIA[17]) since major advances in ICU care and in ECMO techniques have occurred in the past 15 years making the two older trials not relevant for comparison.[10, 20, 21] In addition the two older trials did not use venovenous ECMO. One used venoarterial ECMO[28] and one used low-flow veno-venous extracorporeal CO_2 removal.[29] Characteristics of patients included in EOLIA and CESAR were comparable regarding ARDS aetiology and disease severity at randomisation. Patients were enrolled early after the initiation of invasive mechanical ventilation and rates of control patients being proned and receiving low-volume low-pressure mechanical ventilation were high. Both EOLIA and CESAR trials showed a comparable survival benefit with ECMO, but neither was individually powered to detect a reasonable survival difference between groups. Specifically, the data safety monitoring board of EOLIA, following pre-specified guidance using a sequential design with a two-sided triangular test based on 60-day mortality, recommended stopping the trial for futility after 75% of the maximal sample size had been enrolled because the probability of demonstrating a 20% absolute risk reduction in mortality with ECMO was considered unlikely. Our meta-analysis, which includes a much larger number of patients and shows higher survival with ECMO in both the intention-to-treat and per-protocol analyses provides strong evidence about the benefit of ECMO in severe ARDS. Our results also extend the conclusions of a post-hoc Bayesian analysis of EOLIA indicating a very high probability of ECMO success in severe ARDS patients, ranging from 88% to 99% depending on the chosen priors.[30] Our results are consistent with two previous aggregated data meta-analyses in the field: one was a network meta-analysis considering different interventions whose impact is limited by the lack of direct comparisons[31] and the other focused on ECMO.[32] Our IPD meta-analyses goes beyond these two previous studies and provides a stronger evidence on the benefit of ECMO in ARDS for the following reasons. IPD meta-analyses provides a higher level of evidence than aggregated data meta-analyses because they are independent of the quality of reporting in included studies and allow evaluation of other important outcomes such as time to death and number of days without organ failures.[33, 34]

In this study, we showed that, beyond mortality, duration and severity of organ failures also favoured ECMO, and these results were highly consistent between the two studies. This observation provides insights into the potential pathophysiological mechanisms of ECMO-associated benefits in severe ARDS.[10] Although extracorporeal gas exchange may rescue some patients dying of profound hypoxemia or in whom high pressure mechanical ventilation has become dangerous, minimization of lung stress and strain associated with positive pressure ventilation may drive most of the improved outcomes observed under ECMO.[10] Ultraprotective ventilation with very low VTs, driving pressures and respiratory rates,[35] and therefore minimized overall mechanical power transmitted to lung alveoli[36] may reduce ventilator-induced lung injury, pulmonary and systemic inflammation and ultimately organ failure leading to death. These data also reinforce the recent recommendation of the World Health Organization (WHO),[37] and the Surviving Sepsis Campaign[38] to consider ECMO support in coronavirus disease 2019 (COVID-19)-related ARDS with refractory hypoxemia if lung protective mechanical ventilation was insufficient to support the patient.[39]

Meta-analyses of individual patient data can also explore outcomes in important subgroups and suggest which population may derive the greatest benefit of a specific intervention, which is very limited in aggregated data meta-analyses.[40] In this study, the mortality of patients with only one or two organs failing at randomisation was almost halved with ECMO (22% vs. 41%) while it was not substantially different between groups in patients with ≥3 organ failures ~~(P=0.006 for interaction)~~. This finding suggests that veno-venous ECMO may not be able to improve the outcomes of ARDS patients with severe shock and multiple organ failure. In EOLIA, patients with baseline PaO_2:FIO_2 >66 mmHg or those enrolled due to severe respiratory acidosis and hypercapnia, seemed to derive the greatest benefit of ECMO.[17]

This analysis has several limitations. First, inclusion criteria were more stringent for the EOLIA trial, in which, for example, ventilator optimization (FIO2>80%, VT at 6 ml/kg predicted body weight and PEEP >10 cm H_2O) was mandatory before enrolment. However, it should be noted that baseline patient characteristics were comparable regarding ARDS severity at inclusion (eTable 4 in the Supplement). Second patient management was not similar in the two studies. In CESAR, 24% of patients randomised to the ECMO arm did not receive ECMO and there was no standardized protocol for mechanical ventilation in the control group. Conversely, in EOLIA, 98% of patients randomised to ECMO received the intervention, the mechanical ventilation strategy in the control group followed a strict protocol, and rescue ECMO was applied to 28% of control group patients who had developed refractory hypoxemia. However, this meta-analysis showed a significantly lower mortality with ECMO in the per-protocol analysis including only patients in whom ECMO had been initiated in the ECMO arm and patients not having ECMO in the control arm. This analysis minimizes the aforementioned management differences, since the least severe patients who did not receive ECMO after MV optimization in CESAR were excluded from the ECMO arm and the most severe patients who needed rescue ECMO in EOLIA were excluded from the control arm. In contrast, ECMO was not associated with a mortality benefit in the as-treated population, but such an analysis strongly disadvantages the ECMO group, which includes the most severe control patients rescued by ECMO. Second, this meta-analysis does not provide detailed data on ECMO-related safety endpoints since they were not reported in CESAR. Death directly related to ECMO cannulation was rare in both studies and the rates of stroke and major bleeding were also low in EOLIA, in which a restrictive anticoagulation strategy was applied.[17] Third, no long-term outcomes beyond 90 days post-randomisation were analysed although the CESAR trial[15] and a retrospective cohort of ARDS patients[41] reported satisfactory long-term health-related quality-of-life after ECMO. Fourth, only the CESAR trial provided a cost-effectiveness analysis that suggested a benefit of the transfer of ARDS patients to a centre with an ECMO-based management protocol.[15] Our results, showing improved survival, with more days alive out of the ICU and without the need for major organ support are in line with CESAR's cost-effectiveness data. Fifth, many conditions such as MV duration >7 days prior to ECMO or major comorbidities were exclusion criteria for enrolment in both CESAR and EOLIA. The indication to initiate ECMO should therefore be carefully evaluated in these situations. Lastly, ECMO should be used in experienced centres and only after proven conventional management of severe ARDS (including lung protective mechanical ventilation and prone positioning) have been applied and failed,[42] except when hypoxemia is immediately life-threatening, or when the patient is too unstable for prone positioning.[43]

In conclusion, this meta-analysis of individual patient data of the CESAR and EOLIA trials showed strong evidence of a clinically meaningful benefit of early ECMO in severe ARDS patients. Another large study of ECMO appears unlikely in this setting and future research should focus on the identification of patients most likely to benefit from ECMO and optimization of treatment strategies after ECMO initiation [44].

The trial was registered at PROSPERO (CRD42019130034) on May 1st 2019.

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See the Supplement for the list of EOLIA and CESAR collaborators.

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Conflict of interest statement

Alain Combes reports grants from Getinge, personal fees from Getinge, Baxter and Xenios outside the submitted work. Matthieu Schmidt reports lecture fees from Getinge, Drager and Xenios outside the submitted work. The other authors declare that they have no conflicts of interest related to the purpose of this manuscript.

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Table 1. Characteristics of the patients at randomisation. *

Characteristic	ECMO group (N = 214)	Control group (N = 215)
Age, years	46.6±15.2	48.3±14.8
Male — no. (%)	138 (65)	143 (67)
Median (interquartile) time since intubation, h	35 [16-95]	36 [16-100]
ARDS aetiology — no. (%)		
Pneumonia	136 (64)	131 (61)
Other	78 (36)	84 (39)
3 or more organs failed†	82 (38)	84 (39)
Predicted mortality‡	0.34±0.23	0.34±0.22
$PaO_2:F_IO_2$	76±35	75±33
pH	7.30±0.37	7.26±0.24
Disorder leading to study entry		
Hypoxia	184 (86%)	192 (89%)
Uncompensated hypercapnia	30 (14%)	23 (11%)
PEEP, cm H_2O	12.3±6.8	12.7±6.8
Respiratory system compliance, ml/cm H_2O	25.8±11.8	25.3±8.8
Murray Score	3.3±0.6	3.3±0.4
Chest radiograph (quadrants infiltrated)	3.4±0.9	3.5±0.8

* Plus–minus values are means ±SD; see eTable 5 the Supplement for missing data.

† number of organ failed (0 to 6) defined as the corresponding component sequential organ failure assessment (SOFA) score > 2.

‡ APACHE2 (CESAR) and SAPS2 (EOLIA) scores were both translated to predicted probability of ICU mortality.

ECMO denotes extracorporeal membrane oxygenation, ARDS the acute respiratory distress syndrome, PaO_2 partial pressure of arterial oxygen, FiO_2 the fraction of inspired oxygen, PaO_2/F_IO_2

the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, PEEP positive end-expiratory pressure.

Missing data were <3% for patients' characteristics at randomisation, except for predicted mortality, respiratory system compliance and Murray score (see eTable 5 in the Supplement).

Table 2. Endpoints.

Endpoint	ECMO group (N = 214)	Control group (N = 215)	Relative Risk or difference (95% CI)	*P*	I^2 (%)
Primary endpoint					
Day 90 mortality — no. (%)	77 (36)	103 (48)	0.75 (0.60 to 0.94)	0.013	0
Secondary endpoints*					
Day 90 treatment failure — no. (%)	77 (36)	119 (55)	0.65 (0.52 to 0.80)		0
Day 28 mortality — no. (%)	50 (23)	88 (41)	0.57 (0.40 to 0.81)		33
Day 60 mortality — no. (%)	73 (34)	101 (47)	0.73 (0.58 to 0.92)		0
Day 1–90 ICU-free days †	36±32	28±33	8 (2 to 14)		0
Day 1–90 hospital-free days †	22±27	18±27	4 (-1 to 9)		0
Day 1–90 ventilation-free days †	40±35	31±34	8 (2 to 15)		0
Day 1–60 vasopressor-free days †‡	35±26	28±27	8 (3 to 13)		0
Day 1–60 RRT-free days †‡	35±27	28±27	7 (2 to 13)		0
Day 1–60 neurological failure-free days †‡£	38±28	31±30	7 (2 to 13)		6

Data are mean (SD) or number (%).

ECMO denotes extracorporeal membrane oxygenation, ICU intensive care unit and RRT renal replacement therapy.

* The width of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment differences.

† Free-days were calculated assigning zero free-days to patients who died during the follow-up period.

‡ Day-by-day follow-up was limited to Day 60 in the EOLIA trial

£ Neurological failure was defined by the number of days without neurological depression requiring system monitoring/support' in CESAR study and the neurologic component of the sequential organ failure assessment (SOFA) score greater than 2.

Table 3. Patients' management and other outcomes.

Endpoint	ECMO group (N = 214)	Control group (N = 215)
Received ECMO — no. (%)	189 (88)	36 (17)
Days under ECMO*	14.3±12.6	16.6±15.0
Received LVLP MV — no. (%)†	205 (98)	181 (85)
Prone position (before and after randomisation) — no. (%)†	114 (54)	151 (71)
iNO or prostacyclin — no. (%)†	84 (40)	110 (51)
Renal replacement therapy — no. (%)†	106 (50)	129 (60)
Steroids — no. (%)†	156 (74)	140 (65)
ICU length of stay, days	29.7±24.6	23.6±35.9
For survivors	35.2±22.5	39.5±26.3
For non-survivors	20.2±17.6	15.4±16.2
Hospital length of stay, days	49.0±43.1	42.7±69.3
For survivors	58.3±23.8	60.0±28.5
For non-survivors	20.2±17.6	15.4±16.2
Cause of death		
Respiratory failure	13 (6)	36 (17)
Multiple organ failure	35 (16)	44 (20)
ECMO cannulation-related	2 (1)	1 (0)
Miscellaneous	27 (13)	22 (10)

Data are mean (SD) or number (%); see eTable 5 in the Supplement for missing data.

* For patients who received ECMO.

† From randomisation to Day 60.

ECMO denotes extracorporeal membrane oxygenation, LVLP MV, low-volume low-pressure mechanical ventilation, iNO inhaled nitric oxide, and ICU intensive care unit.

Missing data were <2.5% for patients' outcomes (see eTable 5 in the Supplement).

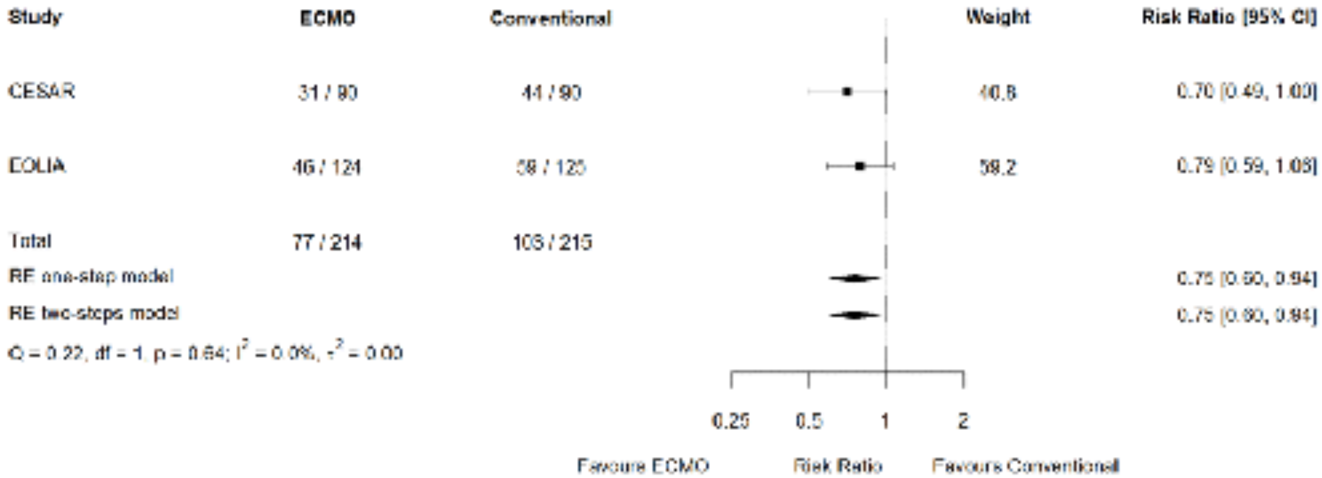
Figure legend

Figure 1. Forest plot of 90-day mortality in the intention-to-treat population.

Figure 2. Kaplan–Meier survival estimates in the intention-to-treat population of the time to death within the first 90 study days.

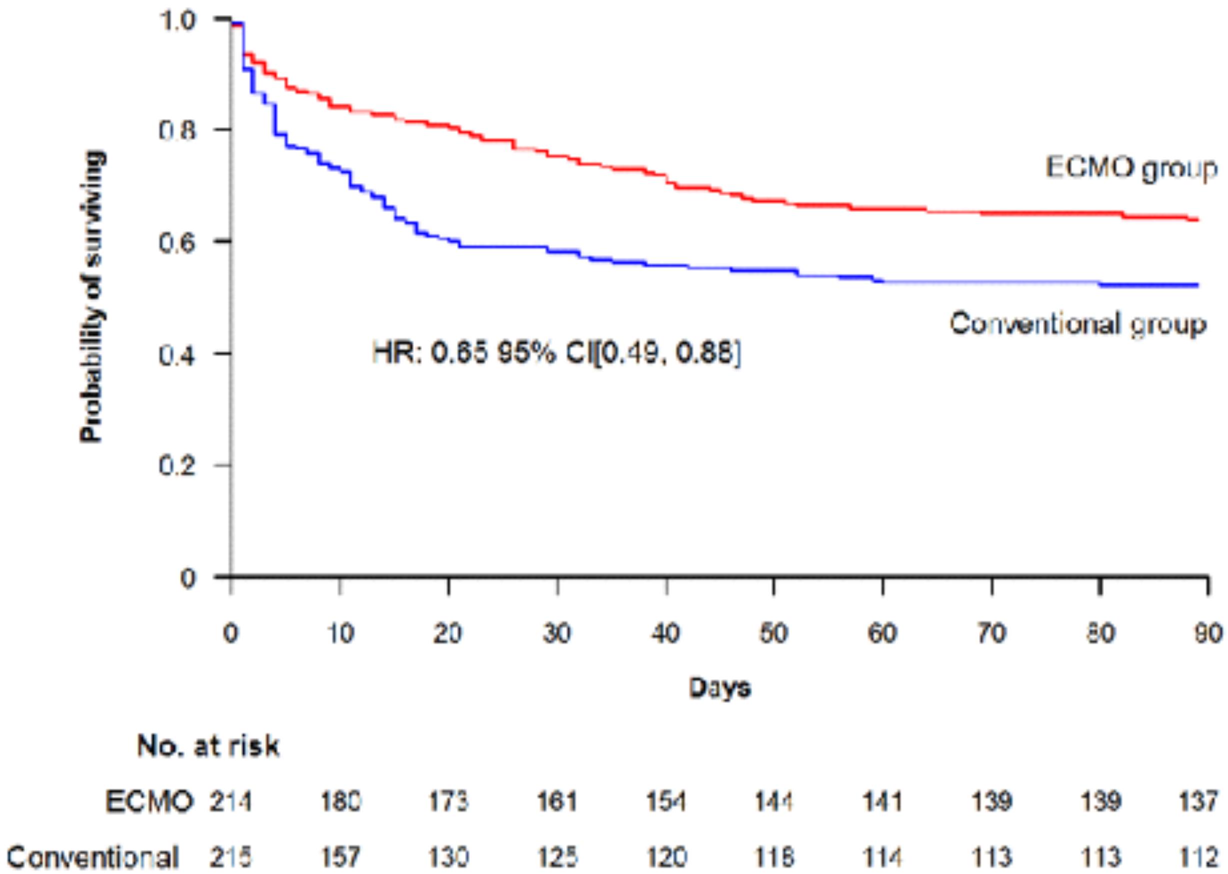
Figure 3. Subgroup analyses for the primary outcome according to baseline characteristics.
MV, mechanical ventilation; number of organ failed (0 to 6) defined as the corresponding component sequential organ failure assessment (SOFA) score > 2; APACHE2 (CESAR) and SAPS2 (EOLIA) scores were both translated to predicted probability of ICU mortality.

Figure 1



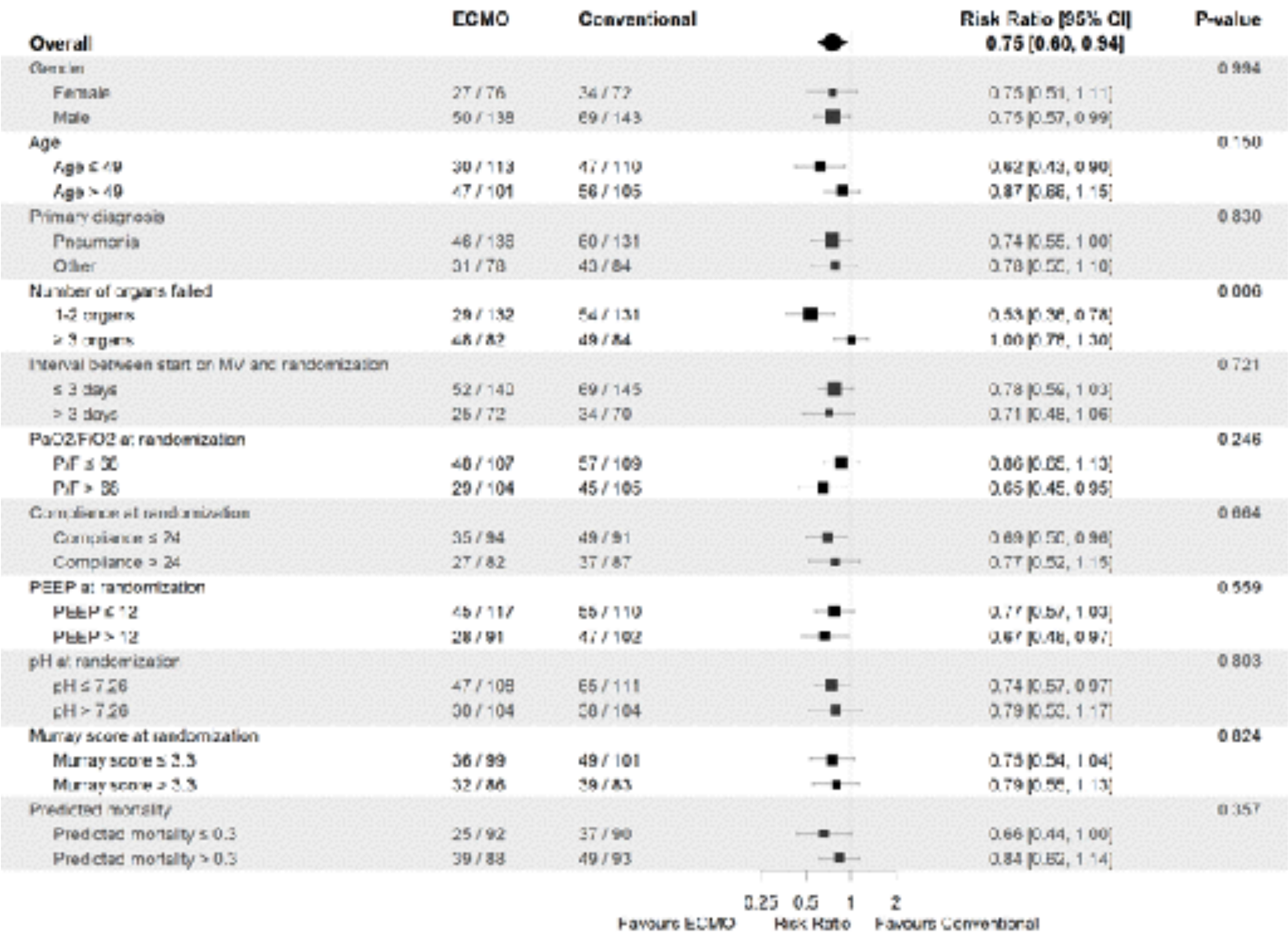
Study
ECMO
Conventional
Weight
Risk Ratio [95% CI]
CESAR
31 / 90
44 / 90
40.8
0.70 [0.49, 1.00]
EOLIA
46 / 124
59 / 125
59.2
0.79 [0.59, 1.06]
Total
77 / 214
103 / 215
RE one-step model
0.75 [0.60, 0.94]
RE two-steps model
0.75 [0.60, 0.94]
Q = 0.22, df = 1, p = 0.64; I² = 0.0%, τ² = 0.00
0.25
0.5
1
2
Favours ECMO
Risk Ratio
Favours Conventional

Figure 2



1.0
0.8
0.6
0.4
0.2
0
Probability of surviving
ECMO group
Conventional group
HR: 0.65 95% CI[0.49, 0.88]
0
10
20
30
40
50
60
70
80
90
Days
No. at risk
ECMO 214 180 173 161 154 144 141 139 139 137
Conventional 215 157 130 125 120 118 114 113 113 112

Figure 3


ECMO
Conventional
Risk Ratio [95% CI]
P-value
Overall
0.75 [0.60, 0.94]
Gender
0.994
Female 27 / 76 34 / 72 0.75 [0.51, 1.11]
Male 50 / 138 69 / 143 0.75 [0.57, 0.99]
Age
0.150
Age ≤ 49 30 / 113 47 / 110 0.62 [0.43, 0.90]
Age > 49 47 / 101 56 / 105 0.87 [0.66, 1.15]
Primary diagnosis
0.830
Pneumonia 46 / 138 60 / 131 0.74 [0.55, 1.00]
Other 31 / 78 43 / 84 0.78 [0.55, 1.10]
Number of organs failed
0.006
1-2 organs 29 / 132 54 / 131 0.53 [0.36, 0.78]
≥ 3 organs 48 / 82 49 / 84 1.00 [0.78, 1.30]
Interval between start on MV and randomization
0.721
≤ 3 days 52 / 140 69 / 145 0.78 [0.56, 1.03]
> 3 days 25 / 72 34 / 70 0.71 [0.48, 1.06]
PaO2/FiO2 at randomization
0.246
48 / 107 57 / 109 0.86 [0.65, 1.13]
29 / 104 45 / 105 0.65 [0.45, 0.95]
Compliance at randomization
0.664
Compliance ≤ 24 35 / 94 49 / 91 0.69 [0.50, 0.96]
Compliance > 24 27 / 82 37 / 87 0.77 [0.52, 1.15]
PEEP at randomization
0.559
PEEP ≤ 12 45 / 117 55 / 110 0.77 [0.57, 1.03]
PEEP > 12 28 / 91 47 / 102 0.67 [0.46, 0.97]
pH at randomization
0.803
pH ≤ 7.26 47 / 108 65 / 111 0.74 [0.57, 0.97]
pH > 7.26 30 / 104 38 / 104 0.79 [0.53, 1.17]
Murray score at randomization
0.824
Murray score ≤ 3.3 36 / 99 49 / 101 0.75 [0.54, 1.04]
Murray score > 3.3 32 / 86 39 / 83 0.79 [0.55, 1.13]
Predicted mortality
0.357
Predicted mortality ≤ 0.3 25 / 92 37 / 90 0.66 [0.44, 1.00]
Predicted mortality > 0.3 39 / 88 49 / 93 0.84 [0.62, 1.14]
0.25 0.5 1 2
Favours ECMO
Risk Ratio
Favours Conventional

Supplementary online material

ECMO for severe acute respiratory distress syndrome: systematic review and individual patient data meta-analysis

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Supplementary online material

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I. AUTHORS' CONTRIBUTIONS

Dr Combes had full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis.

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II. EOLIA AND CESAR TRIALS GROUPS

1. EOLIA

The EOLIA trial[1] was supported by the Direction de la Recherche Clinique et du Développement (DRCD), Assistance Publique–Hôpitaux de Paris (APHP), with a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique number, PHRC 2009 081224), the EOLIA Trial Group, the Réseau Européen en Ventilation Artificielle (REVA) and the International ECMO Network (ECMONet, http://www.internationalecmonetwork.org).

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2. CESAR

The CESAR trial was supported by the UK NHS Health Technology Assessment, English National Specialist Commissioning Advisory Group, Scottish Department of Health, and Welsh Department of Health.

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III. SUPPLEMENTARY DATA

1. METHODS

Ethical Aspects

The study protocol for the systematic review and IPD meta-analysis was approved by the relevant independent ethics committees: in France, Comité de Protection des Personnes CPP Ile de France VI, Pitié-Salpêtrière, on 04/19/2018, Ref #12 and in the UK by the Ethics committee of the London School of Hygiene and Tropical Medicine, on 04/12/2019, LSHTM Ethics Ref: 17159.

Only patient characteristics and outcomes already evaluated in the trials were combined in this systematic review and meta-analysis.

Study Design

The protocol followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P) and was registered in PROSPERO (CRD42019130034).

Eligibility criteria

Type of Studies

We included only randomised controlled trials (RCTs) published or whose primary completion date is after 2000. This choice is justified by major progress in intensive care treatment in general and in ECMO techniques in particular that have considerably modified the prognosis of patients.[2] We considered all types of RCTs whether they are published or not and whatever their language of publication.

Population

We included trials of patients with ARDS fulfilling the American–European Consensus Conference definition[3] or the Berlin definition for ARDS,[4] who were endotracheally intubated and who had signs of severe hypoxemia or hypercapnia.

We excluded trials involving only patients aged <18 years; with mechanical ventilation for >7 days; pregnancy; weight >1 kg/cm (height), or body mass index >45 kg/square meter; long-term chronic respiratory insufficiency treated with oxygen therapy or non-invasive ventilation; cardiac failure requiring venoarterial-ECMO; history of heparin-induced thrombocytopenia; malignancy with life expectancy <5 years; patient moribund on the day of randomisation or with a simplified acute physiology score (SAPS II) >90; non-drug–induced coma following cardiac arrest; irreversible neurological injury; decision to withhold or withdraw life-sustaining therapies; expected difficulty in obtaining vascular access for ECMO in the femoral or jugular vein; or ECMO device not immediately available.

Intervention in the Experimental Group

We included trials evaluating in the experimental group early veno-venous cannulation and ECMO initiation with adjustment of mechanical ventilator settings to allow low-volume, low-pressure ventilation.

Intervention in the Control Group

We included trials evaluating in the control group conventional ventilatory management.

Data Sources

Electronic Search

We searched MEDLINE via PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (Central) from 2000 (see justification above) to 30 September 2019 using a search algorithm developed for the purpose of this study and adapted to each database. The search algorithm included both key-words relevant to this topic and free text words as well as the sensitive filter developed by the Cochrane Collaboration to identify RCTs. The search algorithm for MEDLINE via PubMed is reported in Table S1.

We also searched trial registries including ClinicalTrials.gov and the International Clinical Trial Registry Platform (ICTRP) for completed and ongoing trials.

Additional Searches

We screened conference proceedings of major critical care societies (American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), Society of Critical Care Medicine (SCCM) and International Symposium on Intensive Care and Emergency Medicine (ISICEM) for the last 5 years.

We also screened reference lists of identified articles as well as systematic or narrative reviews on the topic and contact experts for further eligible trials.

Selection Process

Selection was conducted by two independent reviewers (DA and MS) on titles and abstracts first and then, on the full text. Any discrepancies between the reviewers was discussed with the help of a third reviewer whenever necessary to reach a consensus on studies to be included.

Endnote (Thomson Reuters) was used to manage references and conduct the selection process.

Data Collection Process

For each included RCT, the corresponding author was contacted by email to request individual patient data. The members of the team conducted the two most important RCTs in the topic (EOLIA[1] and CESAR[5]). For each RCT, we asked for fully anonymized IPD for all randomised participants as well as format, coding and signification of any variables. To check data and ensure reproducibility of results, we re-analyzed each included trial in collaboration with each principal investigator, data manager and statistician. In particular, we evaluated data consistency and completeness as well as baseline imbalance (for risk of bias assessment as detailed below). We reviewed the individual study protocols, case report forms and definition of variables to harmonize databases. Whenever necessary, we transformed variables to have homogeneous variable coding across trials in order to merge IPD into one single database.

We planned a strategy in case we identified eligible RCTs but could not obtain individual patient data but this situation was not encountered. Two reviewers would have independently extracted for each outcome of interest, aggregated data from the full text of each RCT with discrepancies solved by discussion with the help of a third reviewer whenever necessary. We would conduct a sensitivity analysis to account for these trials using a two-step approach.

Risk of Bias

For each eligible RCT, risk of bias was evaluated independently by two reviewers using the updated version of the Risk of bias tool developed by the Cochrane Collaboration[6] (www.cochrane.org).

We initially planned to use the first version of the tool but the updated version was made available while we were conducting this systematic review and we decided to use this updated version. We evaluated the following domains: risk of bias arising from the randomisation process (using full-text articles and IPD), risk of bias due to deviations from the intended interventions (using full-text articles and protocols), risk of bias due to missing outcome data (using full-text articles and IPD), risk of bias in measurement of the outcome (using full-text articles and protocols), risk of bias in selection of the reported result (using full-text articles, protocols and registration). We focused on our primary outcome for this evaluation.

Study Outcomes and planned analyses

The primary endpoint was mortality 90 days after randomisation in the intention-to-treat population.

The following outcomes were defined as secondary endpoints of interest: time to death up to 90 days after randomisation, treatment failure up to 90 days, defined as crossover to ECMO or death for patients in the control group, and death for patients in the ECMO group, number of days alive and out of hospital, between randomisation and day 90, number of days alive without mechanical ventilation, renal replacement therapy and vasopressor support between randomisation and day 90. Other secondary outcomes included mortality at 28 and 60 days after randomisation, number of days alive and out of the ICU between randomisation and day 90, number of days alive without respiratory failure, neurological failure, cardiovascular failure, liver failure, renal failure and coagulation failure, defined as the corresponding component sequential organ failure assessment (SOFA) score greater than 2 between randomisation and day 90.

Description of patients' management in each group included duration of ECMO support up to

90 days, durations of ICU and hospital stay, rate of patients who received and duration of inhaled nitric oxide, recruitment maneuvers, prone position, high frequency oscillation ventilation, almitrine infusion and low-volume low-pressure ventilation strategy up to 90 days post-randomisation. Causes of death were analyzed and deaths directly attributed to the ECMO procedure were defined as those occurring in the setting of ECMO-device failure: massive gas emboli, cardiac arrest due to massive circuit clotting, septic shock due to ECMO cannulation–site infection, cerebral or meningocerebral hemorrhage, pneumothorax during cannula insertion, or massive hemorrhage requiring transfusion of at least ≥10 units of pack red blood cells. Safety outcomes included: pneumothorax, stroke, ECMO cannula insertion-site infections, cannula thrombosis, ECMO circuit change, intravascular hemolysis, ventilator-associated pneumonia, severe hemorrhagic complications and red blood cells transfusion.

Only outcomes already evaluated in trials were combined in meta-analyses. There were no additional data collected for this systematic review and individual patient data meta-analysis.

Study Outcomes Modified or Not Evaluated in Meta-Analysis Because of Unavailability in Included Studies

Because only two trials were eligible and included, we combined in the meta-analysis only predefined outcomes available in both trials. In EOLIA,[1] the day-by-day follow-up was limited to Day 60, except for mortality, mechanical ventilation, and ICU/hospital duration. Thus, the time-frame was shrunk up to day 60 for the following outcomes: number of days alive without RRT, number of days alive without vasopressors, number of days alive without respiratory failure, number of days alive without neurological failure, and number of days alive without cardiovascular failure.

Number of days alive without liver failure, number of days alive without renal failure, and number of days alive without coagulation failure were not available in the CESAR study,[5] these outcomes were thus excluded from the meta-analysis.

Statistical Analysis

The statistical analysis was performed for each outcome of interest using individual patient data. An intention-to-treat analysis was used for all outcomes, whereby all randomised patients were analyzed in the groups to which they were randomised. The measures of treatment effect were risk ratios for binary outcomes, hazard ratios for time-to-event outcomes and mean differences for quantitative outcomes. The primary endpoint, mortality up to 90 days, was defined as a binary outcome. For the primary endpoint, the analysis involved both one step (as primary analysis) and two steps (as sensitivity analysis) methods. In the one step method, we analyzed all studies simultaneously to obtain the combined treatment effect with 95% CIs and p-values by using a generalized linear mixed effect model to account for the clustering of data within each trial with a random effect. In the two steps method, we first analyzed separately each study using IPD before combining them using a random effects meta-analysis model to account for variability between studies. For convenience reasons and due to the number of analyses, only the two-step method was used for all secondary endpoints. Heterogeneity was evaluated with the Cochran's Q-test, I^2 and between study variance τ^2. Survival curves for the time to death up to 90 days were generated using IPD and the Kaplan-Meier method.

Sensitivity analyses according to different populations of analysis (per-protocol, as-treated) were conducted. The per-protocol population included all randomised patients having received the treatment attributed by randomisation (i.e., patients having received ECMO in the ECMO arm and patients not having ECMO in the control arm). The as-treated population compared patients receiving ECMO to those who did not receive ECMO, whatever the randomisation arm. We planned a sensitivity analysis excluding trials at high risk of bias for each domain but we did not conduct it because only two trials were included and because they were judged at low risk of bias.

We explored whether the effect of ECMO on 90 day mortality varies according to the following baseline characteristics: age, gender, partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO2/FIO2), interval between initiation of mechanical ventilation and randomisation, driving pressure, respiratory system compliance, positive end-expiratory pressure (PEEP), pH, number of organs failed, Murray score, acute physiology score and chronic health (APACHE) II or SAPS II predicted mortality, pneumonia vs. other etiologies of ARDS and use of prone position. For each subgroup, the treatment-subgroup interaction was tested in the one step model. For quantitative baseline characteristics, we used the median values to define the subgroups. All these subgroup analyses (except for the subgroup of patients who received lung protective ventilation) were preplanned as registered in the PROSPERO database (CRD42019130034). We added a post hoc exploratory analysis of 90-d mortality restricted to patients having received lung protective ventilation. Alpha risk was set at 5%. We defined a single primary outcome and did not correct alpha risk for multiple testing. As such all secondary outcomes, subgroup and sensitivity analyses should be considered as exploratory. All analyses involved use of R version 3.6.1.

Grading of the Evidence

For each key outcome (the primary outcome and the 6 most important prespecified secondary outcomes), the quality of evidence was graded using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach and GRADEpro GDT ((GRADEpro GDT:

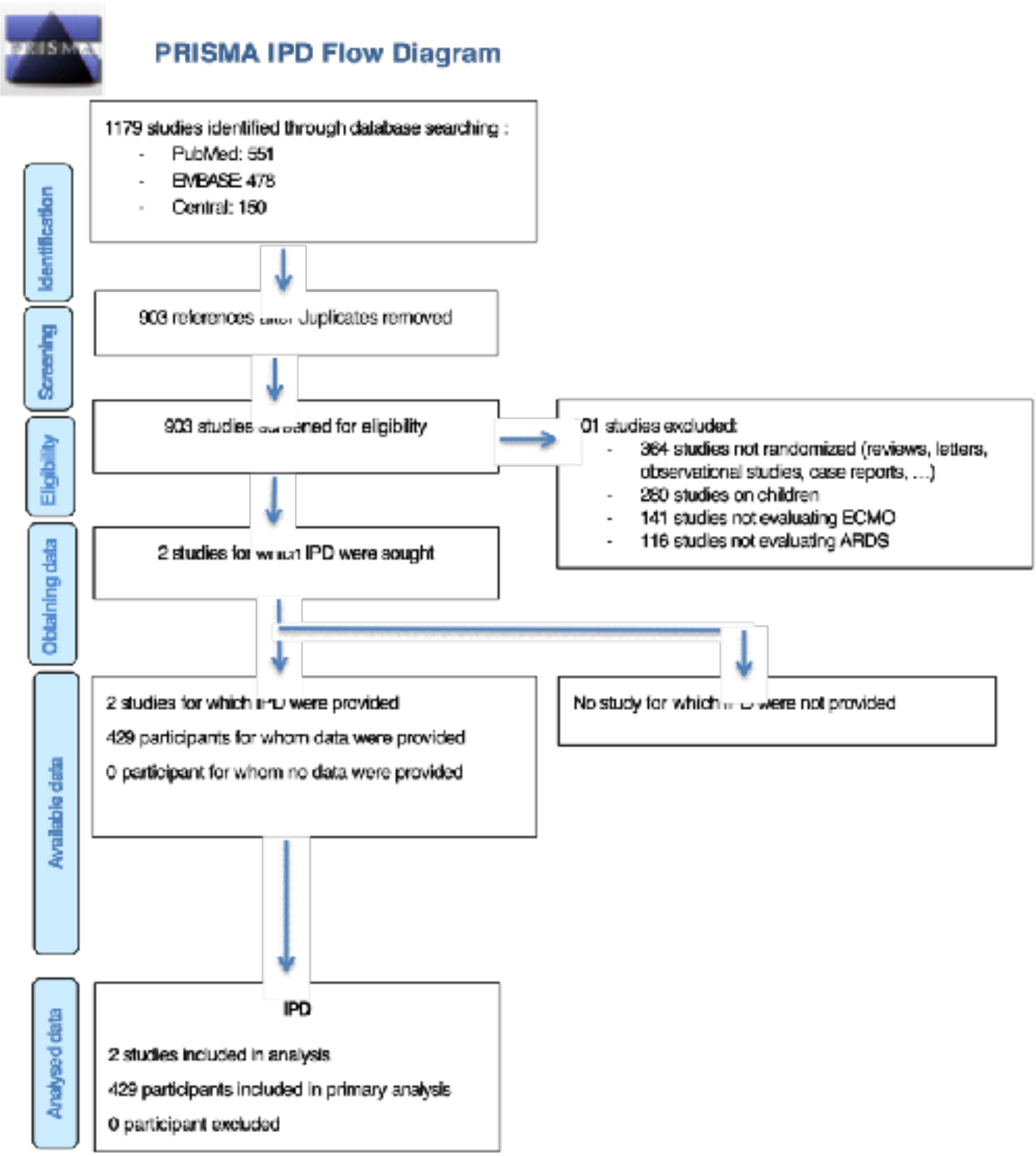
GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org). A summary of findings table (Table S5) summarizes these results.

The primary outcome was mortality up to 90 days after randomisation. The 6 most relevant secondary outcomes were defined as:

- Time to death up to 90 days after randomisation;
- Treatment failure up to 90 days, defined as crossover to ECMO or death for patients in the control group, and death for patients in the ECMO group;
- Number of days alive and out of hospital, between randomisation and day 90;
- Number of days alive without mechanical ventilation between randomisation and day 90;
- Number of days alive without renal replacement therapy between randomisation and day 90;
- Number of days alive without vasopressor support between randomisation and day 90.

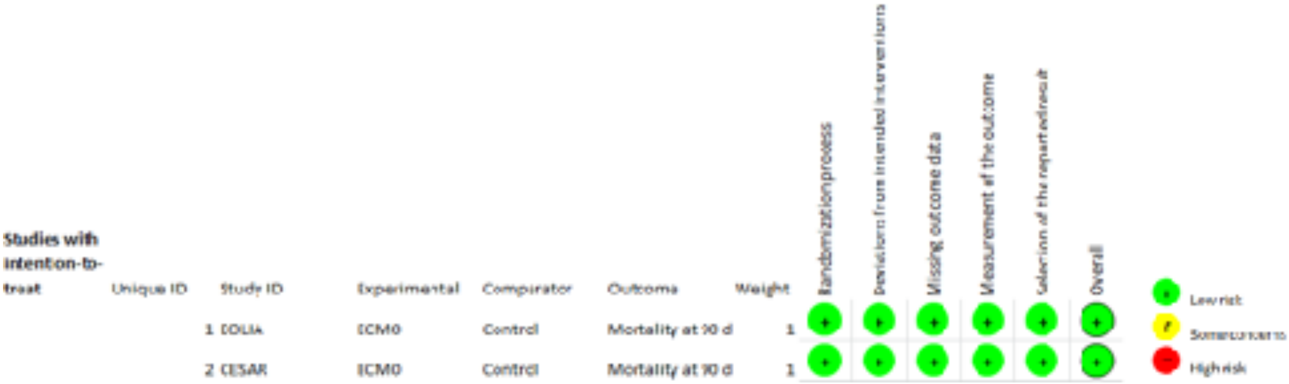
2. FIGURES

eFigure 1. Flow chart of study selection.



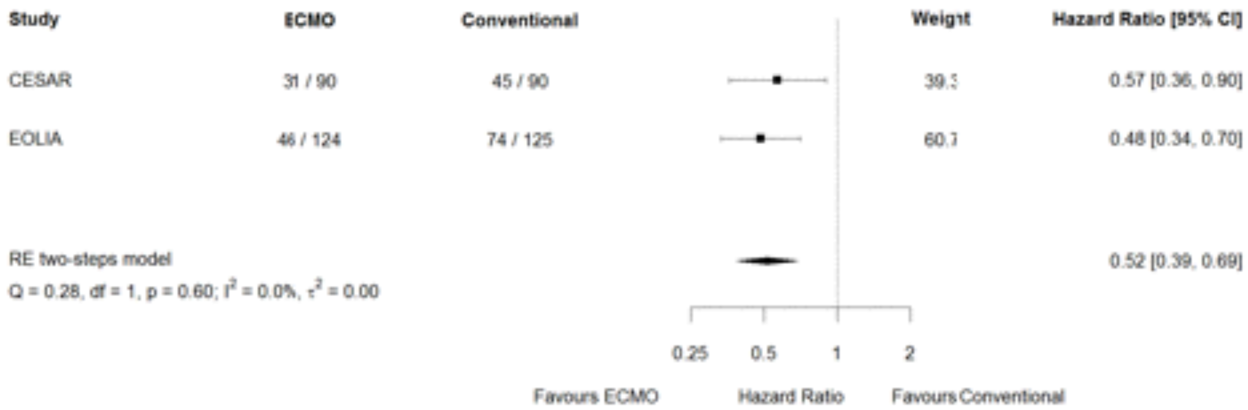
The PRISMA IPD flow diagram

eFigure 2. Risk of bias in the trials included in the analysis.

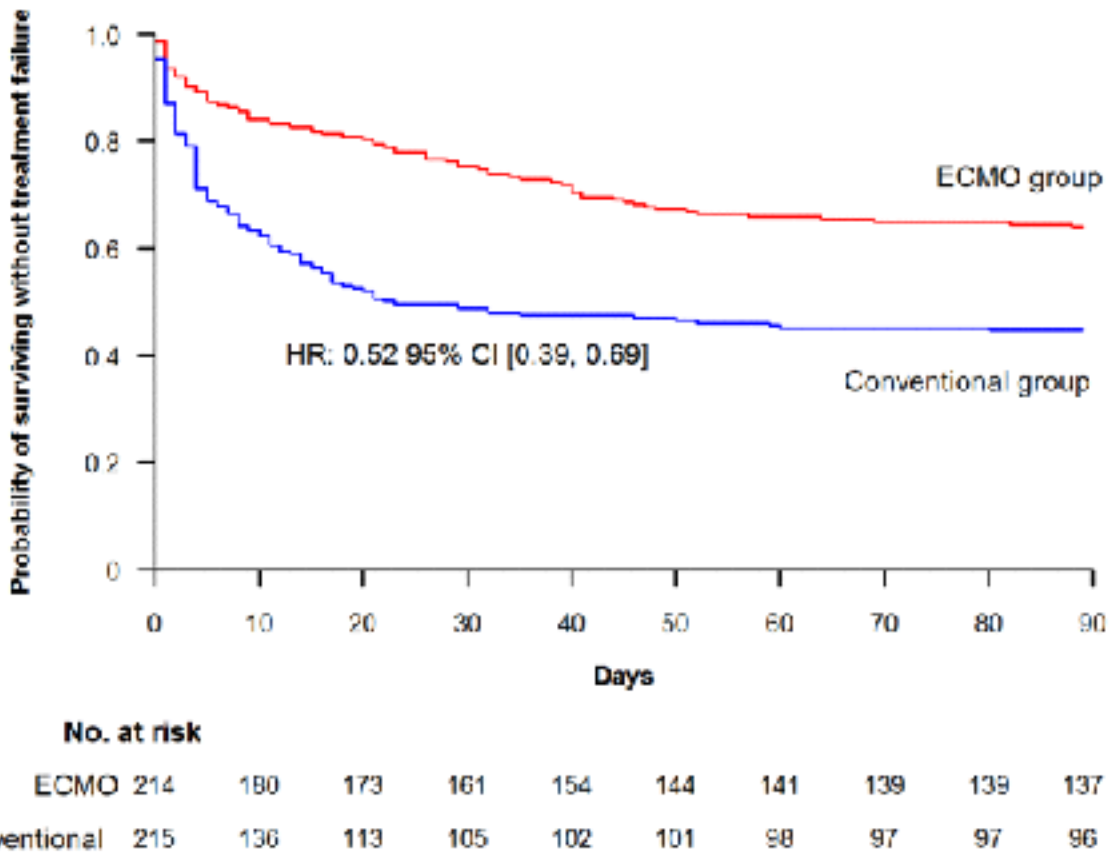


eFigure 3. Forest plot (A) and Kaplan–Meier survival estimates (B) in the intention-to-treat population of the time to treatment failure within the first 90 study days.

A

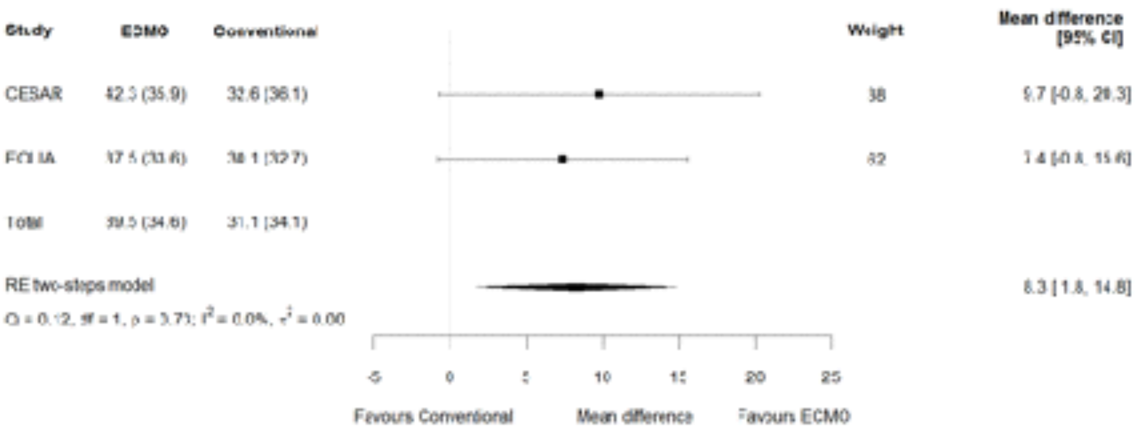


B

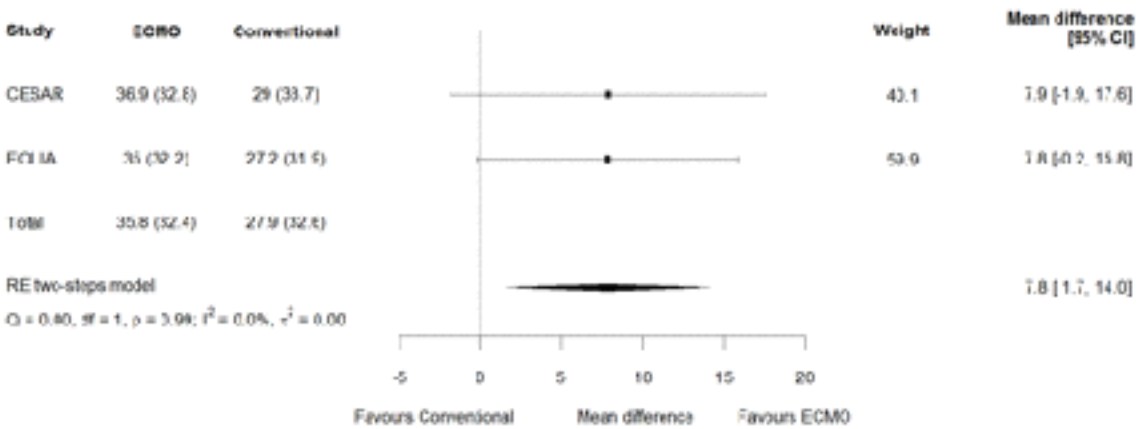


eFigure 4. 90-day free-days of mechanical ventilation (A), ICU (B), and hospital (C).

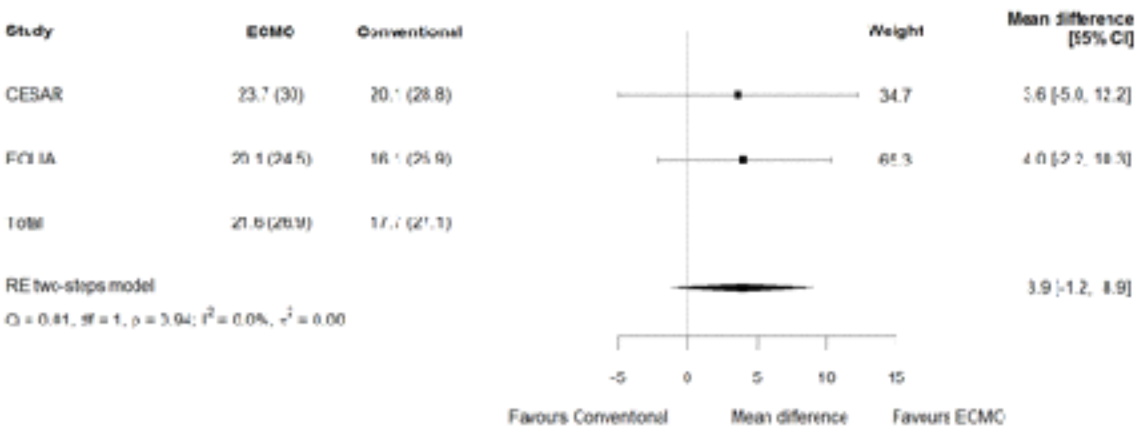
A



B

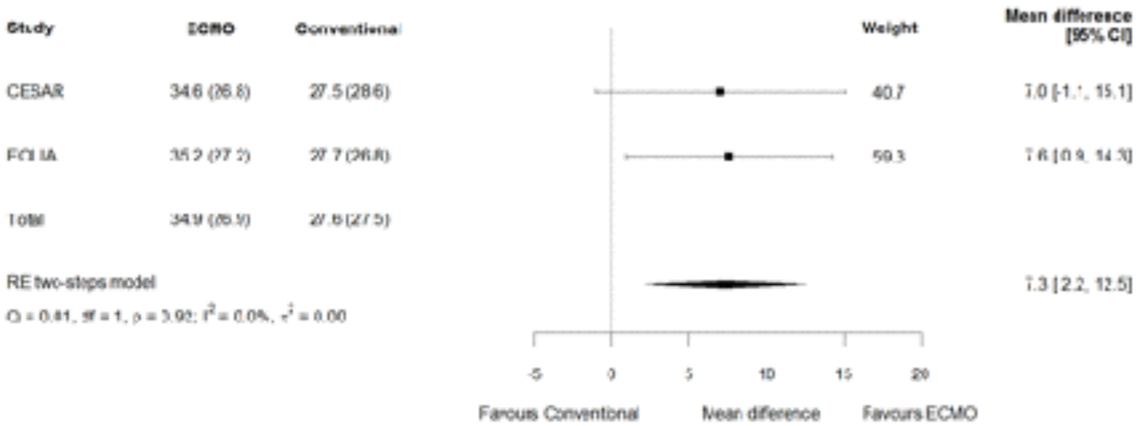


C

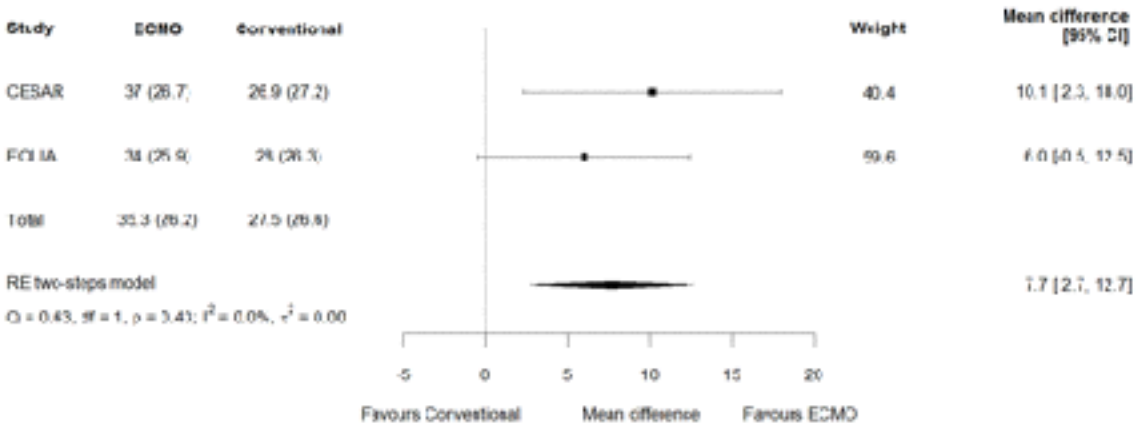


eFigure 5. 60-day free-days of renal replacement therapy (A), vasopressors (B), and neurological failure (C). Neurological failure was defined by the number of days without neurological depression requiring system monitoring/support' in CESAR study and the neurologic component of the sequential organ failure assessment (SOFA) score greater than 2.

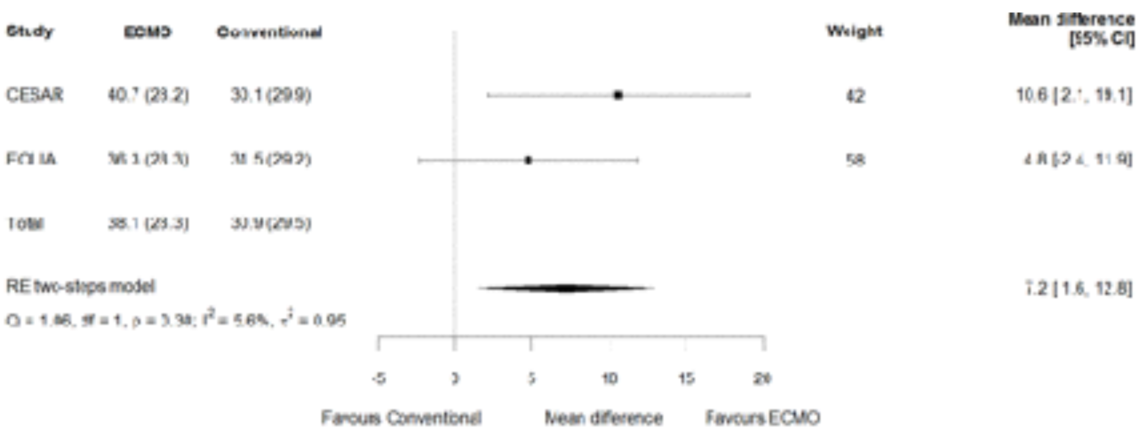
A



B

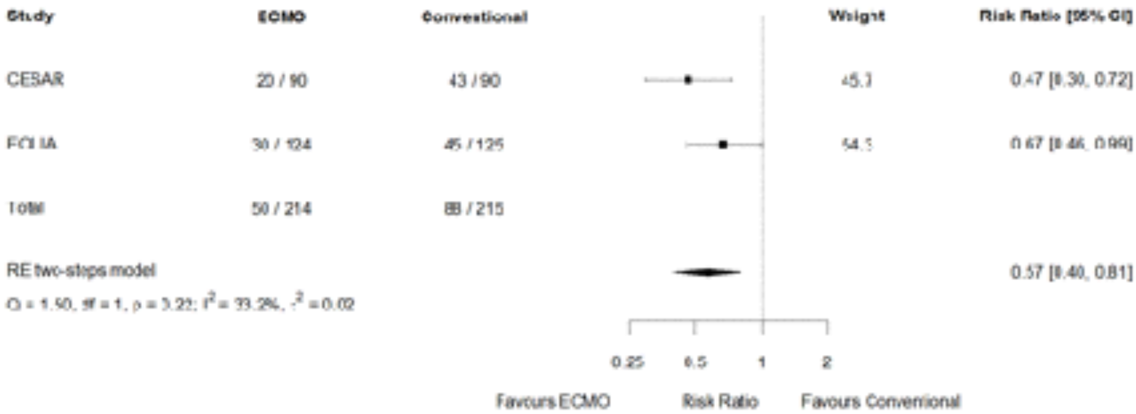


C

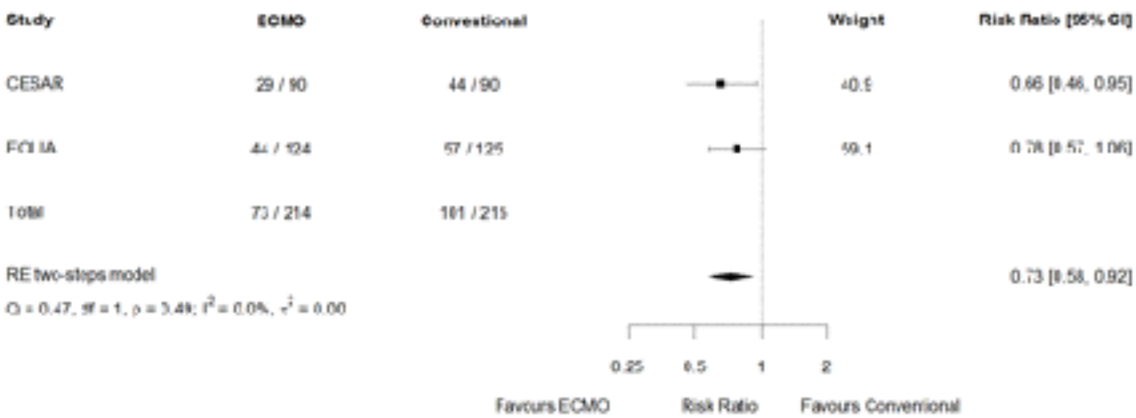


eFigure 6. Forest plot of 28-day (A) and 60-day (B) mortality in the intention-to-treat population.

A

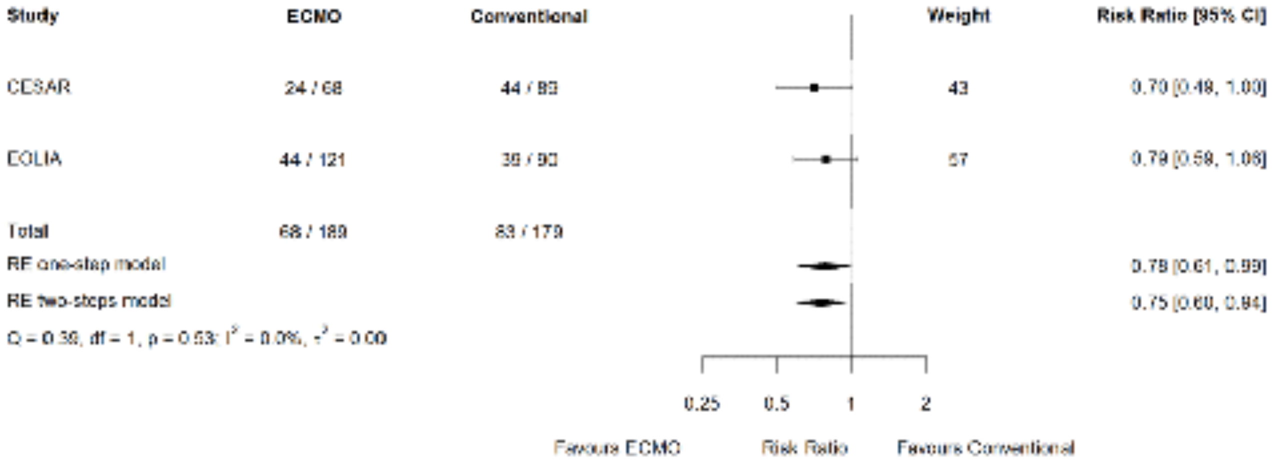


B

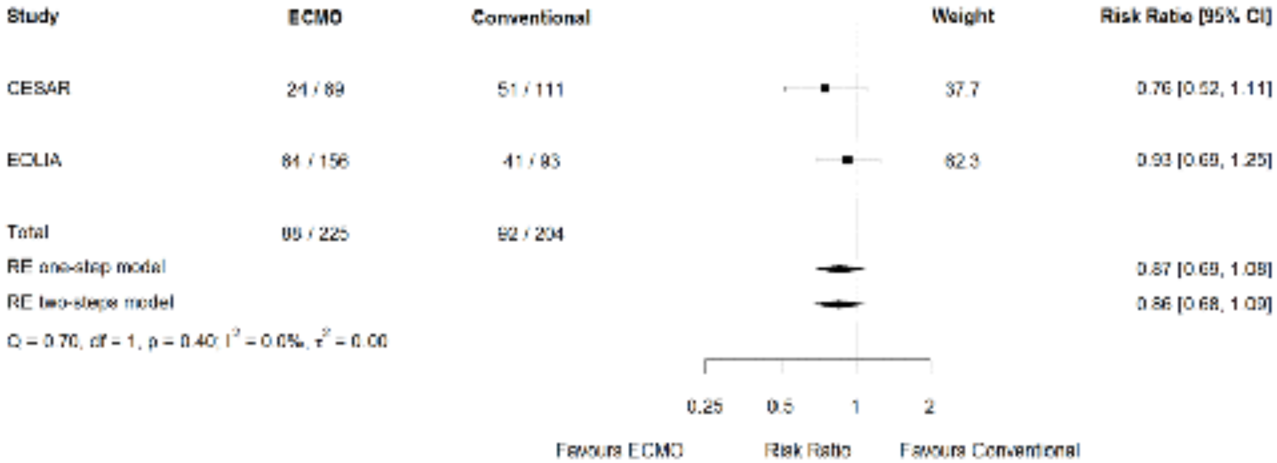


eFigure 7. Forest plot of 90-day mortality for per-protocol (A) and as-treated (B) populations.

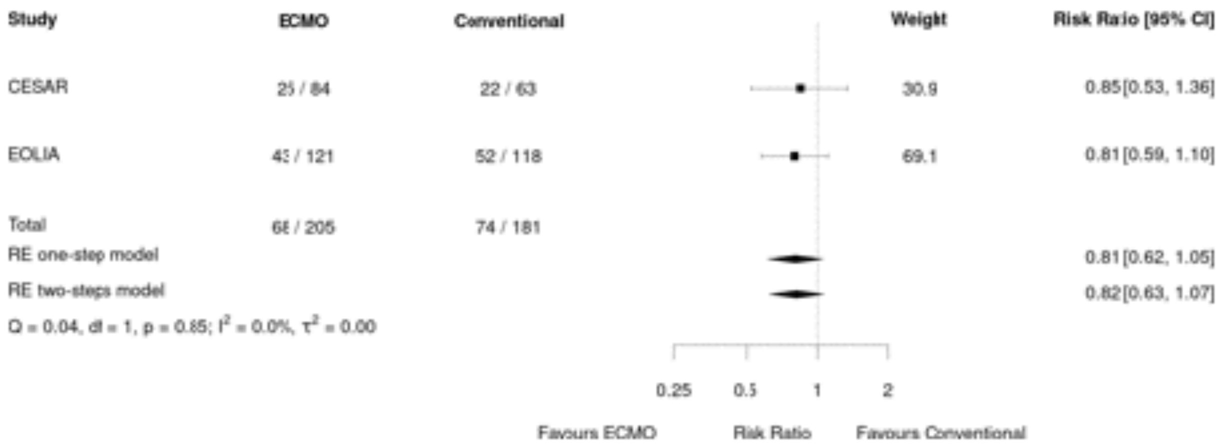
A



B



eFigure 8. Post-hoc analysis of 90-day mortality in the subgroup of patients who received lung protective ventilation.



3. TABLES

eTable 1. PRISMA-IPD checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD).

PRISMA-IPD Section/ topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	4
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	4
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	4 4
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	4 5
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	6
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	7
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	7 Suppl. 7-8

Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	7 Suppl. 7-8
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eTable 2
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	7 Suppl. 7-8
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	7; Suppl. 7-8
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	NA
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	Suppl. 8
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	Suppl. 7-9
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	7 Suppl. 10
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	7-8 Suppl. 11-12

Synthesis methods	14	Describe the meta-analysis methods used to synthesize IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	8-9 Suppl. 12-14
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	9 Suppl. 13
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	9 Suppl. 13
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	9 eFig 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	eTable 4
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	NA
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	9 eFig 2

Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Fig 1 eFig 2-6
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	Fig 1 eFig 2-6
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	10
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	10-11
Discussion			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome.	12
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	13-14
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	14-15
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	14-15
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	15

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

eTable 2. Search algorithm for the MEDLINE via PubMED search.

1. Extracorporeal membrane oxygenation [mh]
2. “Extracorporeal membrane oxygenation” [tiab]
3. ECMO [tiab]
4. “extracorporeal life support” [tiab]
5. “extracorporeal gas exchange” [tiab]
6. respiratory insufficiency [mh]
7. Respiratory distress syndrome, adult [mh]
8. “respiratory insufficiency” [tiab]
9. “respiratory failure” [tiab]
10. “respiratory distress syndrome” [tiab]
11. randomized controlled trial [pt]
12. controlled clinical trial [pt]
13. randomized [tiab]
14. placebo [tiab]
15. drug therapy [sh]
16. randomly [tiab]
17. trial [tiab]
18. groups [tiab]
19. 11 OR 12 OR13 OR 14 OR 15 OR 16 OR 17 OR 18
20. animals [mh] NOT humans [mh]
21. 19 NOT 20

22 1 OR 2 OR 3 OR 4 OR 5

23 6 OR 7 OR 8 OR 9 OR 10

24 21 AND 22 AND 23

eTable 3. Summury of the trial design of the 2 included studies.

First author, year	Setting	Design	Recruitment period	Population	Intervention in the experimental group	Intervention in the control group	Primary outcome	Number of patients randomised
Peek, 2009	UK, multicentre trial (103 centres)	Pragmatic RCT 1:1 ratio	July 2001-August 2006	- Aged 18-65 years - Severe but potentially reversible respiratory failure - Murray score ≥ 2.5 or hypercapnia with pH <7.20	Transfer to ECMO centre and ECMO using venovenous mode with percutaneous cannulation	Best critical care practice with advice on using low volume low pressure ventilation strategy	Death or severe disability at 6 months	180 ECMO group: 90 Control group: 90
Combes, 2018	International (France, USA, Australia, Canada), multicentre trial (43 centres)	RCT 1:1 ratio Sequential design with pre-specified stopping rules	December 2012, April 2017	- ARDS - Endotracheal intubation - Ventilation <7 days - Disease-severity criteria	ECMO with percutaneous venovenous cannulation	Ventilatory treatment according to the increased recruitment strategy of the EXPRESS trial	Mortality at 60 days	249 ECMO group: 124 Control group: 125

eTable 4. Characteristics of the patients at randomisation in the 2 included trials and in the individual patient data meta-analysis.

Characteristic	CESAR ECMO group (N = 90)	EOLIA ECMO group (N = 124)	IPDMA ECMO group (N = 214)	CESAR Control group (N = 90)	EOLIA Control group (N = 125)	IPDMA Control group (N = 215)
Age, years	39.3±13.5	51.9±14.2	46.6±15.2	40.0±13.4	54.4±12.7	48.3±14.8
Male — no. (%)	51 (57)	87 (70)	138 (65)	53 (59)	90 (72)	143 (67)
Time since intubation, h	35 [18-104]	34 [15-88]	35 [16-95]	37 [16-98]	34 [17-100]	36 [16-100]
ARDS etiology — no. (%)						
Pneumonia	56 (62)	80 (65)	136 (64)	53 (59)	78 (62)	131 (61)
Other	34 (38)	44 (36)	78 (36)	37 (41)	47 (38)	84 (39)
3 or more organs failed†	28 (31)	54 (44)	82 (38)	27 (30)	57 (46)	84 (39)
Predicted mortality‡	0.37±0.19	0.32±0.25	0.34±0.23	0.38±0.18	0.31±0.24	0.34±0.22
PaO_2:FIO_2	80±40	73±30	76±35	78±43	72±24	75±33
pH	7.37±0.54	7.24±0.13	7.30±0.37	7.28±0.34	7.24±0.12	7.26±0.24
Disorder leading to study entry						
Hypoxia	85 (94%)	99 (80%)	184 (86%)	87 (97%)	105 (84%)	192 (89%)
Uncompensated hypercapnia	5 (6%)	25 (20%)	30 (14%)	3 (3%)	20 (16%)	23 (11%)
PEEP, cm H_2O	13.3±9.6	11.7±3.4	12.3±6.8	14.0±9.4	11.8±3.4	12.7±6.8
Respiratory system compliance, ml/cm H_2O	26.9±12.0	25.0±11.6	25.8±11.8	25.2±8.6	25.4±11.0	25.3±8.8
Murray Score	3.4±0.7	3.3±0.4	3.3±0.6	3.4±0.4	3.3±0.4	3.3±0.4
Chest radiograph (quadrants infiltrated)	3.4±0.9	3.3±0.9	3.4±0.9	3.6±0.8	3.4±0.8	3.5±0.8

† number of organ failed (0 to 6) defined as the corresponding component sequential organ failure assessment (SOFA) score > 2.

‡ APACHE2 (CESAR) and SAPS2 (EOLIA) scores were both translated to predicted probability of ICU mortality.

ECMO denotes extracorporeal membrane oxygenation, ARDS the acute respiratory distress syndrome, PaO_2 partial pressure of arterial oxygen, FiO_2 the fraction of inspired oxygen, PaO_2/FIO_2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, PEEP positive end-expiratory pressure, LVLP MV, low-volume low-pressure mechanical ventilation, iNO inhaled nitric oxide, and ICU intensive care unit.

eTable 5. Missing data for characteristics of the patients included in the 2 trials and in the meta-analysis

Characteristic	CESAR ECMO group (N = 90)	EOLIA ECMO group (N = 124)	IPDMA ECMO group (N = 214)	CESAR Control group (N = 90)	EOLIA Control group (N = 125)	IPDMA Control group (N = 215)
Age, years	0	0	0	0	0	0
Male	0	0	0	0	0	0
Median (interquartile) time since intubation, h	2	0	2	0	0	0
ARDS etiology	0	0	0	0	0	0
3 or more organs failed†	0	0	0	0	0	0
Predicted mortality‡	33	1	34	29	3	32
PaO_2:FIO_2	2	1	3	1	0	1
pH	1	1	2	0	0	0
Disorder leading to study entry	0	0	0	0	0	0
PEEP, cm H_2O	6	0	6	1	2	3
Respiratory system compliance, ml/cm H_2O	10	28	38	7	30	37
Murray Score	0	29	29	0	31	31
Chest radiograph (quadrants infiltrated)	3	0	3	1	3	4
Received ECMO	0	0	0	0	0	0
Received LVLP MV	2	3	5	1	1	2
Prone position	2	0	2	1	0	1
iNO or prostacyclin	2	0	2	1	0	1
Renal replacement therapy	2	0	2	0	0	0
Steroids	2	0	2	0	0	0
ICU length of stay, days	1	0	1	0	0	0
Cause of death	0	0	0	0	0	0

† number of organ failed (0 to 6) defined as the corresponding component sequential organ failure

assessment (SOFA) score > 2.

‡ APACHE2 (CESAR) and SAPS2 (EOLIA) scores were both translated to predicted probability of ICU mortality.

ECMO denotes extracorporeal membrane oxygenation, ARDS the acute respiratory distress syndrome, PaO_2 partial pressure of arterial oxygen, FiO_2 the fraction of inspired oxygen, PaO_2/F_IO_2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, PEEP positive end-expiratory pressure, LVLP MV, low-volume low-pressure mechanical ventilation, iNO inhaled nitric oxide, and ICU intensive care unit.

eTable 6: Summary of findings table.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with ECMO**				
Mortality up to 90 days after randomization follow up: 90 days	479 per 1 000	**359 per 1 000** (287 to 450)	**RR 0.75** (0.60 to 0.94)	429 (2 RCTs)	⨁⨁⨁⨁ HIGH	Despite the low number of included studies, there was a high level of evidence because results were highly consistent in both studies, with no heterogeneity. Both studies had a low risk of bias.
Time to death up to 90 days after randomization follow up: 90 days	0 per 1 000	**NaN per 1 000** (NaN to NaN)	**HR 0.65** (0.49 to 0.88)	429 (2 RCTs)	⨁⨁⨁⨁ HIGH	Despite the low number of included studies, there was a high level of evidence because results were highly consistent in both studies, with no heterogeneity. Both studies had a low risk of bias.
Treatment failure up to 90 days follow up: 90 days	553 per 1 000	**360 per 1 000** (288 to 443)	**RR 0.65** (0.52 to 0.80)	429 (2 RCTs)	⨁⨁⨁⨁ HIGH	Despite the low number of included studies, there was a high level of evidence because results were highly consistent in both studies, with no heterogeneity. Both studies had a low risk of bias.
Number of days alive and out of hospital follow up: 90 days	The mean number of days alive and out of hospital was **18** days	MD **4 days more** (1 fewer to 9 more)	-	429 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Results were downgraded because of imprecision
Number of days alive without mechanical ventilation follow up: 90 days	The mean number of days alive without mechanical ventilation was **31** days	MD **8 days more** (2 more to 15 more)	-	429 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Results were downgraded because of imprecision
Number of days alive without renal replacement therapy follow up: 60 days	The mean number of days alive without renal replacement therapy was **28** days	MD **7 days more** (2 more to 13 more)	-	429 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Results were downgraded because of imprecision
Number of days alive without vasopressor support follow up: 60 days	The mean number of days alive without vasopressor support was **28** days	MD **8 days more** (3 more to 13 more)	-	429 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Results were downgraded because of imprecision

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with ECMO**				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. there was imprecision

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