



# Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study

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## ABSTRACT

### OBJECTIVE

To estimate the effect of extracorporeal membrane oxygenation (ECMO) compared with conventional mechanical ventilation on outcomes of patients with covid-19 associated respiratory failure.

### DESIGN

Observational study.

### SETTING

30 countries across five continents, 3 January 2020 to 29 August 2021.

### PARTICIPANTS

7345 adults admitted to the intensive care unit with clinically suspected or laboratory confirmed SARS-CoV-2 infection.

### INTERVENTIONS

ECMO in patients with a partial pressure of arterial oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) ratio  $<80$  mm Hg compared with conventional mechanical ventilation without ECMO.

### MAIN OUTCOME MEASURE

The primary outcome was hospital mortality within 60 days of admission to the intensive care unit. Adherence adjusted estimates were calculated using marginal structural models with inverse probability weighting, accounting for competing events and for baseline and time varying confounding.

### RESULTS

844 of 7345 eligible patients (11.5%) received ECMO at any time point during follow-up. Adherence

adjusted mortality was 26.0% (95% confidence interval 24.5% to 27.5%) for a treatment strategy that included ECMO if the  $\text{PaO}_2/\text{FiO}_2$  ratio decreased  $<80$  mm Hg compared with 33.2% (31.8% to 34.6%) had patients received conventional treatment without ECMO (risk difference  $-7.1\%$ , 95% confidence interval  $-8.2\%$  to  $-6.1\%$ ; risk ratio 0.78, 95% confidence interval 0.75 to 0.82). In secondary analyses, ECMO was most effective in patients aged  $<65$  years and with a  $\text{PaO}_2/\text{FiO}_2$   $<80$  mm Hg or with driving pressures  $>15$  cmH<sub>2</sub>O during the first 10 days of mechanical ventilation.

### CONCLUSIONS

ECMO was associated with a reduction in mortality in selected adults with covid-19 associated respiratory failure. Age, severity of hypoxaemia, and duration and intensity of mechanical ventilation were found to be modifiers of treatment effectiveness and should be considered when deciding to initiate ECMO in patients with covid-19.

### Introduction

About 40% of patients with covid-19 admitted to the intensive care unit develop severe acute respiratory failure.<sup>1 2</sup> In patients without covid-19 who develop progressive acute respiratory failure despite optimal support with conventional mechanical ventilation, extracorporeal membrane oxygenation (ECMO) reduces mortality by maintaining gas exchange and mitigating ventilator induced lung injury while the lungs recover.<sup>2-6</sup> Reports of poor survival rates in case series of patients with covid-19 associated acute respiratory failure treated with ECMO, however, discouraged clinicians from using ECMO early in the pandemic and even led some to call for a moratorium on its use in patients with covid-19, especially given limited resources during a pandemic.<sup>7</sup> However, an early report from the Extracorporeal Life Support Organization showed that the mortality of patients receiving ECMO for covid-19 associated acute respiratory failure might be closer to 40%.<sup>8</sup> Moreover, subsequent observational studies reported outcomes with ECMO in covid-19 associated acute respiratory failure that were similar to previous observations on the effect of ECMO in patients with acute respiratory failure from other causes, although mortality rates have varied over time and across jurisdictions during the pandemic.<sup>9-14</sup> Nevertheless, data to guide clinical decisions about patient selection for ECMO are lacking, and established protocols are largely based on the results from a recent randomised

## WHAT IS ALREADY KNOWN ON THIS TOPIC

The optimal indications for extracorporeal membrane oxygenation (ECMO) and modifiers of treatment effectiveness in patients with acute respiratory failure from covid-19 are currently unknown

Established protocols for the initiation of ECMO are largely based on a randomised controlled trial in patients without covid-19

## WHAT IS THIS STUDY ADDS

In this registry based cohort study of 7345 patients with covid-19 associated acute respiratory failure, ECMO in those with partial pressure of arterial oxygen to fraction of inspired oxygen ratio  $<80$  mm Hg was associated with a reduction in hospital mortality by 7.1% compared with conventional mechanical ventilation without ECMO

Age and severity of hypoxaemia, as well as duration and intensity of mechanical ventilation were modifiers of treatment effectiveness and should be considered when deciding to initiate ECMO in patients with covid-19

controlled trial in patients with acute respiratory failure without covid-19, which suggested a benefit of ECMO in patients with severe hypoxaemic acute respiratory failure, characterised by a partial pressure of arterial oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) ratio  $<80$  mm Hg.<sup>3 4</sup>

Using observational data to emulate a target trial represents an established statistical approach to estimate treatment effectiveness across populations in an uncontrolled setting.<sup>15 16</sup> This analysis approach provides an attractive complement to randomised controlled trials<sup>17</sup> and can yield important and more generalisable information, especially when the conduct of a randomised trial is challenging (eg, slow enrolment rates, crossovers, restrictive inclusion criteria, and lack of equipoise), particularly when investigating a complex and resource intensive intervention such as ECMO during a global pandemic.<sup>3 18 19</sup>

In this registry based cohort study of adults with covid-19 related acute respiratory failure, we compared hospital mortality and the probability of being discharged alive between ECMO treatment in patients with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $<80$  mm Hg and a treatment strategy where all patients received conventional mechanical ventilation without ECMO. In additional analyses, we investigated if age, pre-existing comorbidities, or the duration of mechanical ventilation preceding ECMO use was associated with modified treatment effectiveness. Finally, we estimated the effectiveness of ECMO when initiated on the basis of various ranges for markers accounting for the severity of acute respiratory failure or intensity of mechanical ventilation that change during a patient's hospital admission.

## Methods

We used data from the international, multicentre COVID-19 Critical Care Consortium registry.<sup>20</sup> Study methods and design of the registry are published elsewhere.<sup>21</sup> Briefly, adults with clinically suspected (determined by attending doctor) or laboratory confirmed SARS-CoV-2 infection (reverse transcriptase polymerase chain reaction or next generation sequencing, or both) were eligible for analysis if they were admitted to an intensive care unit between 3 January 2020 and 29 August 2021. We excluded patients from countries that did not provide ECMO during the observation period and patients who were missing all baseline and longitudinal measurements, as counterfactual outcomes could not be reliably determined.

Participating hospitals obtained approval from their local institutional review board. Because the study was observational, with only deidentified data recorded in a central repository, waivers of informed consent were granted for all patients.<sup>21</sup>

## Primary analysis

We compared hospital mortality and the probability of being discharged alive between a treatment

strategy where ECMO was initiated if the  $\text{PaO}_2/\text{FiO}_2$  ratio dropped below 80 mm Hg and a treatment strategy where all patients had received conventional mechanical ventilation without ECMO. As we wanted to measure the causal effect of ECMO on outcomes (as in a per protocol analysis of a randomised controlled trial), adherence adjusted estimates were calculated for the primary analysis. We also conducted an "as treated" analysis and compared outcomes between treatment as received (which could have included ECMO) and treatment with conventional mechanical ventilation without ECMO. The primary outcome was hospital mortality, and patients were followed from admission to the intensive care unit (time point zero for the analysis) until either death, hospital discharge alive, or 60 days, whichever occurred first. Discharge alive was considered a competing event for hospital mortality because patients who were discharged could not then die in hospital.

## Secondary analyses

In secondary analyses, we investigated if age, pre-existing comorbidities (diabetes, obesity, and arterial hypertension), and duration of mechanical ventilation were potential effect modifiers. Also, we estimated the effectiveness of ECMO when initiated based on different time varying markers of disease severity. The  $\text{PaO}_2/\text{FiO}_2$  ratio was used as marker of the severity of acute respiratory failure. As a marker for the intensity of mechanical ventilation, we used static driving pressure, calculated as plateau airway pressure minus positive end expiratory pressure.<sup>22</sup> In addition to the primary analysis, we investigated two additional ranges for the  $\text{PaO}_2/\text{FiO}_2$  ratio as a basis to initiate ECMO:  $\geq 80$  and  $<120$  mm Hg,  $\geq 120$  and  $<150$  mm Hg. Four thresholds were used for static driving pressure:  $>12$  cmH<sub>2</sub>O,  $>15$  cmH<sub>2</sub>O,  $>17$  cmH<sub>2</sub>O, and  $>20$  cmH<sub>2</sub>O. The supplementary appendix provides further details.

## Statistical analyses

To answer the research questions, we emulated a pragmatic randomised controlled trial using observational data and calculated adherence adjusted estimates using a three step analytical procedure (see supplementary figure S1), similar to a per protocol analysis of randomised controlled trial. This robust analysis approach, which eliminates immortal time bias in the estimation of absolute and relative risks, has been well described.<sup>16 23 24</sup>

Firstly, we created clones of each patient and assigned these clones to the different treatment strategies: ECMO, defined as ECMO being initiated if the  $\text{PaO}_2/\text{FiO}_2$  ratio was  $<80$  mm Hg, or conventional mechanical ventilation (without ECMO). Secondly, we censored clones that were non-adherent to their assigned treatment strategy during follow-up (eg, initiation of ECMO in the group treated with conventional mechanical ventilation). To mitigate the risk of violating the positivity assumption (patients rarely receive a cannula if they have already undergone a prolonged course of mechanical

ventilation), clones were eligible for censoring during the first 21 days in the intensive care unit. Thirdly, we used inverse probability weighting to deal with selection bias introduced by censoring non-adherent clones. For each day we calculated the probability of not being censored, based on factors that might have been considered by the treatment team to decide whether ECMO should be initiated or not, such as physiological characteristics, disease severity, ventilation variables, specific treatments, and time (see supplementary appendix for additional details). Weighted marginal structural models were used to calculate absolute risks, differences in absolute risks, and risk ratios. The results were reported for the primary outcome (direct effect on hospital mortality) and for the competing event (indirect effect mediated by hospital discharge on mortality), thereby giving a better understanding of the total effect of ECMO on outcomes.<sup>25</sup> Percentile based 95% confidence intervals were obtained using non-parametric bootstrapping with 500 resamples.

We conducted sensitivity analyses to detect residual confounding, control for country specific heterogeneity in treatment, and measure the influence of missing data and multiple imputation. Supplementary table S1 provides details on covariates included in the models, calculations of the inverse probability weights, and sensitivity analyses, as well as information on missing data and how such data were handled. The article is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology

guidelines.<sup>26</sup> Analyses were performed in R version 4.0.4.

### Patient and public involvement

No patient representatives or members of the public were involved in the design, conduct, or reporting plans of this research project. We aim to involve patients and members of the public in the development of an appropriate method of dissemination.

### Results

Data on 7847 patients were recorded in the registry. We excluded 502 (6.4%) patients—150 were from countries that did not enrol patients requiring ECMO during the observation period and 352 had no baseline or longitudinal measurements. A total of 7345 (93.6%) patients were included in the analysis (see supplementary figure S2). The median age was 59 (interquartile range 49-68) years, and 2265 (30.8%) patients were women. The median PaO<sub>2</sub>/FiO<sub>2</sub> ratio at baseline was 130 (interquartile range 88-193) mm Hg. The median length of hospital stay was 16 (interquartile range 6-30) days. The cumulative probability of death at 60 days was 35.3% (95% confidence interval 33.9% to 36.7%). A total of 844 patients (11.5%) received ECMO at any time point during follow-up. The median duration of ECMO was 13 (interquartile range 5-26) days. For patients who received ECMO during follow-up, median length of hospital stay was 29 (interquartile range 15-49) days, the cumulative probability of death at 60 days was 50.0% (95% confidence interval 46.2% to 54.1%), and the cumulative probability of remaining in hospital at 60 days was 16.0% (95% confidence interval 13.0% to 19.7%). Table 1 and supplementary tables S2 to S8 provide details on patient characteristics and ventilation variables at baseline.

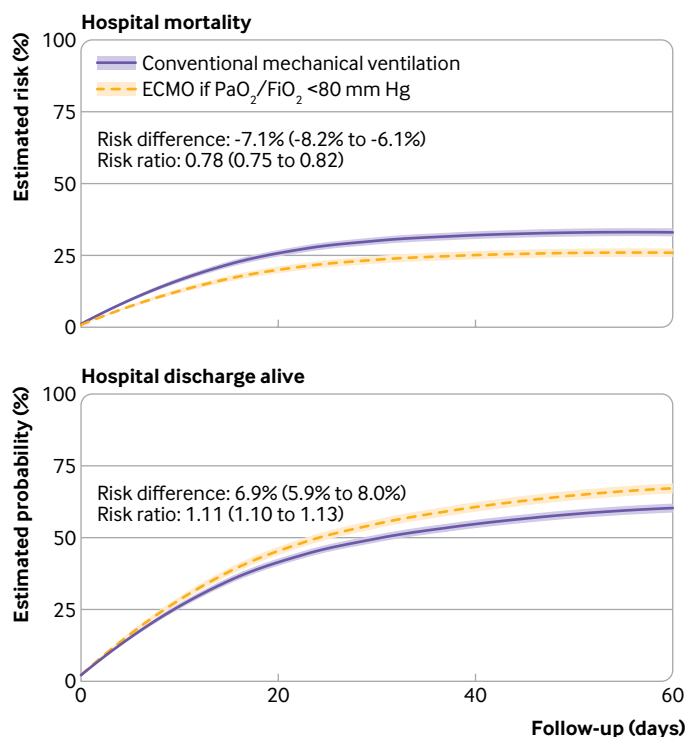
### Primary analysis

Adherence adjusted hospital mortality was 26.0% (95% confidence interval 24.5% to 27.5%) for a treatment strategy that included ECMO if the PaO<sub>2</sub>/FiO<sub>2</sub> ratio dropped below 80 mm Hg compared with 33.2% (31.8% to 34.6%) had patients received conventional treatment without ECMO (risk difference -7.1%, 95% confidence interval -8.2% to -6.1%; risk ratio 0.78, 95% confidence interval 0.75 to 0.82) (fig 1). The probability of being discharged alive was 67.5% (95% confidence interval 65.7% to 69.3%) for patients in the treatment strategy with ECMO compared with 60.6% (59.0% to 62.2%) had patients received conventional treatment without ECMO (risk difference 6.9%, 95% confidence interval 5.9% to 8.0%; risk ratio 1.11, 95% confidence interval 1.10 to 1.13). Estimated hospital mortality at 60 days under treatment as received was 34.8% (95% confidence interval 33.4% to 36.1%), and the estimated probability of being discharged alive was 58.3% (95% confidence interval 56.8% to 59.7%), similar to treatment with conventional mechanical ventilation without ECMO (fig 2 and supplementary table S9).

**Table 1 | Patient characteristics at baseline, treatments, and outcomes. Values are median (interquartile range) unless stated otherwise**

| Characteristics                                                               | Estimate (n=7345) |
|-------------------------------------------------------------------------------|-------------------|
| No (%) women                                                                  | 2265 (30.8)       |
| Age (years)                                                                   | 59 (49-68)        |
| SOFA score                                                                    | 4 (3-6)           |
| APACHE II score                                                               | 14 (10-18)        |
| Ventilation variables at baseline:                                            |                   |
| Tidal volume (mL/kg predicted bodyweight)                                     | 6.4 (5.8-7.1)     |
| FiO <sub>2</sub> (%)                                                          | 60 (49-76)        |
| Positive end expiratory pressure (cmH <sub>2</sub> O)                         | 10 (8-12)         |
| Airway plateau pressure (cmH <sub>2</sub> O)                                  | 22 (20-25)        |
| Respiratory rate per minute                                                   | 24 (20-28)        |
| Gas exchange at baseline:                                                     |                   |
| PaO <sub>2</sub> /FiO <sub>2</sub> ratio (mm Hg)                              | 130 (88-193)      |
| PaO <sub>2</sub> (mm Hg)                                                      | 79 (64-100)       |
| SaO <sub>2</sub> (%)                                                          | 94 (91-96)        |
| Arterial pH                                                                   | 7.41 (7.35-7.45)  |
| PaCO <sub>2</sub> (mm Hg)                                                     | 39 (34-47)        |
| Serum bicarbonate (mmol/L)                                                    | 24 (22-27)        |
| Lactate (mmol/L)                                                              | 1.4 (1.1-1.9)     |
| No (%) of specific treatments recorded for at least one day during follow-up: |                   |
| Prone position                                                                | 1117 (15.2)       |
| Neuromuscular blockade agent                                                  | 1707 (23.2)       |
| Inhaled nitric oxide                                                          | 72 (1.0)          |
| Vasoactive drugs                                                              | 1590 (21.6)       |
| Renal replacement therapy                                                     | 738 (10.0)        |
| Corticosteroids                                                               | 2961 (40.3)       |

SOFA=sequential organ failure assessment; APACHE=acute physiology and chronic health evaluation; FiO<sub>2</sub>=fraction of inspiratory oxygen; PaO<sub>2</sub>=arterial partial pressure of oxygen; SaO<sub>2</sub>=arterial oxygen saturation; PaCO<sub>2</sub>=arterial partial pressure of carbon dioxide.



**Fig 1 |** Treatment with extracorporeal membrane oxygenation (ECMO) if ratio of partial pressure of arterial oxygen to fraction of inspiratory oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) was  $<80$  mm Hg, was compared with treatment with conventional mechanical ventilation without ECMO. Adherence adjusted estimates are reported for differences in hospital mortality and probability of hospital discharge alive in 7345 patients with covid-19 associated acute respiratory failure. Shaded areas represent 95% confidence intervals

### Secondary analyses

Treatment effectiveness of ECMO was shown to decrease with increasing patient age. In patients aged  $<50$  years, the risk ratio for mortality was 0.71 (95% confidence interval 0.62 to 0.81) when ECMO was compared with conventional mechanical ventilation. In contrast, the risk ratio for mortality in patients aged  $\geq 65$  years was 0.84 (0.81 to 0.88) (fig 3 and supplementary table S10).

For patients with pre-existing comorbidities, we estimated the following risk ratios when mortality was compared between ECMO and conventional mechanical ventilation: for arterial hypertension 0.75

(95% confidence interval 0.71 to 0.80), for diabetes 0.79 (0.74 to 0.84), and for obesity 0.72 (0.65 to 0.80) (fig 3 and supplementary tables S11 and S12). The risk ratio for mortality of patients without any comorbidities was 0.80 (95% confidence interval 0.70 to 0.91).

Treatment effectiveness was seen to decrease with increasing duration of mechanical ventilation before cannulation (fig 4). In patients who were mechanically ventilated for one day or less the risk ratio for mortality was 0.91 (0.88 to 0.94) when ECMO was compared with conventional mechanical ventilation. In patients who were mechanically ventilated for seven days, effectiveness of ECMO was observed to decrease, and the risk ratio for mortality was 0.97 (0.95 to 0.98) (supplementary table S13).

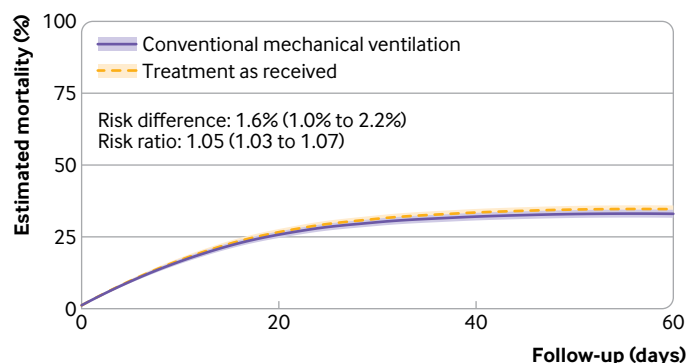
We compared different treatment strategies, when ECMO had been initiated according to either time dependent  $\text{PaO}_2/\text{FiO}_2$  ratio or driving pressure levels, with conventional mechanical ventilation without ECMO. The risk ratio for mortality was 0.87 (0.84 to 0.91) for ECMO initiated in patients with a  $\text{PaO}_2/\text{FiO}_2$  ratio of 80-119 mm Hg (fig 5). In contrast, the risk ratio for mortality was 1.05 (1.02 to 1.08) if ECMO had been initiated in patients with a  $\text{PaO}_2/\text{FiO}_2$  ratio of 120-149 mm Hg, suggesting reduced effectiveness of ECMO in patients with less severe hypoxaemic respiratory failure (see supplementary table S14). We also compared ECMO treatment strategies initiated in patients with higher time dependent driving pressure levels with conventional mechanical ventilation without ECMO. The following risk ratios for mortality were measured if ECMO had been initiated according to the four prespecified thresholds for driving pressure:  $>12$   $\text{cmH}_2\text{O}$ , 0.95 (0.89 to 1.00);  $>15$   $\text{cmH}_2\text{O}$ , 0.89 (0.86 to 0.93);  $>17$   $\text{cmH}_2\text{O}$ , 0.91 (0.89 to 0.93), and  $>20$   $\text{cmH}_2\text{O}$ , 0.99 (0.98 to 1.01) (fig 6 and supplementary table S15).

### Sensitivity analyses

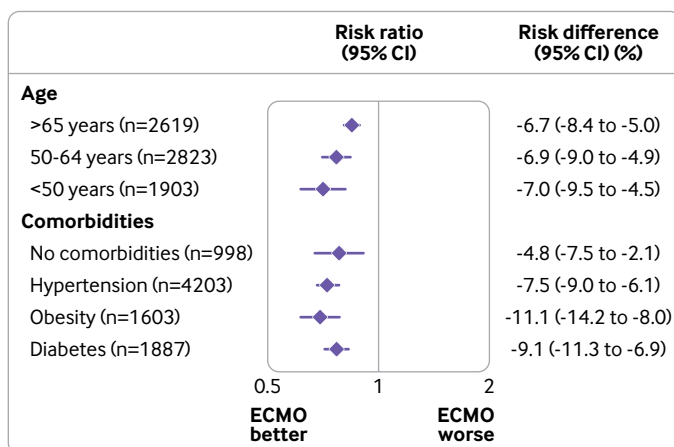
Our findings were robust in several sensitivity analyses. Firstly, no effect was observed in an analysis using a random outcome variable with a 50:50 probability for which by design no causal relationship with ECMO existed (see supplementary figure S3). Detection of a treatment effect in such an analysis would have suggested important uncontrolled confounding. Secondly, similar results to the primary analysis were found in an analysis using an alternative set of covariates for the estimation of the inverse probability weights (see supplementary figure S4). Thirdly, estimates consistent with the primary analyses were measured in sensitivity analyses to detect the potential influence of country specific heterogeneity (see supplementary figure S5). Finally, supplementary figure S6 and table S16 describe the missing data patterns. Similar results to the primary analyses were measured in a complete case analysis without multiple imputation (see supplementary figure S7).

### Discussion

In this registry based cohort study of 7345 adults with covid-19 associated acute respiratory failure, treatment



**Fig 2 |** As treated analysis in 7345 patients, with hospital mortality compared between treatment as received, which could have included treatment with extracorporeal membrane oxygenation (ECMO), and treatment with conventional mechanical ventilation without ECMO. Shaded areas represent 95% confidence intervals

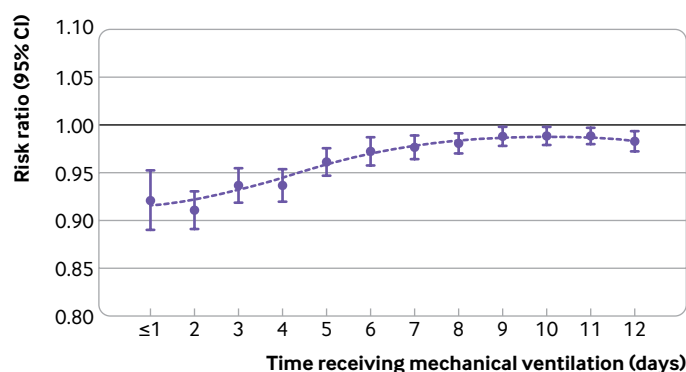


**Fig 3 | Treatment with extracorporeal membrane oxygenation (ECMO) if ratio of partial pressure of arterial oxygen to fraction of inspiratory oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) was  $<80$  mm Hg compared with conventional mechanical ventilation without ECMO. Adherence adjusted effects (95% confidence intervals) on hospital mortality within 60 days reported by age groups and baseline comorbidities**

with ECMO in those with  $\text{PaO}_2/\text{FiO}_2 < 80$  mm Hg was associated with a 7.1% reduction in hospital mortality (95% confidence interval 6.1% to 8.1%) compared with conventional mechanical ventilation without ECMO (risk ratio 0.78, 95% confidence interval 0.75 to 0.82). In secondary analyses, we found that ECMO would have been most effective if consistently provided to well selected patients with more severe hypoxaemia (ie,  $\text{PaO}_2/\text{FiO}_2 < 80$  mm Hg) or with exposure to higher intensities of mechanical ventilation (ie, driving pressure levels  $>15$   $\text{cmH}_2\text{O}$ ).

### Primary analysis

In the primary analysis, we reported adherence adjusted estimates as in a per protocol analysis of a randomised trial. Adherence adjusted mortality was lower than observed mortality under the natural course or mortality of patients treated with a strategy that did not include ECMO. This finding suggests that adherence to our treatment strategy (initiation of ECMO if the  $\text{PaO}_2/\text{FiO}_2$  ratio was  $<80$  mm Hg) was associated with



**Fig 4 | Treatment with extracorporeal membrane oxygenation (ECMO) if ratio of partial pressure of arterial oxygen to fraction of inspiratory oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) was  $<80$  mm Hg compared with conventional mechanical ventilation without ECMO. The influence of duration of mechanical ventilation preceding ECMO is illustrated using risk ratios with 95% confidence intervals. Dots represent a loess curve**

a reduction in mortality compared with conventional mechanical ventilation without ECMO. Our analysis approach assigned clones for all observed patients to each of the two treatment strategies, censoring only when the assigned treatment was violated (assignment to the other treatment). In both treatment strategies, we considered patients fully adherent in the primary analysis if they maintained a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\geq 80$  mm Hg and were not treated with ECMO. Both treatment groups comprised patients whose  $\text{PaO}_2/\text{FiO}_2$  ratio never dropped below 80 mm Hg or received ECMO during follow-up (ie, they only developed a mild to moderate but never a severe form of covid-19 acute respiratory distress syndrome), which explains the difference between adherence adjusted estimates for mortality reported in the target trial analysis and survival probabilities conditional on the receipt of ECMO at any time point during follow-up.

### As treated analysis

We also conducted an as treated analysis comparing treatment as received (which could have included ECMO) with conventional mechanical ventilation that could have included ECMO. Interestingly, treatment under real world conditions resulted in similar outcomes compared with a treatment strategy in which none of the patients had received ECMO. This finding might be explained by factors related to patient selection for ECMO and by influences related to country specific and temporal heterogeneity in decision making and treatment capacity.<sup>27 28</sup> For example, clinicians might have been hesitant to use ECMO early in the pandemic after reports of poor survival rates in the initial case series of patients with covid-19 associated acute respiratory failure. Moreover, many countries may have been overwhelmed by the sheer volume of critically ill patients requiring admission to an intensive care unit during the pandemic, resulting in resource intensive interventions such as ECMO being restricted to those patients who it was thought would benefit the most. This as treated analysis should be interpreted with caution, however, because one treatment strategy does not represent an active intervention but reflects the real world situation (ie, treatment as received). This analysis might be more susceptible to bias from uncontrolled confounding than the primary analysis where two active interventions were compared.<sup>16</sup> For the inverse probability weighting, we modelled the decision making process for the initiation of ECMO (ie, the daily probability that a patient would receive a cannula for ECMO) rather than individual patient outcomes, considering the challenges to model the different course of the pandemic in different countries. Importantly, we excluded from the analysis those patients from countries that did not provide ECMO during the observation period. While baseline risk levels for the multiple countries and centres might vary, we report estimates for the effect of ECMO that are consistent with previous findings. The ECMO to Rescue Lung Injury in Severe ARDS trial reported a risk ratio of 0.76 (95% confidence interval 0.55 to 1.04)

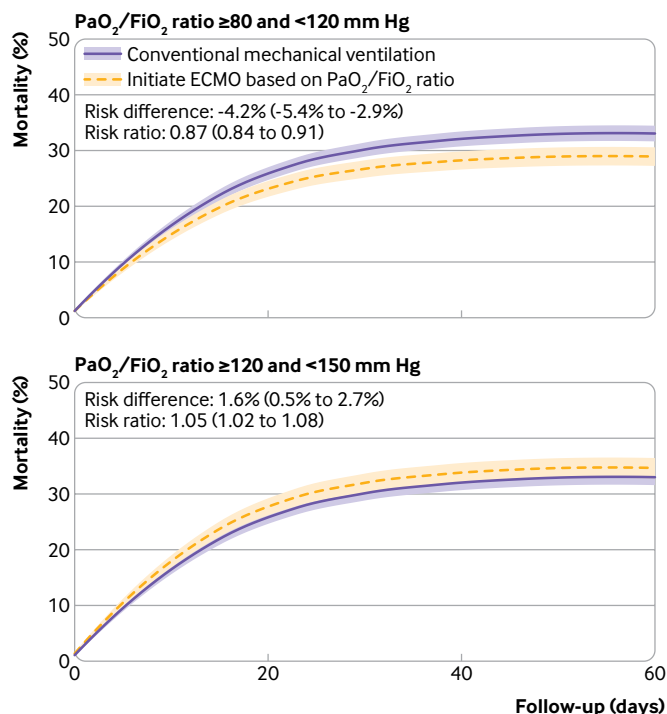


Fig 5 | Treatment with extracorporeal membrane oxygenation (ECMO) if ratio of partial pressure of arterial oxygen to fraction of inspiratory oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) was  $<80$  mm Hg compared with conventional mechanical ventilation without ECMO. The primary analysis was repeated with different  $\text{PaO}_2/\text{FiO}_2$  ratio thresholds for initiation of ECMO. Shaded areas represent 95% confidence intervals

for patients with acute respiratory distress syndrome from causes other than covid-19,<sup>3</sup> whereas another study reported an adjusted hazard ratio of 0.55 (95%

confidence interval 0.41 to 0.74) for the same duration of follow-up in patients with covid-19 associated acute respiratory failure,<sup>9</sup> suggesting that the identified range of values for the causal effect estimated in our analysis aligns well with evidence from previous studies. Also, the results of our primary analysis were confirmed in a sensitivity analysis, adjusted for country specific heterogeneity in treatment, as well as in an analysis that excluded patients from the United States, underlining the robustness of our findings and methodological approach.

### Secondary analyses

In secondary analyses, we investigated if age, pre-existing comorbidities, and duration of mechanical ventilation preceding ECMO initiation were associated with modified treatment effectiveness. Furthermore, we estimated the effectiveness of ECMO when initiated based on markers accounting for the severity of acute respiratory failure or intensity of mechanical ventilation that change during a patient's admission. The use of ECMO was highly effective in patients younger than 65 years, and to a lesser extent potentially also in older patients. Interestingly, although comorbidities such as obesity, diabetes, and arterial hypertension are associated with more severe covid-19,<sup>29</sup> ECMO was also observed to be effective at reducing mortality in these patients. Although hypothesis generating, our analyses question whether ECMO should be strictly limited to patients with covid-19 who have a  $\text{PaO}_2/\text{FiO}_2 < 80$  mm Hg for at least six hours and only during the first seven days of mechanical ventilation, as recommended by the current guidelines from the Extracorporeal Life

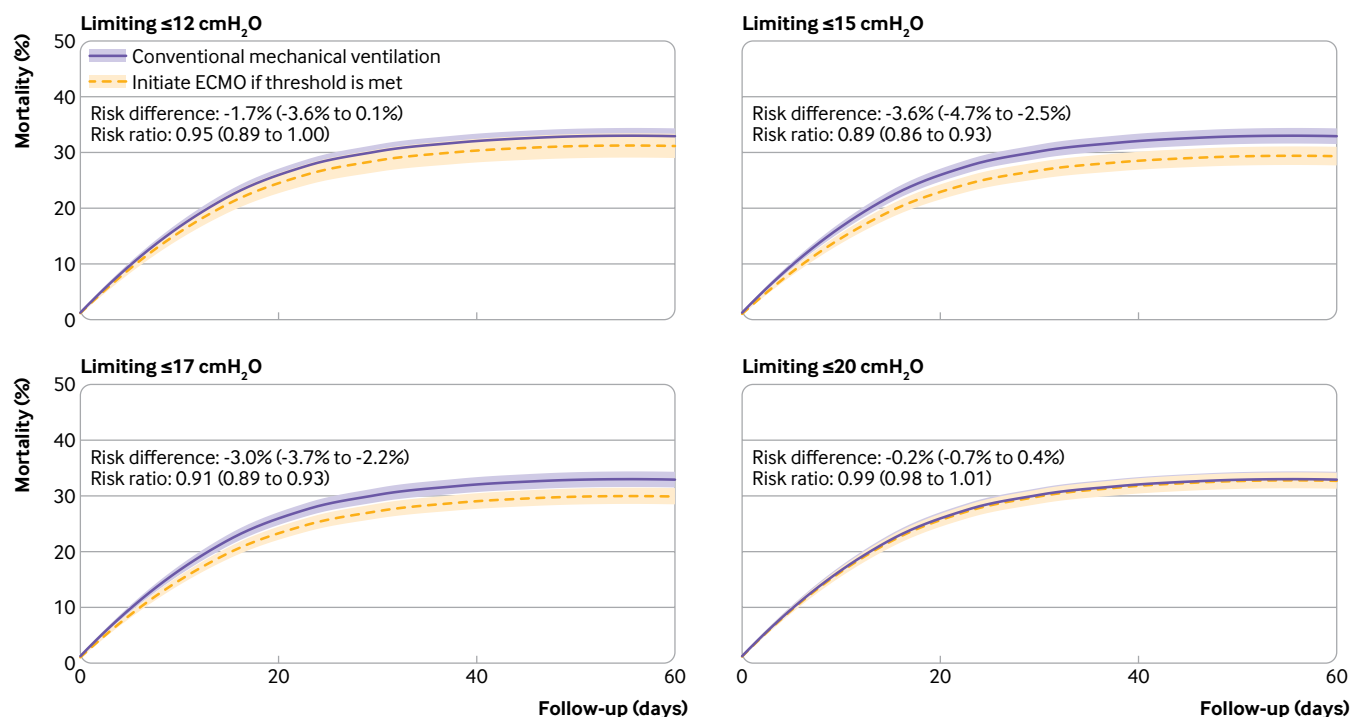


Fig 6 | Treatment with extracorporeal membrane oxygenation (ECMO) if ratio of partial pressure of arterial oxygen to fraction of inspiratory oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) was  $<80$  mm Hg compared with conventional mechanical ventilation without ECMO. Treatment strategies, when ECMO was initiated based on various thresholds for driving pressure, were compared with conventional mechanical ventilation. Shaded areas represent 95% confidence intervals

Support Organization, which are based on the results of the ECMO to Rescue Lung Injury in Severe ARDS trial.<sup>3 4</sup> We found a potential beneficial effect of ECMO in patients with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio <120 mm Hg, and even if support was initiated up to 10 days after the start of mechanical ventilation. In addition, we found that ECMO was associated with improved survival in patients with potentially injurious intensities of mechanical ventilation (ie, a driving pressure >15 cmH<sub>2</sub>O), likely mitigating the risk of ventilator induced lung injury.<sup>22</sup>

### Comparison with other studies

Our study agrees with and builds on findings from previous reports on the effectiveness of ECMO in patients with acute respiratory distress syndrome from causes other than covid-19,<sup>3</sup> as well as the results of a previous single country cohort study from the US<sup>9</sup> investigating the effectiveness of ECMO in patients with covid-19 and more severe acute respiratory failure. Moreover, our study expands the current knowledge on clinical criteria that might be considered before initiating ECMO and on factors influencing the effectiveness of such treatment in patients with covid-19. Importantly, our results should be confirmed in future randomised controlled trials and should be seen as complementary information recorded in an uncontrolled setting under real world conditions. However, the conduct of such randomised controlled trials might be challenging owing to constraints on time and resources, along with the changing epidemiology of the pandemic and potential transition to endemicity of covid-19 as effective vaccines become more widely available.<sup>30 31</sup> Finally, our findings might also provide valuable insights for future study design, as well as the potential utility of ECMO in patients with acute respiratory failure of other causes, such viral pneumonia from seasonal influenza viruses or Middle East respiratory syndrome coronavirus.<sup>32</sup>

### Limitations of this study

Our study has several important limitations. Firstly, residual confounding, limitations in modelling complex interventions such as ECMO, missing data, and imputation of missing values might have influenced the results of our analyses. Daily measurements were routinely collected during the pandemic and made available for our analysis. These measurements might not necessarily reflect the worst or best value of the day. Also, the measurements might or might not align with the time point of cannulation for ECMO. Similar to findings in patients with acute respiratory distress syndrome of causes other than covid-19, airway plateau pressures and driving pressures were often missing and might only have been measured in patients with more severe illness.<sup>33</sup> Our secondary analyses on thresholds of driving pressures should therefore be interpreted with caution. Our results, however, were robust in sensitivity analyses with control outcomes, in an analysis with alternative sets of covariates to calculate the inverse probability weights,

and in a complete case analysis.<sup>16</sup> Secondly, some of the patients might have been transferred to long term acute care facilities after hospital discharge. The mortality of patients after transfer to long term acute care hospitals might be substantial.<sup>34</sup> For this reason, we considered discharge alive to be a competing event for hospital mortality in our analysis and not treated as a censoring event. Also, a major portion of patients remained in hospital and at risk of experiencing the primary outcome at the end of follow-up. Finally, the estimated effects of ECMO in patients with prolonged preceding duration of mechanical ventilation or in elderly patients, should be interpreted with caution considering that only highly selected patients in our cohort had received ECMO under such circumstances. The results of these secondary analyses are therefore hypothesis generating and require further validation.

### Conclusions

In this international, registry based cohort study of patients with covid-19 associated acute respiratory failure, ECMO was associated with a reduction in mortality by 7.1% (95% confidence interval 6.1% to 8.1%) compared with conventional mechanical ventilation without ECMO. Furthermore, ECMO would have improved outcomes if consistently provided to well selected patients with more severe hypoxaemia or with exposure to higher intensities of mechanical ventilation. Age, severity of hypoxaemia, intensity of mechanical ventilation, and duration of mechanical ventilation should be considered when deciding to initiate ECMO to mitigate the risk of ECMO associated harm and to maximise effectiveness of ECMO in patients with covid-19.

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**Contributors:** MU, JFF, and EF designed and planned the study. MU wrote the analysis code. AGB ran the analysis. AGB and EF supervised the analysis. MU, AGB, NDF, and EF interpreted the data. MU and EF wrote the initial manuscript draft. All authors were involved in critical revision of the final manuscript. MU, EF, AGB, and JFF are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Data sharing:** An independent research team collects data of the international, multicentre COVID-19 Critical Care Consortium registry. Deidentified registry data may be obtained for research purposes on approval of a formal proposal. Derived data supporting the findings of this study may be available from the corresponding author upon request.

The lead authors (MU and EF) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that

no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**Dissemination to participant and related patient and public communities:** The result of this work will be disseminated among the members of the COVID-19 Critical Care Consortium, Extracorporeal Life Support Organization, and International ECMO Network, as well as through our Twitter and other social media accounts.

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**Supplementary information:** Additional information, tables, figures, and lists of collaborators and contributors