Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome associated with COVID-19: An Emulated Target Trial Analysis

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Abbreviations

ARDS, acute respiratory distress syndrome

COVID-19, Coronavirus disease 2019

ECMO, extracorporeal membrane oxygenation

VV-ECMO, veno-venous membrane oxygenation

ICU, intensive care unit

IMV: invasive mechanical ventilation

IPC weighting: the inverse probability of censoring weighting

PEEP: positive end-expiratory pressure

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

IQR: interquartile range

Keywords: extracorporeal membrane oxygenation; acute respiratory distress syndrome (ARDS); COVID-19; SARS-CoV-2; emulated target trial.

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At a Glance Commentary

Scientific Knowledge on the Subject

Extracorporeal membrane oxygenation (ECMO) is currently used for patients with coronavirus disease 2019 (COVID-19) related to acute respiratory distress syndrome. However, whether COVID patients may benefit from ECMO compared with mechanical ventilation associated with other adjunct therapies such as prone positioning and neuromuscular blockade remains unknown, as no randomized controlled trial has been performed in that population.

What This Study Adds to the Field

In an emulated trial based on a nationwide COVID-19 cohort, we found differential survival over time of an ECMO compared with a non-ECMO strategy for COVID-19. However, ECMO was consistently associated with better outcomes when performed in high-volume centers, in regions with ECMO capacities specifically organized to handle high demand, in profoundly hypoxemic patients, and if initiated early after intubation.

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Abstract (250 words)

Rationale: Whether COVID patients may benefit from extracorporeal membrane oxygenation (ECMO) compared with conventional invasive mechanical ventilation (IMV) remains unknown.

Objectives: To estimate the effect of ECMO on 90-Day mortality vs IMV only

Methods: Among 4,244 critically ill adult patients with COVID-19 included in a multicenter cohort study, we emulated a target trial comparing the treatment strategies of initiating ECMO *vs.* no ECMO within 7 days of IMV in patients with severe acute respiratory distress syndrome (PaO_2/FiO_2 <80 or $PaCO_2$ ≥60 mmHg). We controlled for confounding using a multivariable Cox model based on predefined variables.

Main results: 1,235 patients met the full eligibility criteria for the emulated trial, among whom 164 patients initiated ECMO. The ECMO strategy had a higher survival probability at Day-7 from the onset of eligibility criteria (87% vs 83%, risk difference: 4%, 95% CI 0;9%) which decreased during follow-up (survival at Day-90: 63% vs 65%, risk difference: -2%, 95% CI -10;5%). However, ECMO was associated with higher survival when performed in high-volume ECMO centers or in regions where a specific ECMO network organization was set up to handle high demand, and when initiated within the first 4 days of MV and in profoundly hypoxemic patients.

Conclusions: In an emulated trial based on a nationwide COVID-19 cohort, we found differential survival over time of an ECMO compared with a no-ECMO strategy. However, ECMO was consistently associated with better outcomes when performed in high-volume centers and in regions with ECMO capacities specifically organized to handle high demand.

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Introduction

Extracorporeal membrane oxygenation (ECMO) has been used for patients with coronavirus disease 2019 (COVID-19) related to severe acute respiratory distress syndrome (ARDS) (1–4). High-volume ECMO centers and large ECMO networks reported similar survival for these patients compared to ECMO-supported patients with non-COVID-19-related ARDS (5, 6). Two randomized controlled trials (5, 7), a post-hoc Bayesian analysis (8), and a systematic review and individual meta-analysis (9) all consistently supported the use of venovenous ECMO in adults with severe ARDS treated in expert centers. Whether COVID patients may benefit from ECMO compared with mechanical ventilation associated with other adjunct therapies such as prone positioning and neuromuscular blockades remains unknown, as no randomized controlled trial has been performed in that population. However, a recent multicenter cohort study of critically ill adults with COVID-19 in the United States found that patients with severe hypoxemic respiratory failure treated with ECMO in the first 7 days of ICU admission had a considerable reduction in mortality compared to those not treated with ECMO (10).

We aimed to use the COVID–ICU-cohort database containing prospectively collected demographic and clinical characteristics, management, and outcomes of patients admitted to ICUs for severe COVID-19 in France, Belgium, and Switzerland, between February and May 2020 (11), to further examine the impacts of ECMO on survival in patients with COVID-19-related severe ARDS. We used the target trial emulation framework and causal inference methodology (12) to compare the treatment strategies of initiating ECMO *vs.* not initiating, among patients who have started invasive mechanical ventilation (IMV) within the past 7 days.

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Methods

Study population and data collection. All consecutive patients over 16 years of age admitted to the participating ICUs between February 25, 2020, and May 4, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were included. Details of the data collected daily in the first 14 days from admission, and then at days 28, 45, 60, and 90 have been described elsewhere (11) and are briefly summarized below. Beyond baseline demographic and clinical information and ICU severity scores, the study investigators recorded time-updated information, including use of ECMO, respiratory support, arterial blood gas, standard laboratory parameters, and use of adjuvant therapies for ARDS. The investigators also recorded information on ECMO-related complications (see online data supplement) and in-ICU organ dysfunction. Patients' vital status (with the exact date of death) was collected by study investigators 90 days after ICU admission, with a call to the patients or their relatives if they were discharged from the hospital before day 90. This study received approval from the ethical committee of the French Intensive Care Society (CE-SRLF 20-23) and Swiss and Belgium ethical committees following local regulations.

Descriptive statistics of individuals who initiated ECMO. A descriptive analysis of the characteristics, management, and outcomes of patients aged ≤ 70 years old, with SAPS II ≤ 90, and who received ECMO within 14 days of ICU admission (whatever other eligibility criteria defined in the next subsection) was performed. This was done overall and according to their survival status at 90 days after ECMO initiation.

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We used the target trial emulation framework, which involves specifying the protocol for a hypothetical randomized trial, and then emulating this using the available observational data described above. The components of the target trial and how it is emulated are summarized below. Full characteristics of a hypothetical target trial and our emulated trial using the COVID-ICU cohort are provided in Table E1 in the online data supplement.

Eligibility criteria and treatment strategies of interest. The first step of any emulated trial is to define the target trial that would have been conducted if randomization was feasible (13). Based on the inclusion criteria of the EOLIA trial (5), our eligibility criteria for this study were: patients in ICU and on IMV, with time spent in ICU $\leq$ 14 days (before ECMO initiation) and time spent on IMV $\leq$ 7 days, age $\leq$ 70 years, Simplified Acute Physiology Score (SAPS) II at ICU admission $\leq$ 90, and $PaO_2/FiO_2 < 80$ mmHg or $PaCO_2 \geq 60$ mmHg. The lowest PaO_2 value (with its corresponding FiO_2) on the day of ECMO initiation/non-initiation or the day before was used. Therefore, a target trial would have aimed to compare strategies of initiating ECMO versus not initiating ECMO in patients with severe ARDS among patients meeting the above criteria. All patients in the COVID-ICU study were considered as potential candidates for ECMO, as ECMO was available in all centers including patients through mobile ECMO teams and retrieval into the ECMO center after cannulation. The organization of ECMO mobile teams and the increase in the offer during that period in Paris and its greater area (Région Ile de France) have been thoroughly described elsewhere (4). An ECMO center that had performed more than 30 venovenous (VV-) ECMO cases in 2019 was considered a high volume center (4, 14).

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Endpoints and estimands. The primary outcome was all-cause mortality. Overall survival time was defined as the time in days from the time of meeting eligibility criteria (i.e. time of inclusion in a given sequential "trial", see the next subsection) up to death. We applied administrative censoring at 90 days. The primary estimands of interest were the marginal survival probabilities up to 90 days under each of the two treatment strategies (i.e., what would have been the survival if all patients meeting the eligibility criteria had started ECMO compared with none of them had) and the corresponding risk difference. The secondary estimand was the hazard ratio (HR) associated with ECMO initiation conditional on variables measured at the time of meeting eligibility criteria.

Analysis using sequential trials approach: data set-up. Data from the COVID-ICU cohort were used to emulate the target trial specified above. The estimands specified in the previous section could be estimated using observational data under several assumptions: conditional exchangeability, positivity, consistency, and no interference (15).

Eligibility criteria were checked daily for each patient, and individuals in the study cohort could meet the eligibility criteria on several days. We took advantage of this feature in our analysis by making use of the 'sequential trials' causal inference approach (10, 16, 17) (see Figure E1 in the online data supplement). Day 1 denoted the first day of IMV. An 'emulated trial' data set was created for each day between Day 1 and Day 7 from IMV initiation, as follows. Among patients who met eligibility criteria on Day-1, those treated with ECMO were following treatment strategy (i) and are referred to as the *treatment* group. The remaining patients who did not initiate ECMO on Day 1 were following treatment strategy (ii) on that day and are referred to

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as the *control* group. Some individuals in the control group on Day 1 subsequently initiated ECMO, therefore deviating from treatment strategy (ii). They were artificially censored the day before initiating ECMO. This process was repeated for each day from Day 2 to Day 7, for alive patients meeting the eligibility criteria and not yet treated by ECMO. A given patient could be included in the *control* group in several trials, but only once in the *treatment* group. Days 1 to 7 were called landmark time points. The final analysis dataset (referred to as the "pooled" dataset) was obtained by pooling the data from the 7 sequential trials.

Analysis using sequential trials approach: estimation. To estimate the effect of ECMO use on survival we needed to account for confounding in this association. We also needed to account for the dependent censoring that is created from our artificial censoring of patients in the control group at the start of a given trial who deviated from the treatment strategy (ii) when ECMO was initiated. These were respectively handled in the analysis by adjustment for confounders measured at the start of each "trial", and by use of time-dependent inverse probability of censoring (IPC) weights. The following prespecified covariates were used to adjust for confounding: age, sex, inclusion period (before or after March 31, 2020), body mass index ($< \text{or} \geq 30$ kg.m^{-2}), time from first symptoms to ICU admission ($\leq \text{or} > 7$ days), time since IMV initiation ($< \text{or} \geq 6$ days), diabetes mellitus, treated hypertension, immunodeficiency, PaO_2/FiO_2 ($< \text{or} \geq 65$ mmHg; $PaO_2/FiO_2 < 65$ mmHg was the first quartile of PaO_2/FiO_2 and therefore identified the most hypoxemic patients in our population), $PaCO_2$ ($< \text{or} \geq 60$ mm Hg), bacterial co-infection, renal and cardiovascular components of the SOFA score ($\leq$ or > 2), any prone position, neuromuscular blockades, and/or corticosteroids use before ECMO initiation/non-initiation (details in the online data supplement). Of these covariates, PaO_2/FiO_2, the

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SOFA score, $PaCO_2$, bacterial co-infection, rescue therapies, and corticosteroids use were varying over time during the follow-up in the emulated trial. These covariates were selected *a priori* based on known prognostic factors of COVID-19 ARDS (11, 18) and severe ARDS rescued by ECMO (19, 20). The analysis used a Cox regression fitted to the pooled dataset, using the time-dependent IPC weights (see below). The model included ECMO status at the start of the trial (i.e. treatment or control) as a covariate, plus measures of all covariates (as recorded at the start of each trial for time-varying covariates). The coefficient for ECMO status was assumed to be identical across the seven trials. We allowed a time-varying coefficient for ECMO, *i.e.* non-proportional hazards. A smooth plot of the Schoenfeld residuals was used to choose a suitable functional form for the log hazard ratio over time (21).

IPC weighting was used to adjust for the artificial informative censoring of patients in the *control* group who initiated ECMO later during follow-up (the "protocol deviation"). Cox regression was used to estimate the denominator of the weights, which was the estimated probability of not being censored up to a given follow-up time conditional on the patient's characteristics at each landmark time-points and during ICU follow-up, using the same set of covariates as in the main analysis. The weights were stabilized by using the estimated probability of not being censored up to a given time obtained from the Kaplan–Meier estimator in the numerator. Individual weights were estimated separately in each trial.

Marginal survival curves for treated and control groups were estimated from the regression coefficients and cumulative baseline hazard estimated from the weighted Cox regression analysis (16, 22). As the pooled dataset included several copies of the same individual that did not correspond to any well-defined population,

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survival curves were estimated on an *evaluation* cohort composed of unique individuals meeting the eligibility criteria at any time, with covariates set to their values at the first time of meeting the eligibility criteria (which may be trials starting on different days for different individuals). For each patient in the evaluation cohort, we estimated two sets of survival probabilities: the probabilities if they had initiated ECMO and the probabilities if they had not. We then calculated the empirical average of these predicted survival probabilities. Our focus was on the time horizon of 90 days, but we also repeated this at each day of follow-up to create estimated marginal (population average for the evaluation cohort) survival curves under the two treatment strategies. Because the same individual may appear in more than one trial and the use of IPC weighting, model-based variance estimators were not appropriate. Non-parametric bootstrap was used to estimate 95% normal-based confidence intervals for marginal survival probabilities and HRs (with 200 bootstrap replications). The estimation of weights and the multivariable Cox model were repeated in each bootstrap sample.

Missing data. Multiple imputations using chained equations were used to replace missing values on covariates, assuming that data are missing at random. Besides, there was no missing data regarding ECMO exposure. Further details on our multiple imputations are provided in the online data supplement.

Sensitivity analyses (SA). We performed several SA. First, by considering the complete cases sample without any missing data imputation (SA1). Second, by performing the analysis without artificial censoring of "crossed-over" control patients (and thus without IPC weighting) (SA2). Third, by using more stringent eligibility criteria: patients with $PaO_2/FiO_2 < 80$ mmHg or $PaCO_2 \geq 60$ mmHg and having

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received at least one prone position session (SA3) and fourth in the most hypoxemic patients with $PaO_2/FiO_2 < 65$ mmHg (SA4).

To allow that ECMO effects may vary over the landmark times, we performed subgroup analyses by restricting the analysis to the first four trials (Day 1 to 4) (SA5) and the last three trials (Day 5 to 7) (SA6).

To explore effect variation of ECMO between centers, analysis was restricted to centers from greater Paris (Région Ile de France) where a specific (re)organization of mobile ECMO teams was set up during that period (4) (SA7), and by separating high and low ECMO volume centers (SA8).

Lastly, marginal survival curves were re-estimated using a multivariable Cox model stratified (instead of adjusted) on the ECMO initiation group (i.e. with separate baseline hazards in the treated and control groups). Similarly to the time-varying coefficient method, this allowed to completely relax the proportional hazards assumption on ECMO initiation (SA9), at the cost of preventing the estimation of an HR associated with ECMO.

Results

Study population and characteristics of patients before ECMO initiation. Among 4,244 patients included in the analysis, 2,858 (67%) met the criteria for inclusion in the target trial (of age ≤ 70 years old and SAPS II ≤ 90) (Figure 1). A total of**Error! Reference source not found.** 269 (9%) patients received ECMO within 14 days of ICU admission. The main characteristics of these patients on ECMO according to their survival status 60 days after ECMO initiation are presented in Table 1. One hundred nineteen (44%) patients died. IMV was started at a median time of 0

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(interquartile range, IQR 0-1) days from ICU admission, and ECMO was initiated 6 (4-8) days after IMV started. Median pre-ECMO PaO_2/FiO_2 was 62 (53-74) whereas $PaCO_2$ was 58 (50-68) mmHg. Noticeably, PaO_2/FiO_2 was < 80 in 81% of the patients. Prone positioning and continuous neuromuscular blockade before ECMO were used in 240 (89%) and 260 (97%) patients, respectively.

Management on ECMO and outcomes. One hundred and eighty-four (68%) patients were proned on ECMO (Table 2). The median ECMO duration was 11 (6-17) days in the ECMO population and 12 (7-20) days in survivors. Noticeably, ECMO durations were 13 (7-20) and 10 (5-17) days in the high and low volume centers, respectively (Table E2). Median ICU and hospital length of stay were 31 (22-50) and 42 (28-63) days among survivors, respectively. Among the survivors 60 days after ECMO initiation, 6 (4%), 26 (17%), and 32 (21%) patients were still on ECMO, on IMV, or in the ICU, respectively. The main in-ICU complications were ventilator-associated pneumonia (64%), the need for renal replacement therapy (40%), and major bleeding (39%).

Effect of ECMO in patients included in the emulated trial. Among the 2,858 included patients included in the above summaries, 2,284 patients received IMV within 14 days after ICU admission (Figure 1**Error! Reference source not found.**). Before imputation of missing data, 1,235 unique patients met the full eligibility criteria of the target emulated trial at least once during the first 7 days of IMV, and, among them, 164 initiated ECMO (Table 3) in 30 ECMO centers. Fifty-nine ECMO patients were treated in three high-volume centers. Their characteristics are reported in Table E2. After imputation of missing data, 1,421 (min/max: 1,414/1,449) unique patients met the full eligibility criteria. The results of the multivariable Cox model

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estimated in the primary analysis are shown in Table E3 of the online data supplement. After inspection of Schoenfeld residuals, we chose to introduce a time-varying coefficient associated with ECMO by including an interaction between ECMO status and the square root of time.

Figure 2 and Table E3 show the estimated marginal survival curves under the two treatment strategies for the *evaluation* cohort. Under ECMO, the estimated survival probability at Day-7 was 87%, (95% CI 83-92%) compared with 83% (95% CI 81-85%) under the alternative treatment strategy of not receiving ECMO (risk difference: 4%, 95% CI 0;9%). Moreover, the survival decreased to 69% (95%CI 62;76%) at Day-28 with ECMO, compared with 68% (95%CI 66%;71%) without ECMO (risk difference: 1%, 95% CI -6;8%). After Day-40, the estimated survival under ECMO was lower than without ECMO. Finally, at Day-90, survival was respectively 63% (95% CI 56%;70%) and 65% (95%CI 62%;68%) with and without ECMO initiation (risk difference: -2%, 95% CI -10%;5%).

Initially, patients who initiated ECMO had a lower conditional hazard of death (HR at Day-1: 0.59, 95% CI 0.37;0.94). However, after 14 days of follow-up, the HR associated with ECMO initiation increased to 1.14 (95% CI 0.85;1.54) and was 1.66 (95% CI 1.12;2.46) and 3.00 (95% CI 1.52;5.94) at Day-28 and Day-60, respectively. Figure E2 shows the estimated hazard ratio over time.

Comparable results to the primary analysis were found in analysis with no missing data imputation (Table E4) and when we did not censor patients in the control group who initiated ECMO later during follow-up (Table E5). However, the survival at day 60 under ECMO was higher when the primary analysis was restricted to patients who had received at least one prone positioning session before ECMO (Table

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E6). Similarly, the protective effect of ECMO was more pronounced and maintained until day-90, despite wider confidence intervals, when analyses were limited to patients with PaO_2/FiO_2 <65 (Table E7) or those with ECMO initiated up to 4 days after intubation (Table E8-E9). When the primary analysis was restricted to patients treated in centers of the Greater Paris, or distinguished patients treated in high vs. low-volume ECMO centers, ECMO was consistently associated with a higher survival rate until day-90 (Table E10-E11; Figure 2-B; Figure E2). Specifically, Day-90 survival was 78% (95% CI 66%;92%) for ECMO patients treated in high volume centers compared to 64% (95%CI 61%;67%) in those not receiving ECMO (risk difference, 14%, 95% CI 0%;27%) (Table E11; Figure 2-B). Lastly, similar results to the primary analyses were observed in an analysis using a multivariable Cox model stratified on the ECMO initiation group (Table E11).

Discussion

In this multicenter cohort study of 4,244 patients with COVID-19-associated ARDS, 269 were treated with ECMO, and survival 60 days following ECMO initiation was 56%. When restricted to patients who fulfilled eligibility criteria for the emulation target trial in this nationwide COVID-19 cohort, the estimated survival after 90 days for patients initiating ECMO was 63% (95%CI 56;70%) which was not better compared to patients without ECMO. Besides the effect of ECMO initiation varied over time. In sensitivity analyses, we observed that ECMO was more effective in patients with more severe hypoxemia (i.e., $PaO_2/FiO_2 \leq 65$ mmHg) or if initiated within four days after intubation. Interestingly, the benefit of ECMO (vs. no initiation of ECMO) was important and remained constant over the 90 days of follow-up for

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patients treated in high-volume ECMO centers or in regions where ECMO services were specifically organized in these times of high demand (4).

In our emulated target trial, ECMO was used in 164 out of 1235 (13%) patients with PaO_2/FiO_2 <80 or $PaCO_2 \geq 60$mmHg within the first 7 days of IMV. However, this incidence was greater than reported in the international LUNGSAFE study, where only 6.6% of the severe ARDS received ECMO (23). A better knowledge of ECMO indications and widespread use of that technique with mobile ECMO teams could explain this finding. Although international organizations (24, 25) and experts in the field (26, 27) recommended ECMO for critically ill COVID-19 patients, and large ECMO cohorts reported acceptable survival rates (2, 3), the benefit of ECMO in that population remains a matter of debate (28, 29), especially in a context of a pandemic with health care resource constraints. Further randomized trials of ECMO in the COVID-19 population would be desirable but are unlikely to be undertaken. Target trial emulation may therefore offer the best evidence based on observational data. When restricting the use of ECMO to EOLIA inclusion criteria (i.e. our eligibility target trial criteria), our 90-Day survival for patients initiating ECMO was in accordance with survival reported in experienced-ECMO centers (3), international ELSO cohort (2), or in a recent worldwide meta-analysis (30). However, the effect of ECMO on patients' outcomes in the whole cohort varied over time with a significantly higher survival during the first weeks, and a similar or even lower 90-day survival when compared to a non-ECMO strategy. These results contrast with the constant benefit of ECMO reported in the EOLIA trial (5) and question whether ECMO improves the outcomes of patients with severe COVID-19 related ARDS. Several lines of evidence may explain these findings. First, despite controlling for the carefully chosen baseline and time-dependent prognostic factors, residual confounding may

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have persisted. Second, specific pathophysiological features of COVID-19 could also explain these results. Indeed, longer duration of ECMO support, higher rates of ECMO-associated complications, including ventilator-associated pneumonia, major bleeding, oxygenator failure, and thromboembolic events, were reported in COVID patients compared to the ECMO arm of the EOLIA trial (2, 3, 31–33). This may reflect the longer duration of mechanical ventilation, specific SARS-CoV-2–induced immunoparalysis, the vascular tropism of that disease, and the need for higher anticoagulation. Alternatively, our observation of a decreased benefit of ECMO over time may be explained by the differential survival of patients treated in experienced vs. less experienced centers. Indeed, while the survival of patients treated in high-volume centers remained consistently higher than that of non-ECMO patients, it was not different in the initial days of support and then was even lower in patients treated in lower case-volume centers than in the non-ECMO patients (Figure 2-B). These results concur with the strong association between higher ECMO volume and lower mortality reported in international non-COVID (14) and COVID cohorts (32), advocating for centralization and regulation of ECMO indications (4).

Our primary results also contrast with other recent observations. In an emulated target trial Shaefi et al (10) showed a considerably lower risk of death in patients treated with ECMO compared to those not treated with ECMO. Several factors may explain these differences. First, we used broader eligibility criteria in our trial with the inclusion of patients up to 14 days in ICU whereas it was the first 7 days in the study of Schaefi et al (10). A shorter time between intubation or ICU admission and ECMO has been consistently associated with better survival in COVID cohorts (19). Similarly, our subgroup analysis of patients for whom treatment was initiated within the first 4 days of IMV showed a more pronounced protective effect of ECMO.

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Second, the pre-ECMO PaO_2/FiO_2 and static compliance of our patients were much lower than those reported by Schaefi *et al*, (10) suggesting a greater respiratory severity. Similarly, the higher use of pre-ECMO prone positioning reported in our study (89% *vs.* 71%) reinforces that point by stressing that our population was refractory to (almost) all pre-ECMO adjunct therapies. The mortality benefit associated with ECMO in severe COVID-19 was also strongly suggested in a series of 90 patients eligible and referred for ECMO to a single center. Mortality was 90% for the 55 (61%) patients who did not receive it due to limited health system capacity, compared to 43% when ECMO capacity was available – despite both groups having young age and limited comorbidities (34).

Despite being based on a large detailed multicenter cohort of critically ill COVID-19 patients with a low rate of missing values, the results of this emulated target trial should be interpreted cautiously. First, our inclusion criteria for the emulated target trial were based on PaO_2/FiO_2 <80 and/or $PaCO_2 \geq 60$mmHg at one point (regardless of the timing of adjunct therapies during that day) which contrasts with the EOLIA trial and expert recommendations which advocate considering the duration of time (i.e > 6 hours) below a PaO_2/FiO_2 or above a $PaCO_2$ threshold (5, 35). This difference could have caused a potential bias towards better outcomes for non-ECMO-treated patients and hampered exchangeability. Second, ECMO patients' management has not been specifically captured by our study and could have differed between ECMO centers. As previously reported in COVID (4) and non-COVID patients (14), venovenous ECMO case volume markedly influenced outcome, with better 90-day survival for patients treated in experienced centers in our study. Third, the use of specific COVID-19 therapies, other than dexamethasone, was not collected in the COVID-ICU cohort. Fourth, although we carefully designed this emulated trial

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based on observational data, applied methodological corrections to each identified source of bias, and performed several sensitivity analyses, we cannot exclude residual confounding which could question the conditional exchangeability assumption. The validity of other assumptions of causal inference may also be discussed. The assumption of no interference (the treatment applied to one unit does not affect the outcome of other units) is likely to be valid in this setting, as the assumption of positivity (by carefully selecting clinically meaningful ECMO eligibility criteria). Assumption of consistency could also have been challenged in a period when hospital strain was intense (34). This potential issue was explored by two sensitivity analyses restricted to centers from greater Paris, and centers with high ECMO volume, reducing potential heterogeneity in ECMO management. The assumptions surrounding missing data may also not be justified. Lastly, because an increase in mortality in COVID-19 patients on ECMO has been recently reported during the second surge of the pandemic (i.e after September 2020) (32, 33, 36), our results might have changed over time with the emergence of SARS-CoV-2 variants associated with more severe forms of ARDS.

In conclusion, we found a differential survival associated with ECMO compared to no ECMO that differs from previous studies in an unselected nationwide cohort of COVID-19 (10, 34). However, an ECMO strategy consistently yielded better outcomes when performed in high volume ECMO centers or in regions where ECMO services had been organized to handle high demand, and if initiated early after intubation and in profoundly hypoxemic patients. Our results reinforce the need for regional ECMO networks and advocate for providing ECMO in experienced centers to optimize the outcomes of these critically ill patients, especially at times of unprecedented strain on health care systems.

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MS, DH, RK, AB, CM, CL, and AC developed the protocol and the statistical analysis plan.

DH performed the statistical analysis of the data

MS, DH, and AC wrote the manuscript.

All authors contributed to the revision, read, and approved the final version of the manuscript.

DH and MS take responsibility for the integrity of the work, from inception to published article.

Disclosures

Matthieu Schmidt reports lecture fees from Getinge, Drager, and Xenios outside the submitted work. Alain Combes reports grants from Getinge, personal fees from Getinge, Baxter, and Xenios outside the submitted work. Saad Nseir reports lecture fees from MSD, Gilead, Pfizer, Biomérieux, Bio Rad, and Fischer and Paykel outside the submitted work. Christophe Guervilly reports lecture fees from 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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Data sharing

Individual patients' data reported in this article will be shared after de-identification

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(text, tables, figures, and appendices), beginning 6 months, and ending 2 years after article publication, to researchers who provide a methodologically sound proposal and after approval of the COVID-ICU internal scientific committee. Proposals should be addressed to matthieu.schmidt@aphp.fr. To gain access, data requestors will need to sign a data access agreement.

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Table 1: Patients' pre-ECMO characteristics according to their survival status 60 days after ECMO initiation

	Missing values, n	All patients (n=269)	60-Day after ECMO initiation survival status		*P*-value
			Alive (n=151)	Dead (n=118)	
Age, years	-	54 (46-59)	53 (43.5-58)	55 (50-62)	<0.001
Male sex	-	207 (77)	109 (72)	98 (83)	0.036
Body mass index, kg/m^2	-	30 (27-34)	30 (28-35)	29 (27-34)	0.322
≥ 30 kg/m^2		139 (54)	84 (58)	55 (49)	0.156
SAPS II score	-	42 (31-57)	45 (31-55)	41 (30-59)	0.780
SOFA score at ICU admission	14	8 (4-12)	8 (4-12)	8 (5-11)	0.945
ICU admission	-				0.685
before March 31, 2020		149 (55)	82 (54)	67 (57)	
after April 1, 2020		120 (45)	69 (46)	51 (43)	
Treated hypertension	1	84 (31)	47 (31)	37 (31)	0.997
Known diabetes	3	63 (24)	29 (19)	34 (29)	0.068
Time between, days :					
First symptoms to ICU admission	19	10 (7-13)	10 (7-13)	9 (7-13)	0.975
ICU admission to invasive MV	-	0 (0-1)	0 (0-0)	0 (0-1)	0.030
Invasive MV to ECMO	-	6 (4-8)	5 (3-7)	6 (5-9)	<0.001
Before ECMO					
VT, mL/kg PBW	15	5.1 (3.0-6.0)	5.2 (3.3-6.0)	4.8 (3.1-6.0)	0.474
Set PEEP, cm H_2O	2	14 (12-15)	14 (12-15)	14 (12-16)	0.707
Plateau pressure, cmH_2O	17	30 (28-33)	30 (28-33)	31 (28-34)	0.327
Driving pressure, cmH_2O [a]	10	18 (15-24)	18 (15-23)	19 (15-24)	0.350
Static compliance, mL/ cmH_2O	15	18 (12-25)	19 (14-25)	17 (11-25)	0.264
Cardiovascular SOFA score	12				0.177
0-2		101 (39)	63 (43)	38 (35)	
3-4		156 (61)	84 (57)	72 (65)	
Renal SOFA score	15				0.397
0-2		212 (83)	126 (85)	86 (81)	
3-4		42 (16)	22 (15)	20 (19)	
Renal replacement therapy	-	44 (16)	18 (12)	26 (22)	0.026
Blood gases					
pH	3	7.30 (7.25-7.36)	7.31 (7.26-7.37)	7.29 (7.22-7.35)	0.005
$PaCO_2$, mmHg	6	58 (50-68)	56 (48-67)	59 (53-72)	0.006
PaO_2/FiO_2	5	62 (53-74)	65 (52-76)	61 (54-70)	0.215
HCO_3, mmol/L	3	27 (23-30)	26 (23-30)	27 (23-31)	0.365
Lactate, mmol/L	4	2 (1.6-2.4)	2 (1.6-2.5)	2 (1.6-2.4)	0.818
Bacterial coinfection	-	90 (33)	49 (32)	41 (35)	0.692
Rescue therapies					
Prone position	-	240 (89)	133 (88)	107 (91)	0.495
Continuous neuromuscular blockade	-	260 (97)	149 (99)	111 (94)	0.045
Nitric oxide	-	135 (50)	70 (46)	65 (55)	0.155
Corticosteroids [b]	-	59 (22)	31 (21)	28 (24)	0.529

Values are expressed as median (interquartile range) or number (%).
ECMO, extracorporeal membrane oxygenation, ICU intensive care unit, FiO_2 the fraction of inspired oxygen, MV, mechanical ventilation, PaO_2/FiO_2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, PEEP positive end-expiratory pressure, PBW predicted body weight, PaO_2 partial pressure of arterial oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, VT, tidal volume, SAPS Simplified Acute Physiology Score, and SOFA Sequential Organ-Function Assessment.

[a] *Defined as plateau pressure minus PEEP.*
[b] *No distinction between corticosteroids types, neither their dose nor the reason for initiation were made*

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Table 2: Management, complications, and outcomes of the patients during ECMO according to their survival status 60 days after ECMO initiation

	All patients (n=269)	60-Day after ECMO initiation survival status		*P*-value
		Alive (n=151)	Dead (n=118)	
First 48 hours on ECMO				
VT, mL/kg PBW	2.8 (1.9-4.0)	3.0 (2.1-4.1)	2.5 (1.8-3.6)	0.012
Set PEEP, cm H_2O	14 (12-16)	13 (11-16)	14 (12-16)	0.422
Plateau pressure, cmH_2O	24 (22-27)	24 (22-26)	24 (21-28)	0.503
Driving pressure, cmH_2O	12 (9-14)	12 (9-13)	12 (9.25-14)	0.432
Prone positioning during ECMO	184 (68)	110 (73)	74 (62)	0.076
Tracheostomy	36 (13)	28 (19)	8 (7)	0.005
Complications within day 60				
Renal replacement therapy	106 (39)	49 (32)	57 (48)	0.008
Pneumothorax	15 (6)	8 (5)	7 (6)	0.822
Major hemolysis	32 (12)	15 (10)	17 (14)	0.261
Ventilator associated pneumonia	171 (64)	106 (70)	65 (55)	0.011
Major bleeding	107 (40)	50 (33)	57 (48)	0.012
Intra cranial bleeding or hemothorax	21 (8)	2 (1)	19 (16)	<0.001
Thromboembolic complications	83 (31)	98 (65)	88 (75)	0.088
Pulmonary embolism	36 (13)	16 (11)	20 (17)	0.129
Proven distal venous thrombosis	55 (20)	42 (28)	13 (11)	<0.001
Cardiac arrest	24 (8)	12 (8)	12 (10)	0.526
Length of stay				
On ECMO, days	11 (6-17)	12 (7-20)	9 (5-14)	0.002
On invasive MV, days	24 (16-37)	27 (20-44)	20 (12-31)	<0.001
In ICU, days	27 (15-41)	31 (23-50)	17 (10-31)	<0.001
In the hospital, days	30 (16-48)	43 (28-62)	20 (12-32)	<0.001
At day 60				
Still on ECMO	6 (2)	6 (4)	0	-
Still on invasive MV	26 (10)	26 (17)	0	-
Still in ICU	32 (12)	32 (21)	0	-
Still in the hospital	63 (23)	63 (42)	0	-
Discharge alive from the hospital	88 (33)	88 (58)	0	-

Values are expressed as median (interquartile range) or number (%).
ECMO, extracorporeal membrane oxygenation, ICU intensive care unit, MV, mechanical ventilation.

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Table 3: Characteristics of patients included in the target trial emulation of ECMO versus no ECMO

		Unique patients		Final cohort	
	Missing values [a], n	ECMO (n=164)	No ECMO (n= 1071)	ECMO (n=164)	No ECMO (n= 2992)
Age, years	-	53 (46-59)	61 (54-66)	53 (46-58)	60 (53-66)
Male sex	-	130 (79)	836 (78)	130 (79)	2341 (78)
SAPS II score	-	41 (31-56)	36 (29-48)	41 (31-56)	37 (29-48)
ICU admission	-				
before March 31		103 (63)	727 (68)	103 (63)	2023 (68)
after April 1		61 (37)	344 (32)	61 (37)	969 (32)
Clinical frailty scale	499	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)
Body mass index, kg/m^2	70	30 (27-34)	29 (26-33)	30 (27-34)	30 (26-33)
≥ 30		89 (56)	477 (47)	89 (56)	1415 (50)
Known diabetes	11	31 (19)	312 (29)	31 (19)	847 (28)
Treated hypertension	13	55 (33)	500 (47)	55 (33)	1379 (46)
Bacterial coinfection [b]	-	18 (11)	120 (11)	56 (34)	870 (29)
Time between					
First symptoms to ICU admission, days	65	9 (6-11)	8 (6-11)	9 (6-11)	8 (6-11)
ICU admission to invasive MV, hours	-	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Invasive MV and inclusion in the emulation trial, days	-	-	-	5 (3-6)	4 (2-6)
Respiratory function [c]					
PaO_2/FiO_2	239	74 (62-126)	78 (63-143)	59 (50-67)	73 (63-107)
< 80		50 (54)	471 (52)	156 (95)	1905 (64)
$PaCO_2$, mmHg	244	44 (40-50)	43 (37-50)	58 (51-68)	60 (46-66)
≥ 60		8 (9)	93 (10)	71 (44)	1503 (51)
Arterial pH	240	7.38 (7.32-7.43)	7.37 (7.31-7.43)	7.30 (7.24-7.34)	7.33 (7.27-7.39)
< 7.25		8 (9)	98 (11)	44 (27)	596 (20)
VT, mL/kg PBW	692	5.9 (5.4-6.3)	6.1 (5.8-6.7)	5.3 (3.4-6.1)	6.1 (5.8-6.7)
Set PEEP, cmH_2O	280	12 (10-14)	12 (10-14)	14 (12-16)	12 (10-15)
Plateau pressure, cmH_2O	513	27 (24-29)	24 (21-27)	31 (29-33)	27 (24-30)
Static compliance, mL/cmH_2O	732	27 (17-33)	32 (22-40)	18 (13-25)	27 (19-37)
Extra-pulmonary functions [c]					
Lactate, mmol/l	273	1.5 (1.2-1.9)	1.3 (1.0-1.6)	2.0 (1.6-2.6)	1.6 (1.2-2.0)
Cardiovascular SOFA score 3-4	249	49 (52)	507 (57)	96 (60)	1548 (54)
Renal SOFA score 3-4	258	4 (4)	75 (9)	30 (19)	423 (15)
Renal replacement therapy		1 (1)	33 (3)	22 (13)	336 (11)
Rescue therapies [b]					
Prone position	-	38 (23)	212 (20)	156 (95)	1907 (64)
Neuromuscular blockade	-	84 (51)	749 (70)	162 (99)	2742 (92)
Nitric oxide	-	8 (5)	23 (2)	89 (54)	466 (16)
Corticosteroids [d]	-	4 (2)	106 (10)	30 (18)	656 (22)

Values are expressed as median (interquartile range) or number (%).
ECMO, extracorporeal membrane oxygenation, ICU intensive care unit, FiO_2 the fraction of inspired oxygen, MV, mechanical ventilation, PaO_2/FiO_2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, PEEP positive end-expiratory pressure, PBW predicted body weight, PaO_2 partial pressure of arterial oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, VT, tidal volume, SAPS Simplified Acute Physiology Score, and SOFA Sequential Organ-Function Assessment.
[a] for the unique patients
[b] Assessed on the day of ICU admission for the unique patients and up to the day of ECMO initiation or non-initiation for the final cohort
[c] Assessed on the day of ICU admission for the unique patients and the day of ECMO initiation or non-initiation for the final cohort
[d] No distinction between corticosteroids types, neither their dose nor the reason for initiation were made

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Figures

Figure 1: Study flow chart

The flowchart describes at each landmark time (defined as the first seven days from invasive mechanical ventilation initiation) the number of patients considered for eligibility, the number of patients who met eligibility criteria of the emulated trial, and the number of patients who initiated ECMO. One patient can contribute several times to the 'Did not initiate ECMO' group but only once to the 'initiated ECMO' group. ECMO, extracorporeal membrane oxygenation, CC: complete cases. MI: number of cases after multiple imputations of missing data (median [min/max]).

Figure 2: Marginal survival curves for A) ECMO-treated versus ECMO non-treated patients; B) ECMO- treated in low or high ECMO volume centers versus ECMO non-treated patients (SA8)

ECMO, extracorporeal membrane oxygenation

Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

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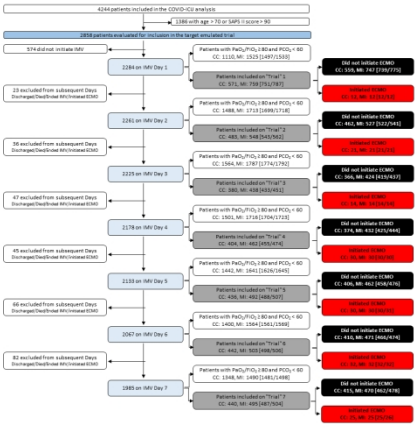

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The flowchart describes at each landmark time (defined as the first seven days from invasive mechanical ventilation initiation) the number of patients considered for eligibility, the number of patients who met eligibility criteria of the emulated trial, and the number of patients who initiated ECMO. One patient can contribute several times to the 'Did not initiate ECMO' group but only once to the 'initiated ECMO' group. ECMO, extracorporeal membrane oxygenation, CC: complete cases. MI: number of cases after multiple imputations of missing data (median [min/max]).

602x338mm (96 x 96 DPI)

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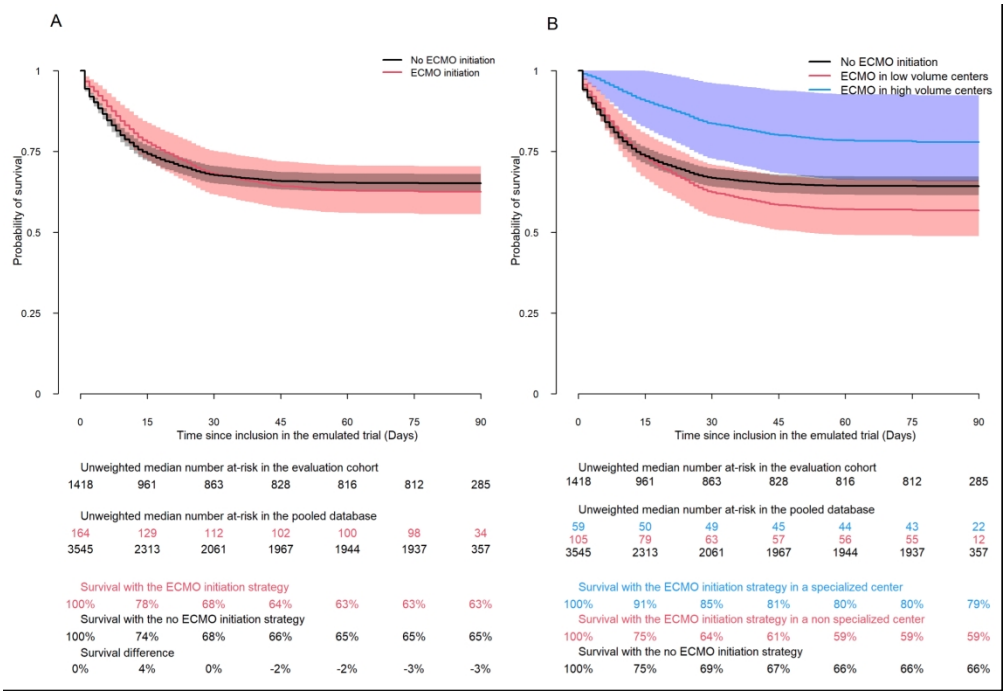

Figure 2: Marginal survival curves for A) ECMO-treated versus ECMO non-treated patients; B) ECMO-treated in low or high ECMO volume centers versus ECMO non-treated patients (SA8)

ECMO, extracorporeal membrane oxygenation
Number at-risk: median number among multiply imputed dataset.
Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.
Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

853x586mm (72 x 72 DPI)

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Online Data Supplement

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome associated with COVID-19: An Emulated Target Trial Analysis

David Hajage, MD, PhD; Alain Combes, MD, PhD; Christophe Guervilly, MD; Guillaume Lebreton, MD, PhD; Alain Mercat, MD PhD; Arthur Pavot, MD; Saad Nseir, MD, PhD; Armand Mekontso-Dessap, MD, PhD; Nicolas Mongardon, MD, PhD; Jean Paul Mira, MD, PhD; Jean-Damien Ricard, MD, PhD; Alexandra Beurton MD; Guillaume Tachon, MD ; Loay Kontar, MD; Christophe Le Terrier, MD ; Jean Christophe Richard, MD, PhD; Bruno Mégarbane, MD,PhD; Ruth H Keogh, DPhil; Aurélien Belot, PhD; Camille Maringe, PhD; Clémence Leyrat, PhD; Matthieu Schmidt, MD, PhD for the COVID-ICU investigators

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Definitions

- Some ECMO-related complications

Major bleeding was defined as bleeding requiring two or more units of packed red blood cells due to an obvious hemorrhagic event, bleeding necessitating a surgical or interventional procedure, an intracranial hemorrhage, or bleeding leading to death.

Severe hemolysis was defined as plasma-free hemoglobin >500 mg/L associated with dark-colored urine or renal insufficiency.

- Some prespecified covariates used to adjust for confounding

- **Immunodeficiency** is defined as hematological malignancies, an active solid tumor or having received specific anti-tumor treatment within a year, solid-organ transplant, human immunodeficiency virus, or immunosuppressants.

- **Corticosteroids use** before ECMO initiation/non-initiation: No distinction between corticosteroids types, neither their dose nor the reason for initiation were made

Missing data imputation

For some patients receiving ECMO, the inclusion in the study cohort was performed by the center providing ECMO, and not by the center that initially admitted the patient to ICU. Consequently, daily time-updated variables (e.g. arterial blood gas) before ECMO initiation were not always available for these transferred patients. However, the date of admission to the first ICU, the date of transfer, and the date of IMV and ECMO initiation were collected for all patients.

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This incomplete time-updated information, as well as other missing data from other sources, were processed by multiple imputations. Because time-dependent covariates were implied (e.g. PaO_2/FiO_2 ratio), we used the procedure described by Murad *et al*. to impute missing covariate values [1]. This procedure is based on multiple imputations chained equations and is thus expected to perform well when the missing at random (MAR) assumption holds true. The procedure multiply imputes the missing values in a time-sequential manner, using covariates from the current and previous days as well as the survival outcome (including the event status and the cumulative baseline hazard estimated by the Nelson-Aalen estimator). Variables used in the imputation model were the same as those used in the multivariable Cox hazard model evaluating the effect of ECMO initiation, as well as pH (which is assumed to inform partial pressure of carbon dioxide [$PaCO_2$] value). Ten copies of the dataset were created with the missing values replaced by imputed values. All the previously described analyses were performed using each dataset (including the selection of eligible subjects, IPCW, Multivariable Cox model, and bootstrap variance estimations) and the results from each dataset were pooled into a final result using Rubin's rules [2]. Of note, the number of eligible patients may vary from one imputed dataset to the other, because the assessment of eligibility makes use of partially observed (but imputed) variables.

References

1 Murad H, Dankner R, Berlin A, Olmer L, Freedman LS. Imputing missing time-dependent covariate values for the discrete time Cox model. *Stat Methods Med Res* 2020; **29**: 2074–86.

2 Sterne JAC, White IR, Carlin JB, *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338**: b2393.

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Table E1: Detailed characteristics of a hypothetical target trial and our emulated trial the COVID-ICU data.

Component	Target trial	An emulated trial using COVID-ICU data
Design	Open-label multicenter two parallel arm superiority randomized trial	Cohort study
Aim	To estimate the effectiveness of ECMO initiation within 10 days of mechanical ventilation on overall survival of patients with Severe Acute Respiratory Distress Syndrome associated with COVID-19 hospitalized in ICU in France	Same
Eligibility	• Age ≤ 70 • SAPS II ≤ 90 • in ICU ≤ 14 days • IMV ≤ 7 days • PaO_2/FiO_2 ratio < 80 mmHg or PaCO2 ≥60 mmHg • Never received ECMO during that hospital stay	Same
Treatment assignment	Random assignment to either: • ECMO initiation or • No ECMO initiation (control group) as soon as eligibility criteria are met.	No random assignment. Treatment strategies are defined based on the treatment received from Day 1 to Day 7 after IMV initiation (landmark times). Patients not initiating ECMO can be assigned to the control group for several days. Patients initiating ECMO are thereafter no more eligible in the subsequent days.
Outcome	All-cause mortality	Same
Type of outcome	Failure time. Time from randomization up to death. Patients alive at 90 days after randomization are censored.	Failure time. • Time from start of IMV to death (Day 1) • Time from each landmark time to death (Day 2 to Day 7) Patients alive at 90 days after inclusion in the study are censored
Adjustment variables	None	Age, sex, inclusion period (before March 31th or after April 1st 2020), body mass index (< or ≥ 30 kg.m^2), time from the first symptom and ICU admission (≤ or > 7 days), time from intubation to inclusion (≤5 or > 5 days), bacterial coinfection, corticosteroids, diabetes mellitus, treated hypertension, immunodeficiency, PaO_2/FiO_2 ratio (< 65 or ≥ 65mmHg), PaCO2 ≥ 60mmHg, renal and cardiovascular components of the SOFA score (≤ or > 2), use prone position before ECMO initiation/non-initiation, use of neuromuscular blockade before ECMO initiation/non-initiation.
Causal	• Intention-to-treat (ITT)	Average Treatment Effect, with censoring of

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contrasts	• Modified ITT: efficacy of receiving the interventions as planned, with censoring of control patients who initiate ECMO later	control patients who initiate ECMO
Estimands	• Difference in probabilities of survival over time • Hazard ratio	Same

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Table E2: Characteristics of the patients on ECMO included in the target trial emulation according to ECMO volume centers

	Unique patients		Final cohort	
	ECMO in high volume centers (n=59)	**ECMO in low volume centers (n= 105)**	**ECMO in high volume centers (n=59)**	**ECMO in low volume centers (n= 105)**
Age, years	49 (40-55)	55 (49-59)	49 (40-55)	55 (49-59)
Male sex	44 (75)	86 (82)	44 (75)	86 (82)
SAPS II score	42 (30-55)	40 (31-57)	42 (30-55)	40 (31-57)
ICU admission before March 31	42 (71)	61 (58)	42 (71)	61 (58)
Clinical frailty scale	2 (1-2)	2 (2-3)	2 (1-2)	2 (2-3)
Body mass index, kg/m^2	31 (28-36)	30 (27-33)	31 (28-36)	30 (27-33)
≥ 30	34 (61)	55 (53)	34 (61)	55 (53)
Known diabetes	13 (22)	18 (17)	13 (22)	18 (17)
Treated hypertension	23 (39)	32 (30)	23 (39)	32 (30)
Bacterial coinfection [b]	4 (7)	14 (13)	13 (22)	43 (41)
Time between First symptoms to ICU admission, days	9 (6-12)	8 (6-10)	9 (6-12)	8 (6-11)
ICU admission to invasive MV, hours	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)
Invasive MV and inclusion in the emulation trial, days	-	-	4 (2-6)	5 (4-6)
Respiratory function [c]				
PaO_2/FiO_2	63 (58-108)	83 (64-134)	58 (50-65)	60 (50-68)
$PaCO_2$, mmHg	48 (39-55)	44 (40-48)	55 (51-65)	60 (52-68)
≥ 60	3 (12)	5 (7)	18 (31)	53 (51)
Arterial pH	7.34 (7.26-7.45)	7.38 (7.33-7.43)	7.30 (7.24-7.34)	7.30 (7.24-7.35)
VT, mL/kg PBW	6.1 (5.2-6.3)	5.8 (5.4-6.3)	4.7 (3.3-6.0)	5.4 (3.5-6.1)
Set PEEP, cmH_2O	12 (10-14)	12 (10-14)	14 (12-15)	14 (12-16)
Plateau pressure, cmH_2O	28 (26-33)	26 (23-29)	33 (30-34)	30 (27-32)
Static compliance, mL/cmH_2O	19 (15-31)	29 (20-34)	18 (14-21)	19 (12-26)
Extra-pulmonary functions [c]				
Lactate, mmol/l	1.7 (1.3-2.1)	1.4 (1.1-1.8)	2.0 (1.6-2.4)	2.0 (1.6-2.6)
Cardiovascular SOFA score 3-4	12 (50)	37 (53)	31 (54)	65 (64)
Renal SOFA score 3-4	1 (4)	3 (4)	12 (21)	18 (18)
Renal replacement therapy	1 (2)	0 (0)	8 (14)	14 (13)
Rescue therapies [b]				
Prone position	11 (19)	27 (26)	54 (92)	102 (97)
Neuromuscular blockade	24 (41)	60 (57)	59 (100)	103 (98)
Nitric oxide	4 (7)	4 (4)	26 (44)	63 (60)
Corticosteroids [d]	3 (5)	1 (1)	7 (12)	23 (22)
ECMO duration, days	13 (7-20)	10 (5-17)	13 (7-21)	9 (5-17)

Values are expressed as median (interquartile range) or number (%).
ECMO, extracorporeal membrane oxygenation, ICU intensive care unit, FiO_2 the fraction of inspired oxygen, MV, mechanical ventilation, PaO_2/FiO_2 the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, PEEP positive end-expiratory pressure, PBW predicted body weight, PaO_2 partial pressure of arterial oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, VT, tidal volume, SAPS Simplified Acute Physiology Score, and SOFA Sequential Organ-Function Assessment.
[a] *for the unique patients*
[b] *Assessed on the day of ICU admission for the unique patients and up to the day of ECMO initiation for the final cohort*
[c] *Assessed on the day of ICU admission for the unique patients and the day of ECMO initiation for the final cohort*

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Table E3: Hazard ratios (HR) of all-cause mortality (primary analysis) associated with ECMO initiation in the whole cohort.

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.02-1.04)
Sex Female (REF: Male)	0.98 (0.77-1.26)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.85 (0.69-1.04)
Diabetes mellitus	1.36 (1.08-1.70)
Treated hypertension	0.90 (0.72-1.11)
ICU admission after April 1 2020 (REF: before March 31 2020)	0.90 (0.73-1.12)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.84 (0.69-1.03)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.20 (1.05-1.38)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.65 (1.41-1.94)
SOFA Renal 3-4 (REF: 0-2)	2.02 (1.64-2.48)
Bacterial infection	1.29 (1.01-1.64)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	1.73 (1.46-2.04)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.81 (0.68-0.96)
Prone position	0.97 (0.81-1.17)
Corticosteroids	1.73 (1.40-2.13)
Neuromuscular blockade	1.02 (0.72-1.44)
ECMO at time 0	0.46 (0.26-0.83)
ECMO time varying HR (with the square root of time, days)	1.27 (1.10-1.47)
ECMO, unadjusted hazard ratio *	1.09 (0.85-1.41)

*no adjustment on covariates, no time dependent effect

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B- Hazard Ratio associated with death on ECMO over time

Computed from the coefficients associated with ECMO (at time zero and time varying) of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	Hazard Ratio (95%CI)
0	0.46 (0.26-0.83)
1	0.59 (0.37-0.94)
7	0.88 (0.63-1.21)
14	1.14 (0.85-1.54)
28	1.66 (1.12-2.46)
60	3.00 (1.52-5.94)

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	83% (81%;85%)	87% (83%;92%)	4% (0%;9%)
14	75% (72%;77%)	78% (73%;84%)	4% (-2%;10%)
28	68% (66%;71%)	69% (62%;76%)	1% (-6%;8%)
40	66% (64%;69%)	65% (59%;73%)	-1% (-8%;6%)
60	65% (63%;68%)	63% (56%;71%)	-2% (-10%;5%)
90	65% (62%;68%)	63% (56%;70%)	-2% (-10%;5%)

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Table E4: Sensitivity analysis on patients with no missing data imputation (complete case analysis) (SA1)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.02-1.04)
Sex Female (REF: Male)	1.01 (0.78-1.30)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.90 (0.73-1.11)
Diabetes mellitus	1.49 (1.20-1.85)
Treated hypertension	0.98 (0.78-1.22)
ICU admission after April 1 2020 (REF: before March 31 2020)	0.88 (0.70-1.11)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.91 (0.74-1.12)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.14 (1.01-1.30)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.58 (1.35-1.86)
SOFA Renal 3-4 (REF: 0-2)	1.96 (1.59-2.41)
Bacterial infection	1.05 (0.85-1.29)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	1.79 (1.50-2.13)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.77 (0.65-0.90)
Prone position	1.07 (0.90-1.28)
Corticosteroids	1.74 (1.42-2.13)
Neuromuscular blockade	1.16 (0.82-1.64)
ECMO at time 0	0.46 (0.28-0.74)
ECMO time varying HR (with the square root of time, days)	1.25 (1.12-1.40)
ECMO, unadjusted hazard ratio*	1.04 (0.81-1.34)

*no adjustment on covariates, no time dependent effect

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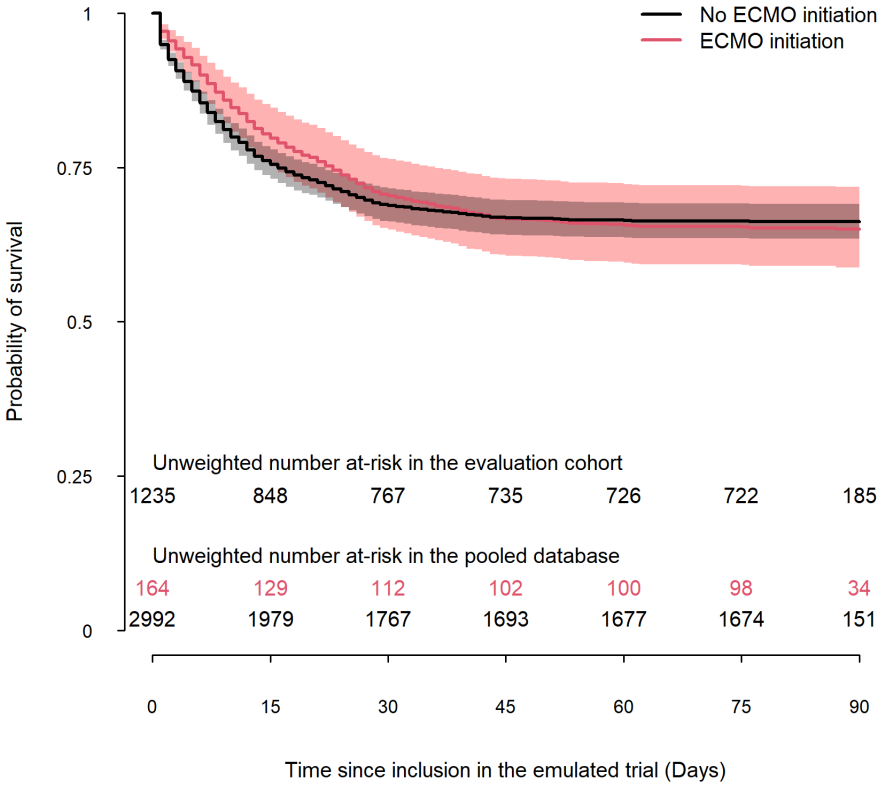
B- Adjusted survival curves



Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	84% (82%;86%)	88% (85%;91%)	4% (1%;8%)
14	77% (75%;79%)	80% (76%;84%)	3% (-2%;7%)
28	70% (68%;73%)	68% (64%;73%)	-2% (-7%;3%)
40	69% (66%;71%)	64% (59%;70%)	-5% (-10%;1%)
60	68% (65%;70%)	61% (56%;67%)	-6% (-12%;-0%)
90	67% (65%;70%)	60% (55%;66%)	-7% (-13%;-1%)

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Table E5: Sensitivity analysis without artificial censoring of "crossed-over" control patients (and without IPC weightings) (SA2)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.01-1.04)
Sex Female (REF: Male)	0.97 (0.76-1.23)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.89 (0.74-1.08)
Diabetes mellitus	1.41 (1.14-1.75)
Treated hypertension	0.87 (0.71-1.07)
ICU admission after April 1 2020 (REF: before March 31 2020)	0.93 (0.76-1.15)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.84 (0.69-1.01)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.17 (1.03-1.33)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.63 (1.40-1.90)
SOFA Renal 3-4 (REF: 0-2)	1.97 (1.62-2.40)
Bacterial infection	1.25 (0.99-1.58)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	1.62 (1.38-1.89)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.85 (0.72-1.00)
Prone position	0.97 (0.81-1.17)
Corticosteroids	1.66 (1.35-2.04)
Neuromuscular blockade	0.95 (0.68-1.32)
ECMO at time 0	0.50 (0.28-0.89)
ECMO time varying HR (with the square root of time, days)	1.22 (1.06-1.40)
ECMO, unadjusted hazard ratio *	0.99 (0.78-1.25)

*no adjustment on covariates, no time dependent effect

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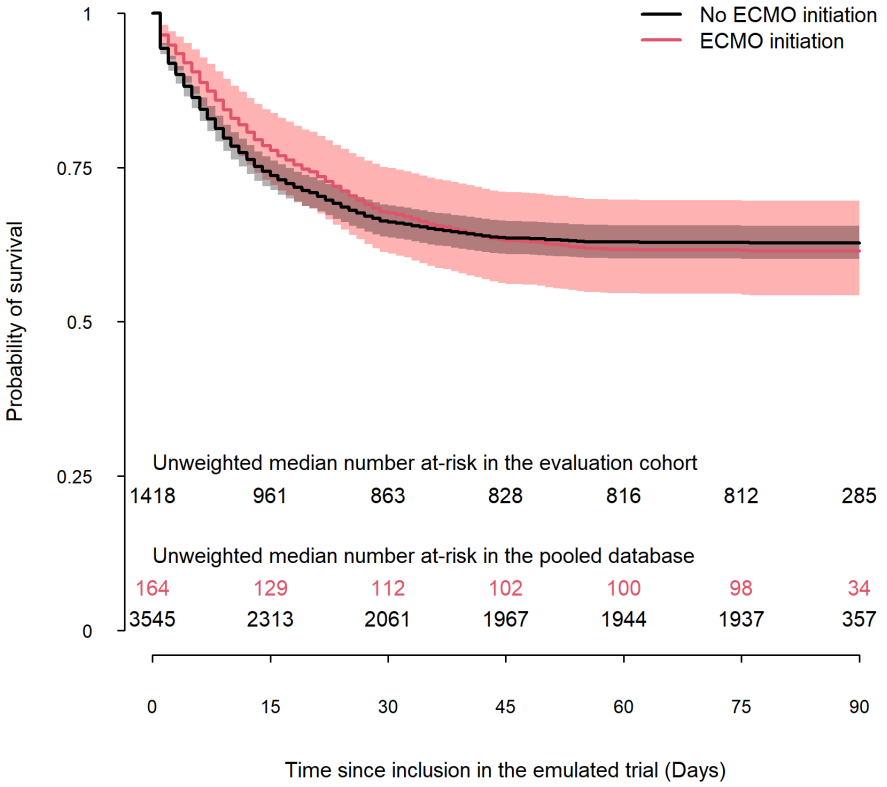
B- Adjusted survival curves



Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

C-Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	83% (81%;85%)	87% (83%;92%)	4% (0%;9%)
14	74% (72%;77%)	79% (73%;84%)	5% (-1%;10%)
28	67% (64%;69%)	68% (62%;76%)	1% (-5%;8%)
40	64% (62%;67%)	64% (58%;72%)	0% (-7%;7%)
60	63% (60%;66%)	62% (55%;70%)	-1% (-9%;6%)
90	63% (60%;66%)	61% (54%;70%)	-2% (-9%;6%)

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Table E6: Sensitivity analysis on patients with $PaO_2/FiO_2 < 80$ mmHg or $PaCO_2 \geq 60$ mmHg and having received at least one prone position session (SA3)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.01-1.04)
Sex Female (REF: Male)	1.06 (0.78-1.45)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.86 (0.68-1.11)
Diabetes mellitus	1.44 (1.09-1.90)
Treated hypertension	0.99 (0.76-1.30)
ICU admission after April 1 2020 (REF: before March 31 2020)	1.00 (0.77-1.30)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.84 (0.65-1.07)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.38 (1.14-1.68)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.89 (1.53-2.34)
SOFA Renal 3-4 (REF: 0-2)	2.03 (1.57-2.62)
Bacterial infection	1.46 (1.09-1.95)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	1.86 (1.47-2.37)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.78 (0.60-0.99)
Corticosteroids	1.68 (1.29-2.19)
Neuromuscular blockade	0.45 (0.24-0.84)
ECMO at time 0	0.55 (0.30-1.03)
ECMO time varying HR (with the square root of time, days)	1.19 (1.01-1.40)
ECMO, unadjusted hazard ratio *	1.00 (0.75-1.35)

*no adjustment on covariates, no time dependent effect

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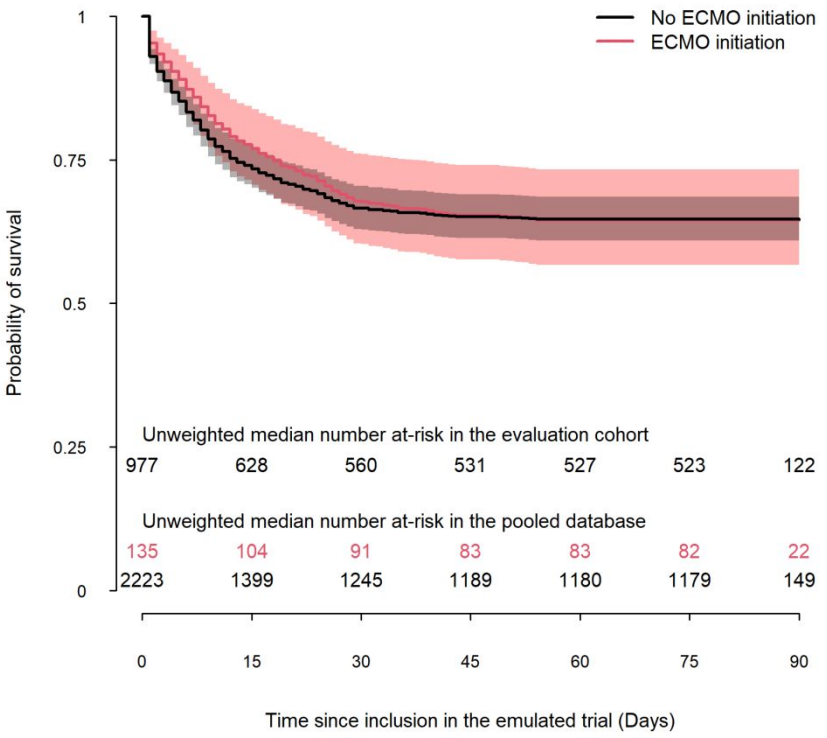
B-Adjusted survival curves



Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	82% (79%;85%)	86% (81%;91%)	4% (-1%;9%)
14	74% (71%;78%)	78% (72%;84%)	4% (-3%;10%)
28	67% (63%;71%)	68% (61%;77%)	1% (-7%;9%)
40	65% (62%;69%)	66% (58%;74%)	1% (-8%;9%)
60	65% (61%;69%)	64% (57%;73%)	-1% (-9%;8%)
90	65% (61%;69%)	64% (57%;73%)	-1% (-9%;8%)

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Table E7: Sensitivity analysis on patients with $PaO_2/FiO_2 < 65$ (SA4)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.02 (1.00-1.03)
Sex Female (REF: Male)	0.95 (0.68-1.34)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.85 (0.64-1.14)
Diabetes mellitus	1.36 (0.98-1.90)
Treated hypertension	0.92 (0.67-1.27)
ICU admission after April 1 2020 (REF: before March 31 2020)	1.01 (0.74-1.38)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.87 (0.65-1.16)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.43 (1.09-1.88)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.60 (1.26-2.03)
SOFA Renal 3-4 (REF: 0-2)	2.17 (1.57-2.99)
Bacterial infection	1.48 (1.08-1.98)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.56 (0.42-0.75)
Prone position	0.90 (0.67-1.22)
Corticosteroids	1.56 (1.14-2.15)
Neuromuscular blockade	1.11 (0.67-1.85)
ECMO at time 0	0.45 (0.24-0.82)
ECMO time varying HR (with the square root of time, days)	1.20 (1.04-1.38)
ECMO, unadjusted hazard ratio *	0.92 (0.67-1.26)

*no adjustment on covariates, no time dependent effect

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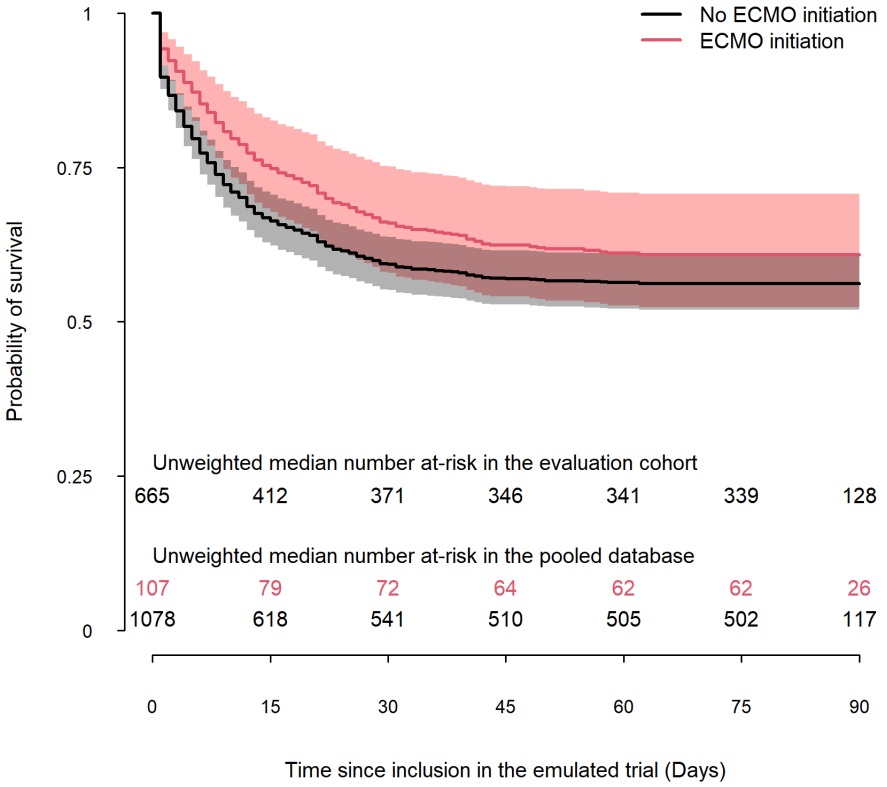
B-Adjusted survival curves



Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	76% (72%;79%)	84% (78%;90%)	8% (2%;15%)
14	67% (63%;71%)	75% (68%;83%)	9% (0%;17%)
28	60% (56%;64%)	67% (59%;76%)	7% (-2%;16%)
40	58% (53%;62%)	63% (55%;73%)	6% (-4%;15%)
60	56% (52%;61%)	61% (53%;71%)	5% (-5%;15%)
90	56% (52%;61%)	61% (52%;71%)	5% (-5%;15%)

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Table E8: Subgroup analysis on patients with ECMO initiated up to day 4 after invasive mechanical ventilation (SA5)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.01-1.04)
Sex Female (REF: Male)	0.86 (0.65-1.14)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.83 (0.66-1.04)
Diabetes mellitus	1.24 (0.98-1.58)
Treated hypertension	0.94 (0.73-1.20)
ICU admission after April 1 2020 (REF: before March 31 2020)	0.78 (0.62-0.99)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.81 (0.65-1.01)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.55 (1.28-1.87)
SOFA Renal 3-4 (REF: 0-2)	2.02 (1.57-2.60)
Bacterial infection	1.40 (1.06-1.84)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	1.48 (1.20-1.83)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.94 (0.74-1.18)
Prone position	0.97 (0.80-1.18)
Corticosteroids	2.10 (1.66-2.65)
Neuromuscular blockade	0.94 (0.67-1.32)
ECMO at time 0	0.35 (0.13-0.95)
ECMO time varying HR (with the square root of time, days)	1.32 (1.05-1.65)
ECMO, unadjusted hazard ratio *	0.92 (0.62-1.34)

*no adjustment on covariates, no time dependent effect

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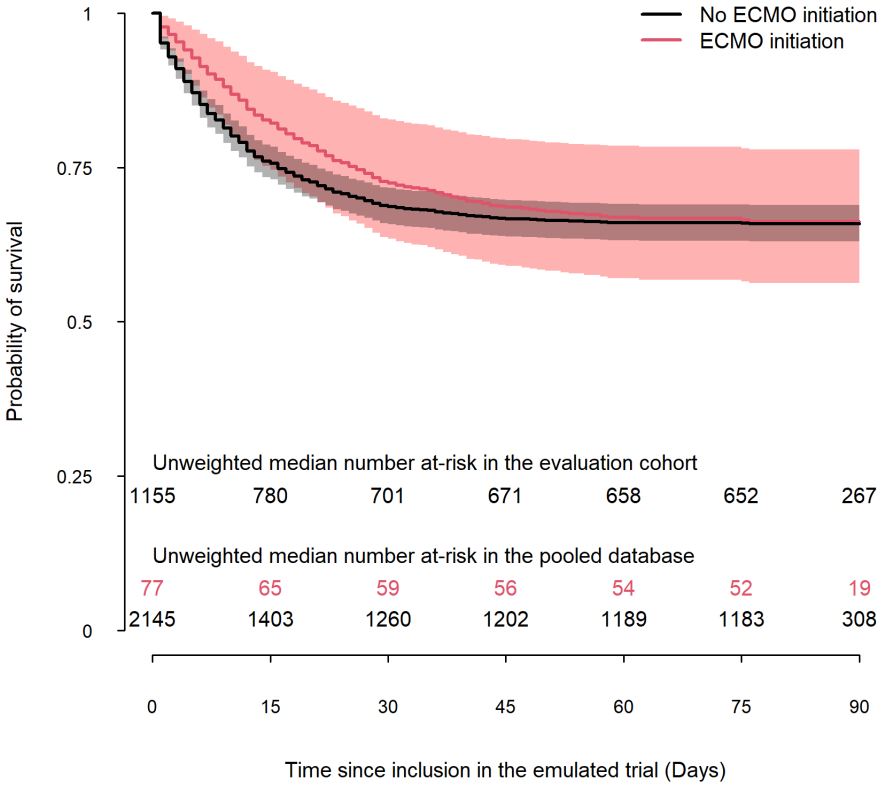
B- Adjusted survival curves



Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 4 sequential trials.

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	84% (81%;86%)	90% (85%;96%)	6% (1%;12%)
14	76% (73%;79%)	83% (75%;91%)	7% (-1%;15%)
28	69% (66%;72%)	73% (64%;83%)	4% (-6%;14%)
40	67% (64%;70%)	70% (60%;80%)	3% (-8%;13%)
60	66% (63%;69%)	67% (57%;78%)	1% (-10%;12%)
90	66% (63%;69%)	66% (56%;78%)	0% (-11%;11%)

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Table E9: Subgroup analysis on patients with ECMO initiated from Day-5 to Day 7 after invasive mechanical ventilation (SA6)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.01-1.05)
Sex Female (REF: Male)	1.22 (0.88-1.69)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.87 (0.67-1.11)
Diabetes mellitus	1.51 (1.13-2.01)
Treated hypertension	0.94 (0.71-1.24)
ICU admission after April 1 2020 (REF: before March 31 2020)	1.06 (0.81-1.40)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.88 (0.68-1.14)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.86 (1.49-2.33)
SOFA Renal 3-4 (REF: 0-2)	2.13 (1.62-2.80)
Bacterial infection	1.22 (0.88-1.70)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	2.27 (1.75-2.95)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.65 (0.50-0.84)
Prone position	0.99 (0.69-1.42)
Corticosteroids	1.41 (1.08-1.82)
Neuromuscular blockade	1.36 (0.59-3.12)
ECMO at time 0	0.63 (0.32-1.27)
ECMO time varying HR (with the square root of time, days)	1.21 (1.00-1.46)
ECMO, unadjusted hazard ratio *	1.20 (0.87-1.64)

*no adjustment on covariates, no time dependent effect

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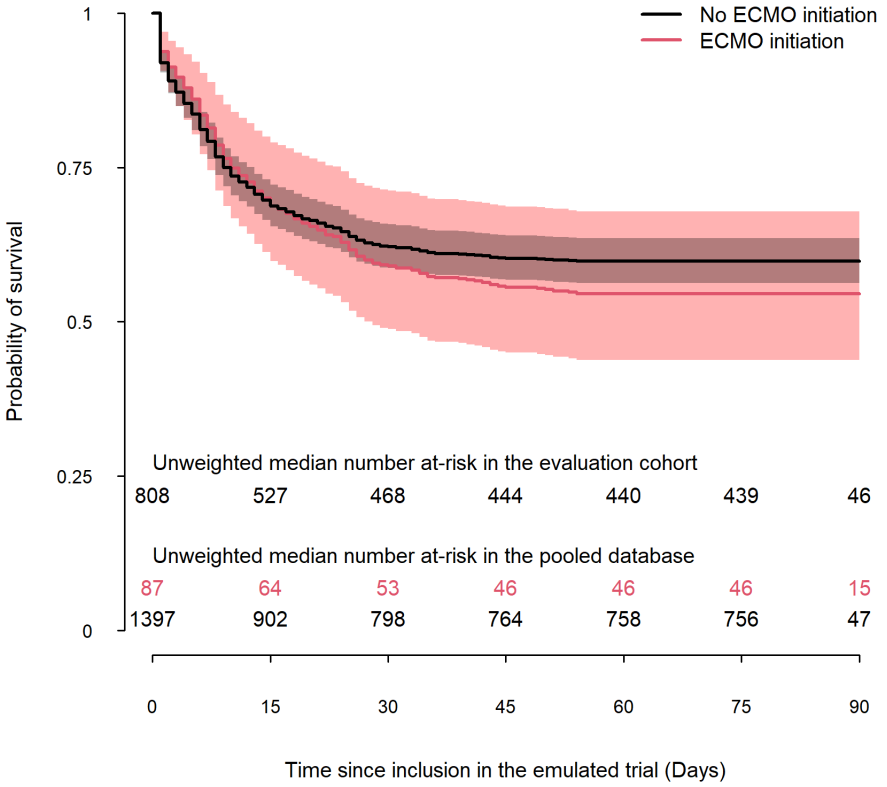
B- Adjusted survival curves



Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 3 sequential trials.

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	79% (76%;82%)	81% (75%;89%)	2% (-5%;9%)
14	70% (66%;73%)	70% (61%;80%)	0% (-9%;10%)
28	62% (59%;66%)	60% (49%;72%)	-2% (-14%;8%)
40	61% (57%;65%)	57% (46%;70%)	-4% (-16%;7%)
60	60% (56%;64%)	55% (44%;68%)	-5% (-17%;7%)

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Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
90	60% (56%;64%)	55% (44%;68%)	-5% (-17%;7%)

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Table E10: Subgroup analysis on patients managed in centers from greater Paris (SA7)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.01-1.04)
Sex Female (REF: Male)	0.86 (0.65-1.14)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.91 (0.72-1.14)
Diabetes mellitus	1.31 (1.01-1.69)
Treated hypertension	0.99 (0.77-1.27)
ICU admission after April 1 2020 (REF: before March 31 2020)	0.83 (0.65-1.07)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.84 (0.68-1.05)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.28 (1.09-1.51)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.55 (1.28-1.88)
SOFA Renal 3-4 (REF: 0-2)	1.66 (1.33-2.08)
Bacterial infection	1.23 (0.92-1.65)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	1.90 (1.59-2.28)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.88 (0.72-1.07)
Prone position	0.90 (0.73-1.11)
Corticosteroids	1.73 (1.39-2.16)
Neuromuscular blockade	1.03 (0.69-1.53)
ECMO at time 0	0.45 (0.22-0.92)
ECMO time varying HR (with the square root of time, days)	1.20 (1.00-1.44)
ECMO, unadjusted hazard ratio *	0.85 (0.63-1.14)

*no adjustment on covariates, no time dependent effect

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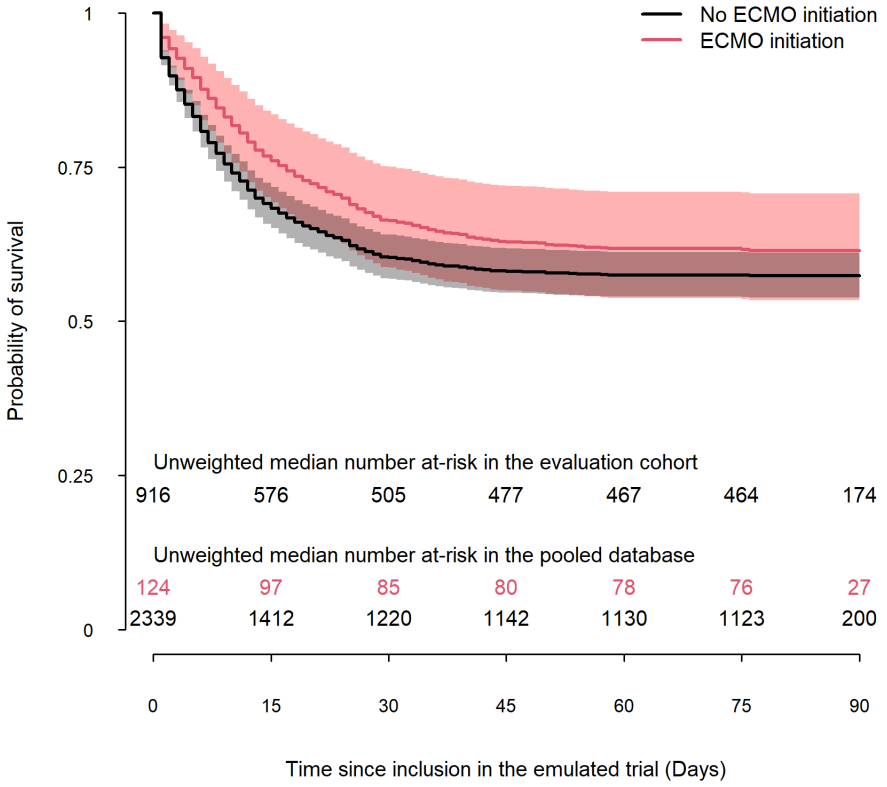
B- Adjusted survival curves



Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	79% (76%;82%)	86% (81%;92%)	7% (1%;13%)
14	69% (66%;72%)	77% (70%;84%)	8% (0%;15%)
28	61% (57%;64%)	67% (59%;76%)	6% (-2%;15%)
40	59% (55%;62%)	64% (56%;73%)	5% (-4%;14%)

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Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
60	58% (54%;61%)	62% (54%;71%)	4% (-5%;13%)
90	57% (54%;61%)	62% (53%;71%)	5% (-5%;13%)

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Table E11: Primary analysis according to low or high ECMO volume centers (SA8)

A- Multivariable Cox model

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.03 (1.02-1.04)
Sex Female (REF: Male)	0.99 (0.77-1.26)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.85 (0.69-1.03)
Diabetes mellitus	1.36 (1.09-1.69)
Treated hypertension	0.90 (0.72-1.11)
ICU admission after April 1 2020 (REF: before March 31 2020)	0.90 (0.72-1.13)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.84 (0.69-1.02)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.19 (1.04-1.37)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.65 (1.41-1.93)
SOFA Renal 3-4 (REF: 0-2)	2.02 (1.64-2.48)
Bacterial infection	1.23 (0.98-1.57)
PaO_2/FiO_2 (mm Hg) < 65 (REF: ≥ 65)	1.72 (1.45-2.04)
$PaCO_2$ (mm Hg) < 60 (REF: ≥ 60)	0.81 (0.68-0.97)
Prone position	0.97 (0.80-1.17)
Corticosteroids	1.73 (1.41-2.12)
Neuromuscular blockade	1.03 (0.73-1.46)
ECMO, low volume center at time 0	0.59 (0.32-1.07)
ECMO, low volume center, time varying HR (with the square root of time, days)	1.25 (1.08-1.45)
ECMO, high volume center at time 0	0.10 (0.00-4.56)
ECMO, high volume center, time varying HR (with the square root of time, days)	1.52 (0.81-2.89)
ECMO, low volume center, unadjusted hazard ratio *	1.33 (1.00-1.77)
ECMO, high volume center, unadjusted hazard ratio *	0.71 (0.45-1.14)

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*no adjustment on covariates, no time dependent effect

B- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO in low volume centers (95%CI)	ECMO in high volume centers (95%CI)	Difference No ECMO vs low volume (95%CI)	Difference No ECMO vs high volume (95%CI)
7	83% (80%;85%)	84% (79%;90%)	96%(90%;100%)	2% (-4%;7%)	13% (7%;19%)
14	74% (72%;77%)	74% (67%;81%)	91%(83%;100%)	-0% (-7%;7%)	17% (8%;26%)
28	67% (65%;70%)	63% (56%;72%)	84% (74%;97%)	-4% (-12%;4%)	17% (5%;29%)
40	65% (63%;68%)	60% (52%;68%)	81% (70%;95%)	-6% (-14%;3%)	16% (3%;29%)
60	64% (62%;67%)	57% (49%;66%)	78% (66%;93%)	-7% (-16%;2%)	14% (0%;28%)
90	64% (61%;67%)	57% (49%;66%)	78% (66%;92%)	-8% (-16%;1%)	14% (0%;27%)

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Table E12: Multivariable Cox hazard model stratified on the ECMO initiation group (SA9)

A- Multivariable Cox model *

Multivariable Cox regression fitted to the pooled dataset, using time-dependent IPC weights.

Covariate	Hazard Ratio (95%CI)
Age (years)	1.05 (1.03-1.07)
Sex Female (REF: Male)	0.90 (0.66-1.22)
Body mass index (kg/m2) ≥ 30 (REF: < 30)	0.91 (0.72-1.16)
Diabetes mellitus	1.45 (1.09-1.92)
Treated hypertension	0.79 (0.59-1.05)
ICU admission after April 1 2020 (REF: before March 31 2020)	0.98 (0.75-1.29)
First symptoms to ICU admission (days) > 7 (REF: ≤ 7)	0.89 (0.70-1.13)
Time since MV initiation 6-7 days (REF: 1-5 days)	1.33 (1.07-1.65)
Bacterial infection	1.65 (1.29-2.15)
SOFA Cardiovascular system 3-4 (REF: 0-2)	1.68 (1.38-2.04)
SOFA Renal 3-4 (REF: 0-2)	2.17 (1.66-2.84)
PaO2,/FiO2, (mm Hg) < 65 (REF: ≥ 65)	1.71 (1.41-2.08)
PaCO2, (mm Hg) < 60 (REF: ≥ 60)	0.94 (0.76-1.17)
Prone position	0.92 (0.73-1.16)
Neuromuscular blockade	1.35 (0.89-2.07)

*Multivariable Cox model stratified on the ECMO initiation group (*i.e.* with separate baseline hazard in the treated and control patients). This model allows to relax the proportional hazards assumption on ECMO initiation, at the cost of preventing the estimation of an HR associated with ECMO.

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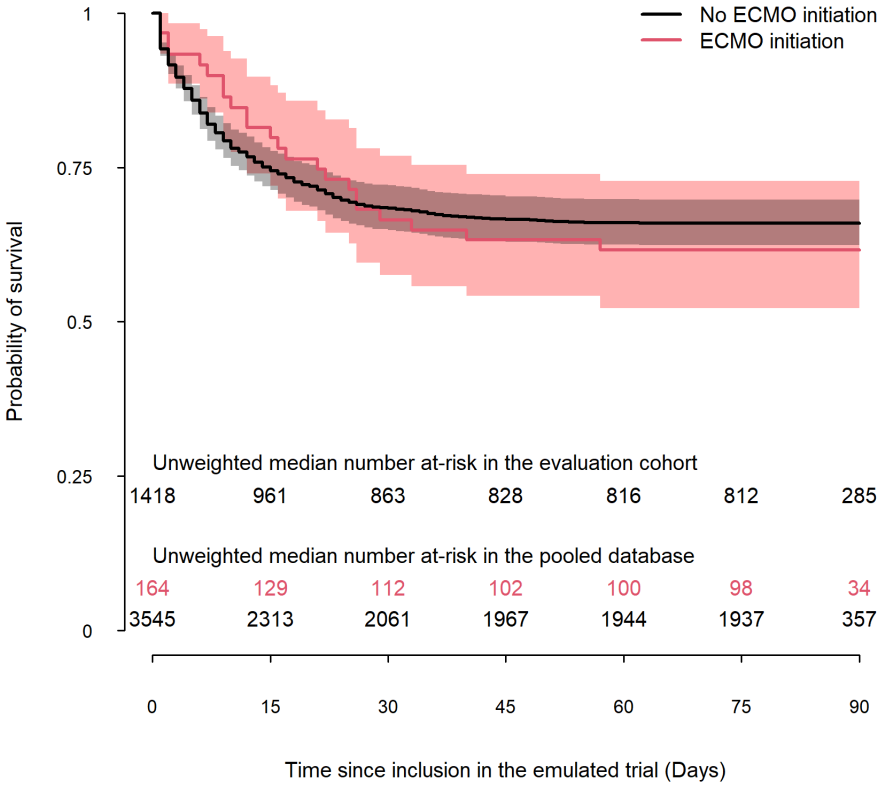
B- Adjusted survival curves



Number at-risk: median number among multiply imputed dataset.

Evaluation cohort: composed of unique individuals at the first time they meet eligibility criteria.

Pooled database: composed of potentially repeated individuals, obtained by pooling the data from the 7 sequential trials.

C- Adjusted survival probability over time

Computed from of the multivariable Cox regression fitted to the pooled dataset.

Time (Days)	No ECMO initiation (95%CI)	ECMO initiation (95%CI)	Difference (95%CI)
7	82% (79%;85%)	90% (84%;96%)	8% (1%;14%)
14	75% (72%;78%)	81% (74%;90%)	6% (-2%;15%)
28	69% (65%;72%)	68% (60%;78%)	-0% (-10%;9%)
40	67% (63%;71%)	63% (54%;74%)	-4% (-14%;7%)
60	66% (62%;70%)	62% (52%;73%)	-4% (-15%;6%)
90	66% (62%;70%)	62% (52%;73%)	-4% (-15%;6%)

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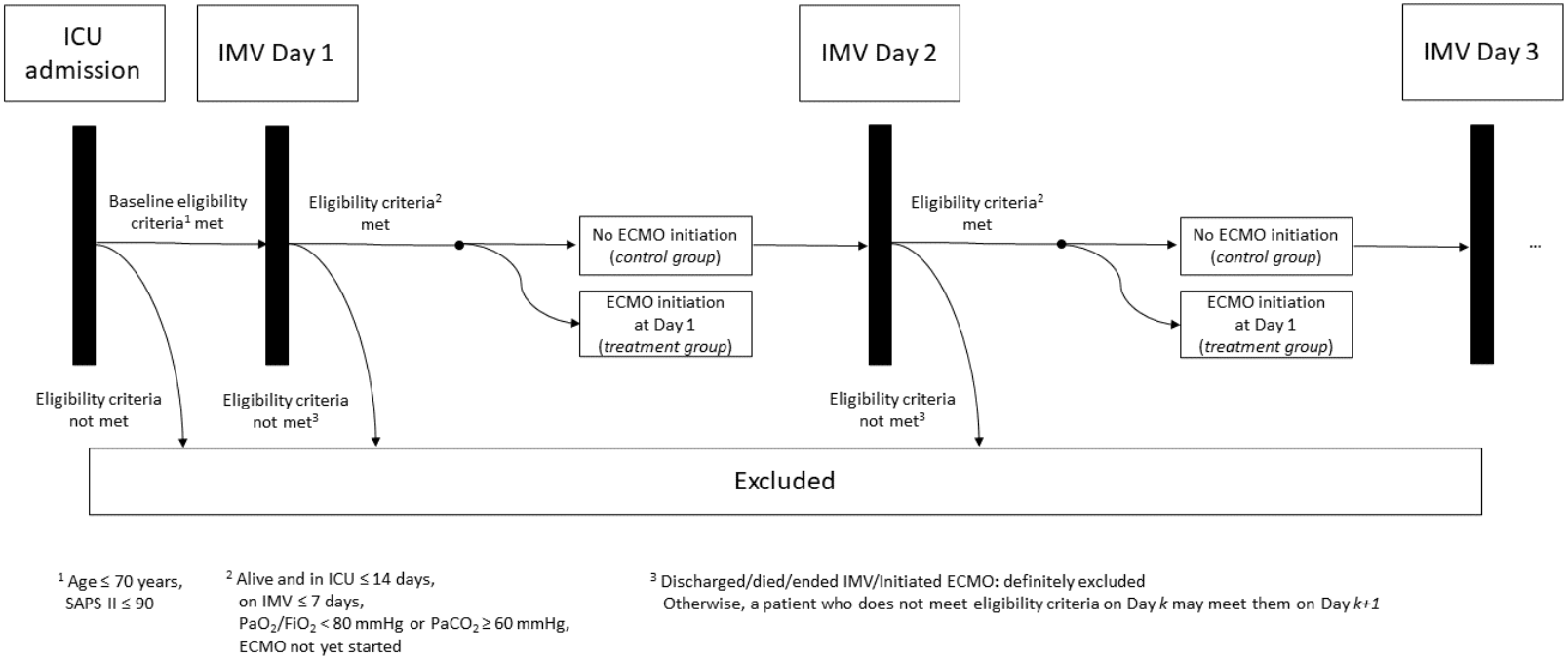
Figure E1: Sequential trial framework



Similar selection process is repeated until IMV Day 7

ECMO, extracorporeal membrane oxygenation ; ICU, Intensive Care Unit; IMV, invasive mechanical ventilation

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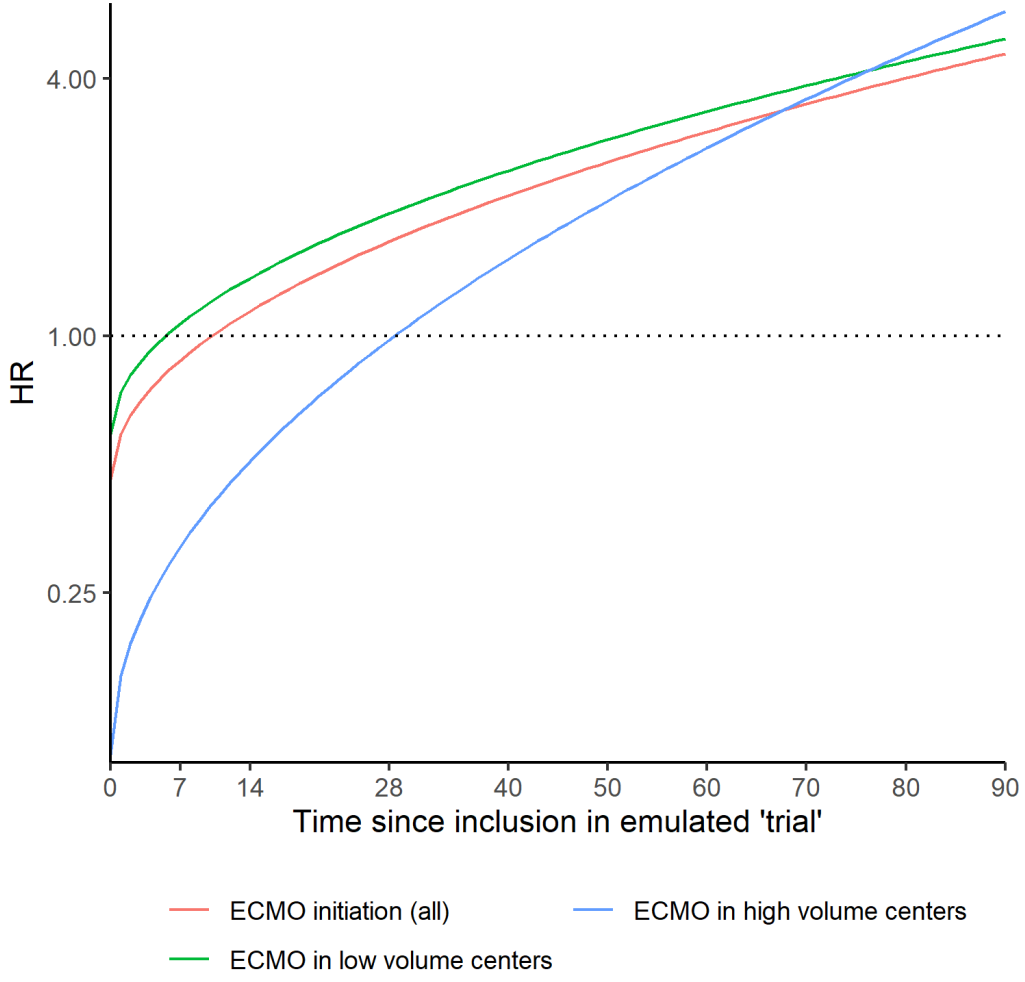
Figure E2: Hazard ratio for 90-day mortality associated with ECMO over time in the total cohort, and in patients treated in high volume centers vs others



ECMO, extracorporeal membrane oxygenation; HR, hazard ratio

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