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Mechanical ventilation management during ECMO for ARDS: An International Multicenter Prospective Cohort

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Running title: Mechanical ventilation management on ECMO

Keywords: ECMO, acute respiratory distress syndrome, mechanical ventilation, outcome, prone position

At a Glance Commentary

Scientific Knowledge on the Subject: Current practices regarding mechanical ventilation and use of adjunct therapies in patients treated with ECMO for ARDS are incompletely understood.

What This Study Adds to the Field: Ultra-protective lung ventilation on ECMO was largely adopted across ECMO centers. In contrast with previous observations in similar patients, mechanical ventilator settings during the first two days of ECMO did not impact the prognosis of the patients.

This article has an online data supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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Abstract

Objectives: To report current practices regarding mechanical ventilation in patients treated with extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS) and their association with 6-month outcomes.

Methods: International, multi-center, prospective cohort study of patients undergoing ECMO for ARDS during a one-year period in 23 international intensive care units (ICUs).

Measurements and Main Results: We collected demographics, daily pre- and per-ECMO mechanical ventilation settings and use of adjunctive therapies, ICU- and 6-month–outcome data for 350 patients (median ± standard deviation pre-ECMO PaO_2/FiO_2 71±34 mmHg). Pre-ECMO use of prone positioning and neuromuscular blockers were 26% and 62%, respectively. Tidal volume (6.4±2.0 vs 3.7±2.0 ml/kg), plateau pressure (32±7 vs 24±7cmH_2O), driving pressure (20±7 vs. 14±4 cmH_2O), respiratory rate (26±8 vs 14±6 breaths/min) and mechanical power (26.1±12.7 vs. 6.6±4.8 J/min) were markedly reduced after ECMO initiation. Six-month survival was 61%. No association was found between ventilator settings during the first 2 days of ECMO and survival in multivariable analysis. A time-varying Cox model retained older age, higher fluid balance, higher lactate, and more need for renal replacement therapy along the ECMO course as being independently associated with 6-month mortality. A higher tidal volume and lower driving pressure (likely markers of static compliance improvement) across the ECMO course were also associated with better outcomes.

Conclusion: Ultra-protective lung ventilation on ECMO was largely adopted across medium to high case-volume ECMO centers. In contrast with previous observations, mechanical ventilation settings during ECMO did not impact patients' prognosis in this context.

Abstract word count: 245

Introduction

Although its use remains controversial, extracorporeal membrane oxygenation (ECMO) may be deployed in severe forms of ARDS to decrease the intensity of mechanical ventilation (MV) or as a rescue therapy for refractory ARDS (1–3). The largest randomized trial of ECMO for severe forms of ARDS failed to demonstrate a statistically significant difference in its pre-specified primary endpoint of 60-day mortality (4). However, the clinically important effect size seen in the EOLIA trial as well as the recent post-hoc Bayesian analysis (5) both suggest that ECMO is efficacious in some patients with severe forms of ARDS. ECMO allows MV with very low tidal volumes, reduced plateau pressures (P_{plat}) and respiratory rates (6) thereby potentially minimizing ventilation–induced lung injury (VILI) (7, 8). However, ventilation strategies during ECMO have received little attention until now (9) and it is not clear how ECMO-treated ARDS patients are managed in routine practice in the broader international context, particularly with regard to MV settings and adjunctive therapies used before and after ECMO initiation. Data currently available in this area has been limited to selected retrospective cohorts (10, 11).

The primary aim of the ventiLatIon management oF patients with Extracorporeal membrane oxyGenation for Acute Respiratory Distress Syndrome (LIFEGARDS) study was to describe the ventilatory management of ECMO-treated ARDS patients in medium to high case-volume international centers. The secondary objective was to investigate the dynamic impact of mechanical ventilation and other organ failures on 6-month mortality. Lastly, we aimed to assess the use of adjunctive therapies before and during ECMO, and ECMO-related complications.

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Methods

Study Design, Patients

LIFEGARDS was an international, multi-center, prospective cohort study conducted in 23 medium to high-volume ECMO ICUs across 10 countries. Centers were invited to participate if their annual hospital ECMO volume in the previous year was ≥ 15 annual cases. The study ICUs represent a convenience sample of those who agreed to participate in the study and had actually enrolled patients. All participating ICUs obtained Institutional Review Board approval in accordance with their local regulations. During a 12-month enrolment period (starting anywhere from September 2014 and January 2016), all consecutive patients over 15 years of age who received extracorporeal lung support (i.e., venoarterial- or venovenous (VV) ECMO) for acute respiratory failure were prospectively screened. Exclusion criteria were ECMO cannulation performed at another center more than 48 hours before inclusion and retrieval to the enrolling center, end-stage chronic respiratory failure and inability to obtain informed consent to participate to this study, when required.

Data collection

Following enrollment, baseline information was collected for the period immediately preceding ECMO implantation and included: age, sex, Acute Physiology And Chronic Health Evaluation (APACHE) II score (12), Sequential Organ Failure Assessment (SOFA) score at cannulation (13), Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score (14), PRedicting dEath for SEvere ARDS on VV-ECMO (PRESERVE) score (15), dates of hospital and ICU admissions, origin of immunodeficiency (if present) and its date of diagnosis, risk factors for ARDS, concomitant therapies before starting ECMO (neuromuscular blocking agents, nitric oxide, prone positioning), date mechanical ventilation started, ventilator settings (mode, PEEP, fraction of inspired oxygen (FiO_2), respiratory rate,

tidal volume, plateau pressure (P_{plat}), peak pressure (P_{peak})), arterial blood gas parameters and standard laboratory parameters. Driving pressure (ΔP) was defined as P_{plat} minus PEEP. If not specified, P_{peak} was considered equal to P_{plat} in pressure-regulated modes other than pressure support ventilation. Mechanical power (J/minute) was calculated using tidal volume, P_{peak}, respiratory rate, and ΔP data:

$$Mechanical\ Power = 0.098 * tidal\ volume * respiratory\ rate * Ppeak - \frac{1}{2} * \Delta P \quad (16).$$

Dead space fraction (Vd/Vt) was estimated using the unadjusted Harris-Benedict equation for the resting energy expenditure (17). Ventilatory ratio was calculated as $\frac{(minute\ ventilation * PaCO2)}{(predicted\ body\ weight * 100 * 37.5)}$ (18) (see details in the electronic supplemental material). The Berlin definition and grading of ARDS were applied.

The case report form (supplemental material) prompted investigators to provide a daily expanded data set including MV settings, arterial blood gas, fluid balance, adjuvant therapies during ECMO and ECMO-related complications until ECMO-day 28, decannulation from ECMO, or death, whichever occurred first. All data were recorded at the same time, normally as close as possible to 10am each day during the ECMO course. Major bleeding was defined as requiring two or more units of packed red blood cells due to an obvious hemorrhagic event, necessitating a surgical or interventional procedure, an intracerebral hemorrhage, or causing a fatal outcome, while massive hemolysis was defined as plasma-free hemoglobin >500 mg/L associated with clinical signs of hemolysis. Patient outcomes included date of ECMO decannulation, date of liberation from mechanical ventilation and vital status at ICU discharge, hospital discharge and 6-month post-ICU admission.

Statistical Analyses

We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations for reporting cohort studies (19). Variables with parametric

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distributions were expressed as mean (standard deviation) whereas continuous variables with non-parametric distributions were expressed as median [25th; 75th percentiles]). Comparison between pre- and post-ECMO continuous variables were undertaken using paired Student t test and the paired Wilcoxon rank sum tests were compared with Wilcoxon rank sum tests. Categorical variables were compared with $\chi 2$ tests or Fisher exact tests.

The primary outcome measure was the prevalence of 6-month mortality after ICU admission. Associations between patients' demographic, clinical and pre-ECMO ventilation characteristics, ECMO ventilation characteristics within the first two days, and laboratory results were tested in bivariable analyses, with odds ratio (OR) quantifying the strength of association. Covariates presumed to be associated with death at 6 months based on previous studies and those associated with mortality at $P \leq 0.20$ were subsequently entered in multivariable logistic regression models. Two different models were built: one including pre-ECMO parameters and the second including early ECMO parameters (first two days of ECMO).

To determine factors associated with 6-month mortality while taking into account the mechanical ventilation variability over time, a Cox model with time-dependent covariates was also performed (with details provided in the electronic supplemental material). Association between those covariates and the hazard of death was measured as a hazard ratio (HR). As a sensitivity analysis, the model was also run after multiple imputation for missing data on pre-ECMO and during the first two days of ECMO (table E1). Results are reported with 95% confidence interval (CI). Statistical analyses were performed with R 3.2.3 (http://www.R-project.org). All *P* values were 2-sided, with *P* values <.05 considered statistically significant.

We planned to enroll at least 300 patients with ECMO-treated ARDS. Based on the estimate that medium to high case-volume centers would have a median of at least 15 VV-ECMO patients during a one-year period, we planned to enroll from at least 20 ICUs

worldwide. Assuming 40% six-month mortality (15, 20), 120 deaths would allow us to evaluate around 12 pre- and early ECMO-associated variables in logistic regressions.

Results

Participating ICUs and Patients Enrolled

Twenty-three ECMO centers from 10 countries participated in the study. Their main characteristics are described in Table E2. Notably, they had a median of 30 (20-52) patients who received ECMO during the previous calendar year, and 20 participating centers provided a referral and retrieval service for patients requiring ECMO support in regional centers. Of the 375 patients receiving ECMO for acute respiratory failure during the enrollment period, 350 patients (age 47±17 years, 65% male, APACHE II score 24±11) with ARDS (325 severe, 22 moderate, and 3 mild) were enrolled (Figure 1). Patient characteristics at ECMO initiation are reported in Table 1 and Table E3. Briefly, viral and bacterial pneumonias were the two main etiologies for ARDS, with 25% patients having extra-pulmonary causes of ARDS. Median (IQR) time between endotracheal intubation and ECMO initiation was 2 (0-5) days

Mechanical Ventilation management during ECMO

Daily MV management was collected for a total of 4211 ECMO days. Before ECMO initiation, 50% of patients received volume-targeted modes of ventilation, whereas 40% were ventilated with pressure-targeted modes (i.e. airway pressure release ventilation/biphasic positive airway pressure; pressure-controlled ventilation, and synchronized intermittent mandatory ventilation with pressure control). Pressure-targeted modes category increased to 69%, 71% and 82% at day 1, day 7, and day 14 during ECMO (Figure E1). Compared to pre-ECMO settings, tidal volume and P_{plat} were both significantly reduced from 6.4±2.0 to 3.7±2.0 mL/kg predicted body weight ($p<0.001$) and from 32±7 to 24±7 cmH_20 ($p<0.001$), respectively, while PEEP was maintained over 10 cmH_20 (Table 1, Table 2, and Figure E2).

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The proportion of patients ventilated with a tidal volume ≤4ml/kg before ECMO and during the first two days of ECMO shifted from 8 to 65%, (Figure 2A). Consequently, ECMO initiation also allowed significant reduction of the ΔP (from 20±7 to 14±4 cmH2O; p<0.001) and mechanical power (from 26.1±12.7 to 6.6±4.8 Joules/minute; p<0.001) (Figure 3). Only 34% patients were ventilated with a ΔP ≤15cmH2O before ECMO, while it increased to 58% during the first two days on ECMO (Figure 2B). Therefore, the combination of a very low tidal volume (≤4ml/kg) and a ΔP ≤15cmH_2O during the first two days of ECMO was obtained in 140 (45%) patients (Figure 2C). It increased to 61% when ΔP ≤15cmH_2O was combined with a tidal volume ≤6ml/kg. In addition, 96% patients were ventilated with a mechanical power≤ 17 J/min. Detailed mean tidal volume and driving pressure per center are reported in the Figure E4 and E5. A significant minute ventilation reduction was also noted after ECMO initiation (p<0.001) (Figure E3). Lastly, fluid balance, static compliance, PaO_2 and $PaCO_2$ obtained during the ECMO evolution with time separated according to 6-month survival are represented in Figures E6, E7, E8 and E9, respectively.

Use of Adjunctive Measures

Before ECMO initiation, neuromuscular blocking agents were used in 62% of the patients, recruitment maneuvers in 37%, and prone position in 26%, with no difference between survivors and non-survivors (Table 1). Continuous neuromuscular blocking agents and prone position were the most frequently used adjuncts (41 and 6% patients, respectively) at ECMO day 1 and day 2. Of note, 15% of the patients received at least one prone session throughout their ECMO course (Table 3).

Patient Outcomes and Predictors of 6-Month Mortality

Six-month status was obtained for all but 2 patients. Two hundred and fifty-nine (74%)

patients were successfully weaned off ECMO, 232 (66%) survived to ICU discharge and 215 (61%) were alive at 6 months. The median duration of ECMO support, mechanical ventilation and hospital stay for 6-month survivors were 9 [6;14], 17 [11;32] and 38 [22;57] days, respectively (Table 3).

Six-month survivors had a shorter duration of MV, as well as ICU and hospital length of stay prior to ECMO ($p<0.05$). Pre-ECMO tidal volume, P_{plat}, driving pressure and mechanical power were similar between 6-month survivors and non-survivors. However, survivors were administered significantly higher PEEP levels, lower respiratory rate, and exhibited higher respiratory system compliance and lower Vd/Vt ratio before ECMO (Table 1). Higher spontaneous respiratory rates during the first two days of ECMO were significantly associated with higher 6-month mortality (Table 2). Of note, non-survivors had a higher fluid balance (Figure E6) and renal replacement therapy was more frequently used during the first two-days on ECMO.

Predictive factors of 6-month mortality were assessed using a multivariable logistic model. Older age, extra-pulmonary sepsis, higher pre-ECMO lactate, delayed time from endotracheal intubation to the initiation of ECMO were jointly selected as being associated with the outcome. Kaplan–Meier survival estimates for ECMO-treated acute respiratory distress syndrome patients. according to the delayed time from endotracheal intubation to the initiation of ECMO is provided in Figure E10. When ECMO management during the first two days was included in the model, higher mean fluid balance was the only additional factor that remained associated with 6–month mortality (Table 4). No association was found between ventilator settings during the first 2 days of ECMO and survival in the multivariable analysis.

The Cox model with time-fixed and time-dependent covariates retained older age, higher fluid balance, higher lactate, and more use of renal replacement therapy (RRT) along the ECMO course as being associated with an increased hazard of death (Table 5). On the

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other hand, higher tidal volume and lower ΔP during the ECMO course were associated with a better outcome. The same analysis was rerun after multiple imputation of missing data with similar results (Table E4).

ECMO-related complications

Major bleeding occurred in 25% patients receiving ECMO with a higher prevalence in non-survivors (p=0.009). Other ECMO related complications such as major hemolysis, cardiac arrest and pneumothorax had also a higher prevalence in non-survivors, occurring in 10, 11, and 9% of the patients, respectively (Table 3).

Discussion

To our knowledge, LIFEGARDS is the largest prospective, international multi-center, cohort with daily data collection of ventilator settings and clinical characteristics of patients with ARDS treated with ECMO in medium to high-case volume centers, and including complications and outcome up to 6 months. The main findings were 1) the low rates of pre-ECMO optimization with the underutilization of prone positioning and continuous neuromuscular blockade; 2) the large application of so-called “ultra-protective ventilation” during ECMO aiming to maintain $\Delta P \leq 15 cmH_2O$, and therefore decreasing mechanical power; 3) the lack of association between mechanical ventilation settings during the first two days of ECMO and survival; and 4) the significant association between tidal volume increase and lower ΔP (likely markers of improvement of the static compliance) during the ECMO course with 6-month mortality.

In a large international, multicenter, unselected, prospective cohort study of patients with ARDS (LUNG SAFE study), only 6.6% of the patients with severe ARDS were treated with ECMO (21). As this technique is currently used primarily as a rescue therapy for severe

or refractory ARDS and given that prone positioning and continuous neuromuscular blockade have both demonstrated improved outcomes (22, 23), such low use of these adjunctive therapies was unexpected in this population. Infrequent use of prone positioning outside the context of ECMO has already been highlighted, as this relatively inexpensive intervention was provided in only 16% of severe ARDS patients in the LUNG SAFE study (21). A recent study focusing on prone positioning reported that clinicians' evaluation of hypoxemia not being severe enough to justify prone positioning, low mean arterial pressure and end-of-life decisions were the main reasons to leave patients supine (24). However, in the context of our severely hypoxemic population treated with an expensive, complex and labor-intensive therapy, it seems difficult to justify not first turning to a proven and less complex and expensive modality. In a small subset of patients, severe hemodynamic instability, or another contraindication, may preclude the use of prone positioning and could justify the prompt application of ECMO when gas exchange is sufficiently impaired (25). Easy access to ECMO and large ECMO experience in the centers involved in our study could also explain this finding and may have biased the treatment indication. On the other hand, logistic regressions retained greater delay from endotracheal intubation to ECMO initiation as being independently associated with 6–month mortality highlighting the need to rapidly recognize when prone positioning and continuous neuromuscular blockers have failed. Taken together, this confirms the challenge of defining the right indication and timing of ECMO initiation within the global management of severe ARDS.

Although ventilation practices in patients supported by VV-ECMO vary across centers internationally, a recent survey reported that "lung rest" was the primary goal of MV during ECMO for the majority of the participating centers (77%) (26). Our results confirm the widespread use of a "lung rest" strategy under ECMO in our medium to high ECMO-volume centers. Most of the patients had pressure-controlled ventilation, which may represent the

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physicians' desire to strictly control ΔP during ECMO. Indeed, this strategy targeting lower mechanical power delivered to the lungs with reduced tidal volume (≤4 ml/kg), respiratory rate (< 20 /min) and airway pressures (P_{plat} <25 cm H_2O and ΔP ≤ 15 cm H_2O) may enhance protection from ventilator-induced lung injury in ARDS patients (8, 27). Notably, pre-ECMO mechanical power (26.1±12.7 J/min) was particularly high, in regard of the increase in the risk of death reported with mechanical power higher than 17.0 J/min (10).

As in non-ECMO patients (28), ΔP during the first days of ECMO had previously been reported as one of the strongest independent risk factor associated with mortality in patients supported by ECMO in the context of H_1N_1-induced ARDS and in an individual patient data meta-analysis of observational studies in adult ARDS patients receiving ECMO (10, 29). Our results were, however, strikingly different, as no association was found between ventilator settings during the first 2 days of ECMO and survival in the multivariable analysis. The recourse to a relatively homogeneous "ultra-protective" ventilation strategy permitted by optimized ECMO settings (providing high level support for gas exchange), in these experienced ECMO centers, may explain this finding. Additionally, when ΔP is set to obtain lower and safer intra-thoracic pressures, and as a way to deliver some pressure to monitor which tidal volume it can generate, it is unlikely to remain a prognostic factor. This is indeed very different from setting ΔP to achieve acceptable gas exchange, which probably still happened in the previous ECMO series (10, 29).

Our main objective was to assess prognostic factors rather than providing any causal estimates. Therefore, we used multivariable regression models including a Cox model with time-dependent covariates, that do not provide any estimate of causal relationship (even if this link could exist), so that our results should not be over-interpreted. Specifically, higher tidal volume and lower ΔP all along the ECMO course were both associated with better survival according to the time-varying Cox model. Thus, this finding more likely reflects the

improvement of respiratory system compliance with pulmonary function recovery (i.e higher volumes obtained with the same or lower pressure applied) rather than the effect of mechanical ventilation *per se* on outcomes. Monitoring tidal volume improvement when constant ΔP is applied may also help determining the timing of ECMO weaning.

The high use of bilevel positive airway pressure—airway pressure release ventilation modes during ECMO permitting the reduction of ΔP while allowing spontaneous ventilation which might prevent respiratory muscles waste, improve hemodynamics and decrease sedation needs (30). However, caution is required in the early phases of severe ARDS, as extracorporeal carbon dioxide removal during full ECMO support might not suffice to control spontaneous respiratory effort and to keep the transpulmonary pressure within safe limits (31–33).

The negative impact of extra-pulmonary organ failure before and during ECMO on outcomes is considerable. Thus, a higher lactate level, a more positive fluid balance, and more frequent RRT requirement on ECMO were all significant in our time-varying Cox model. Given that ECMO should be restricted to the most severe patients with refractory ARDS, a tight control of fluid balance during the early ECMO period appears desirable (34). Similarly, the negative impact of RRT, and elevated lactates levels prior to ECMO insertion have been previously highlighted in a single center retrospective study (35). However, it is worth noting that these data should be interpreted in the light of the hemodynamic status and the vasopressors received, which were not uniformly collected daily in our study.

Our study also reinforces the key role of pre-ECMO patient characteristics and management to identify patients who are more likely to benefit from ECMO. Similar to previous studies, higher age and a greater delay from endotracheal intubation to the initiation of ECMO were independently associated with a worse outcome (14, 15). One may argue that more frequent use of adjuvant therapies, such as prone positioning or perhaps neuromuscular

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blockade, may have extended this delay, however, it might also have obviated the need for ECMO in some cases. A randomized controlled trial would be needed to answer to this important question on ECMO timing. To date, as suggested by the recent EOLIA results (4), lack of significant improvement after one or two sessions of prone positioning should probably urge clinicians to propose VV-ECMO in these severe ARDS patients. Lastly, immunocompromised status remained associated with a lower survival, as previously demonstrated (36).

Our study has several limitations. Only medium to high-volume ECMO centers participated and may have specific patient selection criteria that may limit generalizability. In addition, we did not have access to the source data for the patients in the enrolling ICUs. We were, therefore, unable to calculate ARDS-based incidence figures for ECMO and directly check the quality of the data sent. To ensure data quality, we sent queries to centers to verify data that appeared inconsistent or erroneous. For logistical reasons, MV settings were collected as point data once a day, which did not capture settings that may have changed rapidly within a 24-hour period, especially at the start of the course of ECMO. Lastly, many variables were collected and subsequently, many comparisons were performed, as commonly done in such prognostic studies, which might have increased the probability of type I error.

In conclusion, we found that pre-ECMO practices in high case-volume centers did not always follow current recommendations for ARDS management (37), with a concerningly low use of prone positioning, whereas ultra-protective lung ventilation on ECMO was largely adopted across centers. By adopting this ventilation strategy targeting $\Delta P \leq 15$ cmH2O, mechanical ventilation settings during ECMO did not impact patients' prognosis in contrast with previous observations. Further studies are now needed to investigate whether strategies such as larger reductions in MV intensity through near-apneic ventilation (27) and/or more

frequent use of prone positioning (38) during ECMO may translate into better outcomes in patients supported by VV-ECMO for severe respiratory failure.

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APPENDIX 1. List of the collaborators of the "LIFEGARDS Study Group".

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AJRCCM Articles in Press. Published on 30-May-2019 as 10.1164/rccm.201806-1094OC

References

1. Abrams D, Bacchetta M, Brodie D. When the momentum has gone: what will be the role of extracorporeal lung support in the future? *Curr Opin Crit Care* 2018;24:23–28.
2. Abrams D, Brodie D. Extracorporeal Membrane Oxygenation for Adult Respiratory Failure: 2017 Update. *Chest* 2017;152:639–649.
3. Karagiannidis C, Brodie D, Strassmann S, Stoelben E, Philipp A, Bein T, Muller T, Windisch W. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med* 2016;42:889–96.
4. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A, EOLIA Trial Group, REVA, and ECMONet. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2018;378:1965–1975.
5. Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, Brodie D, Slutsky AS, Combes A. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial. *JAMA* 2018;doi:10.1001/jama.2018.14276.
6. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med* 2011;365:1905–14.
7. Marhong JD, Munshi L, Detsky M, Telesnicki T, Fan E. Mechanical ventilation during extracorporeal life support (ECLS): a systematic review. *Intensive Care Med* 2015;41:994–1003.

8. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009;111:826–835.
9. Schmidt M, Pellegrino V, Combes A, Scheinkestel C, Cooper DJ, Hodgson C. Mechanical ventilation during extracorporeal membrane oxygenation. *Crit Care* 2014;18:203.
10. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, Cazati DC, Cordioli RL, Correa TD, Pollard TJ, Schettino GPP, Timenetsky KT, Celi LA, Pelosi P, Gama de Abreu M, Schultz MJ, PROVE Network Investigators. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. *Intensive Care Med* 2018;44:1914–1922.
11. Schmidt M, Stewart C, Bailey M, Nieszkowska A, Kelly J, Murphy L, Pilcher D, Cooper DJ, Scheinkestel C, Pellegrino V, Forrest P, Combes A, Hodgson C. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study. *Crit Care Med* 2015;43:654–664.
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
13. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707–10.

AJRCCM Articles in Press. Published on 30-May-2019 as 10.1164/rccm.201806-1094OC

14. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, Scheinkestel C, Cooper DJ, Brodie D, Pellegrino V, Combes A, Pilcher D. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med* 2014;189:1374–82.
15. Schmidt M, Zogheib E, Roze H, Repesse X, Lebreton G, Luyt CE, Trouillet JL, Brechot N, Nieszkowska A, Dupont H, Ouattara A, Leprince P, Chastre J, Combes A. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med* 2013;39:1704–13.
16. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E, Chiumello D, Quintel M. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42:1567–75.
17. Beitler JR, Thompson BT, Matthay MA, Talmor D, Liu KD, Zhuo H, Hayden D, Spragg RG, Malhotra A. Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. *Crit Care Med* 2015;43:1026–1035.
18. Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, Kallet RH. Physiological Analysis and Clinical Performance of the Ventilatory Ratio in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2018;doi:10.1164/rccm.201804-0692OC.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007;4:e296.
20. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D. Efficacy and economic

assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374:1351–1363.

21. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, LUNG SAFE Investigators, ESICM Trials Group. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315:788–800.
22. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guerin C, Prat G, Morange S, Roch A. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107–16.
23. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–68.
24. Guérin C, Beuret P, Constantin JM, Bellani G, Garcia-Olivares P, Roca O, Meertens JH, Maia PA, Becher T, Peterson J, Larsson A, Gurjar M, Hajjej Z, Kovari F, Assiri AH, Mainas E, Hasan MS, Morocho-Tutillo DR, Baboi L, Chrétien JM, François G, Ayzac L, Chen L, Brochard L, Mercat A, investigators of the APRONET Study Group, the REVA Network, the Réseau recherche de la Société Française d'Anesthésie-Réanimation (SFAR-recherche) and the ESICM Trials Group. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. *Intensive Care Med* 2018;44:22–37.

AJRCCM Articles in Press. Published on 30-May-2019 as 10.1164/rccm.201806-1094OC

25. Abrams D, Fan E, Ferguson ND, Brodie D. Unproven and Expensive May Still Be Justifiable. *Am J Respir Crit Care Med* 2018;doi:10.1164/rccm.201801-0112LE.

26. Marhong JD, Telesnicki T, Munshi L, Del Sorbo L, Detsky M, Fan E. Mechanical ventilation during extracorporeal membrane oxygenation. An international survey. *Ann Am Thorac Soc* 2014;11:956–61.

27. Araos J, Alegria L, Garcia P, Cruces P, Soto D, Erranz B, Amthauer M, Salomon T, Medina T, Rodriguez F, Ayala P, Borzone GR, Meneses M, Damiani F, Retamal J, Cornejo R, Bugedo G, Bruhn A. Near-Apneic Ventilation Decreases Lung Injury and Fibroproliferation in an Acute Respiratory Distress Syndrome Model with Extracorporeal Membrane Oxygenation. *Am J Respir Crit Care Med* 2019;199:603–612.

28. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–55.

29. Pham T, Combes A, Roze H, Chevret S, Mercat A, Roch A, Mourvillier B, Ara-Somohano C, Bastien O, Zogheib E, Clavel M, Constan A, Marie Richard JC, Brun-Buisson C, Brochard L. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013;187:276–85.

30. Putensen C, Zech S, Wrigge H, Zinserling J, Stüber F, Von Spiegel T, Mutz N. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med* 2001;164:43–49.

31. Mauri T, Bellani G, Grasselli G, Confalonieri A, Rona R, Patroniti N, Pesenti A. Patient-ventilator interaction in ARDS patients with extremely low compliance undergoing ECMO: a novel approach based on diaphragm electrical activity. *Intensive Care Med* 2013;39:282–91.

32. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, Tucci MR, Zin WA, Kavanagh BP, Amato MB. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:1420–7.
33. Yoshida T, Fujino Y, Amato MBP, Kavanagh BP. Fifty Years of Research in ARDS. Spontaneous Breathing during Mechanical Ventilation. Risks, Mechanisms, and Management. *Am J Respir Crit Care Med* 2017;195:985–992.
34. Schmidt M, Bailey M, Kelly J, Hodgson C, Cooper DJ, Scheinkestel C, Pellegrino V, Bellomo R, Pilcher D. Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. *Intensive Care Med* 2014;40:1256–66.
35. Haneya A, Diez C, Philipp A, Bein T, Mueller T, Schmid C, Lubnow M. Impact of Acute Kidney Injury on Outcome in Patients With Severe Acute Respiratory Failure Receiving Extracorporeal Membrane Oxygenation. *Crit Care Med* 2015;43:1898–1906.
36. Schmidt M, Schellongowski P, Patroniti N, Taccone FS, Reis Miranda D, Reuter J, Prodanovic H, Pierrot M, Dorget A, Park S, Balik M, Demoule A, Crippa IA, Mercat A, Wohlfarth P, Sonneville R, Combes A, International ECMO Network (ECMONet), the REVA Research Network and the IDEA Study Group. Six-month Outcome of Immunocompromised Severe ARDS Patients Rescued by ECMO. An International Multicenter Retrospective Study. *Am J Respir Crit Care Med* 2018;doi:10.1164/rccm.201708-1761OC.
37. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, Adhikari NKJ, Amato MBP, Branson R, Brower RG, Ferguson ND, Gajic O, Gattinoni L, Hess D, Mancebo J, Meade MO, McAuley DF, Pesenti A, Ranieri VM, Rubenfeld GD, Rubin E, Seckel M, Slutsky AS, Talmor D, Thompson BT, Wunsch H, Uleryk E, Brozek J, Brochard LJ, *et al.* An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical

AJRCCM Articles in Press. Published on 30-May-2019 as 10.1164/rccm.201806-1094OC

Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2017;195:1253–1263.

38. Prone positioning and extracorporeal membrane oxygenation for severe acute respiratory distress syndrome: time for a randomized trial? - *Intensive Care Med* 2019: Mar 5

Figure Legends

Figure 1: Flow chart of the study
Definition of abbreviations: ARDS= adult respiratory distress syndrome; ECMO= extra-corporeal membrane oxygenation; ICU= intensive care unit; MV= mechanical ventilation.

Figure 2: Mechanical ventilation during the first two days on ECMO
Cumulative frequency distribution of A) tidal volume, and B) driving pressure before ECMO and during the first two days on ECMO. C) represents the distribution of day-1 and day-2 tidal volume vs driving pressure for each patient for which these data are available. 140 patients (mortality 39%) fell within the limits for ultra-protective ventilation, defined as driving pressure less than or equal to 15 cm H_2O and tidal volume of less than or equal to 4 mL/kg of predicted body weight

Figure 3: Median and interquartile range of the mechanical power (A) and the driving pressure (B) during the ECMO course according to time and ICU outcome.
Green boxplots represent ICU survivors whereas red boxplots are non-survivors

Mechanical power (MP) was calculated as proposed previously (ref), using VT, peak pressure (Ppeak), respiratory rate (RR), and driving pressure (ΔP) data: MP (J/minute) = 0.098 × VT × RR× (Ppeak−1/2 × ΔP).
Driving pressure is defined as Plateau pressure – positive end-expiratory pressure
ECMO, extracorporeal membrane oxygenation

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Table 1. Baseline Characteristics, Clinical and Biological Findings at the Time of ECMO Initiation According to 6-Month Survival Status

Characteristics	All patients (*n=350*)	Status 6 Months Post-ICU Admission		*P* Value
		Non survivors (*n=133*)	Survivors (*n=215*)	
Male sex	227 (65)	89 (67)	136 (63)	0.56
Age, years	46±17	52±18	43±15	<0.001
APACHE II score	24±11	27±12	22±10	<0.001
SOFA score at ICU admission	7.8±4.1	7.8±4.4	7.9±3.8	0.90
Body mass index, kg/m^2	28.7±8.5	27.0±7.4	29.8±9.2	0.002
Immunodeficiency	79 (23)	50 (38)	29 (13)	<0.001
ARDS etiologies				0.02
Bacterial pneumonia	116 (33)	49 (37)	65 (30)	
Viral pneumonia‡	90 (26)	21 (16)	69 (32)	
Aspiration pneumonia	41 (12)	15 (11)	26 (12)	
Trauma/burns	17 (5)	9 (7)	8 (4)	
Post-lung transplantation	13 (4)	3 (2)	10 (5)	
Pancreatitis	4 (1)	2 (1)	2 (1)	
Pulmonary vasculitis	4 (1)	2 (1)	2 (1)	
Miscellaneous	65 (19)	32 (24)	33 (15)	
Pre-ECMO ventilation parameters				
FiO_2, %	100 [100;100]	100 [100;100]	100 [100;100]	0.91
Mechanical power, J/minute ‡	26.1±12.7	25.9 ±13.1	26.1 ±12.5	0.91
Tidal volume, ml/kg IBW	6.4±2.0	6.2±1.8	6.5±2.1	0.16
Respiratory rate, breaths/min	26±8	27±8	25±7	0.02
Spontaneous respiratory rate, breaths/min	9±13	10±14	7±13	0.06
Plateau pressure, cm H_2O #	32±7	32±8	32±7	0.77
PEEP, cm H_2O	12±4	12±4	13±4	0.01
Driving pressure, cm H_2O*	20±7	20±7	19±8	0.28
Static compliance, ml/cm H_2O†	24±12	22±11	25±12	0.01
Vd/Vt ratio	0.70 [0.59-0.77]	0.73 [0.62;0.80]	0.67 [0.58;0.75]	0.001
Ventilatory ratio	2.7±1.3	2.8±1.3	2.6±1.3	0.09
Pre-ECMO blood gases				
pH	7.24±0.15	7.22±0.15	7.26±0.14	0.01
$PaCO_2$, mm Hg	68±27	66 ±26	62 ±27	0.17
HCO_3^-, mmol/L	26±7	25±7	26±7	0.54
SaO_2, %	89 [83;93]	89 [82;93]	89 [83;94]	0.62
Arterial lactate, mmol/L	3.0±3.0	3.1±2.6	3.0±3.3	0.66
PaO_2/FiO_2, mmHg	71±34	72±36	70±32	0.48
Adjuvant therapies				
Neuromuscular blockers	215 (62)	78 (59)	135 (63)	0.48
Recruitment maneuvers	131 (37)	46 (35)	84 (39)	0.45
Nitric oxide	109 (31)	48 (36)	61 (28)	0.17
Prone positioning	90 (26)	31 (23)	58 (27)	0.51
High-dose corticosteroids	87 (25)	41 (31)	46 (21)	0.07
HFOV	17 (5)	10 (7)	7 (3)	0.13
Pre-ECMO renal replacement therapy	51 (15)	26 (19)	24 (11)	0.05
Pre-ECMO cardiac arrest	21 (6)	12 (9)	9 (4)	0.11
SOFA at cannulation	10.4±4.0	11.2±4.3	10.0±3.7	0.01
RESP score	1.7±3.4	0.2±3.0	2.6±3.3	<0.001
Interval, days				
ICU admission–ECMO	2 [1;6]	3 [1;8]	2 [1;5]	0.02
MV–ECMO	2 [0;5]	2 [1;7]	1 [0;4]	0.01
Venovenous-ECMO	342 (98)	128 (96)	212 (99)	0.27
Femoral–jugular	261 (75)	102 (77)	159 (74)	0.43
Femoral–femoral	62 (18)	18 (13)	43 (20)	0.91
Dual lumen cannula	25 (7)	13 (10)	11 (5)	0.17
Mobile ECMO team	192 (55)	68 (51)	123 (57)	0.23

Definition of abbreviations: APACHE II = Acute Physiology And Chronic Health Evaluation II; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; HCO3 = bicarbonate; HFOV = high frequency oscillation ventilation; IBW = ideal body weight; ICU = intensive care unit; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; PRESERVE = PRedicting dEath for SEvere ARDS on VV-ECMO; RESP = Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; SOFA = Sequential Organ Failure Assessment; SaO2, arterial saturation in oxygen; Vd/Vt = Dead space fraction, estimated using the unadjusted Harris-Benedict equation for the resting energy expenditure.

Results are expressed as n (%) or median [25th;75th percentiles].
‡ Available for 197 patients
# Available for 271 patients
* Available for 259 patients
† Available for 241 patients

Table 2. ECMO Management and ECMO-Related Complications during the first two days According to 6-Month Survival Status

		Status 6 Months Post-ICU Admission		
Parameter	**All patients *(n=350)***	**Non survivors *(n=133)***	**Survivors *(n=215)***	***P* Value**
Fluid balance, ml	1191±2184	1857±2477	783±1879	<0.001
Ventilation settings				
FiO_2, %	50 [40;68]	54 [40;66]	54 [40;67]	0.79
Mechanical power, J/minute ‡	6.6±4.8	6.7±5.0	6.5±4.5	0.77
Tidal volume, ml/kg IBW	3.7±2.0	3.5±1.8	3.8±2.0	0.17
Total respiratory rate, breaths/min	14±6	14±6	13±5	0.17
Spontaneous respiratory rate, breaths/min †	8±11	10±13	6±10	0.01
Plateau pressure, cmH_2O *	24±7	24±7	25±6	0.30
Static compliance, ml/cm H_2O £	19±12	18±12	20±11	0.25
PEEP, cmH_2O	11±3	11±3	11±3	0.04
Driving pressure, cmH_2O #	14±4	14±5	14±5	0.64
ECMO settings				
Blood flow, l/min	4.2±1.0	4.1±1.1	4.2±1.0	0.27
Sweep gas flow, l/min	5.2±2.3	5.4±2.2	5.1±2.3	0.25
FdO_2, %	100 [100;100]	100 [100;100]	100 [100;100]	0.77
Blood gas				
pH	7.40±0.07	7.38±0.09	7.41±0.06	0.004
$PaCO_2$, mmHg	42±7	41±8	42±6	0.16
PaO_2, mmHg	93±33	94±36	92±31	0.57
HCO_3^-, mmol/L	26±5	24±6	26±5	0.003
SaO_2, %	95 [93;97]	95 [93;97]	95 [93;97]	0.84
Arterial lactate, mmol/L	2.5±2.5	3.3±3.3	2.1±1.6	<0.001
Neuromuscular blockers	142 (41)	56 (42)	85 (39)	0.72
Prone positioning	20 (6)	8 (6)	12 (6)	0.85
Renal replacement therapy	113 (32)	55 (41)	57 (26)	0.006
ECMO-related major bleeding	29 (8)	15 (11)	14 (6)	0.17
Major hemolysis	5 (1)	4 (3)	13 (6)	0.07

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; FdO_2 = fraction of delivered oxygen from the blender; FiO_2 = fraction of inspired oxygen; HCO3 = bicarbonate; IBW = ideal body weight; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; PEEP = positive end-expiratory pressure; SaO2, arterial saturation in oxygen.

Results are presented as n (%) or median [25th;75th percentiles].

‡ available for 317 patients
† available for 348 patients
* available for 342 patients
£ available for 319 patients
available for 322 patients

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Table 3. Ventilatory adjuvant therapies on ECMO and ECMO-Related Complications According to 6-Month Survival Status

	Status 6 Months Post-ICU Admission			
Parameter	**All patients *(n=350)***	**Non survivors *(n=133)***	**Survivors *(n=215)***	***P* Value**
Ventilatory adjuvant therapies on ECMO				
Neuromuscular blockers	179 (51)	77 (58)	101 (47)	0.06
Prone positioning	53 (15)	17 (13)	36 (17)	0.40
First day of proning	4 [2-6]	4 [2-6]	4 [2-7]	0.956
Proned within 3 days of ECMO	25 (7)	9 (7)	16 (7)	0.900
Nitric oxide/prostacyclin	53 (15)	20 (15)	33 (15)	1.00
Refractory hypoxemia within 7days of ECMO*	49 (14)	31 (14)	17 (13)	0.78
Renal replacement therapy on ECMO	177 (51)	84 (63)	92 (43)	<0.001
Tracheotomy on ECMO	162 (46)	58 (44)	103 (48)	0.54
ECMO-related major bleeding	87 (25)	44 (33)	43 (20)	0.009
Transfused RBC units	5 [2;11]	8 [4;20]	4 [1;7]	<0.001
Transfused platelet units	0 [0;5]	1 [0;12]	0 [0;2]	<0.001
Fibrinogen transfusion on ECMO	28 (8)	9 (7)	19 (9)	0.63
Others complications on ECMO				
Major hemolysis	34 (10)	19 (14)	15 (7)	0.04
Cardiac arrest	37 (11)	29 (22)	8 (4)	<0.001
Pneumothorax	33 (9)	19 (14)	14 (6)	0.03
Outcomes				
ECMO duration, days	10 [6;18]	14[6;28]	9 [6;14]	<0.001
Successful weaning	259 (74)	42 (32)	215 (100)	<0.0001
Mechanical ventilation duration, days	18 [11;34]	21 [10;36]	17 [11;32]	0.25
Alive at ICU discharge	232 (66)	15 (11)	215 (100)	<0.0001
ICU length of stay, days	24 [14;39]	24 [11;41]	24 [15;39]	0.39
Hospital length of stay, days	35 [20;55]	32 [14;50]	38 [22;57]	0.02

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; RBC = red blood cell; ICU = intensive care unit.
Results are presented as n (%) or median [25th;75th percentiles].

* Refractory hypoxemia was defined as PaO_2<80 mm Hg despite a fraction of inspired oxygen and a fraction of delivered oxygen from the blender both set at 100%

Table 4. Predictors of 6-Month Mortality of severe ARDS Patients Rescued by ECMO A) Pre-ECMO variables and B) pre and early post-ECMO variables.

A)

Variable	OR (95%CI)	P Value
Age, per additional year	1.03 (1.02-1.05)	<0.001
Immunocompromised condition	3.85 (2.11-7.17)	<0.001
Extra-pulmonary sepsis	2.32 (1.18-4.56)	0.014
Delay from intubation to the initiation of ECMO, for each day	1.08 (1.03-1.14)	0.004
pH, for 0.01 unit	0.98 (0.96-0.99)	0.004

B)

Variable	OR (95%CI)	P Value
Age, per additional year	1.03 (1.01-1.05)	<0.001
Immunocompromised condition	3.81 (2.10-7.02)	<0.001
Extra-pulmonary sepsis	2.61 (1.30-5.30)	0.007
Delay from intubation to the initiation of ECMO, for each day	1.11 (1.05-1.18)	<0.001
Lactate in the first 2 days on ECMO, for one mmol/l	1.15 (1.01-1.33)	0.043
Fluid balance in the first 2 days on ECMO, for one liter	1.28 (1.11-1.50)	0.001

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; OR = odds ratio; CI = confidence interval.

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Table 5. Multivariable Cox model with time-fixed and time-dependent covariates

Variable	HR (95%CI)	P Value
Time fixed		
Age, per additional year	1.01 (1.01-1.03)	0.003
Immunocompromised condition	1.43 (0.94-1.02)	0.09
Time from intubation to the initiation of ECMO, for each day	0.99 (0.96-1.01)	0.343
APACHE 2 score	1.00 (0.98-1.02)	0.828
Time dependent		
Driving pressure, for one cmH2O	1.03 (1.01-1.07)	0.03
Tidal volume, for 1ml/kg PBW	0.71 (0.65-0.78)	<0.001
Fluid balance, for one liter	1.11 (1.04-1.18)	0.003
Lactate, for one mmol	1.30 (1.24-1.37)	<0.001
Renal replacement therapy	1.64 (1.21-2.48)	0.003

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; HR = hazards ratio; CI = confidence interval, PBW, predicted body weight

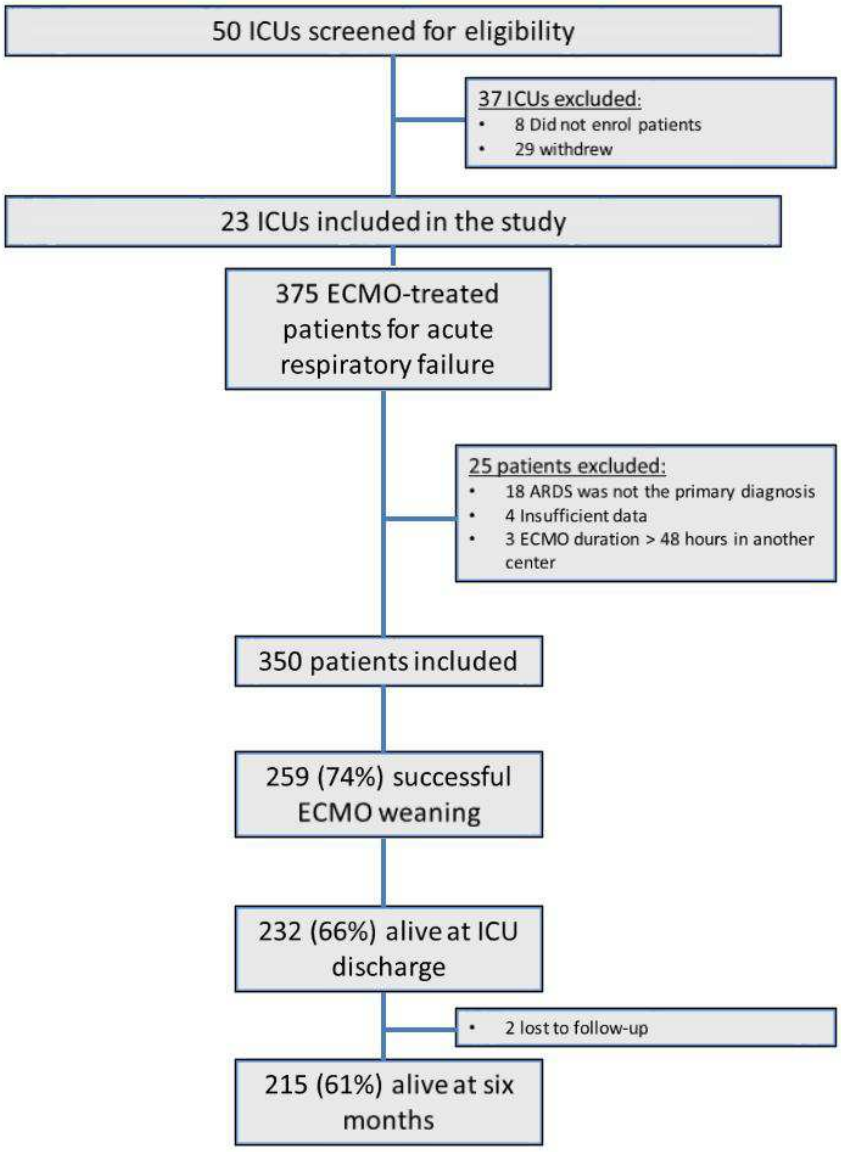

Figure 1: Flow chart of the study
Definition of abbreviations: ARDS= adult respiratory distress syndrome; ECMO= extra-corporeal membrane oxygenation; ICU= intensive care unit; MV= mechanical ventilation.

190x254mm (96 x 96 DPI)

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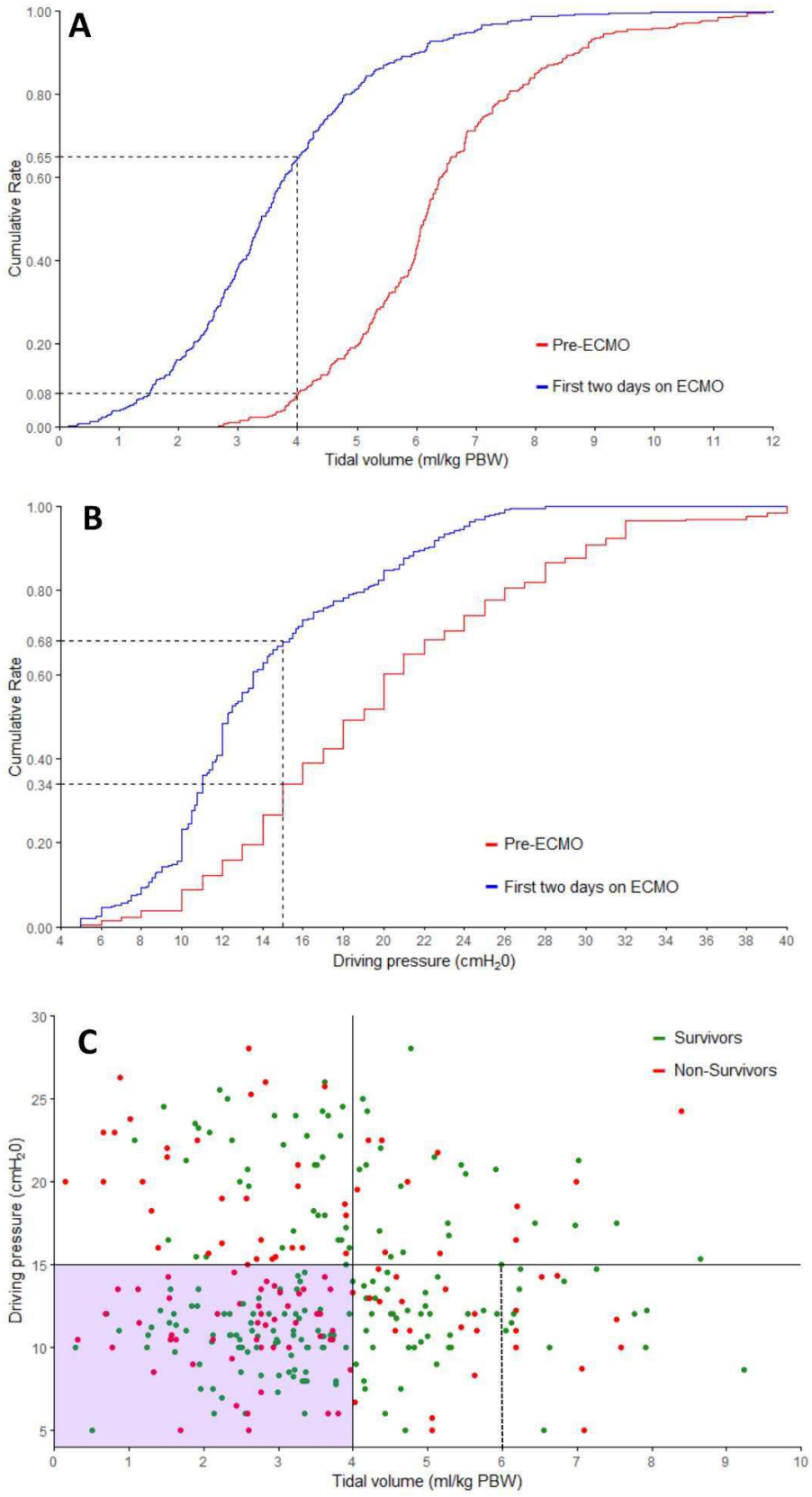

Figure Two

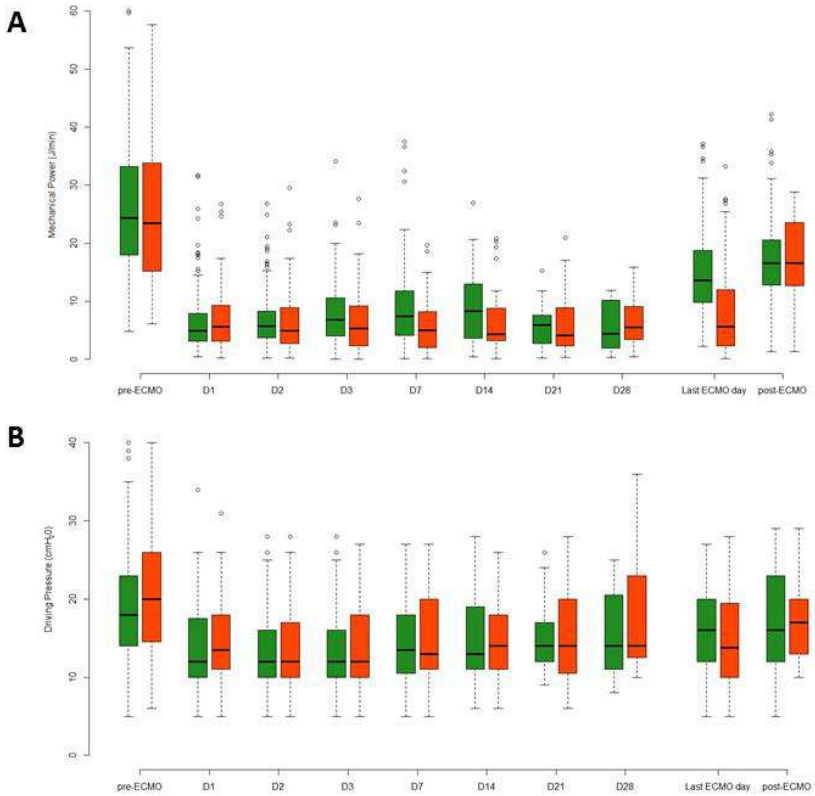

Figure 3: Median and interquartile range of the mechanical power (A) and the driving pressure (B) during the ECMO course according to time and ICU outcome.
Green boxplots represent ICU survivors whereas red boxplots are non-survivors

Mechanical power (MP) was calculated as proposed previously (ref), using VT, peak pressure (Ppeak), respiratory rate (RR), and driving pressure (ΔP) data: MP (J/minute) = 0.098 × VT × RR× (Ppeak−1/2 × ΔP).
Driving pressure is defined as Plateau pressure – positive end-expiratory pressure
ECMO, extracorporeal membrane oxygenation

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ONLINE DATA SUPPLEMENT

Mechanical ventilation management during ECMO for ARDS: An International Multicenter Prospective Cohort

Methods

Data collection

Dead space fraction (Vd/Vt) was estimated using the unadjusted Harris-Benedict equation for the resting energy expenditure (REE): 1- $\frac{0.863 * VCO2}{RR * Vt * PaCO2}$ with VCO2=$\frac{REE}{\left(\frac{5.616}{RQ}\right) + 1.584}$; REE for males= 66.473 +13.752 (weight in kg)+5.003 (height in cm)− 6.755 (age in years); REE for females= 655.096 + 9.563 (weight in kg)+ 1.850 (height in cm)− 4.676 (age in years); and RQ=0.8. Ventilatory ratio was calculated as [minute ventilation (mL/min) * arterial PCO2 (mmHg)] / [predicted body weight * 100 * 37.5].

Lastly, immunodeficiency included hematological malignancies, active treatment for solid tumor, solid-organ transplant, acquired immunodeficiency syndrome, or long-term or high-dose corticosteroids or immunosuppressants. Long-term corticosteroids was defined as >7.5 mg of prednisone/day for >3 months, with high-dose defined as >1 mg/kg for >1 week within the last 3 months. Immunosuppressants had to have been taken during the 6 months before ECMO or within the first 48 hours after ECMO cannulation.

Statistical Analyses

Patients' demographic, clinical and pre-ECMO ventilation characteristics, ECMO ventilation characteristics within the first two days, and laboratory results were tested in bivariable logistic regression analyses for association with death within 6 months after ICU admission. All clinically relevant factors (achieving P≤0.20) were subsequently entered into the multivariable models in a stepwise logistic regression. The candidate variables for the multivariable model before ECMO and during the first two days after cannulation were: "age; extra-pulmonary infection; time between intubation and cannulation; body mass index;

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APACHE 2 score; SOFA score; chronic liver failure; main cause for ARDS; dead space ratio or ventilatory ratio; extra-pulmonary infection; tidal volume (per kg of predicted body weight); PEEP or plateau pressure or driving pressure or mechanical power; lactate; pH; fluid balance in the first two days; respiratory rate; proning; renal replacement therapy“. Multiple forward and backward-stepwise logistic-regression analyses eliminated variables with an exit threshold set at $P \geq 0.05$. Multicollinearity was assessed calculating a variance inflation factor of each variable and ruled out if the variance inflation factor was lower than 2. Lastly, these final models were based on data from patients with complete information available for all variables, assuming completely missing at random data.

Cox model with time-dependent covariates

In order to consider time variation of parameters such as mechanical ventilation settings or respiratory system mechanics over time, we performed a Cox model with time dependent covariates. This model aimed at determining variables associated with the hazard of death within 6 months after ICU admission, taking into account the variation over time of those covariate values. First, we split the time on ECMO in one day-intervals and covariates included in the model were separated in 2 groups: 1) time-fixed variables, i.e. baseline covariates that remained unchanged along the course of ECMO (such as age); 2) time-varying variables, i.e. covariates that could differ from one day to the next (such as tidal volume). Covariates known to be associated to mortality in ICU patients or in ECMO patients were forced into the model, as described below.

The time-fixed variables tested in the model were the following:

- Age
- Body-mass index

- Immunodeficiency
- Cause of ARDS (pulmonary versus extrapulmonary)
- APACHE 2 score
- SOFA score
- Time elapsed between intubation and ECMO (expressed in days)
- Chronic liver disease

The time-dependent covariates tested in the model were the following:

- Tidal volume
- Actual respiratory rate
- Spontaneous respiratory rate
- Driving pressure
- Plateau pressure
- PEEP
- Peak inspiratory pressure
- Compliance
- Renal replacement therapy
- Arterial pH
- Arterial lactate
- Fluid balance from the last 24 hours

Parameters highly correlated such as driving pressure and plateau pressure; driving pressure and peak inspiratory pressure; arterial pH and arterial lactate, etc., were tested in separated models.

We forced into the model immunodeficiency, time elapsed from intubation to the initiation of

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ECMO and APACHE 2 score that are well known to be associated with mortality in ICU patients overall or in patients with ARDS treated with ECMO in particular.

The final model retained the following covariates: immunodeficiency, time from intubation to the initiation of ECMO, APACHE 2 score, age, driving pressure, tidal volume, fluid balance, arterial lactate, renal replacement therapy.

Results

Patient Outcomes and Predictors of 6-Month Mortality

Pre-ECMO predictors of 6-month mortality were immunodeficiency, older age, extra-pulmonary sepsis, greater delay from endotracheal intubation to the initiation of ECMO, and lower pH (Table 4). While integrating data from the two first days on ECMO, early predictors of 6-month mortality were immunodeficiency, older age, extra-pulmonary sepsis, higher ECMO lactate on ECMO, greater delay from endotracheal intubation to the initiation of ECMO, and higher fluid balance on ECMO (Table 4). Lastly, no association was found between ventilator settings and survival during the first 2 days of ECMO in the logistic regression model.

Table E1: Amount of missing data for each Pre-ECMO and first two ECMO days variables included in the analysis

Variables	Available data (n)	Missing data (%)
Pre ECMO		
Age	350	0
Immunodepression status	350	0
Delay intubation-ECMO	349	0.3
BMI	349	0.3
APACHE II	338	3.4
SOFA at Cannulation	327	6.6
Tidal volume (mL/kg)	305	12.9
Total respiratory rate	316	9.7
Spontaneous respiratory rate	221	36.9
PEEP	320	8.6
FiO_2	339	3.1
Plateau pressure	290	17.1
Driving pressure	286	18.3
Mechanical power	221	36.9
Static compliance	267	23.7
pH	328	6.3
PO_2	339	3.1
PCO_2	330	5.7
Bicarbonate	281	19.7
Lactate	270	22.9
PaO_2/FiO_2 ratio	339	3.1
Prone before	349	0.3
Neuromuscular before	349	0.3
Renal replacement therapy	348	0.6
Vd/Vt	287	18
First two days on ECMO		
Fluid balance	334	4.6
Tidal volume (mL/kg)	343	2
Total respiratory rate	337	3.7
Spontaneous respiratory rate	254	27.4
PEEP	347	0.9
FiO_2	348	0.6
Plateau pressure	343	2
Static compliance	319	8.9
Driving pressure	337	3.7
Mechanical power	332	5.1
pH	348	0.6
PO_2	348	0.6
PCO_2	348	0.6
Bicarbonate	345	1.4
Lactate	327	6.6

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Prone	349	0.3
Neuromuscular	349	0.3
Renal replacement therapy	350	0
Last day on ECMO		
Fluid balance	333	4.9
Tidal volume (mL/kg)	292	16.6
Total respiratory rate	287	18
Spontaneous respiratory rate	224	36
PEEP	289	17.4
FiO_2	293	16.3
Plateau pressure	343	2.0
Driving pressure	274	21.7
Mechanical power	260	25.7
pH	287	18
PO_2	287	18
PCO_2	286	18.3
Bicarbonate	277	20.9
Lactate	244	30.3

Table E2. Characteristics of the 23 International ECMO Centers

	Number (%) or median [IQR]
Characteristics of the Center	
University hospital	22 (96)
Number of hospital beds	850 [700–1034]
Number of ICU beds	21 [16;24]
Number of ICU admissions per year	1400 [850;1905]
Number of ECMO per year	30 [20;52]
Number of adult ECMO patients treated primarily for respiratory indications per year	12 [9;27]
Number of adult ECMO patients treated primarily for cardiac indications per year	20 [4;26]
Number of $ECCO_2R$-treated patient admitted in the last calendar year	2.5 [2.0;6.5]
No. of ICU physicians (day shift)	8 [5;14]
No. of ICU physicians (night shift)	3 [2;4]
Patient-to-nurse ratio	2.0 [1.0;2.5]
Patient-to-nurse ratio for patients receiving ECMO	1[1;2]
Mobile ECMO team available	20 (87)
Cannulation performed by surgeons	13 (56)
Cannulation performed by intensivists	10 (43)

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; $ECCO_2R$ = extracorporeal CO_2 removal; ICU. intensive care unit; IQR. interquartile range.

Results are expressed as n (%) or median [25^{th};75th percentiles].

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Table E3: Additional Baseline Characteristics, Clinical and Biological Findings at the Time of ECMO Initiation According to 6-Month Survival Status

Characteristics	All patients *(n=350)*	Status 6 Months Post-ICU Admission		*P* Value
		Non survivors *(n=133)*	Survivors *(n=215)*	
Thoracic origin of the ARDS	262 (75)	90 (68)	170 (79)	0.02
Surgery <7 days before cannulation	52 (15)	18 (13)	34 (16)	0.67
Berlin definition				0.42
Mild ARDS	3 (1)	2 (1)	1 (1)	
Moderate ARDS	22 (6)	10 (7)	12 (6)	
Severe ARDS	325 (93)	121 (91)	202 (94)	
PRESERVE score	4.0±2.9	5.3±2.7	3.0±2.6	<0.001
SOFA hemodynamic at cannulation	3 [0;3]	3 [0;3]	3 [0;3]	0.87
Hematocrit, %	32±7	31±7	33±6	0.005
Creatinine, µmol/l	135 ±110	140 ±118	131±103	0.51
Interval, days				
Hospital admission–ECMO	4 [1;10]	7 [2;17]	3 [1;7]	<0.001
Main indication for ECMO				0.10
Refractory hypoxemia	301 (86)	108 (81)	191 (89)	
Uncompensated hypercapnia	32 (9)	14 (10)	18 (8)	
Uncontrolled plateau pressure	11 (3)	7 (5)	4 (2)	
Respiratory and cardiac failure	6 (2)	4 (3)	2 (1)	

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Table E4. Cox model with time-dependent covariates after multiple imputation

Variable	HR (95%CI)	P Value
Age. per additional year	1.02 (1.01-1.04)	<0.001
Driving pressure. for one cmH_2O	1.04 (1.01-1.07)	0.014
Tidal volume. for 1ml/kg PBW	0.71 (0.65-0.77)	<0.001
Fluid balance. for one liter	1.11 (1.04-1.18)	0.002
Lactate. for one mmol	1.31 (1.24-1.37)	<0.001
Renal replacement therapy	1.68 (1.19-2.37)	0.003
Immunocompromised condition	1.36 (0.91-2.03)	0.14
Time from intubation to the initiation of ECMO. for each day	0.99 (0.96-1.01)	0.32
APACHE 2 score	1.00 (0.98-1.02)	0.98

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; OR = odds ratio; CI = confidence interval. PBW. predicted body weight

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Figure E1: Mechanical ventilation modes set during the ECMO course.

ACV. Assist-control in volume; APRV/Bi-level positive airway pressure; airway pressure release ventilation/ bi-level positive airway pressure; PCV. pressure-controlled ventilation; PSV. pressure support ventilation; SIMV/PC. synchronized intermittent mandatory ventilation with pressure control; SIMV/VC. synchronized intermittent mandatory ventilation with volume control. VCV. volume controlled ventilation.

Figure E2: Median and interquartile range of tidal volume (A), respiratory rate (B), and positive end-expiratory pressure (C) targeted during the ECMO course according to time and 6-month outcome.

Green boxplots represent ICU survivors whereas red boxplots are non-survivors

ECMO, extracorporeal membrane oxygenation

Figure E3: Median and interquartile range of minute ventilation targeted during the ECMO course according to time and 6-month outcome.

Green boxplots represent ICU survivors whereas red boxplots are non-survivors

D=day

Figure E4: Median and interquartile range of tidal volume during the first two days on ECMO according to center.

Figure E5: Median and interquartile range of driving pressure during the first two days on ECMO according to center

Figure E6: Median interquartile range of fluid balance during the ECMO course according to time and 6-month outcome.

Green boxplots represent ICU survivors whereas red boxplots are non-survivors

Figure E7: Median and interquartile range of static compliance observed during the ECMO course according to time and 6-month outcome.

Green boxplots represent ICU survivors whereas red boxplots are non-survivors

D=day

Figure E8: Median and interquartile range of PaO_2 obtained during the ECMO course according to time and 6-month outcome.

Green boxplots represent ICU survivors whereas red boxplots are non-survivors

D=day

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Figure E9: Median and interquartile range of $PaCO_2$ obtained during the ECMO course according to time and 6-month outcome.

Green boxplots represent ICU survivors whereas red boxplots are non-survivors

D=day

Figure E10: Kaplan–Meier survival estimates for ECMO-treated acute respiratory distress syndrome patients. according to the delayed time from endotracheal intubation to the initiation of ECMO

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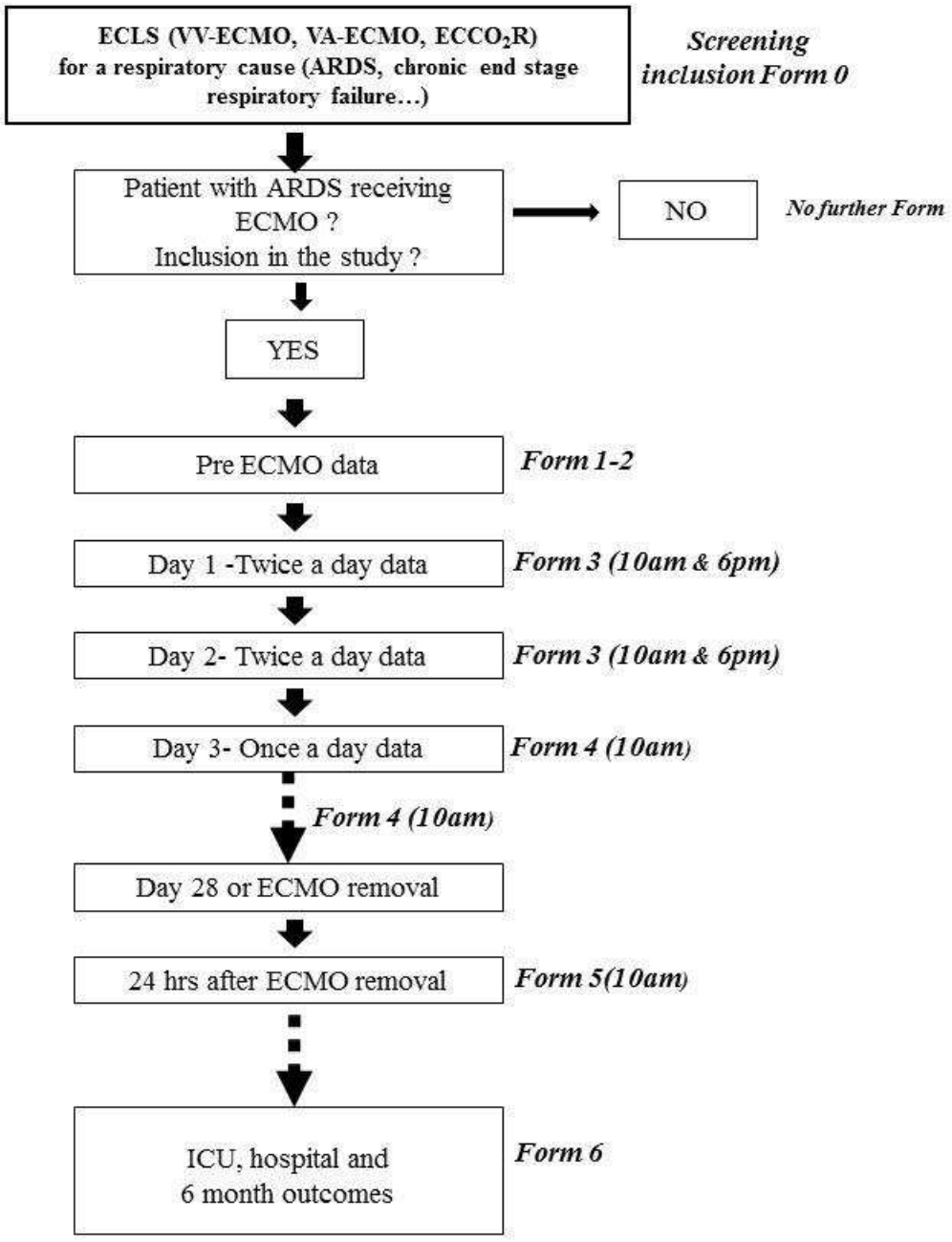
Case report form

Mechanical ventilation management during ECMO for ARDS – The LIFEGARDS study –



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Screening data for inclusion (screening form)

(all patients with ECLS for acute respiratory failure)

Patient Initials : __ __ __ Gender : M/F S1

Year of birth: _ _ _ _ S2

Centre : _____ S3 | APD number (for ANZ sites): _ _ _ _ _ _ _ _ _ S4

Simultaneous inclusion in others ECLS or mechanical ventilation studies:
□ None □ EOLIA □ LUNG-SAFE □ Other: _____ S5

Pre-existing pulmonary disease (*limited at two answers*) □ None
□ asthma □ cystic fibrosis □ chronic obstructive lung disease
□ chronic restrictive lung disease □ documented pulmonary hypertension S6

Primary diagnosis
□ ARDS/ALI □ Chronic end stage respiratory failure □ Other:_____ S7

Risk factor for primary diagnosis *(select ONLY one answer)*
□ Bacterial Pneumonia □ Viral Pneumonia □ Trauma/burns □ Pancreatitis □ Asthma
□ Aspiration pneumonia □ Pulmonary vasculitis □ Pre lung transplantation (respiratory chronic disease) □ Post lung transplantation □ COPD decompensation Other S8

Indications for ECMO / CO2 removal devices □ respiratory failure with heart failure
□ Refractory hypoxemia □ Uncompensated hypercapnia □ Uncontrolled plateau pressure S9

ECMO Assessment

Date and time ECMO cannulation :
_ _/_ _/2 0 _ _ _ _:_ _

□ VV ECMO □ VA ECMO □ VV-CO_2R
□ VA-CO_2R □ others

Details of site of VV ECMO cannulation
□ F-F □ F-J □ F-SC □ F-F-J □ JJ

Location of the first ECMO cannulation
□ Theatre □ Your ICU □ Other ICU by a mobile ECMO team

Drainage cannula size (venous): _ _ Fr Return cannula size: _ _ Fr S10

Inclusion criteria *(All must be 'Yes' for inclusion into study)*

ARDS is the primary diagnosis for ECMO? □ yes □ no
ECMO cannulation < 48 hours? □ yes □ no S11

Exclusion Criteria *(All must be 'No' for inclusion into study*

< 15 years of age □ yes □ no
Death is imminent and inevitable? □ yes □ no S12

Inclusion in the study

□ yes □ no S13

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Date and time of inclusion _ _/_ _/_ _ _ _ _ _: _ _ **(24 h clock)** S14

If the patient is included in the study. please answers to Form 1 to 6 during the ECMO duration

Did the patient receive an ECMO for ARDS? □ yes □ no 1-1

If no the patient cannot be included in this study. Please answer only to the screening form

Form 1 - Patient characteristics

Weight : _ _ _kg 1-2 | **Height : _ _ _cm** 1-3

ICU admission score

APACHE II : _ _ _

For definition. see the appendix section 1-4

SOFA first ICU admission:

Resp _ _ Neuro _ _ CV _ _ Liver _ _ Renal_ _ Hemato_ _

SOFA at the time of ECMO cannulation:

Resp _ _ Neuro _ _ CV _ _ Liver _ _ Renal_ _ Hemato_ _ 1-5

Post-operative (< 7 days) □ yes □ No 1-6

Pregnancy or peri-partum □ yes □ No □ N/A 1-7

History of the disease

Pre-existing immunosuppression □ None

□ hematologic malignancies □ solid tumor □ solid organ transplantation

□ high-dose or long term steroids □ immunosuppressive agents □ HIV 1-8

Comorbidities □ None □ diabetes mellitus □ chronic renal failure (dialysis)

□ heart failure: NYHA classes III-IV □ chronic liver failure (Child-Pugh Class C)

□ neurological impairment 1-9

Primary causes of ARDS *(select ONLY one)*

□ Bacterial Pneumonia □ Viral Pneumonia □ Trauma/burns

□ Pancreatitis □ Aspiration pneumonia □ Pulmonary vasculitis

□ Post lung transplantation □ Other: _____ 1-10

□ Mild ARDS □ Moderate ARDS □ Severe ARDS 1-11 | *For definition. see the appendix section*

Date of your hospital admission: _ _/_ _/2 0 _ _ 1-12

Your ICU admission: _ _/_ _/2 0 _ _ 1-13

Date and time intubation: _ _/_ _/2 0 _ _ _ _:_ _ 1-14

If patient transferred from another hospital ? □ yes □ No

Date of Admission to that hospital _ _/_ _/2 0 _ _

Date of ICU Admission in that hospital _ _/_ _/2 0 _ _ 1-15

Date and time ECMO cannulation :

_ _/_ _/2 0 _ _ _ _:_ _ 1-16

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Form 2 - Before ECMO cannulation for ARDS patients

□ ***No invasive MV***	NIV during the previous 24hrs? □ Yes □ No		2-1
□ ***Volume control ventilation*** □ ***Assist control*** □ ***SIMV-Volume control***	Mech tidal volume : _ _ _ mL Plateau pressure: _ _ cmH_2O Inspiratory pressure : _ _ cmH_2O Spont respiratory rate: _ _ $n.min^{-1}$	Mech respiratory rate: _ _ $n.min^{-1}$ Peak pressure: _ _ cmH_2O Spont tidal volume : _ _ _ mL	2-2
□ ***Pressure control ventilation*** □ ***PRVC*** □ ***SIMV-Pressure control***	Inspiratory pressure : _ _ cmH_2O Mech tidal volume : _ _ _ mL Spont tidal volume : _ _ _ mL Plateau pressure: _ _ cmH_2O	Mech respiratory rate: _ _ $n.min^{-1}$ Peak pressure: _ _ cmH_2O Spont respiratory rate: _ _ $n.min^{-1}$	2-3
□ ***Airway pressure release ventilation*** □ ***Bi-LEVEL***	High pressure: _ _ cmH_2O Time High: _ _ ._ sec Mech tidal volume : _ _ _ _ mL	Low pressure or PEEP : _ _ cmH_2O Time Low: _ _. _ sec Mech respiratory rate: _ _ $n.min^{-1}$	2-4
□ ***Pressure support ventilation***	Inspiratory Pressure : _ _ cmH_2O Spont Respiratory rate: _ _ $n.min^{-1}$	Spont Tidal volume : _ _ _ _ mL	2-5
	□ ***Other mode (PAV. NAVA…)***		2-6
PEEP : _ _ cmH_2O	FiO_2 : _ _ _ %	Is the patient triggering the ventilator? □ Yes □ No	2-7
End Tidal CO_2: _ _ mmHg	□ N/A		2-8
Worse Mean Arterial Pressure immediately prior to ECMO cannulation: _ _ _ mmHg			2-9
Extra pulmonary (co)-infection (bacterial. parasitic. fungal...)	□ Yes	□ No	2-10
Cardiac arrest before ECMO cannulation	□ Yes	□ No	2-11

Last blood gas immediately prior to ECMO cannulation

FiO_2 : _ _ _ %	pH: _._ _	pO_2: _ _ _ mmHg	
pCO_2: _ _ _ mmHg	HCO3: _ _ mmol/L	SaO2 : _ _ _ %	
	Lactate: _ _ _ mmol/L		2-12

Last biological values immediately prior to ECMO cannulation

Serum Creatinine: _ _ _ µmol/L	Total Billirubin: _ _ _ µmol/L	Hematocrit: _ _ %	
2-13	2-14		2-15
The worst PaO_2/FiO_2 ratio: _ _ _mmHg			2-16

Therapies prior to ECMO initiation (within 48 hrs)

Recruitment manoeuvres :	□ Yes □ No	Continuous NM blocking agents :	□ Yes □ No	
Prone positioning :	□ Yes □ No	Prostacyclins	□ Yes □ No	
Nitric oxide:	□ Yes □ No	High dose corticosteroids	□ Yes □ No	
HFO ventilation :	□ Yes □ No	Almitrine besylate	□ Yes □ No	
Bicarbonate infusion :	□ Yes □ No	Renal replacement therapy	□ Yes □ No	2-17

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Form 3 - Twice a day data (Day 1 and Day 2) 1/2

Is the patient still on ECMO? □ yes □ no *If No. answer Form 5-6* *3-1*

Complete a separate Form 3 for each day up to study day 2 (D1-D2)

Day _ _ _ _/_ _/20 _ _ *3-2*	**Fluid balance of the previous 24hrs: +/- _ _ _ _ _ mL** *3-3*

Morning ventilator settings (Closest to 10AM)		**Evening ventilator settings (Closest to 6PM)**	
RASS +/- _ _ *3-4*		**RASS +/- _ _** *3-5*	
□ **No invasive MV**	□ NIV during the past 24h *3-6*	□ **No invasive MV**	□ NIV during the past 24h *3-7*
□ **Volume control ventilation** □ **Assist control** □ **SIMV-Volume control**	Mech tidal volume: _ _ _ mL Mech respiratory rate: _ _ Plateau pressure: _ _ cmH_2O Peak pressure: _ _ cmH_2O Insp pressure : _ _ cmH_2O Spont tidal volume: _ _ _ mL 3-8	□ **Volume control ventilation** □ **Assist control** □ **SIMV-Volume control**	Mech tidal volume: _ _ _ mL Mech respiratory rate: _ _ Plateau pressure: _ _ cmH_2O Peak pressure: _ _ cmH_2O Insp pressure : _ _ cmH_2O Spont tidal volume: _ _ _ mL 3-9
□ **Pressure control ventilation** □ **PRVC** □ **SIMV-Pressure control**	Insp pressure : _ _ cmH_2O Mech tidal volume: _ _ _ mL Mech respiratory rate: _ _ Peak pressure: _ _ cmH_2O Spont tidal volume: _ _ _ mL Spont respiratory rate: _ _ Plateau pressure: _ _ cmH_2O 3-10	□ **Pressure control ventilation** □ **PRVC** □ **SIMV-Pressure control**	Insp pressure : _ _ cmH_2O Mech tidal volume: _ _ _ mL Mech respiratory rate: _ _ Peak pressure: _ _ cmH_2O Spont tidal volume: _ _ _ mL Spont respiratory rate: _ _ Plateau pressure: _ _ cmH_2O 3-11
□ **Airway pressure release ventilation** □ **Bi-LEVEL**	High pressure: _ _ cmH_2O Low pressure or PEEP: _ _cmH_2O Time High: _ _ ._ sec Time Low: _ _. _ sec Tidal volume : _ _ _ _ mL Mech respiratory rate: _ _ 3-12	□ **Airway pressure release ventilation** □ **Bi-LEVEL**	High pressure: _ _ cmH_2O Low pressure or PEEP : _ _cmH_2O Time High: _ _ ._ sec Time Low: _ _. _ sec Tidal volume : _ _ _ _ mL Mech respiratory rate: _ _ 3-13
□ **Pressure support ventilation**	Insp pressure : _ _ cmH_2O Spont tidal volume: _ _ _ mL Spont respiratory rate: _ _ 3-14	□ **Pressure support ventilation**	Insp pressure : _ _ cmH_2O Spont tidal volume: _ _ _ mL Spont respiratory rate: _ _ 3-15
□ **Other mode (PAV. NAVA…)** 3-16		□ **Other mode (PAV. NAVA…)** 3-17	
PEEP : _ _ cmH_2O 3-18	FiO_2 : _ _ _ % 3-19	PEEP : _ _ cmH_2O 3-20	FiO_2 : _ _ _ % 3-21
Is the patient triggering the ventilator? 3-22 □ Yes □ No		Is the patient triggering the ventilator? 3-23 □ Yes □ No	
End Tidal CO_2: _ _ mmHg □ N/A 3-24		End Tidal CO_2: _ _ mmHg □ N/A 3-25	

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Form 3 - Twice a day data (Day 1 and Day 2) *2/2*

Morning ECMO settings (Closest to 10AM)	**Evening ECMO settings (Closest to 6PM)**
Flow: _ . _ L/min Sweep gas flow: _ _ L/min ECMO FiO2: _ _ _ % 3-26	Flow: _ . _ L/min Sweep gas flow: _ _ L/min ECMO FiO2: _ _ _ % 3-27
Blood gas (Closest to 10AM)	**Blood gas (Closest to 6PM)**
FiO_2 : _ _ _ % pH: _._ _ pCO_2: _ _ _ mmHg pO_2: _ _ _ mmHg HCO_3: _ _ mmol/L SaO_2 : _ _ _ % Lactate: _ _ _ mmol/L 3-28	FiO_2 : _ _ _ % pH: _._ _ pCO_2: _ _ _ mmHg pO_2: _ _ _ mmHg HCO_3: _ _ mmol/L SaO_2 : _ _ _ % Lactate: _ _ _ mmol/L 3-29

Major Adverse events during the past 24hrs

Death □ Yes □ No

Major hemolysis □ Yes □ No

Major hemolysis is an hemolysis which needed to change the ECMO circuit

Major bleeding event □ Yes □ No

- □ Hemothorax
- □ Oro-nasal bleeding
- □ Gastric ulcer
- □ Other

Major bleeding event is defined as a life-threatening bleeding which lead to an haemostatic treatment (pleural drainage. oropharyngeal packing. arterial embolization and gastrointestinal endoscopy). or a transfusion > to 5 blood packs or catecholamine increasing/introduction

Cardiac arrest : □ Yes □ No

Pneumothorax □ Yes □ No

Worse hemoglobin value of the day: _ _. _ _ g/dL Number of red blood cells units transfused : _ _ 3-30

Mechanical ventilation setting modifications during the past 24hrs

MV weaning □ Yes MV removal □ Yes 3-31

ECMO circuit modifications during the past 24hrs

ECMO weaning □ Yes ECMO removal □ Yes *If yes then answer Form 5-6*

ECMO settings modification □ Yes □ No

- □ Add a third cannula
- □ Switch mode VV to VA or VA to VV
- □ Change of circuit
- □ Other

3-32

Associated treatment during the past 24hrs

Renal replacement therapy :	□ Yes □ No	Continuous NM-blocking drug :	□ Yes □ No
Mobilisation out of bed :	□ Yes □ No	Surgical intervention:	□ Yes □ No
Prone positioning :	□ Yes □ No	HFO ventilation :	□ Yes □ No
Nitric oxide/prostacyclin	□ Yes □ No		3-33

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Form 4 - once a day data (from D3 to ECMO removal or D28)

Day _ _ _ _/_ _/20 _ _ 4-1	Fluid balance of the previous 24hrs: +/- _ _ _ _ _ mL 4-2	**RASS +/- _ _** 4-3

Morning ventilator settings (Closest to 10AM)

□ **No invasive MV**	NIV during the previous 24hrs? □ Yes □ No		4-4
□ **Volume control ventilation** □ **Assist control** □ **SIMV-Volume control**	Mech tidal volume : _ _ _ mL Plateau pressure: _ _ cmH_2O Inspiratory pressure : _ _cmH_2O Spont respiratory rate: _ _ $n.min^{-1}$	Mech respiratory rate: _ _ $n.min^{-1}$ Peak pressure: _ _ cmH_2O Spont tidal volume : _ _ _ mL	4-5
□ **Pressure control ventilation** □ **PRVC** □ **SIMV-Pressure control**	Inspiratory pressure : _ _cmH_2O Mech tidal volume : _ _ _ mL Spont tidal volume : _ _ _ mL Plateau pressure: _ _ cmH_2O	Mech respiratory rate: _ _ $n.min^{-1}$ Peak pressure: _ _ cmH_2O Spont respiratory rate: _ _ $n.min^{-1}$	4-6
□ **Airway pressure release ventilation** □ **Bi-LEVEL**	High pressure: _ _ cmH_2O Time High: _ _ ._ sec Tidal volume : _ _ _ _ mL	Low pressure or PEEP : _ _ cmH_2O Time Low: _ _. _ sec Mech respiratory rate: _ _ $n.min^{-1}$	4-7
□ **Pressure support ventilation**	Inspiratory Pressure : _ _ cmH_2O Spont Respiratory rate: _ _ $n.min^{-1}$	Spont Tidal volume : _ _ _ _ mL	4-8
□ **Other mode (PAV. NAVA…)**			4-9
PEEP : _ _ cmH2O	FiO_2 : _ _ _ %	Is the patient triggering the ventilator? □ Yes □ No	4-10
End Tidal CO2: _ _ mmHg	□ N/A		4-11

Blood gas (Closest to 10AM)

FiO_2 : _ _ _ %	pH: _ . _ _	pO_2: _ _ _ mmHg	
pCO_2: _ _ _ mmHg	HCO_3: _ _ mmol/L	SaO_2 : _ _ _ %	
	Lactate: _ _ _ mmol/L		4-12

Morning ECMO settings (Closest to 10AM)

Flow: _ . _ L/min	Sweep gas flow: _ _ L/min	ECMO FiO2: _ _ _ %	4-13

Major events of the past 24hrs

Death: □ Yes Major hemolysis □ Yes Major Bleeding event □ Yes if Yes type: _____

Cardiac arrest : □ Yes Pneumothorax □ Yes Worse hemoglobin value: _ _. _ _ g/dL

Number of red blood cells units transfused : _ _

MV weaning □ Yes □ No MV removal □ Yes □ No

ECMO weaning □ Yes □ No ECMO removal □ Yes □ No *if yes then answer Form 5-6*

ECMO settings modification □ Yes □ No

□ Add a third cannula □ Switch mode VV to VA or VA to VV □ Change circuit □ Other 4-14

Associated treatment during the past 24hrs

Renal replacement therapy :	□ Yes □ No	Continuous NM-blocking drug :	□ Yes □ No
Mobilisation out of bed :	□ Yes □ No	Surgical intervention:	□ Yes □ No
Prone positioning :	□ Yes □ No	HFO ventilation :	□ Yes □ No
Nitric oxide/prostacyclin	□ Yes □ No		4-15

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Form 5 - 24hrs after ECMO removal

Day _ _ _ _/_ _/20 _ _ 5-1	Fluid balance of the previous 24hrs: +/- _ _ _ _ _ mL 5-2	**RASS +/- _ _** 5-3

Morning ventilator settings (Closest to 10AM)

□ ***No invasive MV***	NIV during the previous 24hrs? □ Yes □ No		5-4
□ ***Volume control ventilation*** □ **Assist control** □ ***SIMV-Volume control***	Mech tidal volume : _ _ _ mL Plateau pressure: _ _ cmH_2O Inspiratory pressure : _ _cmH_2O Spont respiratory rate: _ _ $n.min^{-1}$	Mech respiratory rate: _ _ $n.min^{-1}$ Peak pressure: _ _ cmH_2O Spont tidal volume : _ _ _ mL	5-5
□ ***Pressure control ventilation*** □ **PRVC** □ ***SIMV-Pressure control***	Inspiratory pressure : _ _cmH_2O Mech tidal volume : _ _ _ mL Spont tidal volume : _ _ _ mL Plateau pressure: _ _ cmH_2O	Mech respiratory rate: _ _ $n.min^{-1}$ Peak pressure: _ _ cmH_2O Spont respiratory rate: _ _ $n.min^{-1}$	5-6
□ ***Airway pressure release ventilation***	High pressure: _ _ cmH_2O Time High: _ _ ._ sec	Low pressure or PEEP : _ _ cmH_2O Time Low: _ _. _ sec	
□ ***Bi-LEVEL***	Tidal volume : _ _ _ _ mL	Mech respiratory rate: _ _ $n.min^{-1}$	5-7
□ ***Pressure support ventilation***	Inspiratory Pressure : _ _ cmH_2O Spont Respiratory rate: _ _ $n.min^{-1}$	Spont Tidal volume : _ _ _ _ mL	5-8
□ ***Other mode (PAV. NAVA…)***			5-9
PEEP : _ _ cmH_2O	FiO_2 : _ _ _ %	Is the patient triggering the ventilator? □ Yes □ No	5-10
End Tidal CO_2: _ _ mmHg	□ N/A		5-11

Blood gas (Closest to 10AM)

FiO_2 : _ _ _ %	pH: _ . _ _	pO_2: _ _ _ mmHg	
pCO_2: _ _ _ mmHg	HCO_3: _ _ mmol/L	SaO_2 : _ _ _ %	
	Lactate: _ _ _ mmol/L		5-12

Major events of the past 24hrs

Death: □ Yes Major hemolysis □ Yes Major Bleeding event □ Yes if Yes type: _____

Cardiac arrest : □ Yes Pneumothorax □ Yes Worse hemoglobin value: _ _. _ _ g/dL

Number of red blood cells units transfused : _ _

MV weaning □ Yes □ No MV removal □ Yes □ No 5-13

Associated treatment during the past 24hrs

Renal replacement therapy :	□ Yes □ No	Continuous NM-blocking drug :	□ Yes □ No
Mobilisation out of bed :	□ Yes □ No	Surgical intervention:	□ Yes □ No
Prone positioning :	□ Yes □ No	HFO ventilation :	□ Yes □ No
Nitric oxide/prostacyclin	□ Yes □ No		5-14

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Form 6 - Outcomes

Tracheotomy? □ Yes □ No

Date and time of tracheotomy : _ _/_ _ /20_ _ □ N/A

6-1

Did the patient require re-cannulation within 48 hrs of ECMO liberation? □ Yes □ No □ N/A

Did the patient require re-cannulation within 48 hrs and ICU discharge after ECMO liberation?

□ Yes □ No □ N/A

ECMO outcome:

□ Successful weaning □ Never weaned □ Bridge to transplantation

Date and time of final ECMO liberation: _ _/_ _ /20 _ _ _ _: _ _ (24 h clock) □ N/A

6-2

Blood products during the ECMO duration:

Number of red blood cells units: __ _ units

Number of platelets units: __ _ units

Number of fresh frozen plasma units: __ _ units

Fibrinogen infusion during the ECMO run : □ Yes □ No

Recombinant factor VIIa **:** □ Yes □ No

6-3

Did the patient require re-intubation within 48 hrs of MV liberation? □ Yes □ No □ N/A

Did the patient require re-intubation within 48 hrs and ICU discharge after MV liberation?

□ Yes □ No □ N/A

Date and time of final ventilator liberation: _ _/_ _ /20 _ _ _ _: _ _ (24 h clock) □ N/A

6-4

Your ICU outcome: □ Alive □ Dead

Date and time of ICU discharge/death: _ _/_ _ /20 _ _ _ _: _ _ (24 h clock)

6-5

Was there a decision to withhold/withdraw life sustaining measure? □ Yes □ No

Date of decision to withhold/withdraw life sustaining measure _ _/_ _ /20_ _

6-6

Your Hospital outcome: □ Alive □ Dead

Date of your hospital discharge/death: _ _/_ _ /20 _ _

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Discharged to: □ home □ another acute ICU □ another hospitals ward □Rehabilitation centre

If transferred to another acute ICU or another hospitals ward

Transferred-hospital outcome: □ Alive □ Dead

Date of ICU discharge/death: _ _/_ _ /20 _ _

Date of hospital discharge/death: _ _/_ _ /20 _ _

6-7

Six months follow-up : date : _ _/_ _ /20 _ _

□ Alive □ Dead

Date of death (if appropriate) : _ _/_ _ /20 _ _ 6-8

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Appendix section

ARDS definition

Mild ARDS	200mmHg <PaO2/FiO2 ≤ 300mmHg with PEEP or CPAP ≥5 cmH_2O
Moderate ARDS	100mmHg <PaO2/FiO2 ≤ 200mmHg with PEEP ≥5 cmH_2O
Severe ARDS	PaO2/FiO2 ≤ 100mmHg with PEEP ≥5 cmH_2O

Richmond Agitation and Sedation Scale (RASS)

+4	***Combative***	Violent. immediate danger to staff
+3	***Very Agitated***	Pulls or remove tube(s) or catheter(s); aggressive
+2	***Agitated***	Frequent non-purposeful movement. fight ventilator
+1	***Restless***	Anxious. apprehensive but movements not aggressive or vigorous
0	***Alert and calm***	
-1	***Drowsy***	Not fully alert. but has sustained awakening to voice (eye-opening and contact ≥ 10 sec)
-2	***Light sedation***	Briefly awakens to voice (eye-opening and contact<10 sec)
-3	***Moderate sedation***	Movement or eye-opening to voice (but no eye contact)
-4	***Deep sedation***	No response to voice. but movement or eye-opening to physical stimulation
-5	***Unarousable***	No response to voice or physical stimulation

Sequential Organ Failure Assessment (SOFA)

	SOFA Score				
Organ System	0	1	2	3	4
Cardiovascular[b] hypotension, mm Hg	MAP: >70 mm without vasopressors	MAP: <70 without vasopressors	Dopamine ≤5 or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Respiratory, Pao_2/Fio_2 mm Hg	>400	<400	<300	<200 with respiratory support	<100 with respiratory support
Renal[c] creatinine, mg/dL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Hematology, platelet count, × $10^3/mm^3$	>150	<150	<100	<50	<20
Hepatic, bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0

SOFA Neuro	Glasgow score
0	15
1	13-14
2	10-12
3	6-9
4	<6

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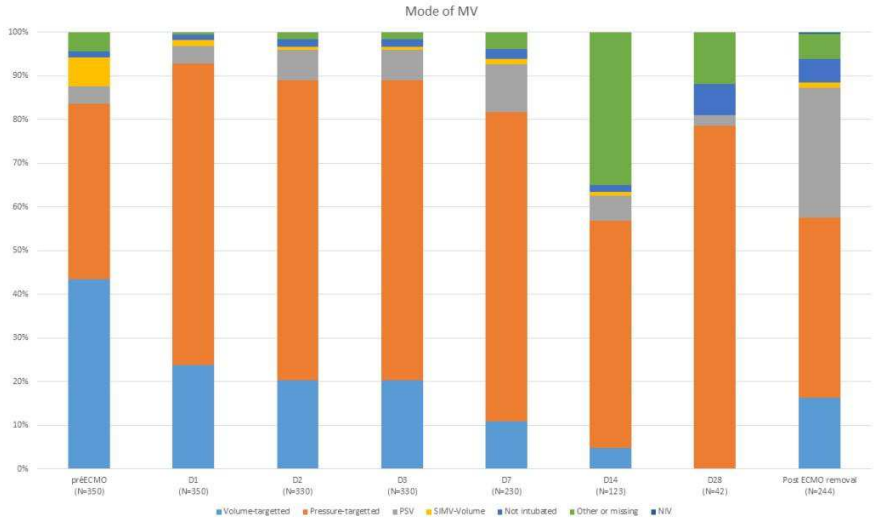

Figure E1: Mechanical ventilation modes set during the ECMO course.
ACV. Assist-control in volume; APRV/Bi-level positive airway pressure; airway pressure release ventilation/ bi-level positive airway pressure; PCV. pressure-controlled ventilation; PSV. pressure support ventilation; SIMV/PC. synchronized intermittent mandatory ventilation with pressure control; SIMV/VC. synchronized intermittent mandatory ventilation with volume control. VCV. volume controlled ventilation.

338x190mm (96 x 96 DPI)

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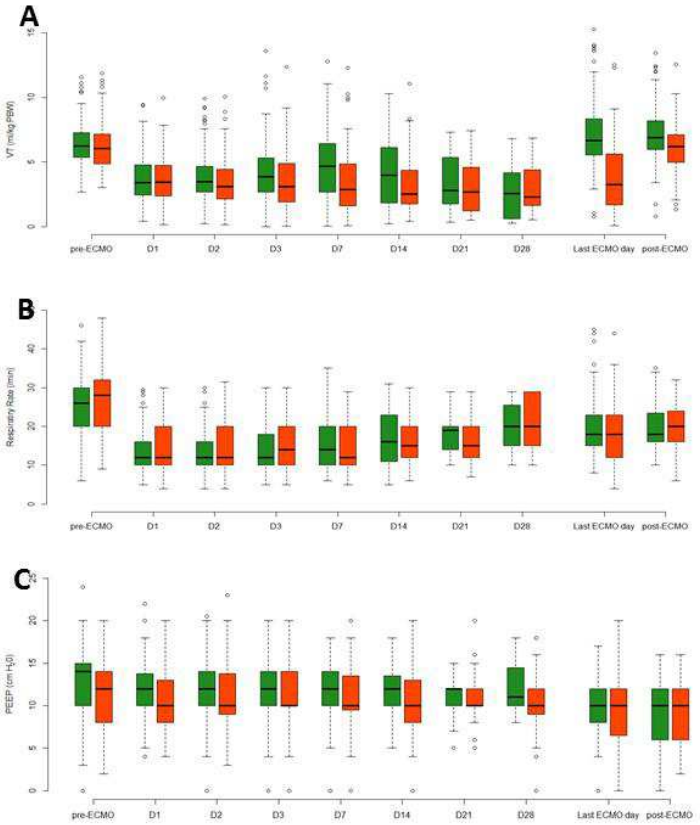

Figure E2: Median and interquartile range of tidal volume (A), respiratory rate (B), and positive end-expiratory pressure (C) targeted during the ECMO course according to time and 6-month outcome. Green boxplots represent ICU survivors whereas red boxplots are non-survivors
ECMO, extracorporeal membrane oxygenation

190x254mm (96 x 96 DPI)

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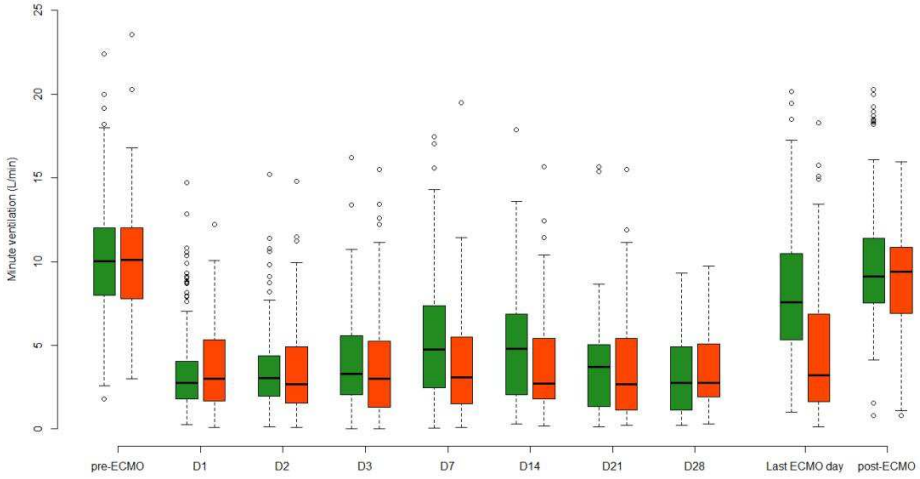

Figure E3: Median and interquartile range of minute ventilation targeted during the ECMO course according to time and 6-month outcome.
Green boxplots represent ICU survivors whereas red boxplots are non-survivors
D=day

370x218mm (96 x 96 DPI)

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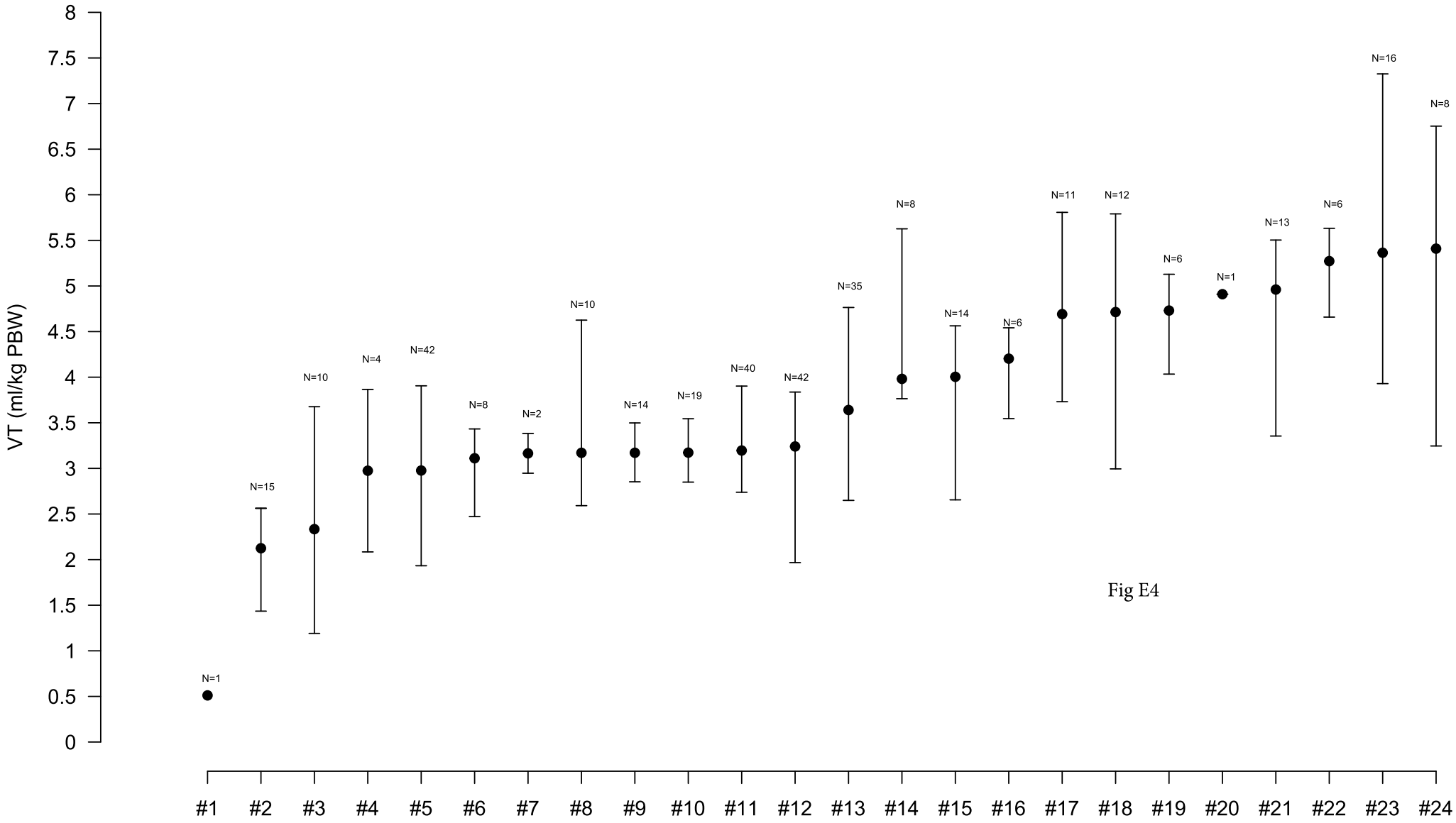

Fig E4

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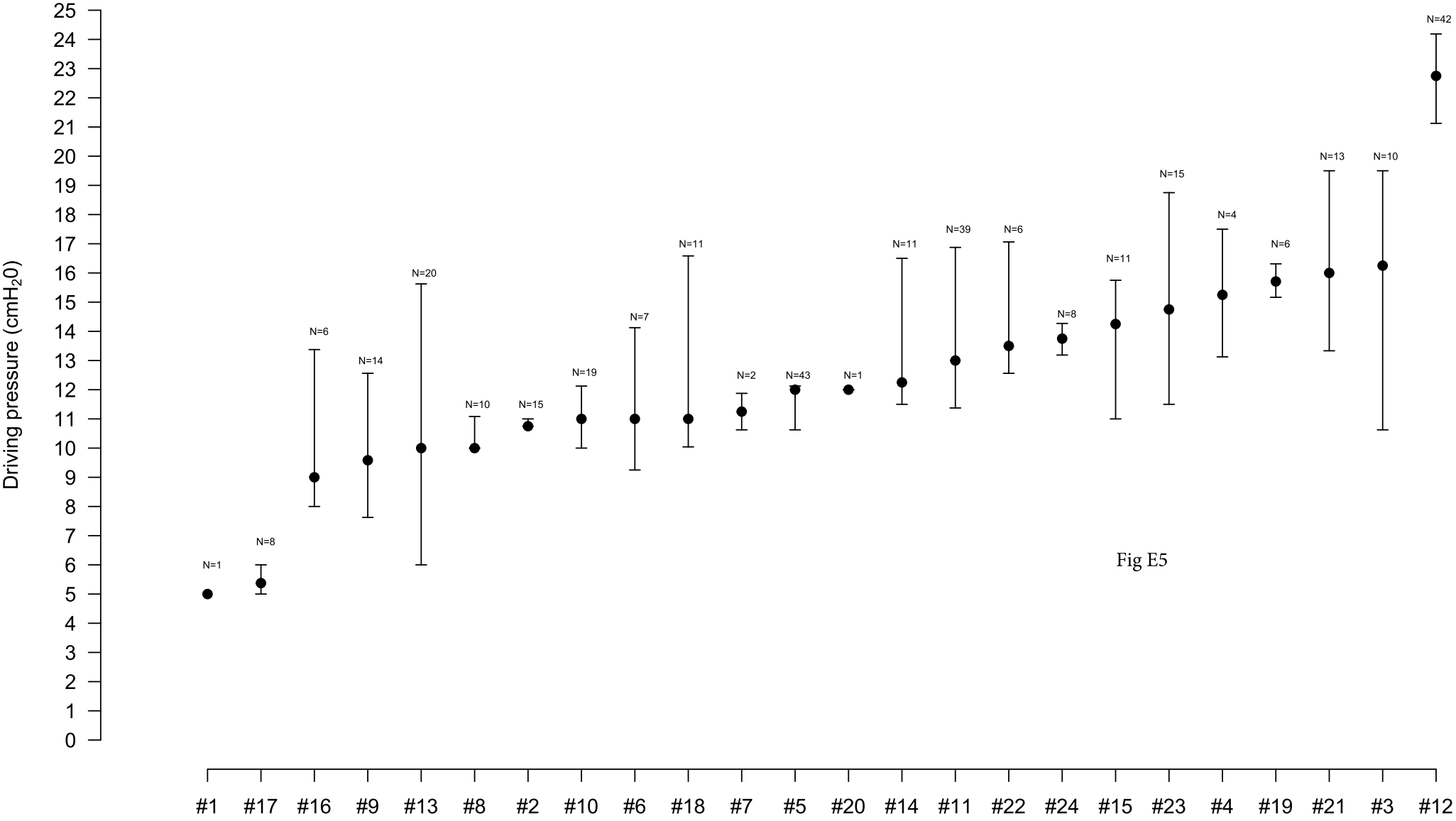

Fig E5

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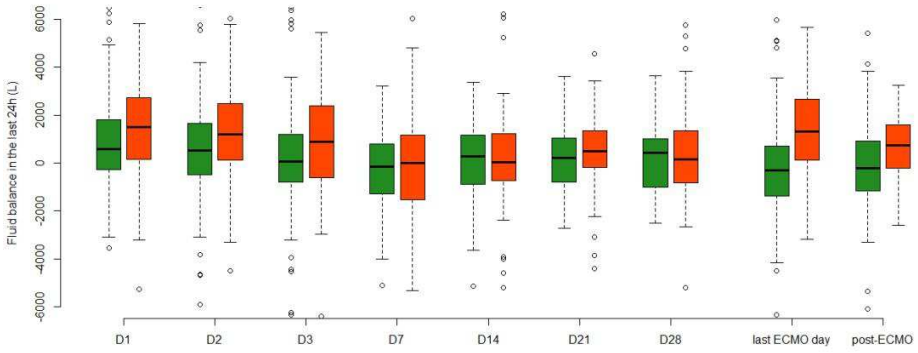

Figure E6: Median interquartile range of fluid balance during the ECMO course according to time and 6-month outcome.
Green boxplots represent ICU survivors whereas red boxplots are non-survivors

350x158mm (96 x 96 DPI)

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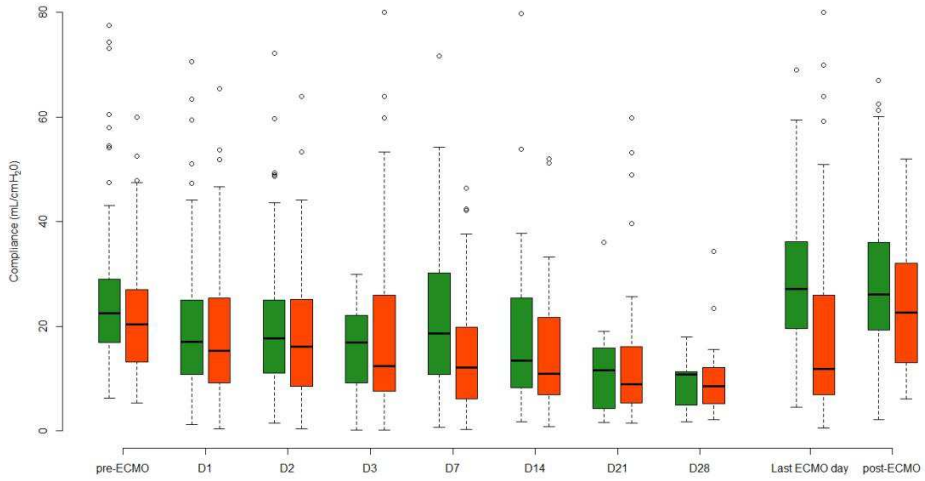

Figure E7: Median and interquartile range of static compliance observed during the ECMO course according to time and 6-month outcome.
Green boxplots represent ICU survivors whereas red boxplots are non-survivors
D=day

370x218mm (96 x 96 DPI)

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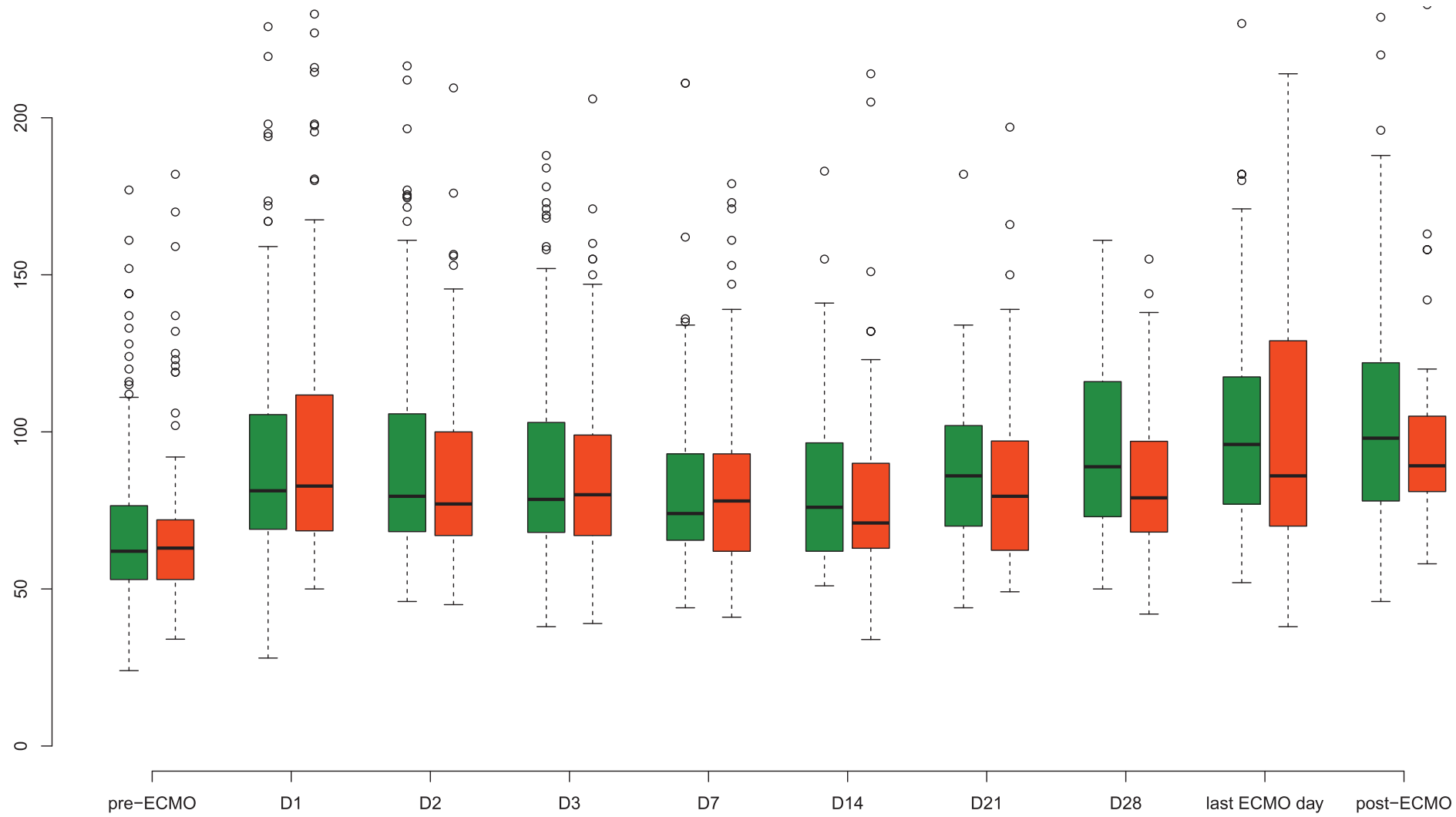

Fig E8

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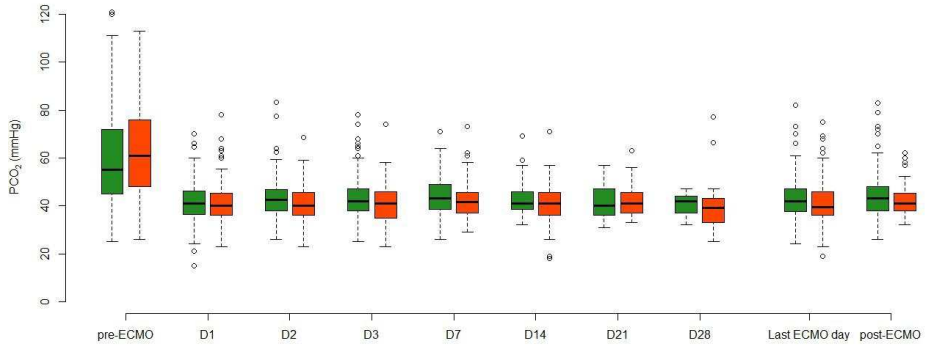

Figure E9: Median and interquartile range of PaCO2 obtained during the ECMO course according to time and 6-month outcome.
Green boxplots represent ICU survivors whereas red boxplots are non-survivors
D=day

350x158mm (96 x 96 DPI)

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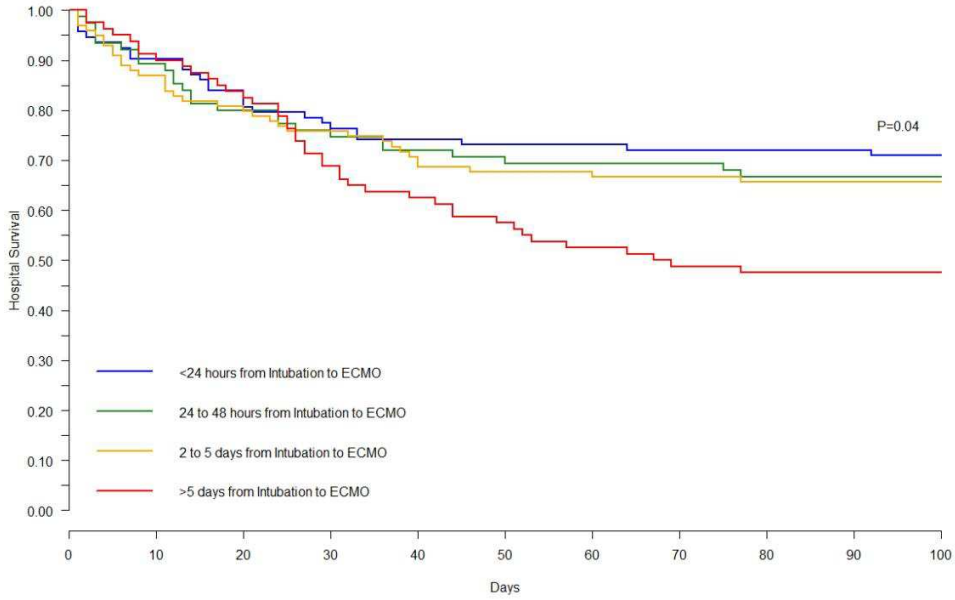

Figure E10: Kaplan–Meier survival estimates for ECMO-treated acute respiratory distress syndrome patients. according to the delayed time from endotracheal intubation to the initiation of ECMO

309x218mm (96 x 96 DPI)