

# Prediction of Long-Term Mortality in Acute Hypercapnic Respiratory Failure with Use of Low-Flow Veno-Venous Extracorporeal CO<sub>2</sub> Removal: A Retrospective Single-Center Study

Anne-Aylin Sigg Stefanie Keiser Shalimar Mila Konopasek  
Stephanie Klinzing Pedro David Wendel-Garcia Marco Maggiorini  
Reto Andreas Schuepbach Matthias Peter Hilty

Institute of Intensive Care Medicine, University Hospital of Zurich, Zurich, Switzerland

## Keywords

Extracorporeal CO<sub>2</sub> removal · Outcome · Hypercapnia · Acute respiratory distress syndrome · Chronic-obstructive pulmonary disease · Cystic fibrosis

## Abstract

**Introduction:** Hypercapnic respiratory failure is associated with high morbidity and mortality. Low-flow extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) has been shown to facilitate lung-protective ventilation or spontaneous breathing. However, three multicenter randomized trials have failed to show benefit which could potentially be a result of patient selection. In this study, we aimed to characterize prognostic scores developed for extracorporeal membrane oxygenation therapy which could potentially assist with the selection of patients for ECCO<sub>2</sub>R. **Methods:** A total of 70 patients admitted to the intensive care unit at the University Hospital of Zurich between 10/2009 and 02/2017 with hypercapnic respiratory failure were treated with ECCO<sub>2</sub>R if pH ≤ 7.25 and/or PaCO<sub>2</sub> ≥ 9 kPa experiencing respiratory exhaustion during spontaneous breathing in obstructive lung disease or reaching the limits of lung protective ventilation (*n* = 22 and *n* = 48) in patients with restrictive lung pathologies. Data including baseline

characteristics and respiratory parameters were collected prospectively. Scores were calculated retrospectively. **Results:** The underlying diseases were acute respiratory distress syndrome (*n* = 27), chronic-obstructive pulmonary disease (*n* = 12), bronchiolitis obliterans syndrome (BOS; *n* = 9), cystic fibrosis (*n* = 10), pulmonary fibrosis (*n* = 8), and other causes (*n* = 4). The 180-day mortality was 45.7% with the highest rate observed in PF and BOS patients as well as in patients who had been mechanically ventilated >6 days before initiation of ECCO<sub>2</sub>R. The modified PRedicting dEath for SEvere hypercapnic respiratory failure on vv-ECCO<sub>2</sub>R (PRESERVE-CO<sub>2</sub>) score differentiated well between survivors and non-survivors (4.3 ± 2.2 vs. 6.9 ± 2.6, *p* < 0.01), whereas the modified Respiratory ECMO Survival Prediction (RESP-CO<sub>2</sub>) score showed no significant distinction. Receiver operating characteristics analysis of the PRESERVE-CO<sub>2</sub> score revealed an area under the curve of 0.78, suggesting a cut-off of 7 points. **Conclusion:** Careful selection of patients for ECCO<sub>2</sub>R therapy may help to improve outcomes. The proposed PRESERVE-CO<sub>2</sub> score may serve as a guide. A score of 7 points or higher is associated with an unfavorable outcome regarding the 180-day mortality in the specific patient cohort of this study, but future studies to externally validate this score are required.

© 2026 The Author(s).  
Published by S. Karger AG, Basel

## Introduction

Hypercapnic respiratory failure in critically ill patients is associated with high morbidity and mortality. Two distinct disease groups are commonly linked to hypercapnic respiratory failure and can be broadly classified as restrictive and obstructive lung disease. The former primarily includes the juxtaposition of maximizing oxygenation and minimizing ventilator induced lung injury in early acute respiratory distress syndrome (ARDS) and the late phase of ARDS as well as less frequent interstitial pulmonary diseases, while the latter encompasses chronic-obstructive pulmonary disease (COPD), bronchiolitis obliterans syndrome (BOS) and other conditions. In both groups the primary treatment goal in the intensive care unit (ICU) is to implement a bridge-to-recovery strategy using the most appropriate technique. In ARDS and other restrictive pulmonary diseases, successful recovery largely depends on minimizing the negative effects of mechanical ventilation (MV), particularly ventilator induced lung injury [1]. In acute exacerbation of COPD or other pulmonary diseases with predominantly chronic disease course, recovery is heavily influenced by preventing neuromuscular deconditioning [2], which depends on the need and duration of sedation and MV [3].

However, balancing the risks and benefits of the treatment options, including MV, extracorporeal membrane oxygenation (ECMO) or low-flow extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R), remains challenging. Regarding ECCO<sub>2</sub>R, three multicenter randomized trials have failed to show an outcome benefit so far, potentially because of poor patient selection [4–6]. But tools for patient selection are missing for ECCO<sub>2</sub>R. Tools such as the PRedicting dEath for SEvere ARDS on vv-ECMO (PRESERVE) score [7, 8] and Respiratory ECMO Survival Prediction (RESP) [9, 10] score provide some guidance on ECMO use, but it remains unclear how to select patients for ECCO<sub>2</sub>R with predominantly hypercapnic respiratory failure. This issue is particularly relevant in case with predominantly hypercapnic respiratory failure where severe oxygenation deficits are absent such as in patients with exacerbation of COPD [11, 12]. These situations are not represented by the current scores, and it remains unclear whether existing scoring systems for ECMO are also applicable to predict outcome after ECCO<sub>2</sub>R treatment in patients suffering from hypercapnic respiratory failure.

In this study, we aimed to characterize prognostic scores developed for ECMO therapy which could potentially assist with the selection of patients for ECCO<sub>2</sub>R.

The two scores were modified to account for awake spontaneously breathing patients (PRESERVE-CO<sub>2</sub> and RESP-CO<sub>2</sub>) [13].

## Methods

All protocols and procedures conformed to the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee at the University of Zurich (BA SEC 2021-00912). Written informed consent for subsequent use of health-related data was obtained from patients and/or relatives as required.

### Study Population and Design

The study was conducted from October 2009 to February 2017 at a tertiary hospital in Zurich Switzerland. All patients treated with low-flow ECCO<sub>2</sub>R for hypercapnic respiratory failure within the study period were prospectively included and treatment data recorded. Modified PRESERVE and RESP scores (PRESERVE-CO<sub>2</sub> and RESP-CO<sub>2</sub> scores) were calculated retrospectively and their predictive power for 180-day mortality was tested. ECCO<sub>2</sub>R therapy was initiated in accordance with the clinical standard operating procedure and the decision of the attending ICU physician [2]. The clinical standard operating procedure defined the following criteria for progressive hypercapnic respiratory failure: (1) in an alert and spontaneously breathing patient, further referred to as awake patient, a pH  $\leq$  7.25 and/or PaCO<sub>2</sub>  $\geq$  9 kPa despite respiratory support with either nasal cannula, high flow oxygen therapy (HFOT) and/or noninvasive ventilation (NIV). (2) in an invasively ventilated patient a pH  $\leq$  7.25 and/or PaCO<sub>2</sub>  $\geq$  9 kPa while reaching the limits of lung protective ventilation. Lung protective ventilation was defined as tidal volumes  $\leq$  6 mL/kg ideal body weight, peak inspiratory pressure (P<sub>peak</sub>)  $\leq$  30 mbar, being a surrogate for inspiratory plateau pressure, driving pressure (dP)  $\leq$  15 mbar and respiratory rate (RR)  $\leq$  25/min. The first criterion was applied for patients with obstructive lung diseases whereas the second one exclusively for patients with restrictive lung diseases. In ARDS patients, we did not aim to achieve ultra-protective ventilation, similar to the publication of Combes et al. [14] in *Critical Care*.

ECCO<sub>2</sub>R therapy could be initiated either as a bridge to recovery or as a bridge to lung transplant. Discontinuation of ECCO<sub>2</sub>R treatment was performed either at recovery of hypercapnic respiratory failure, defined as a pH  $>$  7.25 and/or PaCO<sub>2</sub>  $<$  9 kPa with compensated

spontaneous breathing in awake patients or lung-protective ventilation in mechanically ventilated patients, at transfer to the operating theater for lung transplant, at upgrade to ECMO therapy or at death, respectively, withdrawal of life-sustaining therapy. Exclusion criteria for ECCO<sub>2</sub>R treatment were thrombocytopenia <100 G/L, contraindications for heparin therapy (such as previous bleedings or heparin antibodies), pregnancy and indication for ECMO therapy according the attending physician following the extracorporeal life support organization guidelines [15].

#### *ECCO<sub>2</sub>R and Respiratory Support Treatment Protocol*

ECCO<sub>2</sub>R treatment was performed using an ultrasound-guided established vascular access, preferably of the right internal jugular or left subclavian vein. Using Seldinger technique, a 13 French double lumen hemofiltration catheter was inserted with its tip positioned at the right atrium by real-time digital fluoroscopy imaging. Treatment with the peristaltic pump low-flow ECCO<sub>2</sub>R system (Prolung, Estor, Milan, Italy), equipped with a polypropylene gas-exchanger membrane, was initiated with a target blood flow of 400 mL/min and a flow of medical air of 10 L/min. Arterial, pre-membrane and post-membrane blood gas analysis were performed at t = 0 (before ECCO<sub>2</sub>R treatment initiation), 1, 4, 8, 16, 24 h, and every 24 h thereafter for the first 120 h of ECCO<sub>2</sub>R treatment. The results were recorded alongside ECCO<sub>2</sub>R blood and airflow rates and extracorporeal circuit pressures, respirator settings in mechanically or noninvasively ventilated patients, RR, heart rate, and mean arterial blood pressure. Anticoagulation was performed using an initial bolus of 5000 IU heparin, and continuous administration afterward with a target of systemic anti-factor Xa activity of 0.3–0.4 IU/mL. The anti-factor Xa activity was monitored every 24 h or every 6 h following any adjustment of heparin dose. Platelet count, plasma fibrinogen concentration, and international normalized ratio were monitored every 24 h.

In the awake group NIV, nasal HFOT, or oxygen supplementation via nasal cannula was additionally used for respiratory support. After establishment of ECCO<sub>2</sub>R treatment, the goal was to achieve respiratory compensation with a reduction of RR and clinically compensated work of breathing. ECCO<sub>2</sub>R airflow was down titrated after weaning of NIV and terminated after a 24-h period of respiratory compensation with reduced airflow. In case of worsening respiratory failure with either failure to reach respiratory compensation or progressive hypoxemia with systemic arterial hemoglobin oxygen

saturation <88% despite FiO<sub>2</sub> >90%, treatment was escalated by intubation and MV and/or veno-venous ECMO (vv-ECMO) [15].

Invasive MV (IMV) was performed using either Hamilton S1 (Hamilton medical, Bonaduz, Switzerland) or Evita IV (Dräger Medical, Lübeck, Germany) respirators. As ventilation modes either a bilevel positive airway pressure mode or Adaptive Support Ventilation® mode were used. After initiation of ECCO<sub>2</sub>R on t = 0, the primary aim was to reduce tidal volumes, Ppeak, dP, and RR within the first hour of treatment while maintaining PaCO<sub>2</sub> < 9 kPa and pH >7.25. ECCO<sub>2</sub>R airflow was down titrated according to pH level by the treating physician. Blood flow was only reduced if mandated by negative catheter inlet pressure. In case of failure to reach lung-protective ventilation or in case of progressive hypoxemia with systemic arterial hemoglobin oxygen saturation <88% with FiO<sub>2</sub> >90%, the treatment was either escalated using vv-ECMO or switched to comfort measures in accordance with the presumed wishes of the patient.

#### *Calculation of the Modified PRESERVE-CO<sub>2</sub> and RESP-CO<sub>2</sub> Scores*

The scores were calculated retrospectively based on values before initiation of ECCO<sub>2</sub>R. For the representation of non-intubated patients with the PRESERVE score and the RESP score the scores were modified accordingly and named PRESERVE-CO<sub>2</sub> score and RESP-CO<sub>2</sub> score (Tables 1, 2). In the PRESERVE-CO<sub>2</sub> score, in the non-intubated patients the criteria for the duration of MV and plateau pressure were scored zero points. The PEEP value was derived from NIV, and for patients receiving HFOT, a PEEP value below 10 mbar was assumed. There were three points assigned for respiratory exhaustion due to hypercapnic respiratory failure, which is the leading cause of intubation in these patients. Accordingly, the total score remained unchanged between the modified and the original version of the PRESERVE score.

Regarding the RESP-CO<sub>2</sub> score for the non-intubated patient the criteria for neuromuscular blockade, inhalative nitric oxide (iNO) and duration of IMV as well as Ppeak ≥42 mbar was scored zero point. For respiratory exhaustion, due to hypercapnic respiratory failure 3 points were added. Accordingly, the total score remained unchanged between the modified and the original version.

#### *Statistical Analysis*

Patient characteristics, respiratory variables, and blood gas measurements were compared between different time points and between treatment protocols

**Table 1.** PRESERVE Score and modification predicting outcomes in patients receiving ECCO<sub>2</sub>R therapy

| Parameter                                                     | PRESERVE score for mechanical ventilated patients at the time of ECCO <sub>2</sub> R insertion | Modified PRESERVE score (PRESERVE-CO <sub>2</sub> ) for awake patients at the time of ECCO <sub>2</sub> R insertion |
|---------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Age <45 years                                                 | 0                                                                                              |                                                                                                                     |
| Age 45–55 years                                               | 2                                                                                              |                                                                                                                     |
| Age >55 years                                                 | 3                                                                                              |                                                                                                                     |
| Body mass index >30                                           | –2                                                                                             |                                                                                                                     |
| Immunocompromised                                             | 2                                                                                              |                                                                                                                     |
| SOFA >12                                                      | 1                                                                                              |                                                                                                                     |
| No prone positioning before ECCO <sub>2</sub> R               | 1                                                                                              |                                                                                                                     |
| MV >6 days                                                    | 1                                                                                              | (0)                                                                                                                 |
| PEEP <10 mbar                                                 | 2                                                                                              | 2                                                                                                                   |
| Plateau pressure >30 cm H <sub>2</sub> O                      | 2                                                                                              | (0)                                                                                                                 |
| Respiratory exhaustion due to hypercapnic respiratory failure | 0                                                                                              | 3                                                                                                                   |

Scoring parameters used to calculate the PRESERVE score and the modified PRESERVE score (PRESERVE- CO<sub>2</sub>) are shown. The PRESERVE score originally developed for mechanical ventilated patients was modified to allow scoring of awake, spontaneously breathing patients. Parameters in parentheses (0) are not applicable and therefore excluded in the modified score. ECCO<sub>2</sub>R, extracorporeal CO<sub>2</sub> removal; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; PRESERVE-CO<sub>2</sub>, modified Predicting death for severe ARDS on vv-ECMO score; SOFA, Sequential Organ Failure Assessment.

and 180-day mortality using one- or two-way linear mixed effect model analysis [16] with the effect in question entered as fixed effects and intercepts for subjects and per-subject random slopes representing the effect on the dependent variables entered as random effects. *p* values were calculated using a likelihood ratio test of the full model with the effect in question against a “null model” that lacks the effect in question [17]. *p* values for individual fixed effects were obtained via the Satterthwaite approximation [18]. The Shapiro-Wilk test was used to test for normal distribution (online suppl. Fig. S2; for all online suppl. material, see <https://doi.org/10.1159/000550776>). For the variables deviating significantly from the normal distribution (online suppl. Table S1), the median (IQR) is reported in Tables 3 and 4. Cut-offs to maximize sensitivity and specificity of the PRESERVE-CO<sub>2</sub> and RESP-CO<sub>2</sub> scores regarding the 180-day mortality were determined via receiver operating characteristics (ROC) curves. The 180-day mortality was compared between patients with high and low scores using a Cox proportional hazards model. A two-sided *p* < 0.05 was considered statistically significant. A competing risk analysis according to the methodology described in detail by Scrucca et al. [19] was performed using the R package “casebase,” version 0.10.6.

Alluvial flow diagrams were used to visualize multi-variable interrelations between categorical treatment variables and outcomes. Fully scripted and reproducible data management pathways within the R environment for statistical computing, version 4.4.2 [20] were used for all statistical analyses. Values are specified as the mean ± standard deviation or median (interquartile range), as appropriate.

## Results

### Patient Characteristics

A total of 70 patients with ECCO<sub>2</sub>R were included in the study, 22 of these patients were awake and 48 were on IMV. The etiology for respiratory failure was ARDS (*n* = 27), COPD (*n* = 12), cystic fibrosis (CF) (*n* = 10), BOS after lung transplantation (*n* = 9), pulmonary fibrosis (PF) (*n* = 8), and others (*n* = 4). The latter included exacerbated bronchial asthma and obesity hypoventilation syndrome (Table 3). The patients suffering from ARDS could be separated in two groups: primary ARDS from pneumonia (*n* = 18) and secondary ARDS postoperative (*n* = 2), due to sepsis (*n* = 4) or due to a hematologic neoplasia (*n* = 3). The overall 180-day

**Table 2.** RESP Score and modification predicting outcomes in patients receiving ECCO<sub>2</sub>R therapy

| Parameter                                                     | RESP score for mechanical ventilated patients at the time of ECCO <sub>2</sub> R insertion | Modified RESP score (RESP- CO <sub>2</sub> ) for awake patients at the time of ECCO <sub>2</sub> R insertion |
|---------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Age 18–49 years                                               | 0                                                                                          |                                                                                                              |
| Age 50–59 years                                               | –2                                                                                         |                                                                                                              |
| Age ≥60 years                                                 | –3                                                                                         |                                                                                                              |
| Immunocompromised                                             | –2                                                                                         |                                                                                                              |
| Acute respiratory diagnosis group                             |                                                                                            |                                                                                                              |
| Viral pneumonia                                               | 3                                                                                          |                                                                                                              |
| Bacterial pneumonia                                           | 3                                                                                          |                                                                                                              |
| Asthma                                                        | 11                                                                                         |                                                                                                              |
| Trauma and burn                                               | 3                                                                                          |                                                                                                              |
| Aspiration pneumonitis                                        | 5                                                                                          |                                                                                                              |
| Other acute respiratory diagnosis                             | 1                                                                                          |                                                                                                              |
| Non-respiratory or chronic respiratory diagnosis              | 0                                                                                          |                                                                                                              |
| CNS dysfunction                                               | –7                                                                                         |                                                                                                              |
| Acute non-pulmonary infection                                 | –3                                                                                         |                                                                                                              |
| HCO <sub>3</sub> infusion                                     | –2                                                                                         |                                                                                                              |
| Cardiac arrest                                                | –2                                                                                         |                                                                                                              |
| PaCO <sub>2</sub> ≥75 mm Hg                                   | –1                                                                                         |                                                                                                              |
| Neuromuscular blockade                                        | 1                                                                                          | (0)                                                                                                          |
| iNO                                                           | –1                                                                                         | (0)                                                                                                          |
| MV <48 h                                                      | 3                                                                                          | (0)                                                                                                          |
| MV 48 h to 7 days                                             | 1                                                                                          | (0)                                                                                                          |
| MV >7 days                                                    | 0                                                                                          | (0)                                                                                                          |
| Ppeak ≥42 cm H <sub>2</sub> O                                 | –1                                                                                         | (0)                                                                                                          |
| Respiratory exhaustion due to hypercapnic respiratory failure | 0                                                                                          | 3                                                                                                            |

This table outlines the original RESP score, used in mechanically ventilated patients at the time of ECCO<sub>2</sub>R initiation and the modified version (RESP-CO<sub>2</sub> score) adapted for awake patients. The modified score omits parameters that are not applicable to awake patients and incorporates an additional point for hypercapnic respiratory failure (3 points). CNS, central nervous system; ECCO<sub>2</sub>R, extracorporeal CO<sub>2</sub> removal; iNO, inspiratory nitric oxide; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; RESP-CO<sub>2</sub>, modified Respiratory ECMO Survival Prediction score.

mortality of the patients was 45.7%. Mortality was 75% for patients with PF, 67% for BOS and 10% for CF patients. A total of 12 patients underwent lung transplantation, one of each suffering from COPD, BOS, and PF and 9 patients with CF.

#### *Clinical Pathways and Outcome of Patients Undergoing ECCO<sub>2</sub>R Therapy*

The clinical courses of the individual patients are illustrated in Figure 1. Figure 1a depicts patient's trajectories from initial diagnosis, ECCO<sub>2</sub>R protocol and

bridging strategy to weaning success or withdrawal of life support therapy. The survivors are shown in turquoise, the non-survivors in red.

In all ARDS patients, ECCO<sub>2</sub>R was implemented with the intention of bridge to recovery but resulted in a 180-day mortality of 59%. In total, 93% (25/27) ARDS patients were mechanically ventilated at the time point of ECCO<sub>2</sub>R implementation. The 2 awake ARDS patients presented clinically primarily with hypercapnic failure in addition to hypoxia, one suffering from a fungal pneumonia, the other from pulmonary sepsis associated

**Table 3.** Patient characteristics and preexisting or acute pulmonary conditions in ECCO<sub>2</sub>R patients

|                                                 | All patients | Awake patients      | Invasively ventilated patients | Estimates ± SE (95% CI) | Survivors           | Non-survivors       | Estimates ± SE (95% CI) | p value         |
|-------------------------------------------------|--------------|---------------------|--------------------------------|-------------------------|---------------------|---------------------|-------------------------|-----------------|
| <i>Patient characteristics</i>                  |              |                     |                                |                         |                     |                     |                         |                 |
| N (%)                                           | 70 (100.0)   | 22 (31.4)           | 48 (68.6)                      |                         | 38 (54.3)           | 32 (45.7)           |                         |                 |
| Age, mean (IQR), years                          | 56.0 (16.9)  | 48.45 (29.44–63.23) | 64.23 (54.67–67.04)            | –                       | 55.76 (40.85–66.08) | 64.59 (54.67–67.84) | –                       | <b>0.07</b>     |
| Weight, mean (IQR), kg                          | 70.7 (23.7)  | 60 (45.75–68.5)     | 70.5 (62–83.5)                 | –                       | 65 (48.25–80)       | 70 (62–79.25)       | –                       | 0.32            |
| Height, mean (SD), cm                           | 169 (8)      | 165 (8)             | 171 (8)                        | 6±2 (2–10)              | 168 (9)             | 171 (8)             | 3±2 (–1–7)              | 0.19            |
| Sex (male), n (%)                               | 45 (64.3)    | 10 (45.5)           | 35 (72.9)                      | 3.2±1.7 (1.1–9.5)       | 20 (52.6)           | 25 (78.1)           | 3.2±1.7 (1.2–9.7)       | <b>0.02</b>     |
| <i>Preexisting conditions</i>                   |              |                     |                                |                         |                     |                     |                         |                 |
| Previous CNS condition = none, n (%)            | 70 (100.0)   | 22 (100.0)          | 48 (100.0)                     | 1                       | 38 (100.0)          | 32 (100.0)          | 1                       | 1               |
| Immunosuppression, n (%)                        | 26 (37.1)    | 7 (31.8)            | 19 (39.6)                      | 1.4±1.72 (0.5–4.3)      | 13 (34.2)           | 13 (40.6)           | 1.32±1.6 (0.5–3.5)      | 0.58            |
| <i>Preexisting or acute pulmonary condition</i> |              |                     |                                |                         |                     |                     |                         |                 |
| Chronic-obstructive pulmonary disease, n (%)    | 12 (17.1)    | 4 (18.2)            | 8 (16.7)                       | 0.9±2.0 (0.3–3.7)       | 10 (26.3)           | 2 (6.2)             | 0.2±2.3 (0.0–0.8)       | <b>0.02</b>     |
| Cystic fibrosis, n (%)                          | 10 (14.3)    | 9 (40.9)            | 1 (2.1)                        | 0.0±3 (0–0.2)           | 9 (23.7)            | 1 (3.1)             | 0.1±3.0 (0.0–0.6)       | <b>&lt;0.01</b> |
| Pulmonary fibrosis, n (%)                       | 8 (11.4)     | 1 (4.5)             | 7 (14.6)                       | 3.6±3.0 (0.6–69.3)      | 2 (5.3)             | 6 (18.8)            | 4.2±2.4 (0.9–29.9)      | 0.07            |
| Bronchiolitis obliterans, n (%)                 | 9 (12.9)     | 5 (22.7)            | 4 (8.3)                        | 0.3±2.1 (0.1–1.3)       | 3 (7.9)             | 6 (18.8)            | 2.7±2.1 (0.7–13.7)      | 0.18            |
| ARDS, n (%)                                     | 27 (38.6)    | 2 (9.1)             | 25 (52.1)                      | 10.9±2.2 (2.8–72.9)     | 11 (28.9)           | 16 (50.0)           | 2.5±1.7 (0.9–6.7)       | 0.07            |
| Others, n (%)                                   | 4 (5.7)      | 1 (4.5)             | 3 (6.2)                        |                         | 3 (7.9)             | 1 (3.1)             |                         |                 |

with an unknown, non-malignant stenotic process in the lung. Both patients survived.

Regarding the patients with PF ECCO<sub>2</sub>R was initiated with the intention of bridge to transplantation in 25% of the patients, these patients all survived. In total, 180-day survival was 25%. Seven of the 8 patients were on IMV.

In all but one COPD patients, ECCO<sub>2</sub>R was initiated with the intention of bridge to recovery. In total, 12 patients with COPD were included. In total, 8 of 12 with the intention of rapid weaning after intubation for MV and 4 of them with the intention to support spontaneous breathing and avoid intubation. Ac-

cording to ECCO<sub>2</sub>R treatment intention, ECCO<sub>2</sub>R treatment duration was 2.1 ± 1.6 days and 8.0 ± 5.1 days, respectively. ECCO<sub>2</sub>R weaning was successful in 10 out of 12 patients and these patients survived 180 days. ECCO<sub>2</sub>R was initiated with the intention of bridge to transplant in all 10 patients with CF. Only one patient was invasively ventilated at that time point. A total of 9 patients were bridged successfully to transplantation, one patient died before transplantation due to a septic shock.

Figure 1b shows secondary airway up- and downgrade as well as the need for secondary upgrade to vv-ECMO. While on ECCO<sub>2</sub>R 9 patients needed intubation for IMV

**Table 4.** Physiological status and treatment-associated factors at the start of ECCO<sub>2</sub>R treatment and outcome with survival time and 180-day mortality

|                                                                       | All patients | Awake patients        | Invasively ventilated patients | Estimates ± SE (95% CI)      | Survivors              | Non-survivors       | Estimates ± SE (95% CI) | p-value         |
|-----------------------------------------------------------------------|--------------|-----------------------|--------------------------------|------------------------------|------------------------|---------------------|-------------------------|-----------------|
| <i>Physiological status at ECCO<sub>2</sub>R treatment start</i>      |              |                       |                                |                              |                        |                     |                         |                 |
| SOFA score, mean (IQR)                                                | 8.4 (4.3)    | 3 (3–6)               | 9 (7–12)                       | –                            | 7 (3–10)               | 9 (7–12.25)         | –                       | <b>&lt;0.01</b> |
| SAPS score, mean (SD)                                                 | 46 (21)      | 29 (16)               | 53 (18)                        | 24±5 (15–33)                 | 39 (22)                | 54 (16)             | 15±5 (6–25)             | <b>&lt;0.01</b> |
| PRESERVE-CO <sub>2</sub> score (SD)                                   | 5.51 (2.7)   | 3.67 (2.2)            | 6.34 (2.5)                     | 2.67±0.63 (1.4–3.9)          | 4.28 (2.7)             | 6.91 (2.6)          | 2.63±0.58 (1.5–3.8)     | <b>&lt;0.01</b> |
| RESP-CO <sub>2</sub> score                                            | –0.97 (3.4)  | 0.19 (3.3)            | –1.49 (3.4)                    | –1.68±0.88 (–3.4–0.1)        | –0.22 (3.3)            | –1.81 (3.4)         | –1.5±0.82 (–3.2–0.01)   | 0.05            |
| Mechanically ventilated before ECCO <sub>2</sub> R [days], mean (IQR) | 6.5 (7.9)    | –                     | 3 (1–10)                       | –                            | 0 (0–1)                | 3 (0–10.25)         | –                       | <b>&lt;0.01</b> |
| Prone positioning before ECCO <sub>2</sub> R, n (%)                   | 4 (6)        | –                     | 4 (8)                          | –                            | 0 (0)                  | 4 (13)              | –                       |                 |
| Neuromuscular blockade before ECCO <sub>2</sub> R, n (%)              | 7 (10.1)     | –                     | 7 (14.9)                       | –                            | 4 (10.8)               | 3 (9.4)             | 0.9±2.2 (0.2–4.2)       | 0.84            |
| iNO before ECCO <sub>2</sub> R, n (%)                                 | 21 (30.0)    | –                     | 21 (43.8)                      | –                            | 8 (21.1)               | 13 (40.6)           | 2.57±1.7 (0.9–7.6)      | 0.07            |
| PEEP [mbar], mean (SD)                                                | 8.0 (3.1)    | 6.0 (1.1)             | 8.5 (3.2)                      | 2.5±1.1 (0.4–4.7)            | 8.14 (3.1)             | 7.91 (3.13)         | –0.23±0.94 (–2.1–1.6)   | 0.81            |
| Ppeak [mbar], mean (IQR)                                              | 30.5 (6.9)   | 18 (15.75–24)         | 32 (30–35)                     | –                            | 29 (25–33)             | 32 (31.75–35)       | –                       | <b>0.02</b>     |
| P/F ratio [mm Hg], mean (IQR)                                         | 169 (95)     | 232.1 (171.69–314.37) | 128.08 (92.1–173.5)            | –                            | 173.86 (102.19–234.18) | 133.85 (105–166.31) | –                       | 0.24            |
| Ventilatory ratio, mean (SD)                                          | 3.58 (1.4)   | 3.17 (1.5)            | 3.66 (1.4)                     | 0.49±0.52 (–0.5–1.5)         | 3.04 (1.5)             | 4.05 (1.2)          | 1.01±0.36 (0.3–1.7)     | <b>&lt;0.01</b> |
| PaCO <sub>2</sub> [kPA], mean (SD)                                    | 9.08 (2.0)   | 9.47 (2.3)            | 8.92 (1.9)                     | –0.56±0.53 (–1.6–0.5)        | 8.92 (2.3)             | 9.27 (1.7)          | 0.35±0.49 (–0.6–1.3)    | 0.47            |
| HCO <sub>3</sub> [mmol/L], mean (SD)                                  | 30.0 (6.8)   | 33.9 (8.0)            | 28.3 (5.5)                     | –5.6±1.7 (–8.9 to –2.4)      | 31.4 (6.8)             | 28.4 (6.7)          | –3.0±1.6 (–6.2–0.2)     | 0.06            |
| <i>Outcome</i>                                                        |              |                       |                                |                              |                        |                     |                         |                 |
| Survival time [days], mean (SD)                                       | 104.0 (84.2) | 145.5 (66.9)          | 85.0 (85.1)                    | –60.6±20.6 (–100.9 to –20.3) |                        |                     |                         |                 |
| 180-day mortality, n (%)                                              | 32 (45.7)    | 5 (22.7)              | 27 (56.2)                      | 3.3±1.6 (1.3–8.5)            |                        |                     |                         |                 |

and 2 patients could be extubated after implementation of ECCO<sub>2</sub>R.

In total, 22.9% (16/70) of the patients needed an upgrade from ECCO<sub>2</sub>R to vv-ECMO. Only 2 of these patients were not invasively ventilated, both were CF patients. Of the vv-ECMO patients, 9 patients were successfully transplanted, 2 recovered and in 5 patients withdrawal of life sustaining therapy was performed. Additionally, we have calculated a combined secondary endpoint "ECCO<sub>2</sub>R success," excluding all patients that have either needed an upgrade to vv-ECMO, have not reached the goal of avoiding intubation, or have died during treatment. Successful bridge-to-transplant was considered ECCO<sub>2</sub>R success. This combined endpoint of ECCO<sub>2</sub>R success was reached in 27/70 patients.

#### *Treatment-Associated Factors and Predictive Value of the PRESERVE-CO<sub>2</sub> and RESP-CO<sub>2</sub> Scores*

Physiological status as well as treatment-associated factors is shown in Table 4 for IMV as well as awake patients. Before initiation of ECCO<sub>2</sub>R SOFA and SAPS scores were significantly ( $p < 0.0001$ ) lower in the awake than in the IMV group. HCO<sub>3</sub> was significantly higher in awake patients (mean 33.9 versus 28.3 mmol/L,  $-5.6 \pm 1.7$  ( $-8.9$  to  $-2.4$ )). Before initiation of ECCO<sub>2</sub>R IMV was performed for a median of 6.5 days. SOFA as well as SAPS Score correlated with survival. IMV duration before ECCO<sub>2</sub>R initiation as well as prone positioning was associated with mortality, whereas neither neuromuscular blockade nor iNO before ECCO<sub>2</sub>R showed an association. Awake patients on NIV had a significantly lower PEEP, Ppeak and P/F ratio. Mean ventilatory ratio, as an assessment of efficiency of ventilation [21], was not statistically different in between the two groups at ECCO<sub>2</sub>R initiation but significantly different between survivors and non-survivors ( $p < 0.01$ ). Also, Ppeak was statistically significant regarding survival. The survival time for awake ECCO<sub>2</sub>R patients was significantly longer with  $145.5 \pm 66.9$  days in comparison to mechanically ventilated patients with  $85.0 \pm 85.1$ . The 180-day mortality was significantly lower in the awake versus the IMV group (22.7% vs. 56.2%).

The PRESERVE-CO<sub>2</sub> score was significantly higher in the ventilation group, whereas there was no significant difference in the RESP-CO<sub>2</sub> score. Regarding 180-day mortality the PRESERVE-CO<sub>2</sub> score differentiated well between survivors and non-survivors ( $4.3 \pm 2.7$  vs.  $7.0 \pm 2.6$ ,  $p < 0.01$ ), while the RESP-CO<sub>2</sub> score did not ( $-1.5 \pm 0.82$  ( $-3.2$  to  $0.01$ ),  $p = 0.05$ ).

ROC analysis revealed an area under the curve of 0.78 and 0.66, suggesting a cut-off of 7 for the PRESERVE-

CO<sub>2</sub> score and 0 for the RESP-CO<sub>2</sub> score (Fig. 2a) to differentiate 180-day mortality. The Kaplan-Meier curves discriminate patients with PRESERVE-CO<sub>2</sub> score  $\geq 7$  points versus  $< 7$  points (Fig. 2b). The survival probability rapidly falls in patients with equal or more than seven points in the PRESERVE-CO<sub>2</sub> score within the first days of ICU treatment.

The competing risk analysis yielded 26 events (death), 32 censorings (survival), and 12 competing events (transplantation). For the PRESERVE-CO<sub>2</sub> score  $\geq 7$ , a hazard ratio of 5.09 was found for prediction of mortality ( $p < 0.0001$ ), considering lung transplantation as a competing risk (online suppl. Fig. S1).

#### *Adverse Events*

One patient developed a heparin-induced thrombocytopenia, and the anticoagulation was switched to bivalirudin (Angiox®). There was one catheter-related thrombosis and a non-catheter-related bleeding in a different patient.

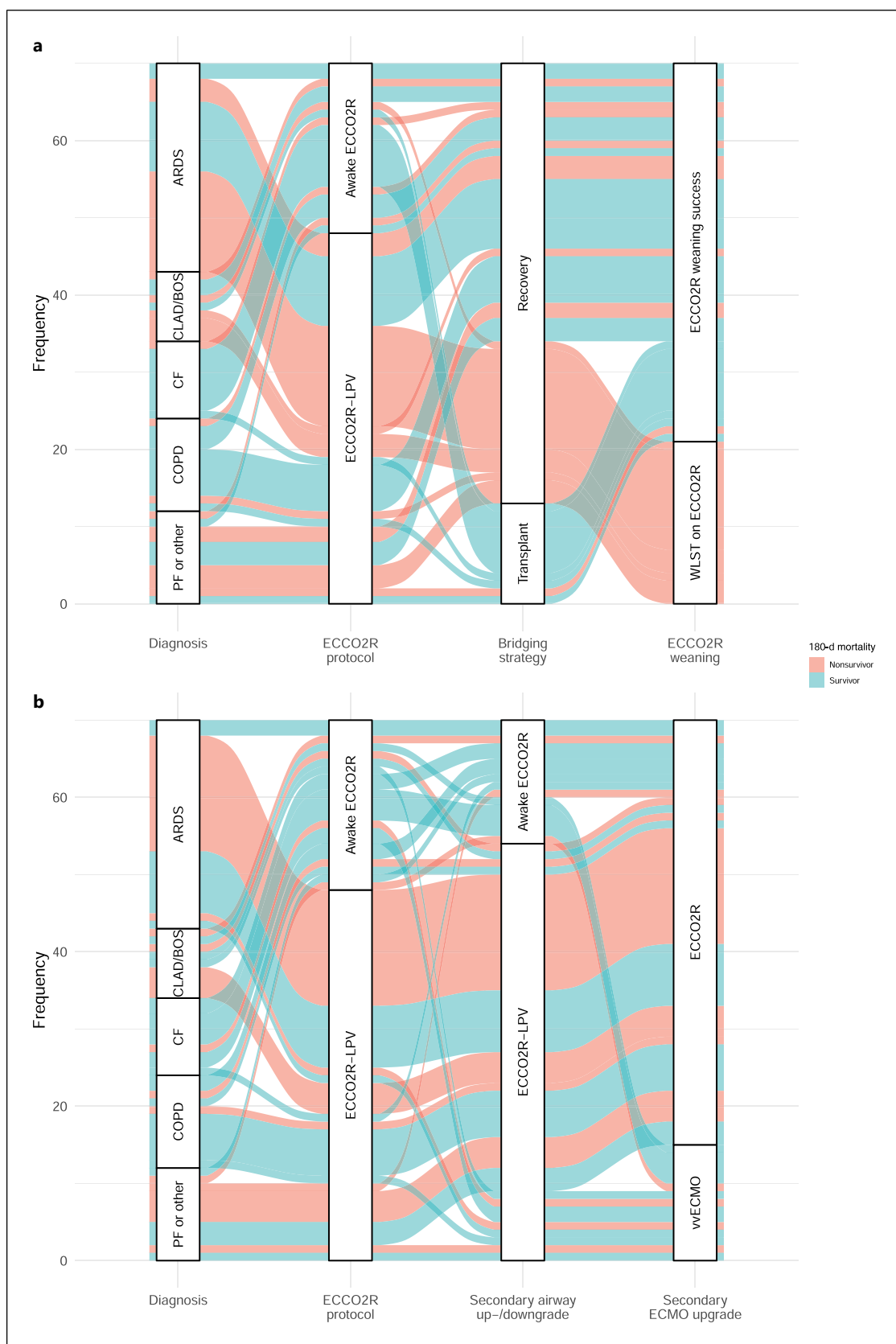
#### **Discussion**

Hypercapnic respiratory failure in critically ill patients remains associated with a high morbidity and mortality. Severe hypercapnia leads to systemic microvascular vasodilation resulting in increased cerebral blood flow and elevated intracranial pressure. Within the pulmonary circulation, hypercapnia induces vasoconstriction, thereby worsening ventilation-perfusion mismatch [22].

Unlike ECMO which supports oxygenation and ventilation ECCO<sub>2</sub>R exclusively removes CO<sub>2</sub>. In contrast to hypoxic respiratory failure, prone positioning and iNO are well established rescue strategies nothing similar exists for hypercapnic respiratory failure [23].

ECCO<sub>2</sub>R is used in clinical practice as bridge to recovery but also as bridge to transplant in selected patients. But to date, no validated scoring system exists to guide patient selection, particularly in awake, spontaneously breathing patients. However, proper patient selection is crucial to minimize poor outcomes and unnecessary therapies. Existing prognostic tools such as the PRESERVE and RESP scores [8–10, 24] were developed for intubated patients with ARDS requiring vv-ECMO therapy and are not applicable in awake spontaneously breathing patients with primarily hypercapnic respiratory failure.

Our study demonstrates that a modified version of the PRESERVE score, the PRESERVE-CO<sub>2</sub> score, can



(For legend see next page.)

predict long-term outcomes prior to ECCO<sub>2</sub>R initiation. Specifically, patients with a PRESERVE-CO<sub>2</sub> score  $\geq 7$  exhibited a 180-day mortality rate exceeding 70%, whereas those with a score  $< 7$  had a mortality of  $< 30\%$ . This clear discrimination suggests that the PRESERVE-CO<sub>2</sub> score may be a valuable tool for guiding clinical decision making regarding ECCO<sub>2</sub>R candidacy.

Interestingly the ROC analysis identified an optimal cut-off of 7 points, consistent with the original PRESERVE score, which was internally and externally [8] validated for prediction of 180-day mortality in patients treated with vv-ECMO for severe ARDS [9]. However, the original PRESERVE score includes variables not applicable in spontaneously breathing patients – such as duration of MV, prone positioning, PEEP, and plateau pressure – making it necessary to modify the score for our target population. This is particularly relevant for patient groups, such as those with severe COPD exacerbation, in whom intubation often leads to prolonged MV, muscle wasting and difficult to wean situation. For such patients, a robust selection tool for initiation of ECCO<sub>2</sub>R is crucial.

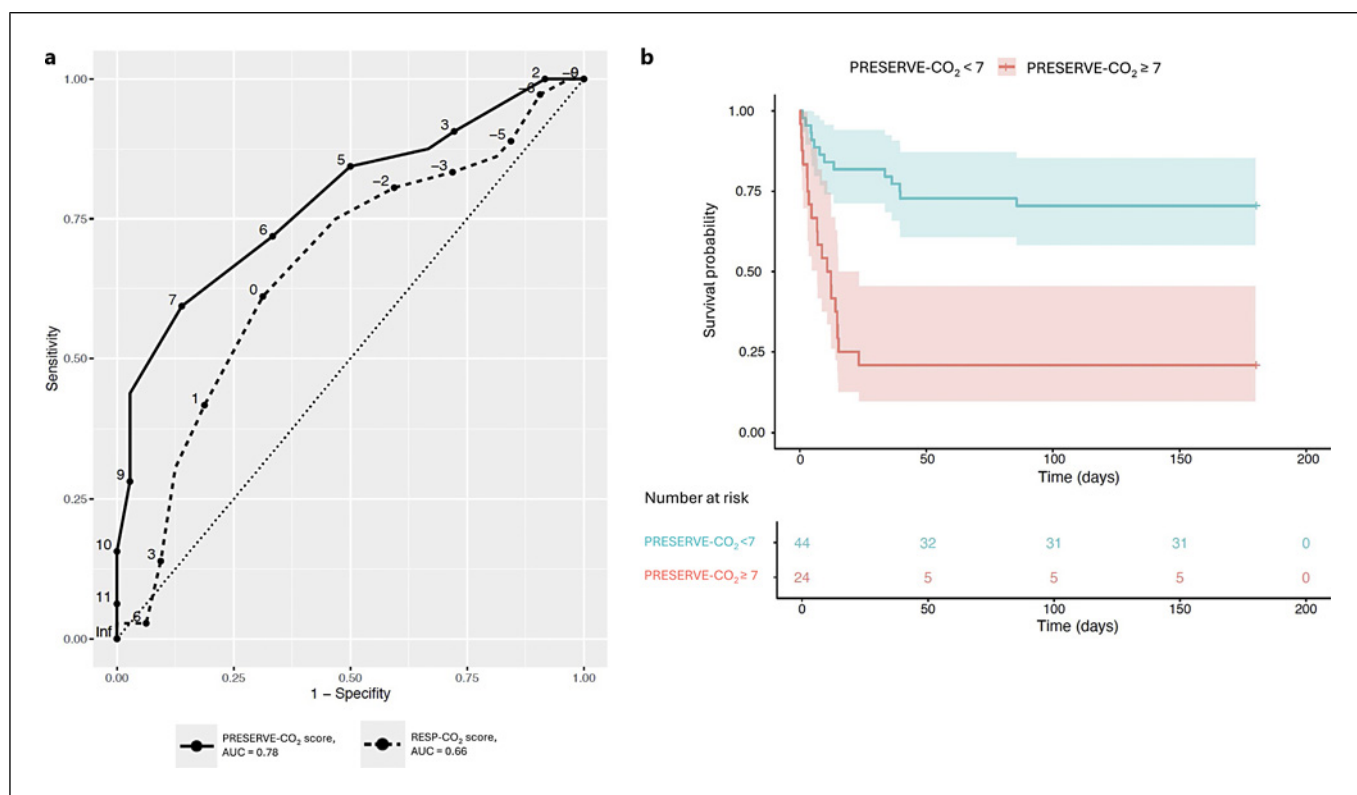
The RESP score was developed to address limitations of the PRESERVE score [10] and includes the respiratory diagnosis, central nervous system dysfunction, non-pulmonary infections, cardiac arrest, neuromuscular blockade, iNO use, bicarbonate use as well as PaCO<sub>2</sub>. The modification of the RESP score, the RESP-CO<sub>2</sub> score did not differentiate between survivors and non-survivors in our study. A possible explanation is that several diagnoses that often lead to primarily hypercapnic respiratory failure, such as COPD, CF, and PF, are not represented in the score. Instead, the diagnoses included in the RESP score primarily lead to hypoxemic respiratory failure. Although the concept of ECCO<sub>2</sub>R was proposed early in the development of extracorporeal support technologies, so far the three performed multicenter trials with more than 500 patients failed to show an outcome benefit or even showed signals of harm in the subgroup undergoing NIV and regarding rate of intracranial hemorrhage [4–6].

Therefore, the ESICM guideline recommend against ECCO<sub>2</sub>R treatment in ARDS outside of clinical trials [23, 25]. But there are some limitations in these studies. First, the device used in the Xtravent trial was a passive arteriovenous device and is not comparable with current devices that are low-flow, veno-venous and use a peristaltic roller pump [5]. This development may lead to a reduction of adverse events due to less coagulation activation [26]. Second, a nonselective population of ARDS patients was included in these trials, but a reduction of VT physiologically benefits only a specific patient group, the group with low respiratory system compliance [6]. A sub-analysis of the REST trial population showed a positive effect on mortality of ECCO<sub>2</sub>R treatment in these patients [27]. Further on the use of ECCO<sub>2</sub>R was limited to tertiary hospitals [28, 29]. However, the risk-benefit ratio remains the core challenge and careful patient selection is the key [14, 30, 31]. As the guidelines state, more research is desperately needed and an individualized approach to ECCO<sub>2</sub>R treatment seems justified.

Our data confirms a high mortality in ARDS patients treated with ECCO<sub>2</sub>R. ECCO<sub>2</sub>R does not address hypoxia a hallmark sign of early ARDS but addresses the core problem of ARDS the limited lung compliance. ECCO<sub>2</sub>R allows lung-protective ventilation despite the reduced lung compliance and leads to less application of mechanical power to the sick lung [32]. Additionally, ARDS patients often suffer from multi-organ failure, while ECCO<sub>2</sub>R like ECMO is most beneficial in cases with isolated respiratory failure [30, 33]. This is supported by our findings showing favorable outcomes in patients with hypercapnic respiratory failure due to COPD and as a bridging to lung transplant strategy in patients with CF. However, with the CF transmembrane conductance regulator modulator therapies cases of severe respiratory failure are becoming increasingly rare in this patient group [34, 35]. In our study the number of complications related to ECCO<sub>2</sub>R was low in contrary to other recent studies having intracranial hemorrhage in 4.5% of the patients [6] or the high

**Fig. 1.** Alluvial plots illustrating clinical trajectories of patients undergoing ECCO<sub>2</sub>R panels (a) and (b) show patient trajectories over different stages of care and clinical decision points associated with ECCO<sub>2</sub>R. Each horizontal axis represents a categorical clinical variable; the width of the flow corresponds to the number of patients. Flow color indicates 180-day mortality (red for non-survivors and blue for survivors). **a** shows the trajectories from the diagnosis to ECCO<sub>2</sub>R therapy, bridging strategy to the weaning outcome, respectively, withdrawal of life-sustaining therapy.

**b** shows details of the clinical course such as secondary airway escalation or de-escalation and upgrade to vv-ECMO. ECCO<sub>2</sub>R, extracorporeal CO<sub>2</sub> removal; vv-ECMO, veno-venous extracorporeal membrane oxygenation; ECCO<sub>2</sub>R-LPV, extracorporeal CO<sub>2</sub> removal extended lung-protective ventilation; ARDS, acute respiratory distress syndrome; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; PF, pulmonary fibrosis; WLST, withdrawal of life-sustaining therapy.



**Fig. 2.** Performance and prognostic value of the PRESERVE-CO<sub>2</sub> and the RESP-CO<sub>2</sub> Score for patients with ECCO<sub>2</sub>R. **a** Receiver operating characteristic (ROC) curves comparing the PRESERVE-CO<sub>2</sub> score and the RESP-CO<sub>2</sub> score. The area under the curve was higher for the PRESERVE-CO<sub>2</sub> score with an optimal cut-off of 7 points. **b** Kaplan-Meier curves stratified by the PRESERVE-CO<sub>2</sub> score cut-off of 7 points. Patients with a PRESERVE-CO<sub>2</sub> score ≥7 points (red curve) had significantly

lower survival compared to those with scores <7 (blue curve). A clear discrimination can be seen within the first days of ICU treatment. AUC, area under the curve; ECCO<sub>2</sub>R, extracorporeal CO<sub>2</sub> removal; ICU, intensive care unit; PRESERVE-CO<sub>2</sub>, modified Predicting death for severe ARDS on vv-ECMO score; RESP-CO<sub>2</sub>, modified Respiratory ECMO Survival Prediction score; ROC, receiver operating characteristic; vv-ECMO, veno-venous extracorporeal membrane oxygenation.

bleeding complication rate as shown in earlier studies using the NOVALUNG device [36].

This study has several limitations. As this study is a small, single-center and observational, the generalizability of the results is not given and the findings should be considered hypothesis-generating. The suggested score cut-off is referential at this stage and a future study with a bigger cohort, or external datasets and prospective studies are needed for external validation of our results. Another important limitation is the heterogeneous population with the case mix of two physiologically distinct populations like the restrictive (ARDS) and obstructive (COPD) lung pathologies.

A further aspect regarding generalizability is the choice of the ventilator modes that are not available in every hospital. Another aspect is the increasing use of prone positioning in non-intubated patients in routine

clinical practice, which is not currently accounted for in existing scoring systems. Additionally, parameters such as the duration and settings of NIV, as well as the duration and flow rates of HFOT could be integrated into future iterations of the score.

Neither the PRESERVE-CO<sub>2</sub> score nor the RESP-CO<sub>2</sub> score incorporates dP, which, according to the Amato et al. [37], is a key predictor of mortality. Likewise, mechanical power of ventilation where RR is a key value is not considered. In spontaneously breathing patients, quantifying the work of breathing may further refine risk stratification and should be implemented in future scores [38]. Another extension of the scores would be to implement other organ dysfunctions as, for example, kidney failure. For optimization of the use of ECCO<sub>2</sub>R, a score should be developed to predict need to upgrade to vv-ECMO besides mortality.

## Conclusions

In hypercapnic respiratory failure, careful selection of patients for ECCO<sub>2</sub>R therapy may help to improve outcomes. The proposed PRESERVE-CO<sub>2</sub> score may serve as a guide. A score of 7 points or higher is associated with an unfavorable outcome regarding the 180-day mortality in the specific patient cohort of this study, but the suggested score cut-off is referential at this stage. Further prospective studies are needed to externally validate the score and refine it further for this specific patient population before using it in a clinical setting.

## Acknowledgments

We thank the team of the ICU of the University Hospital of Zurich for their support for research projects.

## Statement of Ethics

The study was conducted under the Declaration of Helsinki, the good clinical practice standard and with ethic approval of the Cantonal Ethics Committee of Zurich (BASEC Nr. 2021-00912). The patients gave written and oral informed consent as needed.

## References

- Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301–8. <https://doi.org/10.1056/NEJM200005043421801>
- Hilty MP, Riva T, Cottini SR, Kleinert EM, Maggiorini A, Maggiorini M. Low flow venovenous extracorporeal CO<sub>2</sub> removal for acute hypercapnic respiratory failure. *Minerva Anestesiol*. 2017;83(8):812–23. <https://doi.org/10.23736/S0375-9393.17.11524-5>
- Urner M, Mitsakakis N, Vorona S, Chen L, Sklar MC, Dres M, et al. Identifying subjects at risk for diaphragm atrophy during mechanical ventilation using routinely available clinical data. *Respir Care*. 2021;66(4):551–8. <https://doi.org/10.4187/respcare.08223>
- Duggal A, Conrad SA, Barrett NA, Saad M, Cheema T, Pannu S, et al. Extracorporeal carbon dioxide removal to avoid invasive ventilation during exacerbations of chronic obstructive pulmonary disease: VENT-AVOID trial - a randomized clinical trial. *Am J Respir Crit Care Med*. 2024;209(5):529–42. <https://doi.org/10.1164/rccm.202311-2060OC>
- Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, et al. Lower tidal volume strategy ( $\approx 3$  ml/kg) combined with extracorporeal CO<sub>2</sub> removal versus “conventional” protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized xtravent-study. *Intensive Care Med*. 2013;39(5):847–56. <https://doi.org/10.1007/s00134-012-2787-6>
- McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, et al. Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs Standard care ventilation on 90-Day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. *JAMA*. 2021;326(11):1013–23. <https://doi.org/10.1001/jama.2021.13374>
- Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J*. 2015;36(33):2246–56. <https://doi.org/10.1093/eurheartj/ehv194>
- Klinzing S, Wenger U, Steiger P, Starck CT, Wilhelm M, Schuepbach RA, et al. External validation of scores proposed for estimation of survival probability of patients with severe adult respiratory distress syndrome undergoing extracorporeal membrane oxygenation therapy: a retrospective study. *Crit Care*. 2015;19:142. <https://doi.org/10.1186/s13054-015-0875-z>
- Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, et al. 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(10):1704–13. <https://doi.org/10.1007/s00134-013-3037-2>
- Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. 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(11):1374–82. <https://doi.org/10.1164/rccm.201311-2023OC>
- Gray E, Menadue C, Piper A, Wong K, Kiernan M, Yee B. Hypercapnia is not excluded by normoxia in neuromuscular disease patients: implications for oximetry. *ERJ Open Res*. 2024;10(4):00927–2023–02023. <https://doi.org/10.1183/23120541.00927-2023>

## Conflict of Interest Statement

The authors declare no conflicts of interest.

## Funding Sources

This study was not supported by any sponsor or funder.

## Author Contributions

Marco Maggiorini, Matthias Peter Hilty, and Anne-Aylin Sigg designed the study. Anne-Aylin Sigg, Matthias Peter Hilty, and Stefanie Keiser analyzed the data and wrote the draft of the manuscript. Shalimar Mila Konopask, Pedro David Wendel-Garcia, and Matthias Peter Hilty collected the data. Anne-Aylin Sigg, Matthias Peter Hilty, Stephanie Klinzing, Pedro David Wendel-Garcia, Marco Maggiorini, Shalimar Mila Konopask, Stefanie Keiser, and Reto Andreas Schuepbach carefully revised and edited the manuscript.

## Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon request.

- 12 Gernhold L, Neurohr C, Tsitouras K, Lutz N, Briese S, Ghiani A. Hypercapnia and lung function parameters in chronic obstructive pulmonary disease. *BMC Pulm Med*. 2024; 24(1):345. <https://doi.org/10.1186/s12890-024-03151-1>
- 13 Konopasek SM, Klinzing S, Wendel Garcia PD, Hilty MP, Maggiorini M. Increased longevity of a novel gas exchanger System for low-flow veno-venous extracorporeal CO<sub>2</sub> removal in acute hypercapnic respiratory failure. *Blood Purif*. 2023;52(3):275–84. <https://doi.org/10.1159/000526582>
- 14 Combes A, Auzinger G, Capellier G, du Cheyron D, Clement I, Consales G, et al. ECCO2R therapy in the ICU: consensus of a European round table meeting. *Crit Care*. 2020;24(1):490. <https://doi.org/10.1186/s13054-020-03210-z>
- 15 Extracorporeal Life Support Organization (ELSO). ELSO Guidelines for adult respiratory failure: supplement to the ELSO general Guidelines. 2013. Available from: <https://static1.squarespace.com/static/57313085a3360c6b87c17029/t/58da7b5b2e69cfe3746ed7ab/1490713437880/ELSO+Guidelines+for+Acute+Respiratory+Failure.pdf>
- 16 Bates D, Mächler M, Bolker B, et al. Fitting Linear Mixed-Effects Models using lme4. *J Stat Software*. 2015;67.
- 17 Baayen RH, Davidson DJ, Bates DM. Mixed-effects modeling with crossed random effects for subjects and items. *J Mem Lang*. 2008; 59(4):390–412. <https://doi.org/10.1016/j.jml.2007.12.005>
- 18 Barr DJ, Levy R, Scheepers C, Tily HJ. Random effects structure for confirmatory hypothesis testing: keep it maximal. *J Mem Lang*. 2013; 68(3). <https://doi.org/10.1016/j.jml.2012.11.001>
- 19 Scrutta L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. *Bone Marrow Transpl*. 2010;45(9):1388–95. <https://doi.org/10.1038/bmt.2009.359>
- 20 R Development Core Team. R: a language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2011. Available from: <http://www.R-project.org/>
- 21 Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2019;199(3):333–41. <https://doi.org/10.1164/rccm.201804-0692OC>
- 22 Contreras M, Masterson C, Laffey JG. Permissive hypercapnia: what to remember. *Curr Opin Anaesthesiol*. 2015;28(1): 26–37. <https://doi.org/10.1097/ACO.0000000000000151>
- 23 Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med*. 2023;49(7):727–59. <https://doi.org/10.1007/s00134-023-07050-7>
- 24 Petran J, Muelly T, Dembinski R, Steuer N, Arens J, Marx G, et al. Validation of RESP and PRESERVE score for ARDS patients with pumpless extracorporeal lung assist (pECLA). *BMC Anesthesiol*. 2020;20(1):102. <https://doi.org/10.1186/s12871-020-01010-0>
- 25 Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, et al. Low-frequency positive-pressure ventilation with extracorporeal CO<sub>2</sub> removal in severe acute respiratory failure. *JAMA*. 1986;256(7): 881–6.
- 26 Schöps M, Groß-Hardt SH, Schmitz-Rode T, et al. Hemolysis at low blood flow rates: in-vitro and in-silico evaluation of a centrifugal blood pump. *J Transl Med*. 2021;19:2.
- 27 Dianti J, McNamee JJ, Slutsky AS, Fan E, Ferguson ND, McAuley DF, et al. Determinants of effect of extracorporeal CO<sub>2</sub> removal in hypoxemic respiratory failure. *NEJM Evid*. 2023;2(5):EVIDoa2200295. <https://doi.org/10.1056/EVIDoa2200295>
- 28 Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE. Control of breathing using an extracorporeal membrane lung. *Anesthesiology*. 1977;46(2):138–41. <https://doi.org/10.1097/0000542-197702000-00012>
- 29 Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, et al. Extracorporeal CO<sub>2</sub> removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med*. 2015;43(1):120–7. <https://doi.org/10.1097/CCM.0000000000000607>
- 30 Staudinger T. Is there still a place for ECCO2R? *Med Klin Intensivmed Notfmed*. 2024;119(Suppl 2):59–64. <https://doi.org/10.1007/s00063-024-01197-x>
- 31 Combes A, Auzinger G, Camporota L, Capellier G, Consales G, Couto AG, et al. Expert perspectives on ECCO2R for acute hypoxemic respiratory failure: consensus of a 2022 European roundtable meeting. *Ann Intensive Care*. 2024;14(1):132. <https://doi.org/10.1186/s13613-024-01353-8>
- 32 Stommel A-M, Herkner H, Kienbacher CL, Wildner B, Hermann A, Staudinger T. Effects of extracorporeal CO<sub>2</sub> removal on gas exchange and ventilator settings: a systematic review and meta-analysis. *Crit Care*. 2024; 28(1):146. <https://doi.org/10.1186/s13054-024-04927-x>
- 33 Lamas T, Fernandes SM, Vasques F, Karagiannidis C, Camporota L, Barrett N. Recent advances and future directions in extracorporeal carbon dioxide removal. *J Clin Med*. 2024;14(1):12. <https://doi.org/10.3390/jcm14010012>
- 34 Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet*. 2019;394(10212):1940–8. [https://doi.org/10.1016/S0140-6736\(19\)32597-8](https://doi.org/10.1016/S0140-6736(19)32597-8)
- 35 Allen L, Allen L, Carr SB, Davies G, Downey D, Egan M, et al. Future therapies for cystic fibrosis. *Nat Commun*. 2023;14(1):693. <https://doi.org/10.1038/s41467-023-36244-2>
- 36 Braune S, Sieweke A, Brettner F, Staudinger T, Joannidis M, Verbrugge S, et al. The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to non-invasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre casM-control study. *Intensive Care Med*. 2016;42(9):1437–44. <https://doi.org/10.1007/s00134-016-4452-y>
- 37 Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747–55. <https://doi.org/10.1056/NEJMs1410639>
- 38 Barrett NA, Murgolo F, Grasso S, Kostakou E, Hart N, Murphy P, et al. Physiological assessment of ECCO2R on the work of breathing in exacerbations of COPD. *COPD J Chronic Obstr Pulm Dis*. 2024;21(1): 2436169. <https://doi.org/10.1080/15412555.2024.2436169>