Mechanical Power During Extracorporeal Membrane Oxygenation and Hospital Mortality in Patients With Acute Respiratory Distress Syndrome

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Research
Abstract

**Background:** Mechanical power (MP) refers to the energy delivered by a ventilator to the respiratory system per unit of time. MP normalized to predicted body weight (PBW) or respiratory system compliance have better predictive value for mortality than MP alone in acute respiratory distress syndrome (ARDS). Our objective was to assess the potential impact of consecutive changes of normalized MP on hospital mortality among ARDS patients receiving extracorporeal membrane oxygenation (ECMO).

**Methods:** We performed a secondary analysis of patients with severe ARDS receiving ECMO in a tertiary care referral center in Taiwan between May 2006 and October 2015. Serial changes of MP during ECMO were recorded.

**Results:** A total of 152 patients with severe ARDS rescued with ECMO were analyzed. Overall hospital mortality was 53.3 %. There were no significant differences between survivors and nonsurvivors in terms of baseline values of MP or other ventilator settings. Cox regression models demonstrated that MP alone, MP normalized to PBW, and MP normalized to compliance during the first 3 days of ECMO were all independently associated with hospital mortality. Higher MP normalized to compliance (HR 2.289 [95% CI 1.214-4.314], p = 0.010) was associated with a higher risk of death than MP itself (HR 1.060 [95% CI 1.018-1.104], p = 0.005) or MP normalized to PBW (HR 1.004 [95% CI 1.002-1.007], p < 0.001). The 90-day hospital mortality of patients with high MP (> 14.4 J/min) during the first 3 days of ECMO was significantly higher than that of patients with low MP (≤ 14.4 J/min) (70.7 % versus 46.8 %, p = 0.004), and the 90-day hospital mortality of patients with high MP normalized to compliance (> 0.53 J/min/ml/cm H$_2$O) during the first 3 days of ECMO was significantly higher than that of patients with low MP normalized to compliance (≤ 0.53 J/min/ml/cm H$_2$O) (63.1 % versus 29.5 %, p < 0.001).

**Conclusions:** MP during the first 3 days of ECMO was the only ventilator setting independently associated with 90-day hospital mortality, and MP normalized to compliance during ECMO was more predictive for mortality than was MP alone.

**Background**

Mechanical ventilation remains the cornerstone of management strategies for acute respiratory distress syndrome (ARDS), and extracorporeal membrane oxygenation (ECMO) is widely used as a salvage therapy for refractory hypoxemia in patients with severe ARDS. ECMO allows the lungs to rest and prevents the risk of ventilator-induced lung injury (VILI) by lowering airway pressure, tidal volume ($V_T$), and FiO$_2$. However, the optimal ventilation strategies for patients with severe ARDS receiving ECMO have yet to be defined [1, 2].

Mechanical power (MP) refers to the amount of energy per unit of time transmitted to the respiratory system by a mechanical ventilator, as determined by volume, pressure, flow, and respiratory rate (RR). It is therefore reasonable to assume that MP is superior to single ventilator parameter in predicting the risk of VILI [3, 4]. VILI originates from the interaction between the energy load (i.e., MP) and the
pathophysiological characteristics of the lungs (size, homogeneity and recruitability) [4, 5]. Therefore, the same MP may have different impact on respiratory system depending on the applied conditions of lungs, and MP should be normalized at least to the functional lung size in order to accurately reflect the actual amount of energy applied to the lungs [6, 7].

Recent studies have shown that MP is independently associated with in-hospital mortality among critically ill patients [8], and high MP levels have been linked to increased mortality in ARDS patients [9]. However, MP alone does not have better predictive value for patients with ARDS, and it is preferable to normalize MP to predicted body weight (PBW) [6] or respiratory system compliance in terms of well-aerated tissue [7].

ECMO enhanced lung-protective ventilation to mitigate the energy load delivered to the respiratory system (i.e., MP); however, researchers have yet to contrast the influence of MP alone and MP normalized to functional lung size on the mortality in ARDS patients undergoing ECMO. Our objective in this study was to assess the role of serial changes in MP (adjusted for PBW or compliance) on hospital mortality in patients with severe ARDS undergoing ECMO.

**Methods**

**Study design and patients**

This study was based on secondary analysis of patients with severe ARDS who had been treated using ECMO between May 2006 and October 2015 at Chang Gung Memorial Hospital (CGMH) in Taiwan. CGMH is a tertiary care referral center with a 3700-bed general ward and 278-bed adult intensive care unit (ICU) with a high volume of venoarterial and venovenous mode ECMO exceeding 100 cases annually. Exclusion criteria were as follows: (1) age < 20 years, (2) malignancies with poor prognosis within 5 years, (3) significant underlying comorbidities or severe multiple organ failure refractory to treatment, and (4) mortality within 3 days after ECMO initiation. The local Institutional Review Board for Human Research approved this study (CGMH IRB No. 201600632B0) and waived the need for informed consent.

**Definitions**

ARDS was defined in accordance with the Berlin criteria [10]. MP was calculated in accordance with the methods [4] based on $V_T$, RR, peak inspiratory pressure (Ppeak), and driving pressure (\(\Delta P\)) using the following equation:

$$\text{MP (Joules/minutes) (J/min) } = 0.098 \times V_T \times RR \times (\text{Ppeak} - 1/2 \times \Delta P).$$

MP normalized to PBW = MP/PBW.

MP normalized to compliance = MP/Compliance.
Ppeak is equivalent to plateau pressure in pressure-controlled ventilation [11-14]. Ppeak has been used as a surrogate for plateau pressure to calculate MP if not specified [15], and similar effect of MP on mortality was demonstrated when considering Ppeak instead of plateau pressure for calculating MP [8]. One recent prospective study used dynamic driving pressure (Ppeak minus PEEP) to calculate MP, referring to the measure as dynamic MP [16]. Hospital mortality refers to all-cause death during the hospital stay. Patients who remained alive for 90 days after discharge from the hospital were regarded as survivors.

Data collection

Demographic data, risk factors for ARDS, underlying comorbidities, Sequential Organ Failure Assessment (SOFA) score, and lung injury score were collected prior to ECMO initiation. The dates of hospital and ICU admission, ARDS onset, mechanical ventilator initiation and liberation, ECMO cannulation and decannulation, ICU and hospital discharge, and time of death were recorded. Arterial blood gas parameters and mechanical ventilator settings were recorded at the time of ECMO initiation and at approximately 10 a.m. on days 1, 2, and 3 after ECMO initiation.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range), and categorical variables were reported as numbers (percentages). A student’s t test or the Mann-Whitney U test was used to compare continuous variables between groups. Categorical variables were tested using the chi-square test for equal proportions or Fisher’s exact test. Paired Student’s t tests were used to compare continuous variables before and after ECMO. Receiver operating characteristic curve and Youden index were used to determine the cutoff to dichotomize continuous variables. Risk factors associated with hospital mortality were analyzed using univariate analysis in the first step, followed by Cox proportional hazard regression model with stepwise selection. The results were presented using the hazard ratio (HR) and 95 % confidence interval (CI). Cumulative mortality curves were generated as a function of time using the Kaplan-Meier approach and compared using the log-rank test. All statistical analysis was performed using SPSS 22.0 statistical software, and a two-sided p value < 0.05 was considered statistically significant.

Results

Patients

A total of 152 patients with severe ARDS rescued by ECMO were included in the analysis, which examined the impact of MP on hospital mortality. Overall all-cause in-hospital mortality was 53.3 %. All patients were deeply sedated and paralyzed, and most cases received pressure-controlled ventilation until attempts at weaning from ECMO.

Comparisons of survivors and nonsurvivors
As shown in Table 1, the mean age of nonsurvivors was higher than that of survivors. Nonsurvivors suffered from ARDS for a longer duration before ECMO initiation, and a higher percentage were immunocompromised. There were no significant differences between the two groups in terms of baseline ventilator settings. After receiving ECMO support, nonsurvivors received significantly higher MP than did survivors, with higher MP normalized to PBW, higher MP normalized to compliance, higher Ppeak, lower dynamic compliance, and higher total RR (all \( p < 0.05 \)). The SOFA scores of nonsurvivors were also significantly higher during the first 3 days of ECMO support.

**Comparing patients receiving high and low mechanical power**

As shown in Table 2, the maximum Youden index value was used to categorize patients according to MP, using a cutoff point of 14.4 J/min during the first 3 days of ECMO: high MP group (41 patients; 27 %) and low MP group (111 patients; 73 %). No significant differences were observed between the two groups in terms of MP or other ventilatory variables prior to ECMO initiation. After ECMO support, the high MP and low MP groups differed significantly in all ventilatory parameters except for PEEP and dynamic compliance (all \( p < 0.001 \)). Patients in the high MP group had significantly fewer ventilator-free days on day 60 than did patients in the low MP group, and hospital mortality was significantly higher.

**Percentage changes in MP and its components after ECMO and correlation between MP and mortality**

Following ECMO initiation, there was a significant reduction in MP among the overall population (49 %, from 23.8 to 12.1 J/min, \( p < 0.001 \)), survivors (55 %, from 24.1 to 10.9 J/min, \( p < 0.001 \)), and nonsurvivors (44 %, from 23.5 to 13.1 J/min, \( p < 0.001 \)). Following ECMO initiation, there was a pronounced decrease in total RR and \( V_T \) (33 % and 22 %, respectively, \( p < 0.001 \)) with a less pronounced decrease in Ppeak (6 %) and no change in PEEP in the overall population (Fig. 1). Hospital mortality was correlated with MP during the first 3 days of ECMO but not with the initial MP value before ECMO, and MP higher than 15.0 J/min during the first 3 days of ECMO showed consistently increasing trends in mortality. The hospital mortality was 89 % among patients with MP exceeding 20 J/min during the first 3 days of ECMO and 49.3 % among patients with MP of less than 20 J/min (Fig. 2a and Fig. 2b).

**Factors associated with hospital mortality**

After adjusting for significant confounding variables, Cox proportional hazard regression models revealed a number of factors that were significantly associated with 90-day hospital mortality: immunocompromised status, ARDS duration before ECMO, SOFA score from days 1-3 on ECMO, MP alone, MP normalized to PBW, and MP normalized to compliance from days 1-3 on ECMO. The risk of death was higher among patients with higher MP normalized to compliance during ECMO compared to those with higher MP alone or higher MP normalized to PBW (HR 2.289, 1.060, and 1.004, respectively, all \( p < 0.05 \)) (Table 3). The overall 90-day survival rate was significantly higher among severe ARDS patients with MP \( \leq 14.4 \) J/min from day 1 to 3 on ECMO than among those with MP > 14.4 J/min (53.2 % versus 29.3 %, \( p = 0.004 \), log-rank test) (Fig. 3a), and the overall 90-day survival rate was significantly higher among severe ARDS patients with MP normalized to compliance \( \leq 0.53 \) J/min/ml/cm \( H_2O \) from day 1 to
3 on ECMO than among those with MP normalized to compliance > 0.53 J/min/ml/cm H₂O (70.5 %
versus 36.9 %, \( p < 0.001 \), log-rank test) (Fig. 3b). MP > 14.4 J/min during the first 3 days of ECMO was
independently associated with higher hospital mortality (Adjusted HR 2.340 [95% CI 1.358-4.031]; \( p =
0.002 \)) (Additional file 1: Table S1), and MP normalized to compliance > 0.53 J/min/ml/cm H₂O during the
first 3 days of ECMO was independently associated with higher hospital mortality (Adjusted HR 2.238
[95% CI 1.224-4.094]; \( p = 0.009 \)) (Additional file 2: Table S2).

**Discussion**

This study analyzed consecutive changes in the ventilator settings for patients with severe ARDS
receiving ECMO. The primary insight in this research was that MP alone, MP normalized to PBW, and MP
normalized to compliance during the first 3 days of ECMO were all independently associated with hospital
mortality. Among the ventilator variables, mechanical power normalized to compliance during the first 3
days of ECMO had the greatest predictive value for mortality.

We hypothesized that excessive MP may contribute to the development of VILI and thereby influence
clinical outcomes [4]. At the time of this study, there was no clearly defined threshold indicating safe MP
values for patients with critical illness or ARDS. One experimental study reported on the development of
lung edema and other forms of lung damage when MP exceeded 12 J/min [3]. It has been shown that in-
hospital mortality is independently associated with higher MP among critically ill patients, which
increases consistently in cases where MP exceeds 17 J/min [8]. In another study using a standardized
screening program, 28-day hospital mortality and 3-year mortality were higher in ARDS cases where MP
exceeded 22 J/min [9]. However, none of the studies mentioned above considered the effects of changes
in MP over time.

ECMO facilitates the use of ultra-protective ventilation, which allows reductions in the contributors of
energy load (i.e., MP) to promote lung healing, mitigate further lung injury [1, 2]. Previous studies have
reported that during the first 3 days of ECMO, higher PEEP [17] and lower driving pressure [12, 18] were
independently associated with lower mortality. However, there was no clearly defined threshold indicating
safe ventilator settings and MP values for patients with severe ARDS undergoing ECMO [2].

In the current study, we found that higher MP values during ECMO (but not before ECMO) were associated
with increased mortality. We observed a significant difference between patients in the low and high MP
groups in terms of mortality but not in terms of baseline MP nor ventilator settings. In a Cox regression
models, MP during the first 3 days of ECMO was independently associated with hospital mortality, and the
predictive power of MP during ECMO exceeded that of all other individual ventilator variables. MP >14.4
J/min during the first 3 days of ECMO was significantly positively correlated with 90-day hospital
mortality and showed greater hazard of death (Adjusted HR, 2.340; 95% CI, 1.358-4.031; \( p = 0.002 \)).
Overall, our findings revealed that MP (indicating a conjunction of ventilator settings parameters) during
ECMO could be considered a predictor of survival and should be taken into account in optimizing
ventilation.
The energy load (MP) delivered to the lungs is not necessarily evenly distributed. The effects of MP on the respiratory system depend not only on the energy load itself but also on the pathophysiology of the lungs (e.g., functional lung size, proportion of inhomogeneity, and the recruitability) [4, 5]. Therefore, MP should be normalized, at least adjusted for functional lung size to reflect the actual amount of energy expected to be delivered to the lungs. Respiratory system compliance is correlated directly with the amount of aerated lung available for tidal ventilation (functional lung size) in patients with ARDS [19]. Zhang et al. reported that MP normalized to PBW was far more accurate than the absolute value of MP in predicting mortality [6]. Coppola et al. reported no causal relationship between MP alone and mortality, whereas both MP and transpulmonary MP normalized to respiratory system compliance or to the amount of well-aerated tissue were independently associated with ICU mortality [7]. However, the above studies were predicated on baseline MP values, they did not account for serial changes in MP during the ICU stay and did not seek to determine whether the link between MP and mortality was independent from other ventilator settings.

Patients with severe ARDS requiring ECMO tended to have more noninflated tissue (i.e., lower functional lung size), greater inhomogeneity, and greater lung recruitability [20]. There have been relatively few studies examining the effects of MP normalized to functional lung size on mortality in severe ARDS patients receiving ECMO. Cox regression models in our study revealed that the risk of death estimates obtained using MP normalized to compliance were higher than those of MP alone or MP normalized to PBW, despite the fact that all three factors were independently associated with mortality (HR 2.289, 1.060, and 1.004, respectively, all \( p < 0.05 \)). It indicated that functional lung size in ARDS patients is not always proportional to body weight [21], and is generally determined by the severity of the disease and is therefore better quantified by compliance [19]. MP normalized to compliance higher than 0.53 J/min/ml/cm H\(_2\)O during the first 3 days on ECMO was significantly associated with greater hazard of death (Adjusted HR, 2.238; 95% CI, 1.224-4.094; \( p = 0.009 \)). Our findings demonstrated that MP normalized to compliance is a superior representation of the actual amount of energy transmitted to the lungs. Precisely defining the safety limits of MP will require further randomized controlled trials to evaluate the correlations between mortality and MP normalized to functional lung size, lung inhomogeneity, and recruitability.

A few studies have examined the effect of RR on VILI and clinical outcomes. Experimental studies have shown that reducing RR ameliorates lung inflammation and lung injury [22] and that the elevated MP resulting from higher RR can induce lung edema and damage [3]. The LUNG SAFE study concluded that increased RR was associated with increased hospital mortality in patients with ARDS [23]. Our study revealed that ECMO had a more pronounced effect on reducing RR than on any other determinants of MP, as mentioned in other recent studies [15, 24, 25]. We also observed that total RR of nonsurvivors was significantly higher than that of survivors during the first 3 days of ECMO.

Besides, the effects of spontaneous breathing could be protective or deleterious, depending on the severity of lung injury and strength of spontaneous activity. This means that lung injury could be worse in cases of severe ARDS, whether receiving ECMO or not, with vigorous spontaneous effort [26]. One recent international study reported mean spontaneous RR of 9 ± 13 breaths/minute before ECMO and 8 ± 11
breaths/minute during the first 2 days of ECMO. This indicated that those patients were not fully sedated and paralyzed, and neuromuscular blocking agents were used in only 41% of cases [15]. In estimating MP values, patients should be completely relaxed; i.e., without any active inspiratory efforts [7]. In our study, the median spontaneous RR before ECMO was 0 (0-7) breaths/minute and 1 (0-4) breath/minute during the first 3 days of ECMO, indicating that our patients were nearly total sedated and paralyzed. At present, the role of spontaneous effort in patients receiving ECMO for severe ARDS remains unclear, and the benefit or harm were likely depending on the patients’ respiratory pattern, patient-ventilator dyssynchrony, pendelluft, and the phase and duration of ARDS [2]. In many cases, implementing a spontaneous breathing ECMO strategy is difficult or clinically infeasible to apply due to the high respiratory drive associated with severe ARDS and the need for deep sedation to mitigate patient self-inflicted lung injury [2, 27, 28].

The most common cause of death among ARDS patients is multiorgan failure [29]. One international multicenter prospective study reported that extrapulmonary organ failure (elevated lactate levels and positive fluid balance) during ECMO had a significantly negative impact on 6-month mortality for patients with ARDS [15]. Our findings revealed that there was no significant difference between survivors and nonsurvivors in terms of MP and SOFA score before ECMO; however, MP and SOFA score were shown to decrease during the first 3 days of ECMO. SOFA score during the first 3 days of ECMO remained independently associated with hospital mortality. These findings indicated that ECMO could facilitate a further reduction in ventilator load (i.e., MP) in order to alleviate VILI by reducing the proinflammatory biotrauma response, thereby preventing multi-organ failure and improving survival [2, 30, 31]. Besides, an immunocompromised status was associated with lower survival, as reported in previous studies in which the 6-month survival rate was only 30% to 37% [15, 32]. The timing of ECMO initiation for severe ARDS with refractory hypoxemia has yet to be defined [1]; however, recent studies have also reported a link between ARDS duration before ECMO and mortality [15, 31]. This is perhaps due to the fact that ECMO promotes lung-protective ventilation, such that any delay in initiating ECMO would increase the likelihood of VILI and subsequent mortality.

This study was hindered by a number of limitations. First, this retrospective study was conducted in one tertiary care referral center with a high annual volume of patients requiring ECMO, thereby limiting generalizability. Second, ventilatory variables were recorded only once a day (at approximately 10 a.m.) during the stay in the ICU and therefore do not necessarily represent dynamic changes in ventilator status, including fluctuations in MP during 24-hour intervals. Third, ultra-protective ventilation with $V_T$ below 4 ml/kg PBW has been recommended for patients with ARDS undergoing ECMO [1, 2]. Nonetheless, mean $V_T$ value in the current study was 6 ml/kg PBW after ECMO, due perhaps to the fact that ultra-protective ventilation was not widely implemented between 2006 and 2015. Fourth, we assessed functional lung size by means of PBW and compliance due to the retrospective study, but computed tomography scan of the lungs may be more accurate way to estimate amount of aerated remaining functional lung, lung inhomogeneity or the recruitability [6, 20]. However, computed tomography scan requires intra-hospital patient transfer from ICU to radiology department and the use of ECMO preclude widespread clinical use. Finally, our objective in this observational study was to identify the factors associated with mortality.
without considering issues pertaining to causality. Any number of residual or confounding variables that were not measured may have influenced the results.

**Conclusions**

Our findings revealed that MP, MP normalized to PBW, and MP normalized to compliance during the first 3 days of ECMO were all independently associated with hospital mortality. MP normalized to compliance provided the most predictive value for hospital mortality. Defining safety limits to minimize VILI and decrease mortality in patients with severe ARDS undergoing ECMO may require larger randomized controlled trials to determine whether MP normalized to functional lung size, lung inhomogeneity, or recruitability is causally related to mortality.

**Abbreviations**

ARDS: acute respiratory distress syndrome; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; ICU: intensive care unit; MP: mechanical power; PBW: predicted body weight; PEEP: positive end-expiratory pressure; SOFA: sequential organ failure assessment; V_T: tidal volume; Ppeak: peak inspiratory pressure; ΔP: driving pressure; RR: respiratory rate; VILI: ventilator-induced lung injury

**Declarations**

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**Availability of data and materials**

The datasets used or analyzed in the study are available from the corresponding author on reasonable request.

**Authors’ contributions**

LCC and KCK assumed responsibility for the accuracy of the data analysis and drafting of the manuscript. LCC, SWL, LPC, HHL, FCT, CHC, and CYH performed the study design and data acquisition. LCC and PHL were responsible for statistical analysis of data. LCC, CSL, SWL, HCH, CCH, HPW, and KCK performed
interpretation of the results. All authors contributed to the completion of the manuscript and have approved the final version.

**Ethics approval and consent to participate**

The local Institutional Review Board for Human Research approved this study (CGMH IRB No. 201600632B0), and the need for informed consent was waived.

**Consent for publication**

Not applicable.

**Competing interests**

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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Tables

Table 1 Background characteristics and clinical variables: survivors and nonsurvivors
| Variables                                      | All  
|                                               | (n = 152) | Survivors  
|                                               | (n = 71) | Nonsurvivors  
|                                               | (n = 81) | p  |
| Age (years)                                   | 50.3 ± 16.4 | 46.0 ± 16.5 | 54.1 ± 15.4 | 0.002 |
| Male (gender)                                 | 103 (67.8 %) | 48 (67.6 %) | 55 (67.9 %) | 0.969 |
| Body mass index (kg/m²)                       | 25.8 ± 5.3 | 26.0 ± 5.8 | 25.6 ± 4.7 | 0.631 |
| ARDS etiologies                               |  |  |  |  |
| Pulmonary cause                               | 118 (78 %) | 59 (83 %) | 59 (73 %) | 0.130 |
| Extrapulmonary cause                          | 34 (22 %) | 12 (17 %) | 22 (27 %) | 0.130 |
| Diabetes mellitus                             | 40 (26 %) | 23 (32 %) | 17 (21 %) | 0.111 |
| Chronic liver disease                         | 21 (14 %) | 6 (9 %) | 15 (19 %) | 0.073 |
| Immunocompromised status                      | 40 (26 %) | 11 (16 %) | 29 (36 %) | 0.005 |
| SOFA score before ECMO                        | 10.8 ± 3.2 | 10.3 ± 3.1 | 11.3 ± 3.2 | 0.067 |
| Lung injury score before ECMO                 | 3.4 ± 0.4 | 3.4 ± 0.4 | 3.3 ± 0.4 | 0.106 |
| ARDS duration before ECMO (h)                 | 28 (7-122) | 10 (4-64) | 54 (17-195) | <0.001 |
| PaO₂/FiO₂ (mm Hg) before ECMO                 | 63 (52-88) | 64 (53-80) | 63 (52-107) | 0.168 |
| Ventilator settings before ECMO               |  |  |  |  |
| MP (J/min)                                    | 23.8 ± 9.6 | 24.1 ± 10.3 | 23.5 ± 9.0 | 0.668 |
| MP/PBW (× 10⁻³ J/min/kg)                      | 416 ± 172 | 410 ± 174 | 423 ± 171 | 0.645 |
| MP/compliance (J/min/ml/cm H₂O)               | 1.27 ± 0.76 | 1.21 ± 0.75 | 1.33 ± 0.78 | 0.380 |
| Tidal volume (ml/kg PBW)                      | 7.7 ± 2.4 | 7.7 ± 2.3 | 7.8 ± 2.5 | 0.658 |
| PEEP (cm H₂O)                                 | 12.0 ± 2.8 | 12.2 ± 2.5 | 11.8 ± 3.0 | 0.288 |
| Peak inspiratory pressure (cm H₂O)            | 33.9 ± 6.5 | 33.6 ± 6.0 | 34.2 ± 6.9 | 0.605 |
| Mean airway pressure (cm H₂O)                 | 18.6 ± 4.4 | 18.4 ± 4.2 | 18.8 ± 4.6 | 0.588 |
| Dynamic compliance (ml/cm H₂O)                | 22.6 ± 11.3 | 23.7 ± 11.6 | 21.8 ± 11.1 | 0.420 |
| Total respiratory rate (breaths/min)          | 24.0 ± 6.9 | 23.7 ± 7.4 | 24.3 ± 6.6 | 0.596 |
| Spontaneous respiratory rate(breaths/min)     | 0 (0-7) | 1 (0-6) | 0 (0-7) | 0.982 |
| Minute ventilation (L/min)                    | 10.6 ± 3.8 | 10.7 ± 4.1 | 10.5 ± 3.6 | 0.816 |
| SOFA score from day 1 to day 3 on ECMO        | 9.6 ± 2.3 | 8.8 ± 1.9 | 10.4 ± 2.4 | <0.001 |
| **PaO₂/FiO₂ (mm Hg) from day 1 to day 3 on ECMO** | 178 (131-240) | 200 (146-247) | 165 (124-211) | 0.588 |
|---|---|---|---|---|
| **Ventilator settings from day 1 to day 3 on ECMO** | | | | |
| **MP (J/min)** | 12.1 ± 6.2 | 10.9 ± 4.3 | 13.1 ± 7.4 | 0.022 |
| **MP/PBW (× 10⁻³ J/min/kg)** | 206 ± 111 | 185 ± 67 | 226 ± 137 | 0.022 |
| **MP/compliance (J/min/ml/cm H₂O)** | 0.73 ± 0.46 | 0.60 ± 0.32 | 0.86 ± 0.53 | <0.001 |
| **Tidal volume (ml/kg PBW)** | 6.0 ± 2.2 | 6.1 ± 2.0 | 6.0 ± 2.4 | 0.914 |
| **PEEP (cmH₂O)** | 12.0 ± 3.3 | 12.3 ± 3.2 | 11.7 ± 3.3 | 0.202 |
| **Peak inspiratory pressure (cm H₂O)** | 31.7 ± 5.6 | 30.6 ± 5.1 | 32.8 ± 5.9 | 0.018 |
| **Mean airway pressure (cm H₂O)** | 17.7 ± 4.0 | 17.4 ± 3.6 | 17.9 ± 4.3 | 0.406 |
| **Dynamic compliance (ml/cm H₂O)** | 19.2 ± 8.1 | 21.1 ± 7.7 | 17.4 ± 8.1 | 0.006 |
| **Total respiratory rate (breaths/min)** | 16.0 ± 4.4 | 15.2 ± 4.1 | 16.7 ± 4.6 | 0.035 |
| **Spontaneous respiratory rate (breaths/min)** | 1 (0-4) | 0 (0-4) | 2 (0-5) | 0.114 |
| **Minute ventilation (L/min)** | 5.7 ± 2.8 | 5.2 ± 2.0 | 6.0 ± 3.2 | 0.068 |

Data are presented as mean ± standard deviation, count or median (interquartile range)

ARDS acute respiratory distress syndrome, ECMO extracorporeal membrane oxygenation, FiO₂ fraction of inspired oxygen, MP mechanical power, PaO₂ partial pressure of oxygen in arterial blood, PBW predicted body weight, PEEP positive end-expiratory pressure, SOFA Sequential Organ Failure Assessment

**Table 2** Ventilator settings, clinical variables, and outcomes as a function of mechanical power during ECMO
| Variables                              | MP during the first 3 days of ECMO |
|----------------------------------------|-------------------------------------|
|                                        | High (n = 41)                      |
|                                        | Low (n = 111)                      |
|                                        | (>).14.4 J/min)                     |
|                                        | (≤ 14.4 J/min)                      |
|                                        | p                                   |
| Ventilator settings before ECMO        |                                     |
| MP (J/min)                             | 25.0 ± 9.5                         |
|                                        | 23.3 ± 9.5                         |
|                                        | 0.339                               |
| Tidal volume (ml/kg PBW)               | 8.3 ± 2.3                           |
|                                        | 7.5 ± 2.4                           |
|                                        | 0.062                               |
| PEEP (cmH₂O)                           | 11.9 ± 2.7                          |
|                                        | 12.0 ± 2.8                          |
|                                        | 0.786                               |
| Peak inspiratory pressure (cm H₂O)     | 34.4 ± 6.5                          |
|                                        | 33.8 ± 6.5                          |
|                                        | 0.568                               |
| Mean airway pressure (cm H₂O)          | 19.2 ± 3.9                          |
|                                        | 18.4 ± 4.5                          |
|                                        | 0.310                               |
| Dynamic compliance (ml/cm H₂O)         | 22.3 ± 8.4                          |
|                                        | 22.7 ± 12.1                         |
|                                        | 0.869                               |
| Total respiratory rate (breaths/min)   | 23.9 ± 6.7                          |
|                                        | 24.0 ± 7.1                          |
|                                        | 0.891                               |
| Spontaneous respiratory rate (breaths/min) | 1 (0-6)                           |
|                                        | 0 (0-7)                             |
|                                        | 0.956                               |
| Minute ventilation (L/min)             | 11.2 ± 3.5                          |
|                                        | 10.3 ± 3.9                          |
|                                        | 0.205                               |
| Arterial blood gas before ECMO         |                                     |
| pH                                     | 7.24 ± 0.16                         |
|                                        | 7.29 ± 0.13                         |
|                                        | 0.056                               |
| PaCO₂ (mm Hg)                          | 56.1 ± 20.0                         |
|                                        | 51.1 ± 18.4                         |
|                                        | 0.150                               |
| PaO₂ (mm Hg)                           | 72.4 ± 33.4                         |
|                                        | 74.5 ± 41.7                         |
|                                        | 0.776                               |
| Saturation (%)                         | 83.2 ± 17.4                         |
|                                        | 85.1 ± 14.4                         |
|                                        | 0.508                               |
| PaO₂/FiO₂ (mm Hg)                      | 66.5 (49.7-85.7)                    |
|                                        | 63 (53-90.7)                        |
|                                        | 0.882                               |
| SOFA score before ECMO                | 11.9 ± 3.1                          |
|                                        | 10.4 ± 3.1                          |
|                                        | 0.013                               |
| Ventilator settings from day 1 to day 3 on ECMO |                                     |
| MP (J/min)                             | 20.3 ± 5.3                          |
|                                        | 9.1 ± 3.0                           |
|                                        | <0.001                              |
| Tidal volume (ml/kg PBW)               | 7.4 ± 2.2                           |
|                                        | 5.6 ± 2.0                           |
|                                        | <0.001                              |
| PEEP (cmH₂O)                           | 11.8 ± 2.5                          |
|                                        | 12.0 ± 3.5                          |
|                                        | 0.653                               |
| Peak inspiratory pressure (cm H₂O)     | 35.2 ± 5.4                          |
|                                        | 30.5 ± 5.1                          |
|                                        | <0.001                              |
| Mean airway pressure (cm H₂O)          | 19.6 ± 3.8                          |
|                                        | 17.0 ± 3.8                          |
|                                        | <0.001                              |
| Dynamic compliance (ml/cm H₂O)         | 19.9 ± 6.5                          |
|                                        | 18.9 ± 8.5                          |
|                                        | 0.520                               |
| Total respiratory rate (breaths/min)   | 20.3 ± 5.4                          |
|                                        | 14.4 ± 3.5                          |
|                                        | <0.001                              |
| Variable                                                                 | Day 1 ECMO | Day 3 ECMO | P-value |
|------------------------------------------------------------------------|------------|------------|---------|
| Spontaneous respiratory rate (breaths/min)                            | 4 (1-9)    | 0 (0-3)    | <0.001  |
| Minute ventilation (L/min)                                             | 8.9 ± 2.5  | 4.5 ± 1.6  | <0.001  |
| Arterial blood gas from day 1 to day 3 on ECMO                         |            |            |         |
| pH                                                                     | 7.42 ± 0.08| 7.44 ± 0.08| 0.286   |
| PaCO₂ (mm Hg)                                                         | 38.6 ± 6.5 | 38.1 ± 4.7 | 0.639   |
| PaO₂ (mm Hg)                                                          | 102.2 ± 65.9| 96.1 ± 39.5| 0.489   |
| Saturation (%)                                                         | 94.8 ± 3.3 | 95.5 ± 2.9 | 0.240   |
| PaO₂/FiO₂ (mm Hg)                                                     | 151 (123-212)| 189 (140-242)| 0.921   |
| SOFA score from day 1 to day 3 on ECMO                                | 10.7 ± 2.2 | 9.2 ± 2.2  | 0.001   |
| ECMO complications, n (%)                                              | 9 (22 %)   | 34 (30.6 %)| 0.292   |
| Duration of ECMO (days)                                                | 7.7 (4.7-11.5)| 9.9 (5.9-15.8)| 0.287   |
| Duration of mechanical ventilator (days)                              | 15.4 (11.8-34)| 22.9 (12.4-39.8)| 0.291   |
| Length of ICU stay (days)                                              | 19 (10-43) | 27 (16-43) | 0.182   |
| Length of hospital stay (days)                                         | 29 (13-63) | 41 (24-65.5)| 0.130   |
| ECMO-free days on day 28                                               | 0 (0-18.2) | 10.1 (0-19.3)| 0.075   |
| Ventilator-free days on day 28                                         | 0 (0-0)    | 0 (0-8.5)  | 0.311   |
| Ventilator-free days on day 60                                         | 0 (0-20.4) | 8.3 (0-40.5)| 0.04    |
| Hospital mortality, n (%)                                              | 29 (70.7 %)| 52 (46.8 %)| 0.004   |

Data are presented as mean ± standard deviation, count or median (interquartile range)

*ECMO* extracorporeal membrane oxygenation, *FiO₂* fraction of inspired oxygen, *ICU* intensive care unit, *MP* mechanical power, *PaCO₂* partial pressure of carbon dioxide in arterial blood, *PaO₂* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment

**Table 3** Cox proportional hazard regression analysis of factors associated with 90-day hospital mortality
| Variables                                      | Univariate analysis | Multivariate analysis model 1 | Multivariate analysis model 2 | Multivariate analysis model 3 |
|-----------------------------------------------|---------------------|-------------------------------|-------------------------------|-------------------------------|
|                                               | HR (95% CI)         | p                             | HR (95% CI)                   | p                             | HR (95% CI)                   | p                             |
| Age (with each year increase)                 | 1.018 (1.004-1.033) | 0.012                         |                               |                               |                               |                               |
| Pulmonary cause                               | 1.989 (1.211-3.216) | 0.007                         |                               |                               |                               |                               |
| Extrapulmonary cause                          | 0.785 (0.475-1.296) | 0.344                         |                               |                               |                               |                               |
| Diabetes mellitus                             | 0.622 (0.358-1.079) | 0.091                         |                               |                               |                               |                               |
| Chronic liver disease                         | 2.085 (1.184-3.670) | 0.011                         |                               |                               |                               |                               |
| Immunocompromised status                      | 2.242 (1.411-3.563) | 0.001                         | 2.564 (1.488-4.419)           | 0.001                         | 2.674 (1.556-4.596)           | <0.001                        | 2.554 (1.471-4.433)           | 0.001                        |
| ARDS duration before ECMO (with each hour increase) | 1.002 (1.001-1.004) | <0.001                        | 1.002 (1.001-1.004)           | 0.003                         | 1.002 (1.001-1.004)           | 0.003                         | 1.001 (1.000-1.003)           | 0.074                        |
| SOFA score from day 1 to 3 on ECMO (with each point increase) | 1.318 (1.178-1.476) | <0.001                        | 1.202 (1.067-1.355)           | 0.003                         | 1.207 (1.074-1.356)           | 0.002                         | 1.222 (1.084-1.377)           | 0.001                        |
| Tidal volume/PBW from day 1 to 3 on ECMO      | 1.001 (0.896-1.118) | 0.992                         |                               |                               |                               |                               |                               |                               |
| PEEP from day 1 to 3 on ECMO                  | 0.945 (0.880-1.015) | 0.120                         |                               |                               |                               |                               |                               |                               |
| Peak inspiratory pressure from day 1 to 3 on ECMO | 1.058 (1.019-1.100) | 0.004                         |                               |                               |                               |                               |                               |                               |
| Dynamic compliance from day 1 to 3 on ECMO     | 0.953 (0.924-0.984) | 0.003                         |                               |                               |                               |                               |                               |                               |
| Total respiratory rate from day 1 to 3 on ECMO | 1.055 (1.003-1.109) | 0.039                         |                               |                               |                               |                               |                               |                               |
|                                | HR     | CI    | P     | CI     |
|--------------------------------|--------|-------|-------|--------|
| MP from day 1 to 3 on ECMO     | 1.054  | 1.017-1.093 | 0.004 |       |
|                                | 1.060  | 1.018-1.104 | 0.005 |       |
| MP/PBW from day 1 to 3 on ECMO (× 10^{-3} J/min/kg) | 1.003  | 1.001-1.005 | 0.002 | 1.004 <0.001 |
|                                | 1.004  | 1.002-1.007 |       | <0.001 |
| MP/compliance from day 1 to 3 on ECMO (J/min/ml/cm H2O) | 3.142  | 1.966-5.020 | <0.001 | 2.289 0.010 |
|                                | 2.289  | 1.214-4.314 |       | 0.010  |

ARDS acute respiratory distress syndrome, CI confidence interval, ECMO extracorporeal membrane oxygenation, HR hazard ratio, MP mechanical power, PEEP positive end-expiratory pressure, PBW predicted body weight, SOFA Sequential Organ Failure Assessment

Multivariate analysis models included age, pulmonary or extrapulmonary cause of ARDS, diabetes mellitus, chronic liver disease, immunocompromised status, ARDS duration before ECMO, SOFA score from day 1 to 3 on ECMO, ventilatory parameters from day 1 to 3 on ECMO (tidal volume/PBW, PEEP, peak inspiratory pressure, dynamic compliance, total respiratory rate)

Model 1: add MP from day 1 to 3 on ECMO

Model 2: add MP/PBW from day 1 to 3 on ECMO (× 10^{-3} J/min/kg)

Model 3: add MP/compliance from day 1 to 3 on ECMO (J/min/ml/cm H2O)