



## Early View

### Research letter

## **Risk factors for mortality in patients with COVID-19 needing extracorporeal respiratory support**

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# Risk factors for mortality in patients with COVID-19 needing extracorporeal respiratory support

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Dear Editor,

Series describing the evolution of patients with severe acute respiratory distress syndrome (ARDS) secondary to COVID-19 and supported with extracorporeal membrane oxygenation (ECMO) during the first wave of the pandemic have reported mortalities ranging from 30 to 60% [1,2]. More recent publications have demonstrated a trend towards a higher mortality in COVID-19 patients receiving support in later periods of the pandemic, even though the overall mortality of the disease seems lower [3,4]. The reasons for this difference are not clear.

The ECMOVIBER study (The use of ECMO during the coVid-19 pandemic in the IBERian peninsula) is a retrospective-prospective observational cohort study which included consecutive adult patients with SARS-CoV-2 infection admitted to the ICU with severe ARDS and rescued with extracorporeal respiratory support from March 1<sup>st</sup> to December 1<sup>st</sup> 2020 across 24 ECMO centers (22 in Spain and two in Portugal). In general, inclusion and exclusion criteria for ECMO were those applied in the EOLIA trial [5]. Patients were followed for six months after ECMO commencement. The aim of the study was to identify factors associated with hospital mortality. The study protocol was approved by the local ethics committees at all the participating centers. The need for informed consent was waived in view of the retrospective nature of the analysis, and because only data available in the medical records were collected. Qualitative variables were described as numbers and percentages. Quantitative variables were described as means and standard deviations or medians and interquartile ranges (IQR). Confidence intervals for all analyses were set at 95%. The Kaplan-Meier method was used for survival analysis. Variables entered in the Cox proportional hazard model were defined on the basis of their univariate p value and their clinical relevance evaluated according to the literature on ECMO and COVID-19. Clinically relevant variables were included in a multivariate Cox model. Statistical analysis was performed with the “R” statistical software [R version 4.0.3 (2020-10-10), Copyright 2015 The R Foundation for Statistical Computing].

A total of 338 patients at the 24 centers received ECMO support during the study period. In 319 (94.4%) cases ECMO was started as a supportive measure for ARDS. Overall mean age was  $53 \pm 10$  years, 258 patients (80.9%) were male, and hypertension was the most common comorbidity [121 (37.9%)]. Patients were cannulated after a median of 5 (3-9) days from the initiation of mechanical ventilation (MV), 7 (4-13) days after ICU admission and 17 (12-22) days after symptom presentation. Coinfection at ECMO initiation was recorded in 95 (29.8%) cases. Ninety-six (30.1%) patients were supported at high-volume centers (>30 ECMO cases/year) and 129 (40.4%) needed ECMO retrieval and transport.

One hundred and eighty (56.4%) patients were successfully decannulated. The median duration of ECMO support was 17 (9-32) days, with 84 (26.3%) runs lasting more than 30 days. One hundred and fifty-six patients (48.9%) were discharged alive, 156 (48.9%) died in the hospital and seven patients were still hospitalized at six-month follow-up (one of whom remained on ECMO).

Associations of variables with hospital mortality are detailed in figure 1 (upper panel). Age, ischemic cardiomyopathy, center case volume, ECMO retrieval, days from symptoms to cannulation, driving pressure prior to ECMO and drainage cannula size were associated with hospital mortality. In contrast, pre-ECMO MV days were not associated with survival (figure 1a). In the multivariate analysis including the wave in which ECMO support was received, the hazard ratio for hospital mortality was four times higher in patients over 65, and the survival rate of patients supported at centers with a volume of 30 cases or above was significantly higher (figures 1b and 1c). Longer time from symptom onset and higher driving pressure before cannulation were associated with a higher risk of hospital mortality, while higher levels of PEEP at day three of ECMO support were associated with a lower risk of hospital mortality. Larger drainage cannula diameter was also associated with a reduced risk of death on ECMO [HR 0.88 (0.80-0.96),  $p=0.005$ ] but not when it was included in the multivariate model for hospital mortality.

In this large multicenter series of COVID-19 patients receiving ECMO support, we detected several factors associated with hospital mortality. The study of these factors might help in the identification of COVID-19 cases who might benefit the most from ECMO and provide valuable information for improving the management of these patients.

Regarding the criteria for indicating the technique, a period of MV longer than 7-10 days prior to ECMO commencement has traditionally been considered as a contraindication. Recently, Díaz et al indicated that length of MV had no impact on survival [6]; however, the study included only 11 patients with prolonged duration of MV prior to ECMO. Our analysis, which includes 72 patients with more than 10 days of pre-ECMO MV, confirmed the absence of this association; in fact, we found an association between longer time between symptom onset and ECMO initiation with a higher risk for hospital mortality. This time frame includes the period of non-invasive oxygen therapy prior to intubation, in which the lung could be further damaged leading to a potential decrease in lung

resilience. Over the course of the pandemic the time of invasive MV initiation changed, with a general tendency for an early start during the first wave and delayed intubation in later periods. In these later phases there was also a dispersion of ECMO cases (4). In this regard, and in agreement with previous results [7], we found that patients supported at centers with a high case volume had a lower mortality. The recommendation to concentrate cases at high-volume centers should include the capability to retrieve the sickest patients admitted in hospitals that do not have access to this technique [8,9]. Not surprisingly, in our series, patients who were retrieved had lower hospital mortality, a finding that reinforces the idea that attention should be centralized. The age cut-off point for ruling out ECMO support has also been a matter of debate [10]. In our series, in agreement with previous reports [11], survival rates were significantly lower in patients aged over 65, and so it seems reasonable to establish age above 65 as a relative contraindication for COVID-19 ECMO support.

Adequate management of the extracorporeal support, together with the pathological condition itself, also have a direct impact on outcome. Lung parenchyma of COVID-19 patients needing ECMO is severely affected, with notably high lung elastance and very low residual function [12,13]. High ECMO flows are needed in this situation in order to ensure adequate oxygen delivery and allow ultraprotective MV. For this reason, the diameter of the drainage cannula has to be large enough to achieve these high ECMO flows. Our analysis found information suggesting that a larger diameter of the drainage cannula was a protective factor. However, this association should be confirmed in further investigations. MV management of patients on ECMO has also been considered [14]. Our multivariate analysis indicated a relation between higher PEEP levels on the third day of ECMO support and a lower risk of hospital mortality. This result is in agreement with those of previous reports including patients with ARDS [15], but no information has been published to date about PEEP titration in COVID-19 ECMO patients.

In conclusion, when indicating ECMO support for ARDS in COVID-19 patients, center case volume, age, driving pressure and the duration of symptoms should be taken into account. Length of MV prior to ECMO *per se* should not be included in this decision. In the management of these patients, PEEP levels should be kept high during the first days.

**Figure 1.**

**Upper panel: Cox model including relevant factors and its association with hospital mortality in critically ill COVID-19 patients with extracorporeal respiratory support.**

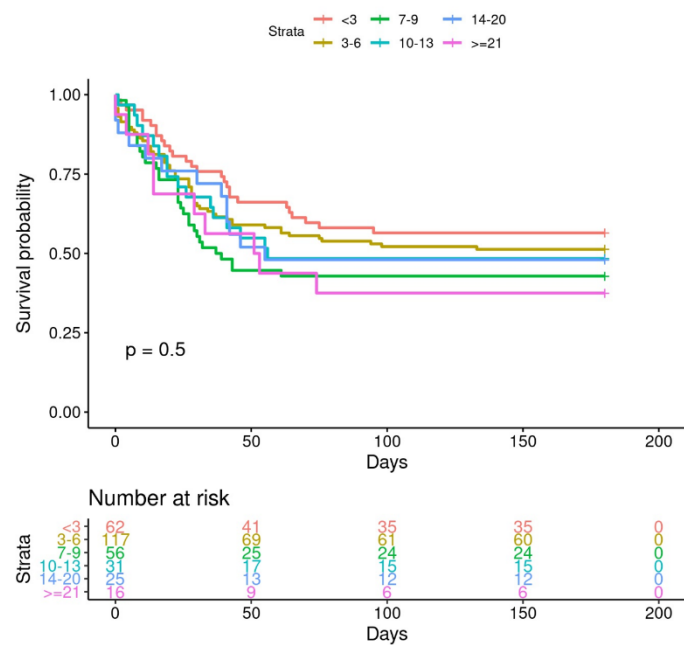
*bmp: breathings per minute; Fr: french; MV: mechanical ventilation PEEP: positive end-expiratory pressure.*

**Lower panel: a) Kaplan–Meier survival estimates according to preECMO mechanical ventilation days. b) Kaplan–Meier survival estimates according to age categories. c) Kaplan–Meier survival estimates according to center volume.**

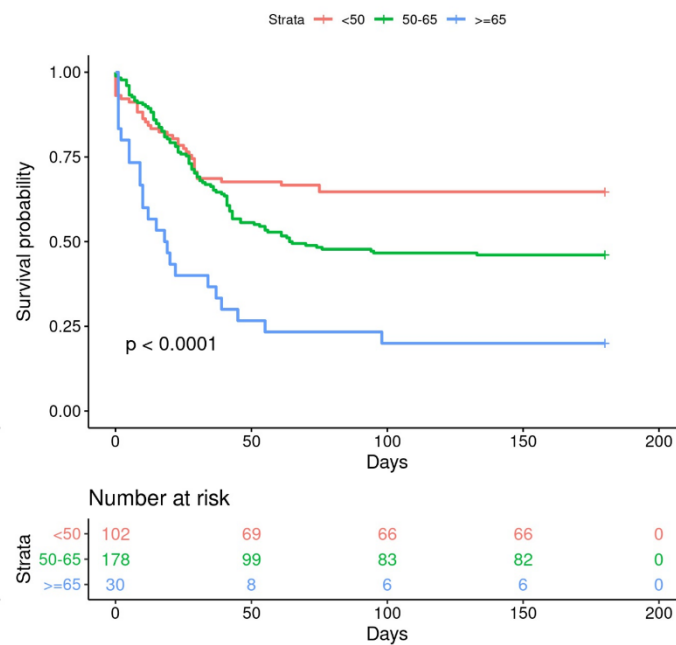
All patients (n=319)	Univariate HR (95% CI)	<i>p</i> value	Multivariate HR (95% CI)	<i>p</i> value
<b>Age (years)</b>	1.035 (1.017-1.053)	< 0.001	-	-
<50 [N=104]	-	-	reference	-
50-65 [N=185]	-	-	1.443 (0.959-2.172)	0.078
≥65 [N=30]	-	-	4.106 (2.341-7.202)	< 0.001
<b>Center volume (cases/year)</b>				
<30 [N=223]	-	-	reference	-
≥30 [N=96]	0.488 (0.331-0.721)	<0.001	0.516 (0.341-0.781)	0.002
<b>Ischemic cardiomyopathy [N=311]</b>	2.485 (1.307 – 4.726)	0.006	-	-
<b>ECMO retrieval (yes) [N=123]</b>	0.570 (0.407-0.798)	0.001	-	-
<b>Coinfection at ECMO initiation [N=95]</b>	1.388 (0.994-1.937)	0.054	1.240 (0.855-1.795)	0.256
<b>Second wave (ECMO start after June 30) [N=168]</b>	1.722 (1.246-2.381)	0.001	1.750 (1.235-2.480)	0.002
<b>MV days prior to ECMO</b>	1.009 (0.991-1.027)	0.33	-	-
<b>Symptom onset to ECMO (days) [N=309]</b>	1.024 (1.011-1.038)	<0.001	1.028 (1.003-1.053)	0.025
<b>PreECMO Driving pressure (cmH<sub>2</sub>O) [N=303]</b>	2.156 (1.172-3.968)	0.014	1.056 (1.017-1.097)	0.005
<b>PreECMO P<sub>a</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ratio (mmHg) [N=312]</b>	0.993 (0.985-1.001)	0.072	-	-
<b>PreECMO P<sub>a</sub>CO<sub>2</sub> (mmHg) [N=308]</b>	1.625 (0.912-2.896)	0.099	-	-
<b>PreECMO Respiratory rate (bpm) [N=307]</b>	0.995 (0.962-1.028)	0.75	-	-
<b>Fr of drainage cannula [N=303]</b>	0.897 (0.8210-0.981)	0.018	0.924 (0.932-1.027)	0.142
<b>Patients alive at day 3 (n=301)</b>	<b>Univariate HR (95% CI)</b>	<b><i>p</i> value</b>	<b>Multivariate HR (95% CI)</b>	<b><i>p</i> value</b>
<b>Fr of drainage cannula [N=301]</b>	0.911 (0.841-0.987)	0.024	0.922 (0.843-1.008)	0.075
<b>Driving pressure at day 3 (cmH<sub>2</sub>O) [N=301]</b>	1.065 (1.008-1.126)	0.025	1.042 (0.986-1.101)	0.145
<b>Tidal volume at day 3 (mL) [N=301]</b>	0.998 (0.997-0.999)	0.03	0.998 (0.997-1.000)	0.080
<b>PEEP at day 3 (cmH<sub>2</sub>O) [N=301]</b>	0.895 (0.840-0.954)	0.001	0.9045 (0.847-0.965)	0.003



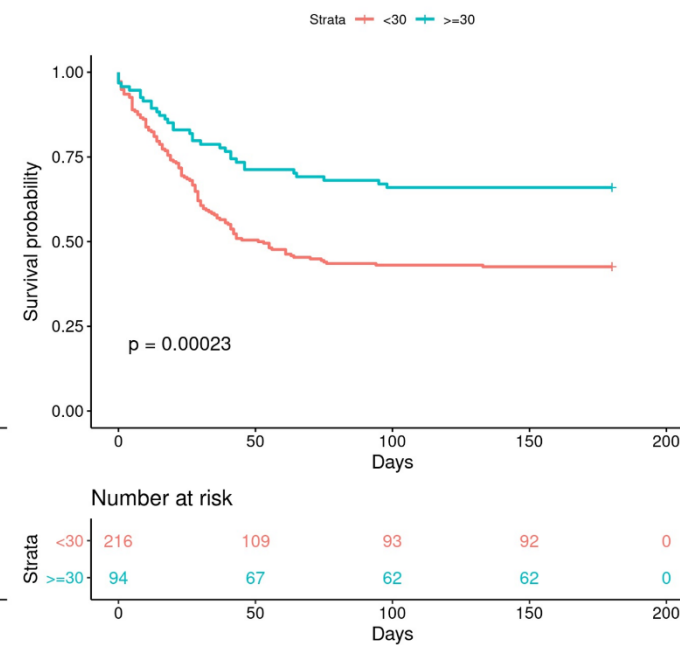
Kaplan-Meier estimate (Pre-ECMO VM days).



Kaplan-Meier estimate (Age categories).



Kaplan-Meier estimate (Center Volume).



**CONFLICT OF INTEREST:**

The authors declare that they have no conflict of interest.

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