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LETTER

Increased mortality in patients with COVID-19 receiving extracorporeal respiratory support during the second wave of the pandemic

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Dear Editor,

In the earliest phases of the pandemic, the use of extracorporeal life support in patients with severe coronavirus disease 2019 (COVID-19) was associated with disastrous outcomes. However, later series have shown better results, with hospital mortality ranging from 30 to 60% [1–3]. These series included patients receiving support during the first wave of the pandemic. Whilst a trend towards lower mortality in the overall COVID-19 population has been observed over time [4], preliminary data from the EuroECMO registry of the EuroELSO organization suggest that outcomes after extracorporeal membrane oxygenation (ECMO) in the second wave of the pandemic have worsened [5]. The present subanalysis examines this situation.

The ECMOVIBER (use of ECMO during the coVid-19 pandemic in the IBERian peninsula) retrospective observational cohort study included data from 24 ECMO centers, 22 in Spain and 2 in Portugal. We established a cut-off date of June 30, 2020 to define the first and second waves. For more information on the study, including the statistical methodology, see the online material. A total of 319 patients received extracorporeal respiratory support due to acute respiratory distress syndrome (ARDS): 151 (47.3%) during the first wave and 168 (52.6%) during the second. Hospital mortality was significantly higher during the second wave (60.1% vs. 41.1%, $p = 0.001$; Figure E3, online material). Patients supported during the second wave were older, had more comorbidities and were less likely to be treated at a high-volume center (Table 1). Time between admission to the intensive care unit (ICU) and ECMO start was longer, but not time since intubation. At ECMO indication, the PaO_2/FiO_2 was significantly higher and levels of COVID-19-associated inflammatory biomarkers were lower. Coinfection, together with new onset pneumonia during ECMO support, was more frequent in patients during the second wave (microbiological profile in table E3, online material).

Although the conclusions derived from an observational study should be treated with caution, these results could be interpreted as follows. The data suggest a certain relaxation of ECMO indication criteria during the second wave, due perhaps to the less demanding context and with the wider acceptance of the use of ECMO in COVID-19 in view of the positive results of early first analyses of large international databases (https://www.euroelso.net/covid-19/covid-19-survey/ and https://www.elso.org/Registry/FullCOVID19RegistryDashboard.aspx). Thus, in the second wave, low-volume centers treated more patients and this tendency for dispersion of ECMO cases may also have negatively affected the results [3]. Another possible influence on the survival difference is the change in the COVID-19 care protocol during the

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The members of "ECMOVIBER Study Group" are presented in the Acknowledgements section.

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Table 1 Patient pre-ECMO characteristics, ECMO management, complications and outcomes according to the wave of the pandemic in which the support was initiated

Variable*	All ($n=319$)	First wave¥ ($n=151$)	Second wave¥ ($n=168$)	p value
Age (years)	53 ± 10.3	51.2 ± 10.5	54.6 ± 9.9	0.004
Older than 65	30 (9.4)	8 (5.3)	22 (13.1)	0.016
Gender (male)	258 (80.9)	117 (77.5)	141 (83.9)	0.187
Active smoker	21 (6.6)	5 (3.3)	16 (9.5)	0.045
Hypertension	121 (37.9)	49 (32.4)	72 (42.8)	0.072
Diabetes mellitus	62 (19.4)	30 (19.9)	32 (19)	0.966
Chronic kidney disease	12 (3.8)	2 (1.3)	10 (5.9)	0.061
COPD	21 (6.6)	4 (2.6)	17 (10.1)	0.014
ICU admission to ECMO (days)	7 [4–12.8]	6 [3–10]	8 [5.5–13.5]	< 0.001
MV days prior to ECMO	5 [3–9]	5 [3–9]	6 [3–9.2]	0.646
Distribution of cases according to center volume				0.049
≥ 30	96 (30.1)	54 (35.8)	42 (25)	
< 30	223 (69.9)	97 (64.2)	126 (75)	
Variables before cannulation				
Coinfection at ECMO initiation	95 (29.8)	36 (23.8)	59 (35.1)	0.041
PaO_2/FiO_2 ratio (mmHg)	76 [63–90]	72 [62–86]	80 [68–93]	0.010
PEEP (cmH_2O)	12 [9–14]	12 [10–14]	10 [9–14]	0.035
Respiratory rate (bpm)	25 [22–30]	26 [22–30]	25 [21–30]	0.321
Driving pressure (cmH_2O)	18 [15–21]	18 [15–22]	17 [15–20]	0.253
Prone-positioning	305 (95.6)	146 (96.6)	168 (100)	0.179
Neuromuscular blockade	314 (98.4)	146 (96.7)	168 (100)	0.048
Corticosteroids				< 0.001
No treatment	54 (16.9)	45 (39.8)	9 (5.3)	
Dexamethasone	217 (68)	70 (46.3)	147 (87.5)	
Methylprednisolone	45 (14.1)	35 (23.2)	10 (5.9)	
Tocilizumab	95 (29.8)	64 (42.4)	31 (18.4)	< 0.001
Anticoagulation therapy	131 (41.1)	55 (36.4)	76 (45.2)	0.138
Arterial pH	7.3 [7.2–7.4]	7.3 [7.2–7.4]	7.3 [7.2–7.4]	0.192
Arterial P_aCO_2 (mmHg)	61 [51–73]	61 [50–71]	61 [51–73]	0.221
Arterial lactate (mmol/L)	1.6 [1.1–2.2]	1.6 [1.1–2.2]	1.6 [1.2–2.2]	0.96
Leukocyte count ($\times 10^9$/L)	12.8 [9.2–16.7]	11.4 [8.1–16.4]	13.2 [9.9–17.1]	0.026
Lymphocyte count ($\times 10^9$/L)	0.8 [0.5–1.2]	0.8 [0.5–1.2]	0.8 [0.5–1.2]	0.526
D-dimer (ng/mL)	2211.5 [1093–3752.5]	2275 [1087–3947]	2080 [1100–3500]	0.836
Ferritin (ng/mL)	1153 [716–1766]	1318 [833.5–2024.5]	1024 [671–1538]	0.031
IL-6 (pg/mL)	125.9 [37.5–564.5]	160 [53.5–1026.8]	100 [37.4–435]	0.062
Complications and outcomes				
New onset pneumonia on ECMO	161 (50.4)	62 (41)	99 (58.9)	0.003
Acute kidney injury	83 (26)	40 (26.5)	43 (25.6)	0.538
Vascular thrombosis	56 (15.6)	19 (12.6)	37 (22)	0.028
Circuit clotting	119 (37.3)	55 (36.4)	61 (36.3)	0.493
Hemorrhagic shock	44 (13.8)	21 (13.9)	23 (13.7)	1
ECMO days	17 [9–32]	16 [8–28]	18 [9–37]	0.107
MV days	36 [20–57]	35 [20–55]	36 [20–58]	0.710
ICU LOS (days)	41 [25–62]	42 [24–61]	41 [24–67]	0.829
Hospital LOS (days)	51 [32–78]	52 [36–76]	48 [29–79]	0.414
ECMO survival	180 (56.4)	100 (66.2)	80 (47.6)	0.001
Hospital survival	156 (48.9)	89 (58.9)	67 (39.9)	0.001
6 months follow up				0.001

Table 1 (continued)

Variable*	All ($n=319$)	First wave¥ ($n=151$)	Second wave¥ ($n=168$)	p value
Home with no oxygen	140 (43.8)	82 (54.3)	58 (34.5)	
Home with oxygen support	15 (4.7)	7 (4.6)	8 (4.8)	
Dead	157 (49.2)	59 (39.1)	98 (58.3)	
Still admitted	7 (0.2)	3 (0.1)	4 (0.2)	

Continuous variables are expressed as means ± standard deviation or median [IQ25–IQ75] and categorical variables as absolute value (percentage)

BMI body mass index (weight in kilograms divided by the square of the height in meters), *bpm* breaths per minute, *COPD* chronic obstructive pulmonary disease or asthma, *IL-6* interleukin 6, *MV* mechanical ventilation, *PEEP* positive end expiratory pressure

*The definition of the different variables is detailed in the Supplement

¥ First wave cases are those in which ECMO support was started before June 30 and second wave cases are those in which ECMO support was started after June 30 and before December 1, 2020

pandemic: for example, the use of corticosteroids and the criteria for intubation. Patients supported during the second wave suffered more coinfections, both at initiation and during extracorporeal support, and this multi-cause lung insult may have had a significant impact on the evolution of cases. Data suggest that in these patients intubation was delayed, and this is known to have potential deleterious effects in ventilated patients.

Our results confirm a higher mortality rate in COVID-19 patients supported with ECMO during the second wave than during the first. Here, we propose possible explanations for this phenomenon, which we feel should be considered in decisions regarding the technique's indication in future patients.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06517-9.

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Compliance with ethical standards

Conflicts of interest
The authors have no conflicts of interest to declare.

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