

SUPPLEMENTARY MATERIALS

Table S1. Bacteria responsible for co-infection at VV-ECMO initiation in C-ARDS patients.

	GRAM +	N	GRAM -	N	GRAM +/GRAM -	N
PNEUMONIA	<i>Streptococcus p.</i>	1	<i>Pseudomonas a.</i>	1		
	MSSA	4	<i>Serratia m.</i>	2		
	MRSA	2	CR- <i>Acinetobacter b.</i>	3		
			<i>Klebsiella p.</i>	1		
			CR-Kp	1		
BSI	<i>E. faecalis</i>	2				
PNEUMONIA + BSI			CR-Kp	1	MRSA	1
					CR- <i>Acinetobacter b.</i>	
ENTERIC COLONIZATION*			CR-Kp	2		
			CR- <i>Acinetobacter b.</i>	1		

*Defined by pathogen isolation in rectal swabs.
List of abbreviations: VV-ECMO: veno-venous extracorporeal membrane oxygenation; C-ARDS: COVID-19 related acute respiratory distress syndrome; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; CR-*Acinetobacter b.*: carbapenem-resistant *Acinetobacter baumannii*; CR-Kp: carbapenem-resistant *Klebsiella pneumoniae*; BSI: bloodstream infection.

Table S2. Trends of ventilator and VV-ECMO setting parameters from day 1 (24 hours after ECMO implantation) to day 14 in C-ARDS patients.

		Day 1 (N=48)	Day 3 (N=46; deaths=2)	Day 7 (N=44; deaths=4)	Day 14 (N=33; deaths=15)
Ventilator setting parameters					
TV/PBW, ml/Kg	Survivors	4.2 (4 - 5.7)	5 (3.0 - 5.2)	5.9 (5.1 - 6.2)	5.7 (4.2 - 6.3)
	Non-survivors	5.4 (4.6 - 6.0)	5.1 (4.2 - 6.0)	4.7 (4.1 - 5.5)	4 (3.6 - 5.4)
RR, breaths/min *	Survivors	10 (8 - 10)	8 (8 - 10)	18 (8 - 22)	20 (14 - 26)
	Non-survivors	10 (8 - 10)	10 (8 - 10)	10 (10 - 15)	14 (10 - 16)
FiO ₂ VENT, %	Survivors	80 (60 - 100)	60 (50 - 90)	50 (45 - 60)	50 (30 - 70)
	Non-survivors	60 (50 - 75)	50 (50 - 80)	60 (50 - 80)	60 (50 - 90)
PEEP, cmH ₂ O *	Survivors	8 (8 - 10)	10 (10 - 15)	8 (6 - 10)	10 (8 - 10)
	Non-survivors	10 (8 - 12)	8 (6 - 12)	8 (5 - 10)	6 (5 - 10)
ECMO setting parameters					
BF, L/min	Survivors	3.8 (3.8 - 4.8)	4.0 (4.0 - 4.3)	3.9 (3.0 - 4.3)	3.8 (3.6 - 5.5)
	Non-survivors	4.0 (3.5 - 4.3)	4.1 (3.6 - 4.5)	4.0 (3.3 - 4.6)	4.1 (3.5 - 4.9)
SG, L/min *	Survivors	4.0 (3.5 - 5.0)	5.0 (3.5 - 5.5)	5.2 (4.0 - 7.0)	6.5 (5.5 - 8.6)
	Non-survivors	3.5 (2.7 - 4.0)	4.0 (3.5 - 5.0)	5 (3.7 - 6.2)	6.2 (5.0 - 7.5)
FiO ₂ ECMO, %	Survivors	100 (80 - 100)	90 (50 - 100)	60 (45 - 100)	100 (75 - 100)
	Non-survivors	90 (80 - 100)	80 (70 - 100)	90 (75 - 100)	100 (70 - 100)

Variables are expressed as median (IQR).

* The parameter significantly differed over the time ($p < 0.05$)

List of abbreviations: C-ARDS: COVID-19 related acute respiratory distress syndrome; VV-ECMO: veno-venous extracorporeal membrane oxygenation; TV/PBW: tidal volume divided by predicted body weight; RR: respiratory rate; FiO₂VENT: ventilator inspired fraction of oxygen; PEEP: positive end-expiratory pressure; BF: blood flow; SG: sweep gas; FiO₂ECMO: ECMO inspired fraction of oxygen.

Table S3. Comparison of the baseline characteristics of patients affected by C-ARDS before VV-ECMO implantation between the first and subsequent waves of COVID-19 outbreak.

VARIABLES	FIRST WAVE* (N = 14)	SUBSEQUENT WAVES* (N = 34)	<i>p-value</i>
Age, years, median (IQR)	53 (50 - 55)	56 (49 - 61)	0.601
Sex, male, n (%)	11 (78.6)	26 (76.5)	0.875
BMI, Kg/m ² , median (IQR)	28.4 (27.6 - 33.5)	30.9 (26.6 - 34.3)	0.812
Pre-existing comorbidities:			
No comorbidity, n (%)	5 (35.7)	2 (5.9)	0.017
Obesity, n (%)	5 (35.7)	18 (52.9)	0.278
Active smoking, n (%)	2 (14.3)	6 (17.6)	0.776
Hypertension, n (%)	4 (28.6)	17 (50)	0.174
CAD, n (%)	0	1 (2.9)	1.000
Lung disease (asthma/COPD), n (%)	1 (7.1)	5 (14.7)	0.656
Diabetes Mellitus, n (%)	2 (14.3)	5 (14.7)	1.000
Hypothyroidism, n (%)	2 (14.3)	2 (5.9)	0.569
Chronic immunosuppression, n (%)	0	1 (2.9)	1.000
Severity score:			
SOFA	10 (7 - 12)	10 (8 - 12)	0.680
APACHE II	24 (22 - 25)	24 (19 - 25)	0.632
Pre-existing bacterial co-infection, n (%)	3 (21.4)	16 (47.1)	0.099
Days from COVID-19 onset to ECMO, median (IQR)	17 (11 - 23)	17 (13 - 21)	0.502
Days from hospitalization to ECMO, median (IQR)	12 (6 - 17)	12 (8 - 17)	0.982
Days of ICU before ECMO, median (IQR)	8 (5 - 14)	6 (3 - 10)	0.116
Mobile ECMO, n (%)	10 (71.4)	31 (91.2)	0.171
Non-invasive ventilatory support (NIS) before intubation, n (%):	10 (71.4)	33 (97.1)	0.021
HFCN, n (%)	1 (7.1)	5 (14.7)	
CPAP, n (%)	6 (42.9)	28 (82.4)	
NIV, n (%)	4 (28.6)	11 (32.4)	
Days of NIS, median (IQR)	3 (0 - 9)	6 (4 - 10)	0.094
Days of invasive mechanical ventilation (IMV), median (IQR)	7 (4 - 9)	3 (2 - 6)	0.021
Total days of ventilation (NIS+IMV), median (IQR)	11 (7 - 17)	11 (8 - 13)	0.955
Rescue therapies:			
LRM, n (%)	12 (85.7)	11 (32.4)	0.001
Pronation, n (%)	12 (85.7)	31 (91.2)	0.621
iNO, n (%)	4 (28.6)	13 (38.2)	0.525
COVID-19 targeted therapies:			
Steroids, n (%)	5 (35.7)	27 (79.4)	0.004
Tocilizumab, n (%)	6 (42.9)	7 (20.6)	0.115
Hyperimmune plasma, n (%)	0	6 (17.6)	0.093
Remdesevir, n (%)	6 (42.9)	8 (23.5)	0.181
Pre-ECMO ventilator setting and arterial blood gases:			
TV/PBW, ml/Kg, median (IQR)	7.2 (6.4 - 8.1)	6.6 (6.1 - 7)	0.038
RR, breaths/min, median (IQR)	25 (18 - 30)	28 (25 - 31)	0.104
PEEP, cmH ₂ O, median (IQR)	12 (10 - 15)	12 (8 - 12)	0.103
FiO ₂ , %, median (IQR)	100 (95 - 100)	100 (100 - 100)	0.868
P _{plat} , cmH ₂ O, median (IQR)	29 (25 - 35)	27 (22 - 30)	0.027
DP, cmH ₂ O, median (IQR)	14 (13 - 22)	16 (12 - 19)	0.256
Static lung compliance, ml/ cmH ₂ O, median (IQR)	28.6 (20.5 - 40.4)	29.2 (24.6 - 37.1)	0.671
pH, median (IQR)	7.33 (7.28 - 7.38)	7.36 (7.30 - 7.41)	0.199
PaO ₂ /FiO ₂ , mmHg, median (IQR)	64 (55 - 70)	64 (54 - 72)	0.904
PaCO ₂ , mmHg, median (IQR)	59 (53 - 73)	59 (54 - 68)	0.958
HCO ₃ ⁻ , mmol/L, median (IQR)	31 (27 - 35)	33 (31 - 37)	0.192
Murray score, median (IQR)	3.4 (3.3 - 3.8)	3.3 (3.0 - 3.5)	0.157

* 'First wave' was defined as the pandemic time between March and August 2020; 'Subsequent waves' comprehended the time between September 2020 and December 2021.

List of abbreviations: C-ARDS: COVID-19 related acute respiratory distress syndrome; VV-ECMO: veno-venous extracorporeal membrane oxygenation; IQR: interquartile range; BMI: body mass index; CAD: coronary artery disease; COPD: *chronic obstructive pulmonary disease*; SOFA: sequential organ failure assessment score; APACHE II: acute physiologic assessment and chronic health evaluation score II; ICU: intensive care unit; NIS: non-invasive ventilatory support; HFNC: high-flow nasal cannula; CPAP: continuous positive airway pressure; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; LMR: lung recruitment maneuvers; iNO: inhaled nitric oxide; TV/PBW: tidal volume divided by predicted body weight; RR: respiratory rate; PEEP: positive end-expiratory pressure; FiO₂: inspired fraction of oxygen; P_{plat}: plateau pressure; DP: driving pressure; PaO₂: arterial pressure of oxygen; PaCO₂: arterial pressure of carbon dioxide; HCO₃: plasma bicarbonate concentrations.

Table S4. Comparison of outcomes of C-ARDS patients treated with VV-ECMO between the first and subsequent waves of COVID-19 outbreak.

OUTCOMES	FIRST WAVE* (N = 14)	SUBSEQUENT WAVES* (N = 34)	<i>p-value</i>
Days on ECMO, median (IQR)	22 (17 - 32)	14 (10 - 23)	0.012
Days on IMV, median (IQR)	35 (24 - 43)	23 (15 - 27)	0.002
Tracheostomy, n (%)	8 (57.1)	8 (23.5)	0.025
LOS in ICU, days, median (IQR)	38 (30 - 49)	24 (17 - 32)	0.005
LOS in Hospital, days, median (IQR)	44 (35 - 58)	28 (21 - 38)	0.005
Mortality at day 28 post-ECMO, n (%)	6 (42.9)	26 (76.5)	0.025
Mortality at day 60 post-ECMO, n (%)	11 (78.6)	30 (88.2)	0.400
Complications:			
ECMO-related:			
Cannula thrombosis, n (%)	1 (7.1)	1 (2.9)	0.503
Membrane clotting, n (%)	3 (21.4)	11 (32.4)	0.449
Circuit change, n (%)	4 (28.6)	9 (26.5)	0.882
Bleeding, n (%)	13 (92.9)	28 (82.4)	0.349
Haemorrhagic stroke, n (%)	1 (7.1)	2 (5.9)	1.000
Haemorrhagic shock, n (%)	1 (7.1)	1 (2.9)	0.503
Superinfection, n (%)	11 (78.6)	32 (94.1)	0.140
Superinfection by MDR, n (%)	5 (35.7)	25 (73.5)	0.014
VAP, n (%)	10 (71.4)	29 (85.3)	0.416
BSI, n (%)	8 (57.1)	10 (29.4)	0.071
Septic shock, n (%)	11 (78.6)	16 (47.1)	0.045
Deep venous thrombosis, n (%)	3 (21.4)	2 (5.9)	0.140
Pulmonary thromboembolism, n (%)	0	3 (8.8)	0.546
Acute kidney disease, n (%)	8 (57.1)	13 (38.2)	0.230
Renal replacement therapy, n (%)	4 (28.6)	7 (20.6)	0.550

* 'First wave' was defined as the pandemic time between March and August 2020; 'Subsequent waves' comprehended the time between September 2020 and December 2021.

List of abbreviations: C-ARDS: COVID-19 related acute respiratory distress syndrome; VV-ECMO: veno-venous extracorporeal membrane oxygenation; IMV: invasive mechanical ventilation; LOS: length of stay; ICU: intensive care unit; MDR: multi-drug resistant pathogens; VAP: ventilator-associated pneumoniae; BSI: bloodstream infection.

Figure S1. Timeline from the start of COVID-19-related symptoms to VV-ECMO implantation in survivor (continuous arrow) and non-survivor (dashed arrow) C-ARDS patients. Time is expressed as days, median (IQR). *List of abbreviations:* C-ARDS: COVID-19 related acute respiratory distress syndrome; VV-ECMO: veno-venous extracorporeal membrane oxygenation; IQR: interquartile range.

