Comparative outcomes of extracorporeal membrane oxygenation for COVID-19 delivered in experienced European centres during successive SARS-CoV-2 variant outbreaks (ECMO-SURGES): an international, multicentre, retrospective cohort study

Matthieu Schmidt, David Hajage, Micha Landoll, Benjamin Pequignot, Elise Langouet, Matthieu Amalric, Armand Mekontso-Dessap, Luis Chiscano-Camon, Katy Surman, Dylan Finnerty, Patricia Santa-Teresa, Antonio Arcadipane, Pablo Millán, Roberto Roncon-Albuquerque Jr, Aaron Blandino-Ortiz, Pablo Blanco-Schweizer, Pilar Ricart, Ricardo Gimeno-Costa, Carlos Luis Albacete, Philip Fortuna, Peter Schellongowski, Dieter Dauwe, Hadrien Winiszewski, Antoine Kimmoun, Bruno Levy, Greet Hermans, Giacomo Grasselli, Guillaume Lebreton, Christophe Guervilly, Gennaro Martucci, Christian Karagiannidis, Jordi Riera, Alain Combes*, for the ECMO-SURGES Investigators†*

Summary

Background To inform future research and practice, we aimed to investigate the outcomes of patients who received extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS) due to different variants of SARS-CoV-2.

Methods This retrospective study included consecutive adult patients with laboratory-confirmed SARS-CoV-2 infection who received ECMO for ARDS in 21 experienced ECMO centres in eight European countries (Austria, Belgium, England, France, Germany, Italy, Portugal, and Spain) between Jan 1, 2020, and Sept 30, 2021. We collected data on patient characteristics, clinical status, and management before and after the initiation of ECMO. Participants were grouped according to SARS-CoV-2 variant (wild type, alpha, delta, or other) and period of the pandemic (first [Jan 1–June 30] and second [July 1–Dec 31] semesters of 2020, and first [Jan 1–June 30] and second [July 1–Sept 30] semesters of 2021). Descriptive statistics and Kaplan-Meier survival curves were used to analyse evolving characteristics, management, and patient outcomes over the first 2 years of the pandemic, and independent risk factors of mortality were determined using multivariable Cox regression models. The primary outcome was mortality 90 days after the initiation of ECMO, with follow-up to Dec 30, 2021.

Findings ECMO was initiated in 1345 patients. Patient characteristics and management were similar for the groups of patients infected with different variants, except that those with the delta variant had a younger median age and less hypertension and diabetes. 90-day mortality was 42% (569 of 1345 patients died) overall, and 43% (297/686) in patients infected with wild-type SARS-CoV-2, 39% (152/391) in those with the alpha variant, 40% (78/195) in those with the delta variant, and 58% (42/73) in patients infected with other variants (mainly beta and gamma). Mortality was 10% higher (50%) in the second semester of 2020, when the wild-type variant was still prevailing, than in other semesters (40%). Independent predictors of mortality were age, immunocompromised status, a longer time from intensive care unit admission to intubation, need for renal replacement therapy, and higher Sequential Organ Failure Assessment haemodynamic component score, partial pressure of arterial carbon dioxide, and lactate concentration before ECMO. After adjusting for these variables, mortality was significantly higher with the delta variant than with the other variants, the wild-type strain being the reference.

Interpretation Although crude mortality did not differ between variants, adjusted risk of death was highest for patients treated with ECMO infected with the delta variant of SARS-CoV-2. The higher virulence and poorer outcomes associated with the delta strain might relate to higher viral load and increased inflammatory response syndrome in infected patients, reinforcing the need for a higher rate of vaccination in the population and updated selection criteria for ECMO, should a new and highly virulent strain of SARS-CoV-2 emerge in the future. Mortality was noticeably lower than in other large, multicentre series of patients who received ECMO for COVID-19, highlighting the need to concentrate resources at experienced centres.

Funding None.

Lancet Respir Med 2023; 11: 163–75

Published Online January 11, 2023 https://doi.org/10.1016/S2213-2600(22)00438-6

This online publication has been corrected. The corrected version first appeared at thelancet.com/respiratory on February 1, 2023

See Comment page 113

*Co-senior authors

†The ECMO-SURGES Investigators are listed in the appendix (pp 23–24)

INSERM, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, Sorbonne Université, Paris, France (Prof M Schmidt MD, Prof G Lebreton MD, Prof A Combes MD); **Service de Médecine Intensive-Réanimation, Institut de Cardiologie, AP-HP Sorbonne Université Hôpital Pitié–Salpêtrière, Paris, France** (Prof M Schmidt, E Langouet MD, Prof A Combes); **Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpitaux Universitaires Pitié Salpêtrière-Charles Foix, Département de Santé Publique, Centre de Pharmacoépidémiologie (Cephepi), Paris, France** (D Hajage MD); **ARDS and ECMO Centre Cologne-Merheim, Witten/Herdecke University, Cologne, Germany** (M Landoll MSc, Prof C Karagiannidis MD);

Department of Cardiovascular Engineering, Institute of Applied Medical Engineering, Medical Faculty, RWTH Aachen University, Aachen, Germany (M Landoll, Prof C Karagiannidis); **Université de Lorraine, CHRU de Nancy, Institut Lorrain du Cœur et des Vaisseaux, Service de Médecine Intensive-Réanimation, U1116, FCRIN-INICRCT, Nancy, France** (B Pequignot MD, Prof A Kimmoun MD, Prof B Levy MD); **Service de Médecine Intensive Réanimation, CHU Hôpital Nord, AP-HM, Marseille, France** (M Amalric MD, C Guervilly MD); **Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri-Mondor, AP-HP, Créteil, France** (Prof A Mekontso-Dessap MD); **Department of Intensive Care, Hospital Universitari Vall d'Hebron, Barcelona, Spain** (L Chiscano-Camon MD); **SODIR, Vall d'Hebron Institut de Recerca, Barcelona, Spain** (L Chiscano-Camon, J Riera MD); **Intensive Care, Division of Surgery, Transplant and Anaesthetics, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK** (K Surman MD, D Finnerty MD); **Department of Intensive Care, Hospital Universitario Gregorio Marañón, Madrid, Spain** (P Santa-Teresa MD); **Department of Anesthesia and Intensive Care, IRCCS-ISMETT (Istituto Mediterraneo per I Trapianti e Terapia ad alta specializzazione), Palermo, Italy** (A Arcadipane MD, G Martucci MD); **Department of Intensive Care, Hospital Universitario La Paz, Madrid, Spain** (P Millán MD); **Department of Intensive Care, São João Universitary Hospital Centre, Porto, Portugal** (R Roncon-Albuquerque Jr MD); **Department of Intensive Care, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain** (A Blandino-Ortiz MD); **Department of Intensive Care Hospital Universitario Rio Hortega, Valladolid, Spain** (P Blanco-Schweizer MD); **Department of Intensive Care Hospital Universitari Germans Trias i Pujol, Badalona – Barcelona, Spain** (P Ricart MD); **Department of Intensive Care, Hospital Universitari i Politècnic La Fe, València, Spain**

Research in context

Evidence before this study

Data from retrospective cohorts of patients with COVID-19 treated with extracorporeal membrane oxygenation (ECMO) during the first few weeks of the pandemic revealed that despite longer ECMO runs and intensive care unit (ICU) length of stay, the mortality of patients with COVID-19 supported by ECMO was similar to that reported in the EOLIA trial and in other large retrospective series of ECMO for non-COVID-19 acute respiratory distress syndrome (ARDS). However, less favourable outcomes were reported in patients treated from July to December, 2020, and a strong effect of patient volume and ECMO centre experience has been noted in most multicentre cohorts published so far, which included almost exclusively patients infected with the wild-type strain of SARS-CoV-2. We aimed to identify all available evidence on the outcomes of patients who received ECMO for severe COVID-19 according to the different SARS-CoV-2 variants, during successive waves of the pandemic. We searched PubMed for articles published in any language in peer-reviewed journals from Jan 1, 2020, up to Aug 8, 2022, with the terms "extracorporeal membrane oxygenation" and either "COVID-19" or "severe acute respiratory syndrome coronavirus 2", and focused on large, multicentre cohort studies that included at least 200 patients treated with ECMO. We found 15 studies, but none of them reported patient outcomes after infection with different variants of SARS-CoV-2.

Added value of this study

Our multicentre, international, retrospective study included 1345 patients who received ECMO in 21 experienced centres in eight European countries. Patient characteristics and management were similar across different variants of SARS-CoV-2, except that the delta group had a younger age and fewer comorbidities than did the groups for other variants. We found that crude 90-day mortality did not differ between variants and was 15–25% lower than the in-hospital mortality reported in other large COVID-19 series. Independent predictors of mortality were age, immunocompromised status, a longer time from ICU admission to intubation, need for renal replacement therapy, and higher Sequential Organ Failure Assessment haemodynamic component score, partial pressure of arterial carbon dioxide, and lactate concentration before ECMO. After adjusting for these variables, mortality was significantly higher with the delta variant than with other variants of SARS-CoV-2.

Implications of all the available evidence

Adjusted mortality of patients with COVID-19-related ARDS treated with ECMO was higher for those infected with the delta variant, who were younger and had fewer comorbidities at ECMO initiation. The higher virulence and poorer outcomes associated with the delta strain might relate to higher viral load and increased inflammatory response syndrome in infected patients, reinforcing the need for a higher rate of vaccination in the population and updated selection criteria for ECMO, should a new and highly virulent strain of SARS-CoV-2 emerge in the future. Mortality in our series of patients treated in experienced ECMO centres was noticeably lower than that in other large multicentre series of patients receiving ECMO for COVID-19, underlying the need to concentrate resources at experienced centres, especially during pandemics that impose substantial burdens on health-care systems.

Introduction

The global pandemic of SARS-CoV-2 started in January, 2020, with the most serious forms of the disease rapidly evolving to severe acute respiratory distress syndrome (ARDS). Based on positive results from randomised controlled trials,[1–3] and a meta-analysis of individual patient data[4] done in non-COVID-19-related ARDS, extracorporeal membrane oxygenation (ECMO) was recommended for patients with COVID-19 who had profound hypoxaemia or high thoracic pressures despite lung-protective mechanical ventilation, including prone positioning.[5–7] Single-centre[8] and multicentre international cohorts[5,9–11] showed that despite longer ECMO runs and length of stay in the intensive care unit (ICU), the mortality of patients with COVID-19 who were treated with ECMO during the first few weeks of the pandemic was similar to that reported in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial[1] and in other large retrospective series of ECMO for non-COVID-19 ARDS.[12–14] However, these encouraging results were challenged by less favourable outcomes in patients treated after July, 2020. For example, the 90-day mortality increased from 36% to 48% between the first and second waves of COVID-19 in patients admitted to hospital at Sorbonne University, Paris, France.[15] Similar increases in mortality were reported in the large cohort of the Extracorporeal Life Support Organization (ELSO)[9] and in patients treated in Spain and Portugal.[16] The reasons for this increase in mortality are still unclear and the respective effects of specific SARS-CoV-2 strains responsible for ARDS, ECMO centre experience, patient characteristics, and patient management have not yet been investigated in detail in large, multicentre cohorts.

The primary objective of this multicentre, international, retrospective study was to analyse, according to different SARS-CoV-2 variants, the characteristics and 90-day mortality of patients with COVID-19 who received ECMO in experienced European centres. Secondary objectives were to report the evolving characteristics, management, and outcomes of these patients during the first 2 years of the pandemic and to determine independent risk factors for mortality.

Methods

Study design and participants

The ECMO-SURGES study was a multicentre, retrospective cohort study done in 21 medium-volume (15–30 venoarterial ECMO [VA-ECMO] or venovenous ECMO [VV-ECMO] cases per year) to high-volume (>30 cases per year) experienced ECMO centres[17] across eight European countries (Austria, Belgium, England, France, Germany, Italy, Portugal, and Spain). Centres were invited to participate if they had an ECMO programme established for at least 5 years and were currently caring for patients with COVID-19 on ECMO. All participating ICUs obtained institutional review board approval in accordance with their local regulations.

All consecutive adult patients with laboratory-confirmed SARS-CoV-2 infection who received VA-ECMO or VV-ECMO for severe ARDS from Jan 1, 2020, to Sept 30, 2021, were included retrospectively. Patients receiving ECMO for isolated refractory cardiogenic shock were excluded. The end of follow-up was Dec 30, 2021.

Time periods and SARS-CoV-2 variants

We defined four periods during the study: Jan 1–June 30, 2020 (first semester of 2020, S1-2020); July 1–Dec 31, 2020 (second semester of 2020, S2-2020); Jan 1–June 30, 2021 (first semester of 2021, S1-2021); and July 1–Sept 30, 2021 (second semester of 2021, S2-2021). SARS-CoV-2 variants were classified as wild type, alpha (B.1.17), delta (B.1.617.2), or other variants. This latter group combined the gamma (P.1), beta (B.1.351), mu (B.1.621), and B.1.160 variants. Because sequencing was not routinely done during the first and second waves of the pandemic, all patients treated before Oct 31, 2020 (when the alpha variant was first reported in England) were considered to have the wild-type variant. When SARS-CoV-2 variant sequencing was not done, patients were categorised as having the predominant variant in the country at the date of admission to the ICU according to the European Centre for Disease Prevention and Control, which reported the number of cases per week and per country in Europe on a weekly basis.

Data collection

We collected patient information on age, sex, body-mass index, comorbidities, SARS-CoV-2 vaccination status, haemodynamic component of the Sequential Organ Failure Assessment (SOFA) score, and dates of first symptom(s) and hospital and ICU admissions. Patients were defined as having an immunocompromised status if they had haematological malignancies, had an active solid tumour or had received specific anti-tumour treatment within the previous year, had undergone solid-organ transplant, were living with HIV, or were on long-term corticosteroids or immunosuppressants. Additionally, we collected pre-ECMO implantation information: previous rescue therapies; date of initiation of high-flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation; and ventilator parameters (mode, positive end-expiratory pressure [PEEP], fraction of inspired oxygen [FiO_2], respiratory rate [RR], tidal volume [V_t], plateau pressure [P_{plat}], arterial blood gas parameters including partial pressure of oxygen [PaO_2] and partial pressure of carbon dioxide [$PaCO_2$], and routine laboratory values). Driving pressure (ΔP) was defined as P_{plat} minus PEEP, and mechanical power (J/min) was calculated using the equation:[18]

$$\text{Mechanical power} = 0{\cdot}098 \times V_t \times RR \times (\text{peak pressure} - 1/2 \times \Delta P)$$

If not specified, peak pressure was considered equal to plateau pressure.

Outcomes

Patient status was recorded 90 days after ECMO initiation. For patients who were still alive at day 90, the following states were defined: on ECMO; on mechanical ventilation and weaned off ECMO; still in hospital and weaned off ECMO and mechanical ventilation; in a rehabilitation centre; or back at home. Causes of death, in-ICU and in-hospital death rates, and the time spent on ECMO, on mechanical ventilation, in the ICU, and in hospital were also noted. Data on mechanical ventilation parameters and other adjuvant therapies were collected on days 1 and 3 after ECMO initiation. ECMO-related complications and organ dysfunction included clogged circuit or membrane, ECMO circuit change, heparin-induced thrombocytopenia, major

(R Gimeno-Costa MD); **Department of Intensive Care, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain** (C L Albacete MD); **Medical Emergency Unit, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal** (P Fortuna MD); **Department of Medicine I, Intensive Care Unit 13i2, Comprehensive Cancer Centre, Centre of Excellence in Medical Intensive Care (CEMIC), Medical University of Vienna, Vienna, Austria** (P Schellongowski MD); **Department of Cardiac Surgery** (D Dauwe MD) **and Medical Intensive Care Unit, Department of General Internal Medicine** (Prof G Hermans MD), **University Hospitals Leuven, Leuven, Belgium; Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Belgium** (Prof G Hermans); **Medical Intensive Care Unit, Besançon University Hospital, Besançon, France** (H Winiszewski MD); **Research Unit EA 3920, University of Franche-Comté, Besançon, France** (H Winiszewski); **Dipartimento di Anestesia, Rianimazione ed Emergenza, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy** (Prof G Grasselli MD); **Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, University of Milan,**

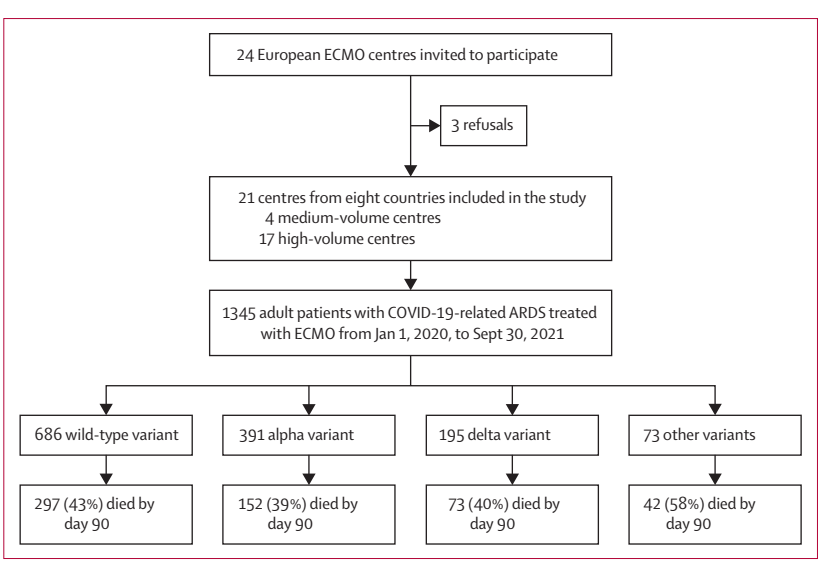

Figure 1: **Study flowchart**
ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation.

Milan, Italy (Prof G Grasselli); **Service de Chirurgie Cardiaque, Institut de Cardiologie, APHP Sorbonne Université Hôpital Pitié–Salpêtrière, Paris, France** (Prof G Lebreton); **CEReSS - Centre for Studies and Research on Health Services and Quality of Life EA3279, Aix-Marseille University, Marseille, France** (C Guervilly)

Correspondence to: Prof Alain Combes, Service de Médecine Intensive–Réanimation, Sorbonne Université, Hôpital Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, F-75013 Paris, France
alain.combes@aphp.fr

See **Online** for appendix

For more on the **Extracorporeal Life Support Organization** see https://www.elso.org/

For more on the **European Centre for Disease Prevention and Control COVID-19 reporting** see https://www.ecdc.europa.eu/en/covid-19

	All patients (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
Age, years	53 (44–59)	54 (46–60)	53 (45–58)	46 (37–55)	55 (49–62)	<0·0001
Sex	..	..	..	..	..	0·261
Male	1035 (77%)	540 (79%)	300 (77%)	143 (73%)	52 (71%)	..
Female	310 (23%)	146 (21%)	91 (23%)	52 (27%)	21 (29%)	..
Body-mass index, kg/m²	30 (27–35)	29 (26–34)	31 (27–37)	31 (28–35)	31 (27–36)	0·017
SOFA cardiovascular component ≥3	573 (53%)	323 (56%)	145 (50%)	75 (51%)	30 (43%)	0·083
COVID-19 vaccination status	..	..	..	..	..	0·0005
1 vaccine dose	24 (2%)	0	5 (1%)	15 (8%)	4 (5%)	..
2 vaccine doses	17 (1%)	0	3 (1%)	12 (6%)	2 (3%)	..
Comorbidities						
Hypertension	555 (41%)	299 (44%)	166 (42%)	55 (28%)	35 (48%)	0·0008
Diabetes	327 (24%)	193 (28%)	89 (23%)	27 (14%)	18 (25%)	0·0005
Ischaemic cardiomyopathy	76 (6%)	41 (6%)	24 (6%)	7 (4%)	4 (5%)	0·589
Chronic respiratory disease*	158 (12%)	77 (11%)	52 (13%)	15 (8%)	14 (19%)	0·045
Immunocompromised†	84 (6%)	41 (6%)	23 (6%)	12 (6%)	8 (11%)	0·407
Pregnant	22 (2%)	7 (1%)	9 (2%)	6 (3%)	0 (0%)	0·102
Time from first symptoms to hospital admission, days	6 (3–8)	6 (3–8)	5 (3–8)	6 (4–8)	6 (3–8)	0·383
Time from ICU admission to intubation, days	1 (0–4)	0 (0–3)	1 (0–5)	1 (0–3)	3 (1–6)	<0·0001
Time from intubation to ECMO, days	4 (1–8)	4 (2–8)	3 (1–7)	4 (1–8)	4 (1–7)	0·017
Retrieval on ECMO by MERT from another hospital	857 (64%)	434 (63%)	252 (64%)	132 (68%)	39 (53%)	0·185
High-flow nasal oxygen	675 (50%)	310 (45%)	199 (51%)	114 (58%)	52 (71%)	<0·0001
Duration, days	1 (0–4)	1 (0–4)	2 (0–5)	1 (0–4)	3 (1–6)	<0·0001
Non-invasive ventilation	567 (42%)	229 (33%)	197 (50%)	100 (51%)	41 (56%)	<0·0001
Duration, days	1 (0–4)	0 (0–3)	1 (0–4)	2 (0–5)	3 (1–6)	0·0009
Ventilation parameters						
FiO_2	100 (100–100)	100 (100–100)	100 (100–100)	100 (95–100)	100 (100–100)	0·581
PEEP, cm H_2O	12 (10–14; n=1157)	12 (10–14; n=608)	12 (10–14; n=327)	12 (10–15; n=162)	12 (10–14; n=60)	0·361
Tidal volume, mL/kg PBW	6·1 (5·5–6·9; n=1068)	6·1 (5·6–7·0; n=569)	6·1 (5·4–6·9; n=303)	6·3 (5·7–7·2; n=151)	6·1 (5·5–7·0; n=56)	0·215
Respiratory rate, breaths per min	26 (23–30; n=1077)	26 (23–30; n=587)	26 (22–30; n=291)	25 (22–28; n=141)	28 (25–30; n=58)	0·0038
Driving pressure, cm H_2O‡	18 (15–22; n=1050)	18 (15–22; n=545)	18 (15–21; n=303)	16 (14–20; n=145)	19 (16–22; n=57)	0·0060
Static compliance, mL/cm H_2O	22·5 (17·5–29·7; n=994)	22·5 (17·6–30·0; n=519)	23·0 (16·9–28·3; n=284)	25·0 (18·5–32·3; n=137)	20·7 (15·2–23·8; n=54)	0·0046
Mechanical power, J/min§	21·7 (17·6–25·9; n=939)	22·1 (18·2–26·3; n=513)	20·9 (17·1–25·2; n=254)	21·1 (16·8–25·7; n=120)	22·2 (17·5–26·4; n=52)	0·086

(Table 1 continues on next page)

bleeding, ischaemic or haemorrhagic stroke, renal replacement therapy, proven pulmonary embolism, pneumothorax, ventilator-associated pneumonia, and bacteraemia. Major bleeding was defined as requiring at least 2 units of packed red blood cells for an obvious haemorrhagic event, an event necessitating a surgical or interventional procedure, an intracerebral haemorrhage, or any other bleeding event leading to death.

Statistical analysis

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for reporting cohort studies. All consecutive adult patients with laboratory-confirmed SARS-CoV-2 infection who received ECMO at the 21 centres during the study period were included, and no sample size calculation was performed. Details of the statistical analyses are provided in the appendix (pp 2–5).

	All patients (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
(Continued from previous page)						
Last blood gas values pre-ECMO						
pH	7·32 (7·24–7·38)	7·31 (7·23–7·39)	7·33 (7·25–7·39)	7·32 (7·25–7·38)	7·34 (7·28–7·38)	0·283
PaO_2/FiO_2 ratio	66 (55–80)	68 (56–81)	65 (51–80)	65 (51–80)	60 (56–67)	0·0008
$PaCO_2$, mm Hg	60 (50–71)	60 (50–74)	60 (50–70)	60 (50–70)	56 (48–64)	0·087
Arterial lactate, mmol/L	1·4 (1·0–2·0)	1·4 (1·1–2·0)	1·4 (1·0–2·0)	1·3 (1·0–2·0)	1·5 (1·2–2·1)	0·084
Bacterial coinfection	476 (35%)	219 (32%)	143 (37%)	86 (44%)	28 (38%)	0·015
Laboratory values						
White blood cell count, $\times 10^9$ cells per L	13·4 (9·4–18·1; n=1109)	12·9 (9·2–17·9; n=594)	13·2 (9·4–18·4; n=306)	14·5 (10·5–20·9; n=141)	14·0 (9·8–18·6; n=68)	0·038
Serum creatinine, µmol/L	70 (53–103; n=1117)	71 (54–109; n=604)	70 (52–98; n=301)	67 (47–96; n=143)	69 (48–111; n=69)	0·274
Serum bilirubin, µmol/L	7 (5–13; n=1041)	7 (5–13; n=559)	7 (4–13; n=283)	8 (5–13; n=131)	7 (5–11; n=68)	0·678
Platelet count, $\times 10^9$ per L	257 (186–342)	249 (178–339)	255 (195–339)	276 (212–360)	240 (171–317)	0·037
Rescue therapy pre-ECMO						
Neuromuscular blockade	1278 (95%)	648 (94%)	370 (95%)	188 (96%)	72 (99%)	0·387
Prone positioning	1203 (89%)	603 (88%)	357 (91%)	179 (92%)	64 (88%)	0·208
Inhaled nitric oxide	371 (28%)	192 (28%)	100 (26%)	49 (25%)	30 (41%)	0·044
Recruitment manoeuvres	334 (25%)	166 (24%)	96 (25%)	58 (30%)	14 (19%)	0·269
Almitrine	20 (1%)	11(2%)	3 (1%)	3 (2%)	3 (4%)	0·190
Renal replacement therapy	67 (5%)	38 (6%)	14 (4%)	10 (5%)	5 (7%)	0·399
Cardiac arrest	58 (4%)	41 (6%)	14 (4%)	3 (2%)	0	0·0040
Pneumothorax	159 (12%)	76 (11%)	49 (13%)	21 (11%)	13 (18%)	0·352

Data are median (IQR) or n (%); the number of patients for whom data were available is specified when less than the total for any group. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. ICU=intensive care unit. MERT=Mobile ECMO Retrieval Team. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2=partial pressure of arterial oxygen. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure. SOFA=Sequential Organ Failure Assessment. *Chronic obstructive pulmonary disease or asthma. †Patients with haematological malignancies or an active solid tumour, those who had received specific anti-tumour treatment within 1 year, those who had undergone a solid-organ transplant, HIV-positive patients, or those on long-term corticosteroids or immunosuppressants. ‡Driving pressure=plateau pressure – PEEP. §Mechanical power (J/min)=0·098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure.

Table 1: **Patients' pre-ECMO characteristics according to SARS-CoV-2 variant**

Patient characteristics are reported as number (percentage) for categorical variables, and median (IQR) for continuous variables. Categorical variables were compared by χ^2 or Fisher's exact test, and continuous variables were compared using Student's t test or the Kruskal-Wallis rank-sum test. Kaplan-Meier overall survival curves until day 90 were computed and were compared using log-rank tests.

Baseline risk factors for death at day 90 were assessed within the whole cohort using multivariable Cox regression models. Baseline variables (ie, those obtained before ECMO initiation) included in the multivariable model were defined a priori (COVID variant and age, sex, body mass index, chronic respiratory disease, treated hypertension, diabetes mellitus, immunocompromised status, time from first symptoms to hospital admission, time from intensive care unit admission to intubation, time from intubation to ECMO, cardiac arrest, haemodynamic component of the SOFA score, renal replacement therapy, bacterial coinfection, mechanical power, pneumothorax, $PaCO_2$, PaO_2/FiO_2 ratio, lactate, platelets, recruitment manoeuvres, prone positioning, inhaled nitric oxide, and neuromuscular blockade), and no variable selection was done. Log linearity was graphically assessed for the quantitative variables' effects using restricted cubic splines. The Cox regression model was stratified on the country variable. Multiple imputations (appendix pp 3–4) were used to replace missing values (appendix pp 6–9), when appropriate. Ten copies of the dataset were created with the missing values replaced by imputed values, based on observed data including outcomes and baseline characteristics of the participants. Each dataset was then analysed and the results from each dataset were pooled to give a final result using Rubin's rule.[19] Hazard ratios and their 95% CIs were estimated on the final pooled dataset using Rubin's rule. Additionally, two prespecified sensitivity analyses were done: one after excluding the 84 patients for whom the variant type was missing and the other with the semester of inclusion in the study instead of the SARS-CoV-2 variant.

All analyses were computed at a two-sided alpha level of 5%. Statistical analyses were done with R version 4.2.0.

	All patients (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
Type of ECMO support	..	..	..	..	..	0·529
VV-ECMO	1318 (98%)	668 (97%)	384 (98%)	194 (99%)	72 (99%)	..
Femoral–jugular	1045 (78%)	539 (79%)	290 (74%)	152 (78%)	64 (88%)	..
VA-ECMO	19 (1%)	13 (2%)	5 (1%)	1 (1%)	0	..
VAV-ECMO	8 (1%)	5 (1%)	2 (0.5%)	0	1 (1%)	..
Ventilation parameters on day 1						
FiO_2	50 (40–70)	50 (40–70)	50 (40–70)	50 (40–60)	50 (40–70)	0·138
PEEP, cm H_2O	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	0·843
Tidal volume, mL/kg PBW	2·9 (2·0–4·2)	3·0 (2·0–4·2)	2·7 (1·9–4·1)	3·1 (2·1–4·7)	2·7 (2·0–3·6)	0·200
Respiratory rate, breaths per min	14 (10–20)	14 (12–20)	14 (10–16)	12 (12–16)	12 (10–20)	0·002
Driving pressure, cm H_2O*	12 (10–14)	12 (11–14)	12 (10–14)	12 (10–14)	12 (10–14)	0·867
Compliance, mL/cm H_2O	15·6 (10·0–23·1)	16·7 (10·7–23·4)	15·0 (9·7–21·9)	15·9 (10·5–23·3)	14·3 (9·8–20·0)	0·097
Mechanical power, J/min†	4·7 (2·9–7·4)	5·1 (3·2–8·2)	4·4 (2·6–6·7)	4·1 (2·9–7·6)	4·0 (2·5–7·0)	0·002
Ventilation mode on day 1	..	..	..	..	..	0·0005
APRV or bilevel PAPV	288 (22%)	167 (25%)	72 (19%)	23 (12%)	26 (38%)	..
Volume control ventilation	279 (21%)	150 (22%)	72 (19%)	29 (15%)	28 (41%)	..
Pressure control ventilation	735 (56%)	350 (52%)	233 (62%)	138 (73%)	14 (21%)	..
Neuromuscular blockade on day 1	860 (67%)	440 (68%)	250 (68%)	123 (67%)	47 (64%)	0·918
Prone positioning on day 1	200 (15%)	76 (11%)	73 (19%)	38 (19%)	13 (18%)	0·0011
Inhaled nitric oxide on day 1	63 (5%)	28 (4%)	23 (6%)	10 (5%)	2 (3%)	0·514
Awake on ECMO on day 1‡	13 (1%)	2 (<1%)	6 (2%)	4 (2%)	1 (1%)	0·032
Ventilation parameters on day 3						
FiO_2	50 (40–60)	50 (40–60)	50 (40–60)	50 (40–60)	50 (40–60)	0·994
PEEP, cm H_2O	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–14)	0·206
Tidal volume, mL/kg PBW	2·9 (1·9–4·4)	2·9 (1·9–4·3)	2·7 (1·8–4·2)	3·2 (1·9–5·0)	3·5 (2·5–5·2)	0·058
Respiratory rate, breaths per min	14 (12–20)	14 (12–20)	14 (10–18)	13 (12–16)	15 (10–20)	0·0102
Driving pressure, cm H_2O*	12 (10–14)	12 (11–14)	13 (10–14)	12 (10–15)	14 (12–15)	0·282
Compliance, mL/cm H_2O	15·8 (10·2–23·3)	16·2 (10·0–23·3)	15·0 (9·0–23·0)	16·0 (10·0–23·0)	17·2 (11·1–26·0)	0·331
Mechanical power, J/min†	4·7 (2·9–7·8)	5·0 (3·1–8·5)	4·3 (2·5–6·6)	4·4 (2·3–7·7)	6·4 (3·3–9·8)	0·0009
Neuromuscular blockade on day 3	736 (57%)	382 (58%)	221 (59%)	91 (48%)	42 (62%)	0·067
Prone positioning on day 3	286 (21%)	113 (17%)	98 (25%)	42 (22%)	33 (46%)	<0·0001
Inhaled nitric oxide on day 3	39 (3%)	19 (3%)	13 (3%)	5 (3%)	2 (3%)	0·935
Awake on ECMO on day 3‡	32 (2%)	8 (1%)	19 (5%)	5 (3%)	0	0·0015

Data are median (IQR) or n (%). APRV=airway pressure release ventilation. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. PAPV=positive airway pressure ventilation. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure. VA-ECMO=venoarterial ECMO. VAV-ECMO=venoarteriovenous ECMO. VV-ECMO=venovenous ECMO. *Driving pressure=plateau pressure – PEEP. †Mechanical power (J/min)=0·098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure. ‡Defined as the patient being awake, cooperative, and performing rehabilitation and physiotherapy.

Table 2: **Patients' characteristics on ECMO day 1 and day 3 according to SARS-CoV-2 variant**

Role of the funding source

There was no funding source for this study.

Results

Among 24 European ECMO centres invited to participate in the ECMO-SURGES study, 21 centres (four medium-volume centres and 17 high-volume centres) from eight countries included patients with COVID-19 treated with ECMO in the study (figure 1). The main characteristics of these centres are described in the appendix (p 10). Notably, the median number of ECMO cases treated in these centres in 2019 was 40 (IQR 30–81), and a mobile rescue team was available in 18 (86%) of 21 centres before the pandemic and in 17 (81%) centres during the pandemic. Most centres followed the EOLIA entry criteria[1] to indicate ECMO. The median upper age to deny ECMO support fell from 70 years (IQR 65–70) before the pandemic to 65 years (65–65) during the pandemic, and more

contraindications to ECMO such as pre-ECMO cardiac arrest and severe immunocompromised status existed during the pandemic than before it (appendix p 10). Thus, between Jan 1, 2020, and Sept 30, 2021, 1345 patients were treated with ECMO in these centres: 324 during S1-2020, 352 during S2-2020, 496 during S1-2021, and 173 during S2-2021. Sequencing was done for 1261 (94%) of 1345 patients and the predominant variant in the country was considered for 84 patients without virus sequencing who were admitted to hospital after Oct 31, 2020. 686 (51%) of 1345 cases were infected with the wild-type variant, whereas alpha, delta, and other

	All (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
Tracheostomy	693 (52%)	347 (51%)	198 (51%)	118 (61%)	30 (41%)	0·0199
Time from intubation to tracheostomy, days	19 (12–29)	20 (13–30)	19 (12–29)	17 (12–23)	20 (11–32)	0·077
Renal replacement therapy	472 (35%)	261 (38%)	124 (32%)	64 (33%)	23 (32%)	0·142
Prone positioning on ECMO	635 (47%)	327 (48%)	193 (49%)	69 (35%)	46 (63%)	0·0003
Number of sessions on ECMO	0 (0–3)	0 (0–3)	0 (0–4)	0 (0–3)	2 (0–5)	0·0008
Received COVID-19-specific treatment*						
Remdesivir	163 (12%)	98 (14%)	47 (12%)	16 (8%)	2 (3%)	0·0079
Tocilizumab	223 (17%)	90 (13%)	51 (13%)	69 (35%)	13 (18%)	<0·0001
Dexamethasone	928 (69%)	345 (50%)	342 (87%)	175 (90%)	66 (90%)	<0·0001
High-dose corticosteroids (Meduri protocol)	451 (34%)	219 (32%)	138 (35%)	61 (31%)	33 (45%)	0·1002
ECMO-related complications						
Clogged circuit or membrane requiring change	449 (33%)	205 (30%)	144 (37%)	89 (46%)	11 (15%)	<0·0001
Number of circuit change(s)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0·0047
Repeat ECMO needed after decannulation	36 (3%)	20 (3%)	8 (2%)	6 (3%)	2 (3%)	0·817
Heparin-induced thrombocytopenia	90 (7%)	35 (5%)	29 (7%)	20 (10%)	6 (8%)	0·058
Major bleeding	432 (32%)	252 (37%)	109 (28%)	53 (27%)	18 (25%)	0·0024
Ischaemic stroke	39 (3%)	15 (2%)	11 (3%)	10 (5%)	3 (4%)	0·147
Haemorrhagic stroke	98 (7%)	49 (7%)	36 (9%)	12 (6%)	1 (1%)	0·097
Pneumothorax on ECMO	202 (15%)	93 (14%)	59 (15%)	35 (18%)	15 (21%)	0·239
Pulmonary embolism	168 (12%)	79 (11%)	55 (14%)	23 (12%)	11 (15%)	0·569
≥1 antibiotic-treated ventilator-associated pneumonia	887 (69%)	421 (66%)	260 (67%)	146 (75%)	60 (82%)	0·0051
≥1 antibiotic-treated bacteraemia episode(s)	571 (44%)	288 (45%)	163 (42%)	87 (45%)	33 (45%)	0·799
Outcomes						
Lung transplant on ECMO	6 (1%)	4 (1%)	1 (<1%)	1 (1%)	0	0·899
ECMO duration, days	21 (10–40)	19 (10–36)	22 (11–43)	25 (13–43)	21 (11–36)	0·021
Mechanical ventilation duration, days	37 (21–58)	36 (21–57)	38 (21–58)	39 (25–62)	33 (22–49)	0·185
ICU length of stay, days	43 (26–63)	42 (25–63)	44 (26–63)	44 (32–68)	42 (28–61)	0·316
Hospital length of stay, days	52 (33–79)	52 (32–79)	51 (34–77)	56 (38–84)	45 (31–67)	0·127
ECMO successfully weaned	812 (60%)	400 (58%)	258 (66%)	119 (61%)	35 (48%)	0·011
ICU discharge survival	737 (55%)	374 (54%)	232 (60%)	103 (55%)	28 (40%)	0·020
Hospital discharge survival	667 (52%)	319 (50%)	226 (59%)	97 (53%)	25 (37%)	0·0023
90-day survival status	..	..	..	..	..	0·0101
Dead	569 (42%)	297 (43%)	152 (39%)	78 (40%)	42 (58%)	..
On ECMO	53 (4%)	37 (5%)	8 (2%)	8 (4%)	0	..
On mechanical ventilation and weaned off ECMO	47 (3%)	26 (4%)	11 (3%)	9 (5%)	1 (1%)	..
Still in the hospital and weaned off ECMO	89 (7%)	43 (6%)	32 (8%)	14 (7%)	0	..
In rehabilitation	120 (9%)	56 (8%)	35 (9%)	19 (10%)	10 (14%)	..
Back home	467 (35%)	227 (33%)	153 (39%)	67 (34%)	20 (27%)	..

(Table 3 continues on next page)

	All (n=1345)	Wild type (n=686)	Alpha (n=391)	Delta (n=195)	Other (n=73)	p value
(Continued from previous page)						
Cause of death (n=592)	..	..	..	..	..	0·0125
Septic shock	165 (28%)	94 (30%)	41 (26%)	19 (23%)	11 (27%)	..
Unspecified multiorgan failure	133 (22%)	73 (23%)	26 (17%)	25 (30%)	9 (22%)	..
Stroke	62 (10%)	28 (9%)	20 (13%)	12 (14%)	2 (5%)	..
Haemorrhagic shock	38 (6%)	20 (6%)	10 (6%)	6 (7%)	2 (5%)	..
Cardiovascular shock	21 (4%)	6 (2%)	5 (3%)	9 (10%)	1 (2%)	..
ECMO device failure	3 (1%)	1 (<1%)	1 (1%)	0	1 (2%)	..
Cannulation complication	9 (2%)	6 (2%)	1 (1%)	0	2 (5%)	..
Transport complication	1 (<1%)	1 (<1%)	0	0	0	..
Persistent respiratory failure other than COVID-19	46 (8%)	31 (10%)	11 (7%)	3 (4%)	1 (2%)	..
Refractory respiratory failure related to COVID-19	108 (18%)	48 (15%)	38 (25%)	10 (12%)	12 (30%)	..
Other	6 (1%)	4 (1%)	2 (1%)	0	0	..

Data are median (IQR) or n (%). ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. *Given before or during ECMO.

Table 3: **ECMO management, complications, and outcomes according to SARS-CoV-2 variant**

variants were responsible for 391 (29%), 195 (14%), and 73 (6%) cases, respectively (table 1). Among the group infected with other variants, 47 were beta, 17 gamma, three mu, and six B.1.160. The wild-type variant accounted for 100% (324/324) of the strains isolated during the first semester of 2020 and for 81% (284/352) of the strains isolated in the second semester of 2020, whereas alpha was predominant in S1-2021 (326 [66%] of the 496 strains isolated) and delta in S2-2021 (169 [98%] of the 173 strains isolated). Variant distribution and main characteristics of the population in the eight countries are provided in appendix (pp 11–12).

Table 1 summarises the main demographic and clinical characteristics of patients according to SARS-CoV-2 variant. Patients with wild-type, alpha, delta, and other variants had similar demographic characteristics, except that patients infected with the delta variant tended to be younger and have less hypertension and diabetes than those with any of the other variants. Overall, the time from ICU admission to intubation, the proportion of patients receiving non-invasive oxygenation strategies (eg, high-flow nasal oxygen and non-invasive mechanical ventilation), and the rate of pneumothorax increased over time (appendix pp 13–15). S2-2021 patients (98% [169/173] of whom were infected with the delta variant) were younger, more frequently vaccinated, and had more frequent bacterial coinfection at cannulation than patients treated during the other semesters (appendix pp 13–15). Neuromuscular blockade and prone positioning were used pre-ECMO in more than 90% of the patients, with no significant difference between variants or semesters (table 1, appendix pp 13–15).

VV-ECMO was administered to 98% of the patients, with the femoral–jugular setting being used in more than 75% of cases (table 2). All patients received ultra-protective mechanical ventilation on ECMO, which aimed to achieve decreases in FiO_2, respiratory rate, tidal volume, and driving pressure, irrespective of the variant or the time period (table 2, appendix pp 16–17). This strategy led to a substantial decrease in ventilation mechanical power (from a median of 21·7 J/min [IQR 17·6–25·9] at baseline to 4·7 J/min [2·9–7·4] on ECMO day 1). Notably, the rate of prone positioning on ECMO increased over time, with a peak number of 278 (58%) of 495 patients being proned during S1-2021 (appendix pp 18–19). Remdesivir treatment decreased over time, with only 12 (7%) of 173 patients receiving this drug during S2-2021. By contrast, the use of tocilizumab and dexamethasone (given before or during ECMO), increased over time (appendix pp 18–19). Of 686 patients with the wild-type variant, only 345 (50%) received dexamethasone and 90 (13%) received tocilizumab, compared with 175 (90%) and 69 (35%) of 195 patients with the delta variant, respectively (table 3).

The rate of clogged circuit or membrane requiring change increased over time, with the highest rate (46%) reported in patients with the delta variant, whereas massive bleeding was most frequently reported in patients with the wild-type strain (37%, p=0·0024; table 3) and during S2-2020 (appendix pp 18–19). The highest rates of ventilator-associated pneumonia were reported in patients with the delta variant (146 [75%] of 195) and in those with other variants (60 [82%] of 73). Of note, rates of ischaemic and haemorrhagic stroke and of bacteraemia were similar between periods and variants (table 3, appendix pp 18–19).

Complete 90-day post-ECMO survival status was available for all patients. 90-day mortality was 42% (569 of 1345 patients died) overall, and 43% (297/686) in patients with wild-type SARS-CoV-2, 39% (152/391) in those with the alpha variant, 40% (78/195) in those with the delta variant, and 58% (42/73) in those with other variants, respectively (log-rank test p=0·008; figure 2A). When compared with other semesters, patients treated during

S2-2020 had the highest 90-day mortality (50% [175/352 died] *vs* 40% [393/993 died] in other semesters [S1-2020: 39% (125/324); S1-2021: 40% (199/496; S2-2021: 40% (69/173], log-rank test p=0·018; figure 2B) and the lowest rates of successful ECMO weaning, ICU survival, and hospital survival. Patients with the delta variant had longer ECMO runs than did those with all other types of variant, despite similar lengths of stay in the ICU and hospital (table 3).

Factors associated with higher mortality according to multivariable analysis are reported in table 4. Age, immunocompromised status, and a longer time between ICU admission and intubation were significantly associated with mortality. Patients needing renal replacement therapy, and those with higher SOFA haemodynamic component score, $PaCO_2$, and lactate concentration before ECMO also had an increased risk of death. After adjusting for these specific variables, the delta variant was associated with a higher likelihood of death, with the wild-type strain as the reference (table 4). Moreover, similar mortality risk factors were found in the two sensitivity analyses, when the model accounted for the semester of inclusion in the study instead of the SARS-CoV-2 strain (appendix p 20), or when excluding patients for whom the variant type was missing (appendix p 21). Kaplan-Meier survival estimates according to tertiles of age, $PaCO_2$, and pre-ECMO time from ICU admission to intubation, and according to whether or not patients received renal replacement therapy, are provided in figure 3 and the appendix (p 22).

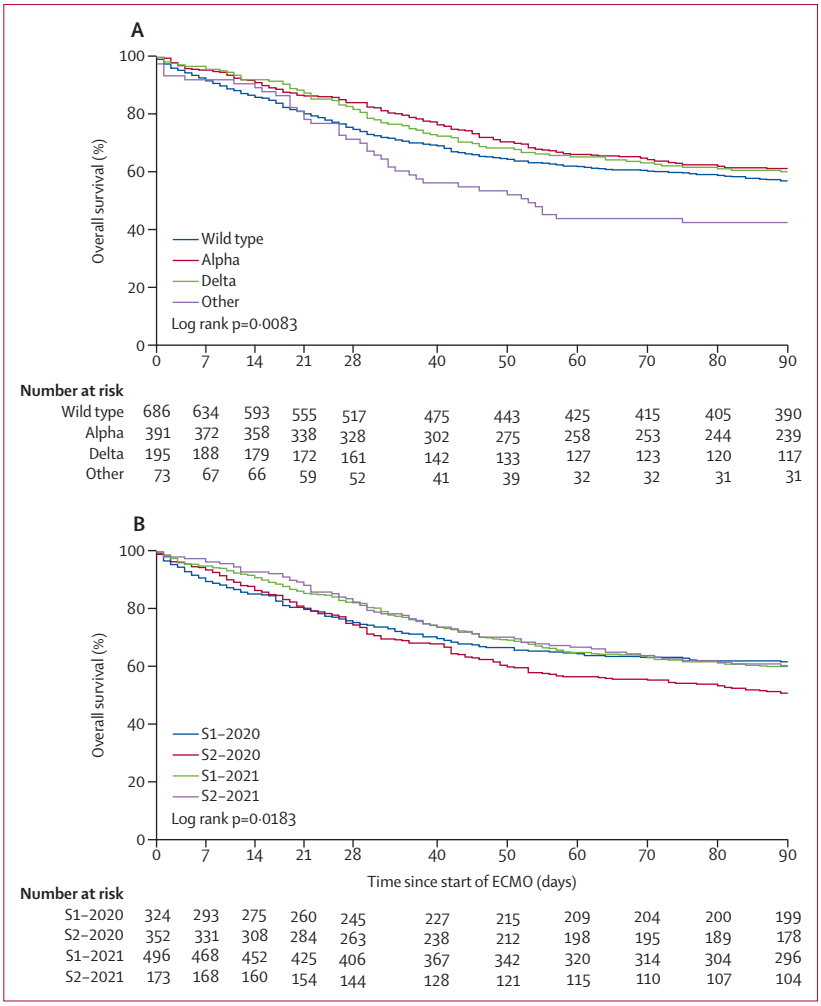

Figure 2: **Survival probability at 90 days according to (A) SARS-CoV-2 variant or (B) study period**
ECMO=extracorporeal membrane oxygenation.

Discussion

This study, reporting the characteristics and outcomes of 1345 patients who received ECMO for severe COVID-19 in 21 experienced European centres, showed no crude difference in 90-day mortality in patients infected with the wild-type, alpha, and delta SARS-CoV-2 variants, which were the three successive dominant viral strains from early 2020 to the second semester of 2021. Notably, mortality was 10% higher (50%) in the second semester of 2020 than in other periods, when the wild-type variant was still dominant. Factors independently associated with 90-day mortality were age, immunocompromised status, longer time between ICU admission and intubation, higher $PaCO_2$ and lactate concentrations, cardiovascular failure, and need for renal replacement therapy at ECMO initiation. After adjusting for these covariates, mortality was higher for patients infected with the delta variant with the wild-type strain as the reference.

Only a few large, multicentre studies[5,9–11,20,21] have reported the outcomes of patients who received ECMO for severe COVID-19. In the international ELSO Registry,[9] in-hospital mortality was 50% among the 4812 patients with COVID-19 who received ECMO, and peaked at 59% for patients treated in less experienced centres in the second semester of 2020. In Germany, the overall in-hospital mortality was 68% among 3397 patients with COVID-19 supported with VV-ECMO from March, 2020, to May, 2021.[21] This high in-hospital mortality was attributed to patients' older mean age (57 years [SD 11]) and to the absence of regulations for ECMO use in the country.[21] Notably, the actual 90-day mortality might have been higher than the reported in-hospital mortality in these series.[9,10,20,21] Additionally, the vast majority of these patients were treated in 2020, when the wild-type SARS-CoV-2 strain was dominant, and no data have previously been reported regarding ECMO patient outcomes after infection with other SARS-CoV-2 variants.

Indeed, infections with the alpha and delta variants of SARS-CoV-2 have been associated with increased transmission, more severe disease, and poorer clinical outcomes compared with the wild-type strain.[22–25] In a large epidemiological study in the US state of Washington, significantly more hospital admissions were reported for infections with the alpha, beta, gamma, or delta strains than with the wild-type variant, with the highest rates associated with the beta and gamma subtypes.[26] Higher

	Multivariable HR (95% CI)	p value
Age, years	1·05 (1·04–1·06)	<0·0001
Male sex	0·97 (0·77–1·22)	0·807
Body-mass index, kg/m^2	1·00 (0·98–1·01)	0·736
Chronic respiratory disease	1·19 (0·92–1·54)	0·195
Hypertension	0·94 (0·78–1·14)	0·527
Diabetes mellitus	1·06 (0·86–1·30)	0·604
Immunocompromised status	1·59 (1·16–2·19)	0·004
Variant	..	0·027
Wild type	..	..
Alpha	0·92 (0·75–1·13)	..
Delta	1·31 (1·00–1·73)	..
Other	1·37 (0·97–1·95)	..
Time from first symptoms to hospital admission, per 1 day	0·99 (0·97–1·01)	0·492
Time from ICU admission to intubation, per 1 day	1·05 (1·02–1·07)	0·0002
Time from intubation to ECMO, per 1 day	1·01 (0·99–1·03)	0·330
Pre-cannulation		
Cardiac arrest	1·04 (0·68–1·63)	0·820
Cardiovascular component of the SOFA score ≥3	1·30 (1·05–1·60)	0·016
Renal replacement therapy	1·55 (1·10–2·17)	0·012
Bacterial coinfection	1·00 (0·82–1·21)	0·928
Mechanical power* (n=939)	1·02 (1·00–1·03)	0·058
Pneumothorax	1·25 (0·96–1·63)	0·096
$PaCO_2$, mm Hg	1·01 (1·00–1·01)	0·011
PaO_2/FiO_2 ratio	1·00 (1·00–1·00)	0·506
Lactate concentration, mmol/L	1·10 (1·02–1·19)	0·011
Platelet count, × 10^9 per L	1·00 (1·00–1·00)	0·382
Recruitment manoeuvres	1·24 (0·95–1·60)	0·109
Prone positioning	1·02 (0·75–1·37)	0·904
Inhaled nitric oxide	1·03 (0·84–1·27)	0·799
Neuromuscular blockade	1·01 (0·65–1·59)	0·944

ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. HR=hazard ratio. ICU=intensive care unit. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2=partial pressure of arterial oxygen. SOFA=Sequential Organ Failure Assessment. *Mechanical power (J/min)=0·098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure.

Table 4: **Predictive factors associated with 90-day mortality in critically ill adults with COVID-19 treated with ECMO**

viral load and increased inflammatory response syndrome have been suggested as potential mechanisms conferring higher virulence to these strains and poorer outcomes in infected patients.[22–25] However, in the most severe forms of COVID-19, patient selection for ECMO, their characteristics at ECMO initiation, and different management and treatments during hospitalisation might also affect outcomes.[9,15,16] In our series, infection with the delta variant was independently associated with higher mortality, with the wild-type strain being the reference in this comparison. However, patients with the delta variant were younger and had fewer comorbidities at ECMO initiation than did those with the other variants. Since the vaccination campaign prioritised the oldest members of the population in all European countries in 2021, it might be speculated that younger patients were less protected than their older counterparts against severe forms of COVID-19 during the delta wave. Indeed, the rate of vaccination remained very low in our patients with COVID-19 on ECMO throughout 2021, with less than 8% of patients with the delta variant having received at least one shot of the vaccine. However, these patients had more frequent ventilator-associated pneumonia and clogged ECMO membrane requiring circuit change during ECMO support than those with all other variant types. These complications might relate to patients' immunosuppressive state, affecting both the innate and adaptive immune systems,[27,28] and to the intense activation of coagulation,[29] which frequently occur during COVID-19, and also to the longer time spent on ECMO.

The higher mortality observed in the second semester of 2020 parallels that reported in previous ECMO series.[9,15,16] In Spain and Portugal,[16] hospital mortality increased (from 41% to 60%) during the second semester of 2020, during which patients being treated with ECMO were older, had more comorbidities and bacterial coinfection at baseline, and were less likely to be treated at a high-volume centre compared with patients treated previously. Their time between admission to the ICU and ECMO start was also longer. In the ELSO Registry,[9] in-hospital mortality increased from 37% before to 52% after May 1, 2020. Patients treated later in 2020 had more frequent diabetes, pre-existing heart disease, immunocompromised status, bacterial pneumonia, and bloodstream co-infection and use of corticosteroids before ECMO than those treated earlier in 2020. They were also more likely to have received non-invasive ventilation before ECMO and had a shorter duration of invasive ventilation before ECMO than those treated earlier in 2020. In our series, the severity of respiratory disease and patient management under ECMO were similar between periods, while the recourse to non-invasive ventilation and steroids increased after June, 2020, and remained constant thereafter. A potential cause of poorer outcomes in the second semester of 2020 might relate to patients' older age and more frequent comorbidities such as diabetes and hypertension. Our multivariable analysis of factors associated with mortality revealed that the time from ICU admission to intubation, a surrogate for the duration of non-invasive respiratory support, which increased significantly in most ECMO series after June, 2020, was a stronger predictor of poor outcome than the time on mechanical ventilation before ECMO. Notably, time on non-invasive respiratory support

was the longest for patients with less common SARS-CoV-2 strains, who had the highest mortality. Indeed, patients who did not improve on non-invasive oxygenation support might have suffered greater self-inflicted lung injury[30] due to strong respiratory efforts and important swings of transpulmonary pressure, which could also explain the increased rate of pneumothorax in the later three semesters of our study. Therefore, the duration of non-invasive respiratory support might be an important consideration in patient selection for ECMO in this context, and warrants further investigation.

Our study has several strengths. First, viral identification was obtained in 94% of cases. Second, we provide details on the ventilatory and general ICU management of our patients in the days following ECMO initiation. Third, patient selection and management was similar in our units over time and variants, with the use of ultraprotective mechanical ventilation under ECMO, with low volume and pressures resulting in very low mechanical power.[13] Fourth, we collected patient outcomes at 90 days (not just in-hospital mortality) in some of the most experienced ECMO centres in Europe, which minimised the volume–outcome effect that had been reported for both patients without COVID-19[17] and those with COVID-19[5,9,16] supported by ECMO. Indeed, the overall 90-day mortality we report here is in line with that of previous non-COVID-19 cohorts of patients with ARDS supported with ECMO.[1,12–14] This mortality rate is also 15–25% lower than the in-hospital mortality observed in recent large COVID-19 series,[9,10,21] despite lower levels of PaO_2 and FiO_2 at baseline.

Our study has also several limitations. First, some patients were still under ECMO or mechanical ventilation at the end of follow-up and mortality might have been higher at later timepoints. Second, we did not evaluate long-term health-related quality of life and other sequelae of COVID-19, which might persist for a long time.[31] Third, we did not collect data after infection with the omicron variant of SARS-CoV-2, which emerged in November, 2021, and has been associated with less severe disease than earlier variants of the virus.[32] Fourth, we inferred the variant based on chronology and geography, and not through direct testing, in 84 (6%) of 1345 patients. Fifth, the calculation of adjusted hazard ratios for mortality among SARS-CoV-2 strains was based on key prognostic factors included in our database, and could have been biased by residual confounders that were not accounted for in our multivariable model. Of note, the hazard ratios associated with these factors should be interpreted with caution because they do not represent the same time of causal effect as that of SARS-CoV-2 strains.[33] Sixth, the strain on health-care systems and ICU resource constraints might have differed during the study period and between countries, leading to differential selection criteria for ECMO or patient management. Lastly, our study was conducted in high-volume European ECMO centres, which might limit the generalisability of our results to centres in other regions of the world.

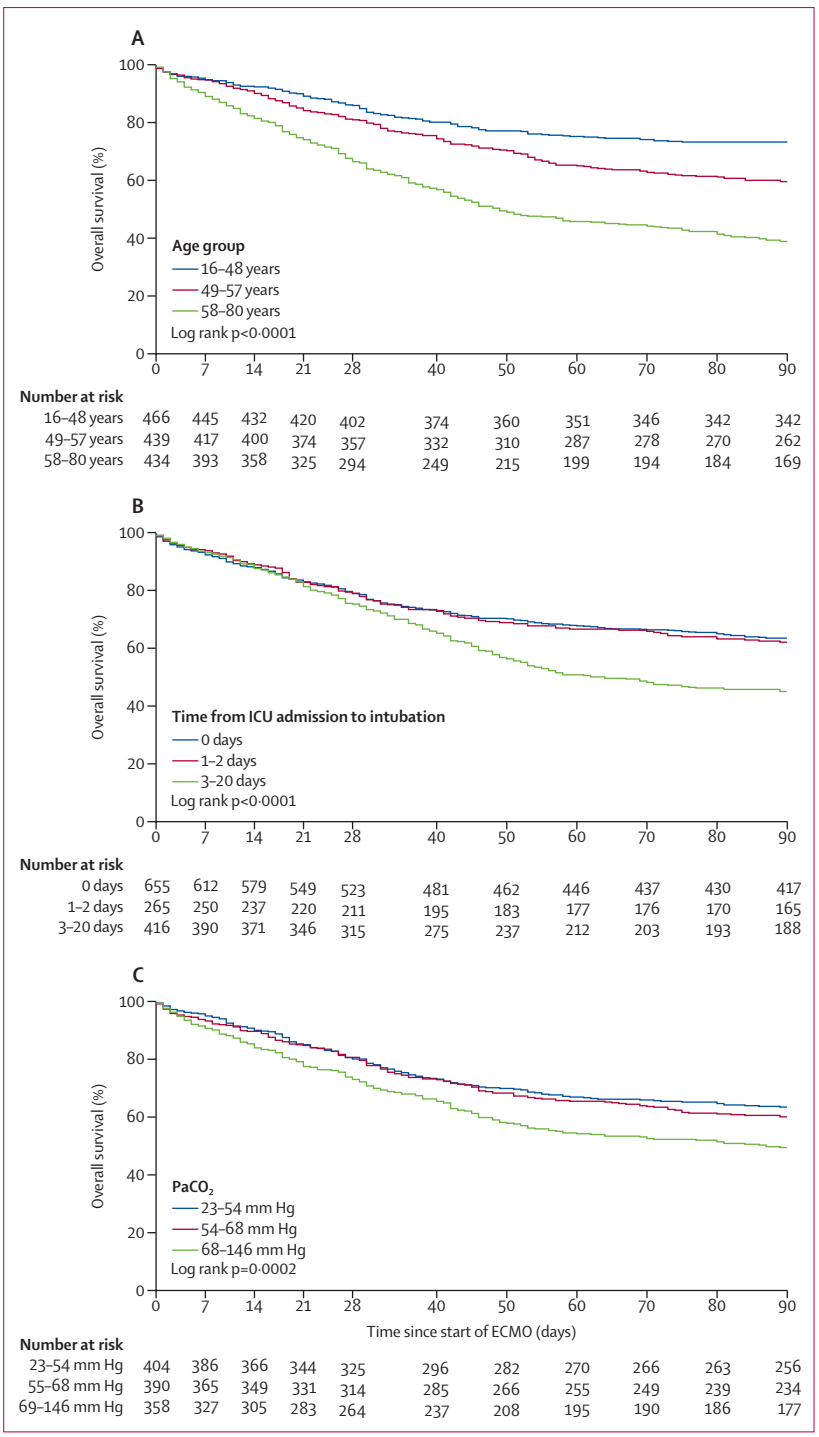

***Figure 3*: Kaplan-Meier survival estimates according to tertiles of (A) age, (B) time from ICU admission to intubation, and (C) pre-ECMO $PaCO_2$**

ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. $PaCO_2$=partial pressure of arterial carbon dioxide. The number of patients censored at each timepoint on all Kaplan-Meier curves was 0, until the final timepoint (90 days) when all patients were censored.

In conclusion, adjusted mortality of patients with COVID-19 treated with ECMO in experienced centres in Europe was higher for those infected with the delta variant, who were younger and had fewer comorbidities at ECMO initiation. The 42% 90-day mortality reported here is lower than that reported for other large series of patients with COVID-19-related ARDS supported with ECMO and in line with cohorts of non-COVID-19 patients on ECMO. This observation reinforces the need to concentrate ECMO resources at experienced ECMO centres in a hub-and-spoke model, especially during pandemics that impose substantial constraints on health-care systems.[11,34,35]

Contributors

All authors were involved in data generation. MS, DH, and AC had direct access to and verified the data. MS, DH, and AC were involved in analysis of the data. MS, DH, and AC wrote the manuscript. All authors contributed to revisions to the manuscript, and read and approved the final version. AC takes responsibility for the integrity of the work as a whole, from inception to published article. AC was responsible for the decision to submit the manuscript for publication. All authors have seen and approved the final text.

Declaration of interests

MS reports lecture fees from Getinge, Drager, and Xenios, outside of the submitted work. AM-D reports grants from Addmedica, Baxter, Ferring, Fisher & Paykel, and Philips, and personal fees from Air Liquide, outside of the submitted work. PSc reports lecture fees from Getinge and scientific grants from the European Society of Intensive Medicine (ESICM) and the European Commission (Horizon 2020 Fast Track to Innovation; NCT04115709), and has co-organised an ARDS fellowship for the ESICM sponsored by Medtronic. BL reports fees from Abiomed, Getinge, Baxter, Novartis, Sanofi, Amomed, and Orion, outside of the submitted work. GG has received personal fees (payment for lectures) from Getinge, Draeger Medical, Biotest, GSK, Pfizer, Fisher & Paykel, and Cook Medical, and research grants from MSD and Fisher & Paykel. CG reports fees from Xenios, outside of the submitted work. JR reports lecture fees from Werfen and Gilead, and advisory fees from Medtronic, outside of the submitted work. AC reports grants from Getinge, and personal fees from Getinge, Baxter, and Xenios, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Individual patient data reported in this Article will be shared after de-identification (text, tables, figures, and appendix), beginning 6 months and ending 2 years after Article publication, to researchers who provide a methodologically sound proposal and after approval by the internal scientific committee. Proposals should be addressed to alain.combes@aphp.fr. To gain access, data requestors will need to sign a data access agreement.

References

1 Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; **378:** 1965–75.

2 Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA* 2018; **320:** 2251–59.

3 Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; **374:** 1351–63.

4 Combes A, Peek GJ, Hajage D, et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. *Intensive Care Med* 2020; **46:** 2048–57.

5 Lebreton G, Schmidt M, Ponnaiah M, et al. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. *Lancet Respir Med* 2021; **9:** 851–62.

6 Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med* 2020; **8:** 518–26.

7 Supady A, Combes A, Barbaro RP, et al. Respiratory indications for ECMO: focus on COVID-19. *Intensive Care Med* 2022; **48:** 1326–37.

8 Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 2020; **8:** 1121–31.

9 Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021; **398:** 1230–38.

10 Urner M, Barnett AG, Bassi GL, et al. Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study. *BMJ* 2022; **377:** e068723.

11 Hajage D, Combes A, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: an emulated target trial analysis. *Am J Respir Crit Care Med* 2022; **206:** 281–94.

12 Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013; **187:** 276–85.

13 Schmidt M, Pham T, Arcadipane A, et al. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome. an international multicenter prospective cohort. *Am J Respir Crit Care Med* 2019; **200:** 1002–12.

14 The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; **302:** 1888–95.

15 Schmidt M, Langouet E, Hajage D, et al. Evolving outcomes of extracorporeal membrane oxygenation support for severe COVID-19 ARDS in Sorbonne hospitals, Paris. *Crit Care* 2021; **25:** 355.

16 Riera J, Roncon-Albuquerque R Jr, Fuset MP, Alcántara S, Blanco-Schweizer P. Increased mortality in patients with COVID-19 receiving extracorporeal respiratory support during the second wave of the pandemic. *Intensive Care Med* 2021; **47:** 1490–93.

17 Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med* 2015; **191:** 894–901.

18 Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016; **42:** 1567–75.

19 Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338:** b2393.

20 Shaefi S, Brenner SK, Gupta S, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. *Intensive Care Med* 2021; **47:** 208–21.

21 Karagiannidis C, Slutsky AS, Bein T, Windisch W, Weber-Carstens S, Brodie D. Complete countrywide mortality in COVID patients receiving ECMO in Germany throughout the first three waves of the pandemic. *Crit Care* 2021; **25:** 413.

22 Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis* 2022; **22:** 35–42.

23 Butt AA, Dargham SR, Chemaitelly H, et al. Severity of illness in persons infected with the SARS-CoV-2 delta variant vs beta variant in Qatar. *JAMA Intern Med* 2022; **182:** 197–205.

24 Patone M, Thomas K, Hatch R, et al. Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. *Lancet Infect Dis* 2021; **21:** 1518–28.

25 Davies NG, Jarvis CI, Edmunds WJ, Jewell NP, Diaz-Ordaz K, Keogh RH. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. *Nature* 2021; **593:** 270–74.

26 Paredes MI, Lunn SM, Famulare M, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. *Clin Infect Dis* 2022; **75:** e536–44.

27 Vacheron CH, Lepape A, Savey A, et al. Attributable mortality of ventilator-associated pneumonia among patients with COVID-19. *Am J Respir Crit Care Med* 2022; **206:** 161–69.

28 Hue S, Beldi-Ferchiou A, Bendib I, et al. Uncontrolled innate and impaired adaptive immune responses in patients with COVID-19 acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020; **202:** 1509–19.

29 Masi P, Hékimian G, Lejeune M, et al. Systemic inflammatory response syndrome is a major contributor to COVID-19-associated Coagulopathy: insights from a prospective, single-center cohort study. *Circulation* 2020; **142:** 611–14.

30 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; **195:** 438–42.

31 Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. *BMJ* 2021; **374:** n1648.

32 Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022; **399:** 1303–12.

33 Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. *Am J Epidemiol* 2013; **177:** 292–98.

34 Brodie D, Abrams D, MacLaren G, et al. Extracorporeal membrane oxygenation during respiratory pandemics: past, present, and future. *Am J Respir Crit Care Med* 2022; **205:** 1382–90.

35 Combes A, Brodie D, Bartlett R, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. *Am J Respir Crit Care Med* 2014; **190:** 488–96.