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HAL Authorization

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

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Abbreviations

ECMO, extracorporeal membrane oxygenation

VV-ECMO, veno-venous membrane oxygenation

ICU, intensive care unit

COVID-19, Coronavirus disease 2019

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

Research in context

Evidence before this study

Data from retrospective cohorts of coronavirus disease 2019 (COVID-19) patients rescued by extracorporeal membrane oxygenation (ECMO) during the first weeks of the pandemic revealed that despite longer ECMO runs and ICU length of stay, the mortality of COVID patients supported by ECMO was similar to that reported in the EOLIA trial or in other large retrospective series of ECMO for non-COVID ARDS. However, less favourable outcomes were reported in patients treated in the second semester of 2020 and a strong volume- and experience-outcome effect existed in most multicentre cohorts published to date, which included almost exclusively patients infected with the wild-type severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) strain. 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 the successive waves of the pandemic. We searched PubMed for articles published in any language in peer-reviewed journals up to August 8, 2022, with the terms “extracorporeal membrane oxygenation” and either “COVID-19” or “severe acute respiratory syndrome coronavirus 2” and focused on the large multicentre cohort studies that included at least 200 ECMO patients. We found 15 studies but none of them reported patients’ outcomes after infection with different variants of the virus.

Added value of this study

Our multicentre international retrospective study included 1345 patients who received ECMO in 21 experienced centres in 8 European countries. Patients’ characteristics and management were similar among variants, except for younger age and less hypertension and diabetes for Delta cases. We found that crude day-90 mortality was not different between variants and was 15-25% lower than the in-hospital mortality reported in other large COVID series.

Independent predictors of mortality were age, immunocompromised status, a longer ICU

admission to intubation time, need for dialysis, and higher hemodynamic SOFA component score, PaCO₂, and lactate before ECMO. After adjusting for these variables, mortality was significantly higher with the Delta variant.

Implications of all the available evidence

Adjusted mortality of COVID patients treated with ECMO for ARDS was higher for those infected with the Delta variant, who were younger and had less comorbidities at ECMO initiation. Mortality in our series of patients treated in experienced ECMO centres was noticeably lower than in other large multicentre series of ECMO for COVID, underlying the need to concentrate resources at experienced centres, especially during pandemics that impose considerable constraint on health care systems.

Summary (248 words)

Background. To inform future research and practice, we aimed to investigate the outcomes of patients who received extracorporeal membrane oxygenation (ECMO) for ARDS due to different variants of Coronavirus disease 2019 (COVID-19).

Methods This retrospective study included patients from January 1, 2020 to December 31, 2021 in 21 experienced ECMO centres from 8 European countries. The primary outcome was mortality 90 days after ECMO. Evolving characteristics, management and outcomes of patients over the first two years of the pandemic and independent risk factors of mortality were also determined.

Findings ECMO was initiated in 1345 patients. Patients' characteristics and management were similar among variants, except for younger age and less hypertension and diabetes for Delta cases. Day-90 mortality was (297/686) 43%, (152/391) 39%, (78/195) 40% and (42/73) 58% for patients with wild-type, Alpha, Delta, and other variants (mainly Beta and Gamma), respectively. Mortality was 10% higher (50%) in the second semester of 2020, when the wild type variant was still prevailing. Independent predictors of mortality were age, immunocompromised status, a longer ICU admission to intubation time, need for dialysis, and higher hemodynamic SOFA component score, PaCO₂, and lactate before ECMO. After adjusting for these variables, mortality was significantly higher with the Delta variant.

Interpretation Although crude mortality was not different between variants, adjusted risk of death was higher for ECMO patients infected with the Delta variant. Mortality was noticeably lower than in other large multicentre series of ECMO for COVID, underlying the need to concentrate resources at experienced centres.

Introduction

The worldwide pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has 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 of randomized controlled trials,¹⁻³ and a meta-analysis on individual patient data⁴ performed in non-COVID ARDS, extracorporeal membrane oxygenation (ECMO) was recommended for COVID-19 patients with profound hypoxemia or high thoracic pressures despite lung-protective mechanical ventilation, including prone-positioning.⁵⁻⁷ Single-centre⁸ and multicentre international cohorts^{5,9-11} revealed that despite longer ECMO runs and ICU length of stay, the mortality of COVID-19 patients rescued by ECMO during the first weeks of the pandemic was similar to that reported in the EOLIA trial¹ or in other large retrospective series of ECMO for non-COVID ARDS¹²⁻¹⁴. However, these encouraging results were challenged by less favourable outcomes in patients treated after July 2020. For instance, the 90-day mortality increased from 36 to 48% between the first and the second COVID wave in patients hospitalized at Sorbonne University, Paris, France.¹⁵ Similar increases in mortality were reported in the large cohort of the Extracorporeal Life Support Organization⁹ or in patients treated in Spain and Portugal.¹⁶ Reasons for this increase in mortality are still unclear and the respective impact of specific SARS-CoV-2 strains responsible for ARDS, ECMO centre experience, patients' characteristics and management has not been investigated in thorough detail in large multicentre cohorts to date.

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

Methods

Study Design

The ECMO-SURGES study was a multicentre, retrospective cohort study conducted in 21 medium (15-30 VA or VV-ECMO cases/year) to high-volume (>30 cases/year) experienced ECMO centres¹⁷ across eight European countries. Centres were invited to participate if they had an established ECMO program for more than five years and were currently caring for COVID-19 patients 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 and who received venoarterial (VA) or venovenous (VV) ECMO for severe ARDS from January 1, 2020, to September 30, 2021, were retrospectively included. ECMO for isolated refractory cardiogenic shock was exclusionary. The end of follow-up was December 30, 2021.

Periods and variants

We defined four periods during the study: January 1 - June 30, 2020 (1st semester of 2020, S1-2020); July 1 - December 31, 2020 (S2-2020); January 1 - June 30, 2021 (S1-2021), and July 1, - September 30, 2021 (S2-2021). COVID-19 variants were classified as wild type, Alpha (B.1.17), Delta (B.1.617.2), or other variants. This latter group combined Gamma (P.1), Beta (B.1.351), Mu (B.1.621), and B.1.160 variants. Because sequencing was not routinely performed during the first and second waves of the pandemic, all patients treated before October 31, 2020 (when the Alpha variant was first reported in England) were considered as wild-type. When COVID-19 variant sequencing was not performed, the predominant variant in the country at the date of ICU admission was considered according to the European Centre for Disease Prevention and Control, which weekly reported the number of cases per week and

per country in Europe (<https://www.ecdc.europa.eu/en/covid-19>).

Pre-ECMO data collection

We collected age, sex, body mass index, comorbidities, COVID-19 vaccination status, hemodynamic component of the Sequential Organ-Failure Assessment (SOFA) score, dates of first symptom(s), and hospital and ICU admissions. Immunocompromised status was defined as haematological malignancies, an active solid tumour or having received specific anti-tumour treatment within 1 year, solid-organ transplant, or human immunodeficiency virus-infected, long-term corticosteroids or immunosuppressant. In addition, we collected pre-ECMO implantation information: previous rescue therapies, date of high flow nasal oxygen, non-invasive ventilation and invasive mechanical ventilation initiation, ventilator settings (mode, PEEP, FiO₂, respiratory rate, tidal volume, plateau pressure (P_{plat}), arterial blood-gas parameters and routine laboratory values. Driving pressure (ΔP) was defined as P_{plat} minus PEEP and mechanical power (J/minute) was calculated as follows: *Mechanical Power* = $0.098 \times tidal\ volume \times respiratory\ rate \times peak\ pressure - \frac{1}{2} \times \Delta P$.¹⁸ If not specified, peak pressure was considered equal to plateau pressure.

Outcomes

Patients status was recorded 90 days after ECMO initiation. For patients alive at day 90, the following states were defined: “on ECMO”, “on mechanical ventilation and weaned-off ECMO”, “still in the hospital and weaned-off ECMO and mechanical ventilation”, “in a rehabilitation centre” or “back home”. Causes of death, in-ICU and in-hospital death rates and the time spent on ECMO, on mechanical ventilation, in the ICU and the hospital, were also noted. Mechanical ventilation settings and other adjuvant therapies were collected on days 1 and 3 after ECMO initiation. ECMO-related complications and organ dysfunction included

clogged circuit/membrane, ECMO-circuit change, heparin-induced thrombocytopenia, major bleeding, ischemic and hemorrhagic stroke, renal replacement therapy, proven pulmonary embolism, pneumothorax, ventilator-associated pneumonia, and bacteremia. Major bleeding was defined as requiring ≥ 2 units of packed red blood cells for an obvious hemorrhagic event, necessitating a surgical or interventional procedure, an intracerebral haemorrhage, or any other bleeding leading to death.

Statistical analyses

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

Patient characteristics are expressed as numbers (percentages) for categorical variables, and median [interquartile range (IQR)] for continuous variables. Categorical variables were compared by chi-square or Fisher's exact test, and continuous variables were compared by Student's t-test or 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 of death at day 90 were assessed within the whole cohort using multivariate Cox regression models. Baseline variables (i.e. obtained before ECMO start) included in the multivariable model were defined *a priori*, and no variable selection was performed. 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 (*Table S1*, 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 participants. Each dataset was then analyzed and the results from each dataset were pooled into a final result using Rubin's rule.¹⁹ Hazard ratios and their 95% confidence interval were estimated. Additionally, two sensitivity analysis were conducted, 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 COVID-19 variant.

All the analyses were computed at a two-sided alpha level of 5%. Statistical analyses were conducted with R v4.2.0.

Role of the funding source

There was no funding for this study. The corresponding author had full access to all data and the final responsibility to submit for publication.

Results

Study population and variant distribution

Among twenty-four European ECMO centres invited to participate in this study, 21 (4 medium and 17 high-volume centres) from eight countries (Austria, Belgium, England, France, Germany, Italy, Portugal, Spain) included COVID-19 patients treated with ECMO in the ECMO-SURGES study (Figure 1). Their main characteristics are described in Table S2 (appendix p 10). Notably, the median number of ECMO cases treated in these centres in 2019 was 40 [IQR 30-81], a mobile rescue team was available in 18 (86%) centres before and 17 (81%) centres during the pandemic. Most centres followed the EOLIA entry criteria to indicate ECMO. The median upper age to deny ECMO dropped from 70 years before to 65 years and more contraindications to ECMO existed during the pandemic (Table S2, appendix p 10). Thus, between January 1, 2020, and September 30, 2021, 1345 ECMO patients were

treated in these centres: 324 during S1-2020, 352 during S2-2020, 495 during S1-2021, and 173 during S2-2021. Sequencing was performed for 1261 (94%) patients and the predominant variant in the country was considered for 84 patients without virus sequencing hospitalized after October 31, 2020. The wild-type variant represented 686 (51%) cases whereas Alpha, Delta, and other variants were responsible for 391 (29%), 195 (14%), and 73 (6%) cases, respectively (Table 1). Among the group named “other variants”, 47 were Beta, 17 Gamma, 3 Mu, and 6 B.1.160 variants. The wild type variant accounted for 100% and 81% of the strains isolated in the first and second semesters of 2020, while Alpha was predominant in S1-2021 and Delta in S2-2021. Variant distribution and main characteristics of the population among the 8 countries are provided in Tables S3 and S4 (appendix pp 11-12).

Patients characteristics before ECMO

Table 1 summarizes main demographic and clinical characteristics of patients according to COVID-19 variants. Patients with wild type, Alpha, Delta, and other variants had similar demographic characteristics, except for younger age and less hypertension and diabetes for Delta patients. Overall, the time between ICU admission to intubation, the proportion of patients receiving non-invasive oxygenation strategies and the rate of pneumothorax increased over time (Table S5, appendix pp 13-15). Noticeably, S2-2021 patients (98% infected with the Delta variant) were younger, more frequently vaccinated (7%) and had more frequent bacterial coinfection at cannulation (Table S5, 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 and semesters.

ECMO management and COVID-19-specific treatment

Venovenous ECMO was applied to 98% of the patients, the femoral-jugular setting being

used in >75% of the cases (Table 2). All patients received ultra-protective mechanical ventilation on ECMO which combined decreases in FiO₂, respiratory rate, tidal volume, and driving pressure whatever the variant or the time period (Table 2 and Table S6, appendix pp 16-17). This strategy led to a considerable decrease in ventilation mechanical power (from [median (IQR)] 21.7 (17.6–25.9) J/min at baseline to 4.7 (2.9-7.4) J/min on ECMO Day 1). Noticeably, the rate of prone positioning on ECMO increased over time with a maximum of 278 (58%) patients being proned during S1-2021 (Table S7, appendix pp 18-19). Remdesivir treatment decreased over time with only 12 (7%) patients receiving this drug during S2-2021. Alternatively, the use of tocilizumab and dexamethasone (given before and/or during ECMO), increased over time (Table S7, appendix pp 18-19). Only 345 (50%) and 90 (13%) wild type patients received dexamethasone and tocilizumab compared to 175 (90%) and 69 (35%) Delta variant patients, respectively (Table 3).

ICU complications and organ support

The rate of clogged circuit/membrane requiring change increased over time, with the highest rate reported in patients with Delta variant, whereas massive bleeding was more frequently reported in patients with the wild type strain (37%, p=0.002) and during S2-2020. 146 (75%) and 60 (82%) patients with Delta and other variants had ventilator-associated pneumonia, respectively. Of note, rates of ischemic and haemorrhagic stroke, and of bacteraemia were similar between periods and variants.

Patient outcomes and factors associated with 90-day mortality

Complete 90-day post-ECMO survival status was available for all patients. Overall 90-day mortality was 42% and was 43%, 39%, 40%, and 58% for patients with wild-type, Alpha, Delta, and other variants, respectively (Figure 2-A, log-rank test p=0.008). When compared

with other semesters, patients treated during S2-2020 had the highest 90-day mortality (50% vs. 40% in other semesters, Log-rank test $p=0.018$; Figure 2-B) and the lowest rates of successful ECMO weaning, ICU and hospital survival. Delta variant patients had longer ECMO runs despite similar ICU and hospital lengths of stay (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 associated mortality. Patients needing renal replacement therapy, and those with higher hemodynamic SOFA component score, PaCO_2 , and lactate before ECMO had also 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 being the reference. Moreover, similar mortality risk factors were found when the model accounted for the semester of inclusion in the study instead of the COVID-19 strain (Table S8, appendix p 20) or when excluding patients for whom the variant type was missing (Table S9, appendix p 21). Kaplan–Meier survival estimates according to tertiles of age, PaCO_2 , and pre-ECMO ICU admission to intubation time and renal replacement therapy are provided in Figure 3 and Figure S1 (appendix p 22).

Discussion

This study reporting the characteristics and outcomes of 1,345 patients who received ECMO for severe COVID-19 in twenty-one 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. Noticeably, mortality was 10% higher (50%) in the second semester of 2020 than in other periods, when the wild type variant was still prevailing. Factors independently associated with 90-day mortality were age, immunocompromised status, longer

time between ICU admission and intubation, higher PaCO₂ and lactate, 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.

Only a few large multicentre studies^{5,9-11,20,21} have reported the outcomes of patients who received ECMO for severe COVID. In the international ELSO registry,⁹ in-hospital mortality was 50% among the 4,812 COVID-19 patients 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 3,397 COVID-19 patients supported with VV-ECMO from March 2020, to May 2021.²¹ This high in-hospital mortality was attributed to patients' older mean age (57±11 years) and to the lack of regulation for ECMO use in the country.²¹ It should be noted that the actual 90-day mortality may have been higher than the reported in-hospital mortality in these series.^{9,10,20,21} In addition, the vast majority of these patients were treated in 2020, when the wild-type SARS-CoV-2 strain was dominant and no data exist to date regarding ECMO patients' outcomes after infection with other SARS-CoV-2 variants.

Indeed, infections with Alpha and Delta 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 epidemiologic study in Washington, significantly more hospitalization were reported for infections with Alpha, Beta, Gamma, or Delta strains, with the highest rates associated with Beta and Gamma subtypes.²⁶ It has been suggested that higher viral load and increased inflammatory response syndrome may be mechanisms conferring higher virulence to these strains and poorer outcomes in infected patients.²²⁻²⁵ However, in the most severe forms of COVID, patients selection for ECMO, their characteristics at ECMO initiation, and different management and treatments during hospitalization may also influence 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. It should however be noted that patients with the Delta variant were younger and had less comorbidities at ECMO initiation. Since the vaccination campaign prioritized the oldest part of the population in all European countries in 2021, it might be speculated that younger patients were less protected against severe forms of COVID during the Delta wave. Indeed, the rate of vaccination remained very low in our COVID patients on ECMO throughout 2021, with less than 8% of Delta patients having received at least one shot of the vaccine. Alternatively, they had more frequent ventilator-associated pneumonia and clogged ECMO membrane requiring circuit change during ECMO support. These complications may relate to the immunosuppressive state, affecting both the innate and adaptive immune systems^{27,28} and to the intense activation of the 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, where ECMO patients were older, had more comorbidities and bacterial coinfection at baseline and were less likely to be treated at a high-volume centre. Their time between admission to the intensive care unit and ECMO start was also longer. In the ELSO registry,⁹ in-hospital mortality increased from 37% before to 52% after May 1st 2020. Patients treated later in 2020 had more frequent diabetes, preexisting heart disease, immunocompromised status, bacterial pneumonia, and bloodstream co-infection and use of corticosteroids before ECMO. They were also more likely to have received non-invasive ventilation before ECMO and had a shorter duration of invasive ventilation before ECMO. In our series, the severity of respiratory disease and patients' management under ECMO was 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 may 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 significantly increased in most ECMO series after June 2020, was a stronger predictor of poor outcome than the time on mechanical ventilation before ECMO. Interestingly, time on non-invasive respiratory support was the longest for patients with less frequent SARS-CoV-2 strains, who had the highest mortality. Indeed, patients failing on non-invasive oxygenation techniques may have suffered greater self-inflicted lung injury³⁰ due to strong respiratory efforts and important swings of transpulmonary pressure, which may also explain the increased rate of pneumothorax in the last three semesters of our study. Therefore, the duration of non-invasive respiratory support may be an important consideration in the selection criteria for ECMO in this context and warrants further investigation.

Our study has several strengths. First, viral identification was obtained in 94% of the 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 day-90 patients' outcomes (not just in-hospital mortality) amongst some of the most experienced ECMO centres in Europe which minimized the volume-outcome effect that had been reported for non-COVID¹⁷ and COVID^{5,9,16} patients supported by ECMO. Indeed, the overall 90-day mortality we report herein is in line with previous non-COVID cohorts of ARDS supported by ECMO.^{1,12-14} It is also 15-25% lower than the in-hospital mortality observed in recent large COVID series,^{9,10,21} despite lower PaO₂/FiO₂ at baseline.

Our study has also limitations. First, some patients were still under ECMO or mechanical ventilation at the end of follow-up and mortality may have been higher at later time points. Second, we did not evaluate long-term health-related quality-of-life and other sequelae of COVID-19, which may persist for a long time.³¹ Third, we did not collect data after Omicron infection, which has been associated with less severe disease.³² Fourth, we inferred the variant based on chronology and geography and not on direct testing in 84 (6%) patients. Fifth, the calculation of adjusted hazard ratios for mortality among SARS-CoV-2 strains was based on key prognosis factors included in our database and may have been biased by residual confounders not taken into account in our multivariable model. Of note, the hazard ratios associated with these factors should be interpreted with caution, as they don't represent the same time of causal effect as that of COVID strains.³³ Sixth, the strain on health-care systems and ICU resource constraints may 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 that may limit generalizability of our results.

In conclusion, adjusted mortality of COVID patients treated with ECMO in experienced centres in Europe was higher for those infected with the Delta variant, who were younger and had less comorbidities at ECMO initiation. The 42% day-90 mortality we report herein is lower than in other large series ARDS patients supported by ECMO for COVID and in line with cohorts of non-COVID 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 considerable constraints on health care systems.^{11,34,35}

Author contributions:

All authors were involved in data generation.

MS, DH, and AC had directly 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 the revision, read and approved the final version of the manuscript.

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. All authors have seen and approved the final text.

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Data sharing

Individual patient data reported in this article will be shared after de-identification (text, tables, figures, and appendices), beginning 6 months and ending 2 years after Article publication, to researchers who provide a methodologically sound proposal and after approval of 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.

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Tables

Table 1. Patients' pre-ECMO characteristics according to their COVID-19 variants

	All (N=1345)	Wild type (N=686)	Alpha (N=391)	Delta (N=195)	Others (N=73)	P-value
Age, years	53 (44-59)	54 (46-60)	53 (45-58)	46 (37-55)	55 (49-62)	<0.001
Male	1035 (77)	540 (79)	300 (77)	143 (73)	52 (71)	0.261
Body mass index, kg/cm²	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
Vaccination						<0.001
1 shot	24 (2)	0 (0)	5 (1)	15 (8)	4 (5)	
2 shots	17 (1)	0 (0)	3 (1)	12 (6)	2 (3)	
Comorbidities						
Hypertension	555 (41)	299 (44)	166 (42)	55 (28)	35 (48)	<0.001
Diabetes	327 (24)	193 (28)	89 (23)	27 (14)	18 (25)	<0.001
Ischemic cardiomyopathy	76 (6)	41 (6)	24 (6)	7 (4)	4 (5)	0.589
Chronic respiratory disease ^a	158 (12)	77 (11)	52 (13)	15 (8)	14 (19)	0.045
Immunocompromised ^b	84 (6)	41 (6)	23 (6)	12 (6)	8 (11)	0.407
Pregnancy	22 (2)	7 (1)	9 (2)	6 (3)	0 (0)	0.102
Time from						
1 st symptoms to hospital admission, days	6 (3–8)	6 (3–8)	5 (3–8)	6 (4–8)	6 (3–8)	0.383
ICU admission to intubation, days	1 (0–4)	0 (0–3)	1 (0–5)	1 (0–3)	3 (1–6)	<0.001
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)	<0.001
Duration, days	1 (0-4)	1 (0-4)	2 (0-5)	1 (0-4)	3 (1-6)	<0.001
Non-invasive ventilation	567 (42)	229 (33)	197 (50)	100 (51)	41 (56)	<0.001
Duration, days	1 (0-4)	0 (0-3)	1 (0-4)	2 (0-5)	3 (1-6)	<0.001

Ventilation parameters						
FiO ₂	100 (100–100)	100 (100–100)	100 (100–100)	100 (95–100)	100 (100–100)	0.581
PEEP, cm H ₂ O ^c	12 (10–14)	12 (10–14)	12 (10–14)	12 (10–15)	12 (10–14)	0.361
Tidal volume, mL/kg PBW ^d	6.1 (5.5–6.9)	6.1 (5.6–7.0)	6.1 (5.4–6.9)	6.3 (5.7–7.2)	6.1 (5.5–7.0)	0.215
Respiratory rate, no./min^e	26 (23–30)	26 (23–30)	26 (22–30)	25 (22–28)	28 (25–30)	0.004
Driving pressure, cm H₂O^f	18 (15–22)	18 (15–22)	18 (15–21)	16 (14–20)	19 (16–22)	0.006
Static compliance, mL/cm H₂O^g	22.5 (17.5–29.7)	22.5 (17.6–30.0)	23.0 (16.9–28.3)	25.0 (18.5–32.3)	20.7 (15.2–23.8)	0.005
Mechanical power, J/min ^h	21.7 (17.6–25.9)	22.1 (18.2–26.3)	20.9 (17.1–25.2)	21.1 (16.8–25.7)	22.2 (17.5–26.4)	0.086
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
PaO₂/FiO₂	66 (55–80)	68 (56–81)	65 (51–80)	65 (51–80)	60 (56–67)	<0.001
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-cell count, G/Lⁱ	13.4 (9.4–18.1)	12.9 (9.2–17.9)	13.2 (9.4–18.4)	14.5 (10.5–20.9)	14.0 (9.8–18.6)	0.038
Serum creatinine, μmol/L ^j	70 (53–103)	71 (54–109)	70 (52–98)	67 (47–96)	69 (48–111)	0.274
Serum bilirubin, μmol/L ^k	7 (5–13)	7 (5–13)	7 (4–13)	8 (5–13)	7 (5–11)	0.678
Platelets, G/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)	0.004
Pneumothorax	159 (12)	76 (11)	49 (13)	21 (11)	13 (18)	0.352

Values are expressed as median (interquartile range) or number (%).

ECMO, extracorporeal membrane oxygenation, ICU intensive care unit, FiO₂ the fraction of inspired oxygen, MERT, Mobile ECMO Retrieval Team, PaO₂/FiO₂ the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, PEEP positive end-expiratory pressure, PBW predicted body weight, PaO₂ partial pressure of arterial oxygen, PaCO₂ partial pressure of arterial carbon dioxide, and SOFA Sequential Organ-Function Assessment.

^a Defined as chronic obstructive pulmonary disease or asthma.

^b Defined as haematological malignancies, active solid tumour or having received specific anti-tumour treatment within 1 year, solid-organ transplant or human immunodeficiency virus-infected, long-term corticosteroids or immunosuppressants

^c N=1157 patients

^d N=1068 patients

^e N=1077 patients.

^f Defined as plateau pressure minus PEEP and available for 1050 patients.

^g N=994 patients

^h 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. N=939 patients.

ⁱ N=1109 patients

^j N=1117 patients

^k N=1041 patients

Table 2. Characteristics of the patients on-ECMO day-1 and day-3 according to their COVID-19 variants

	All (N=1345)	Wild type (N=686)	Alpha (N=391)	Delta (N=195)	Others (N=73)	P-value
Type of ECMO support						0.529
venovenous ECMO	1318 (98)	668 (97)	384 (98)	194 (99)	72 (99)	
Femoral–jugular	1045 (78)	539 (79)	290 (74)	152 (78)	64 (88)	
Venoarterial ECMO	19 (1)	13 (2)	5 (1)	1 (0.5)	0 (0)	
venoarterial–venous ECMO	8 (1)	5 (1)	2 (0.5)	0 (0)	1 (1)	
Ventilation parameters Day 1						
FiO ₂	50 (40–70)	50 (40–70)	50 (40–70)	50 (40–60)	50 (40–70)	0.138
PEEP, cm H ₂ O	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, no./min	14 (10–20)	14 (12–20)	14 (10–16)	12 (12–16)	12 (10–20)	0.002
Driving pressure, cm H ₂ O	12 (10–14)	12 (11–14)	12 (10–14)	12 (10–14)	12 (10–14)	0.867
Compliance, mL/cm H ₂ O	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 Day 1						<0.001
APRV/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 Day 1	860 (67)	440 (68)	250 (68)	123 (67)	47 (64)	0.918
Prone-positioning Day 1	200 (15)	76 (11)	73 (19)	38 (19)	13 (18)	0.001
Inhaled nitric oxide Day 1	63 (5)	28 (4)	23 (6)	10 (5)	2 (3)	0.514
Awake on ECMO Day 1^a	13 (1)	2 (0.3)	6 (2)	4 (2)	1 (1)	0.032
Ventilation parameters Day 3						
FiO ₂	50 (40–60)	50 (40–60)	50 (40–60)	50 (40–60)	50 (40–60)	0.994
PEEP, cm H ₂ O	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, no./min	14 (12–20)	14 (12–20)	14 (10–18)	13 (12–16)	15 (10–20)	0.010
Driving pressure, cm H ₂ O	12 (10–14)	12 (11–14)	13 (10–14)	12 (10–15)	14 (12–15)	0.282
Compliance, mL/cm H ₂ O	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)	<0.001
Neuromuscular blockade Day 3	736 (57)	382 (58)	221 (59)	91 (48)	42 (62)	0.067
Prone-positioning Day 3	286 (21)	113 (17)	98 (25)	42 (22)	33 (46)	<0.001
Inhaled nitric oxide Day 3	39 (3)	19 (3)	13 (3)	5 (3)	2 (3)	0.935
Awake ECMO Day 3 ^a	32 (2)	8 (1)	19 (5)	5 (3)	0 (0)	0.001

Values are expressed as median (interquartile range) or number (%).

APRV denotes airway pressure release ventilation; ECMO extracorporeal membrane oxygenation, FiO₂ the fraction of inspired oxygen, PEEP positive end-expiratory pressure, PaO₂ partial pressure of arterial oxygen, PaCO₂ partial pressure of arterial carbon dioxide, PAPV positive airway pressure ventilation, and PBW predicted body weight,

^a Defined as the patient being awake, cooperative, performing rehabilitation and physiotherapy

Table 3. ECMO management, complications and outcomes according to COVID-19 variants

Parameter	All (N=1345)	Wild type (N=686)	Alpha (N=391)	Delta (N=195)	Others (N=73)	P-value
Tracheostomy	693 (52)	347 (51)	198 (51)	118 (61)	30 (41)	0.020
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)	<0.001
No. of sessions on ECMO	0 (0-3)	0 (0-3)	0 (0-4)	0 (0-3)	2 (0-5)	<0.001
Received COVID-19 specific treatment ^a						
Remdesivir	163 (12)	98 (14)	47 (12)	16 (8)	2 (3)	0.008
Tocilizumab	223 (17)	90 (13)	51 (13)	69 (35)	13 (18)	<0.001
Dexamethasone	928 (69)	345 (50)	342 (87)	175 (90)	66 (90)	<0.001
High-dose corticosteroids (Meduri protocol)	451 (34)	219 (32)	138 (35)	61 (31)	33 (45)	0.100
ECMO-related complications						
Clogged circuit/membrane requiring change	449 (33)	205 (30)	144 (37)	89 (46)	11 (15)	<0.001
Number of circuit change(s)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	0.005
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)	0.002
Ischemic 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)	0.005
≥1 antibiotic-treated bacteraemia episode(s)	571 (44)	288 (45)	163 (42)	87 (45)	33 (45)	0.799
Outcomes						
Lung transplant on ECMO	6 (0.45)	4 (0.6)	1 (0.2)	1 (0.5)	0 (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)	0.002
90-day survival status						0.010
Dead	569 (42)	297 (43)	152 (39)	78 (40)	42 (58)	
On ECMO	53 (4)	37 (5)	8 (2)	8 (4)	0 (0)	
On mechanical ventilation & weaned-off ECMO ^a	47 (3)	26 (4)	11 (3)	9 (5)	1 (1)	
Still in the hospital & weaned-off ECMO	89 (7)	43 (6)	32 (8)	14 (7)	0 (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)	
Cause of death^b						0.010
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 (0.5)	1 (0.3)	1 (0.6)	0 (0)	1 (2)	
Cannulation complication	9 (2)	6 (2)	1 (0.6)	0 (0)	2 (5)	
Transport complication	1 (0.2)	1 (0.3)	0 (0)	0 (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)	0 (0)	

Values are expressed as median (interquartile range) or number (%).

ECMO, extracorporeal membrane oxygenation, and SOFA Sequential Organ Function Assessment

^a given before and/or during ECMO; ^b Available in 592 patients

Table 4: Predictive Factors Associated with 90-day mortality in critically ill adults with COVID-19 treated with ECMO.

	Multivariate HR (95% CI)	P value
Age, years	1.05 (1.04 – 1.06)	<0.001
Male	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		
1 st symptoms to hospital admission, per one day	0.99 (0.97 – 1.01)	0.492
ICU admission to intubation, per one day	1.05 (1.02 – 1.07)	<0.001
Intubation to ECMO, per one day	1.01 (0.99 – 1.03)	0.330
Pre-cannulation		
Cardiac arrest	1.04 (0.68 – 1.63)	0.820
Hemodynamic 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 ^a	1.02 (1.00 – 1.03)	0.058
Pneumothorax	1.25 (0.96 – 1.63)	0.096
PaCO₂, mmHg	1.01 (1.00 – 1.01)	0.011
PaO ₂ /FiO ₂ , mmHg	1.00 (1.00 – 1.00)	0.506
Lactate, mmol/l	1.10 (1.02 – 1.19)	0.011
Platelets, G/l	1.00 (1.00 – 1.00)	0.382
Recruitment maneuvers	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

BMI, body mass index; CV, cardiovascular; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; HR, hazard ratio; CI, confidence interval

^a 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. N=939 patients.

Figure Legends

Figure 1. Study flowchart.

Medium volume centres are performing 15-30 and high-volume centres >30 VA or VV-ECMO cases/year.

Figure 2. Survival probability at 90 days according to A) COVID-19 variants or B) Study periods.

Survival curves (Kaplan-Meier estimate) of COVID-19 patients treated with ECMO during the first semester of 2020 (S1-2020, blue line), second semester of 2020 (S2-2020, red line), first semester of 2021 (S1-2021, green line) and second semester of 2021 (S2-2021, orange line).

Figure 3. Kaplan–Meier survival estimates according to tertiles of A) age, B) ICU admission to intubation time and C) pre-ECMO PaCO₂.

Figure 1.

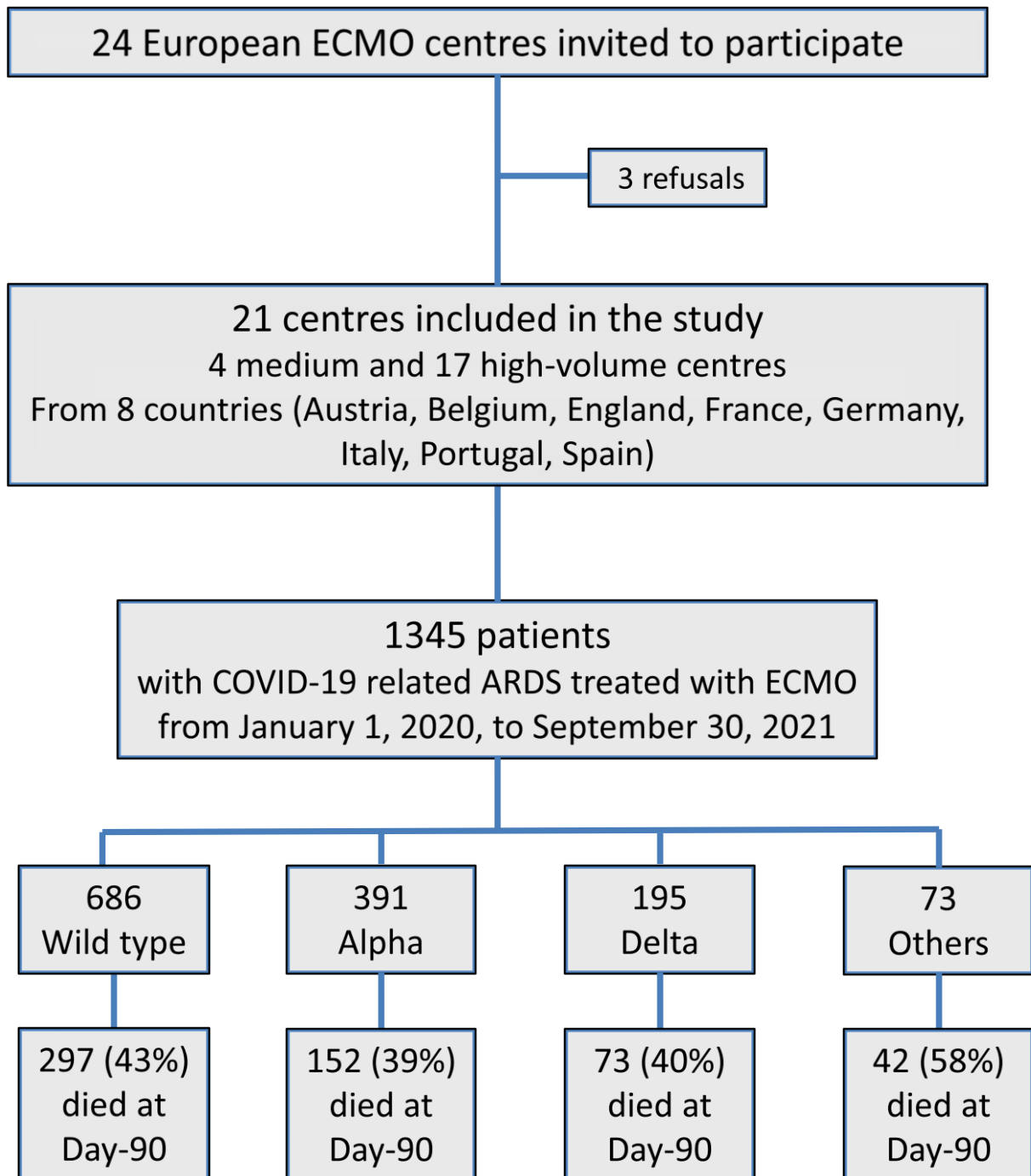
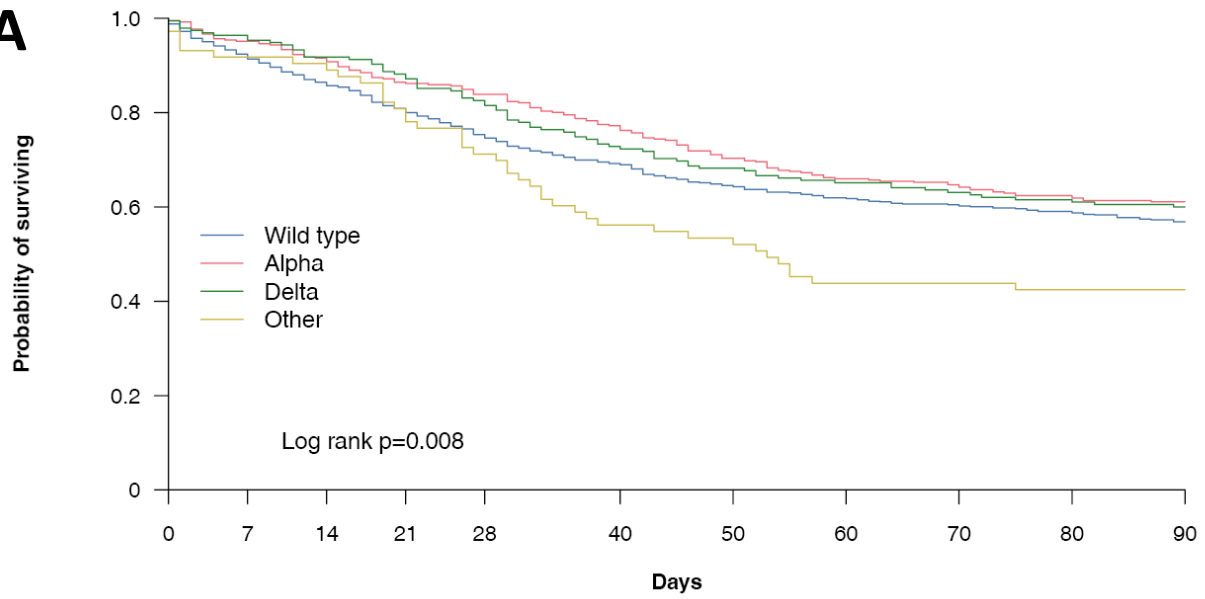


Figure 2.

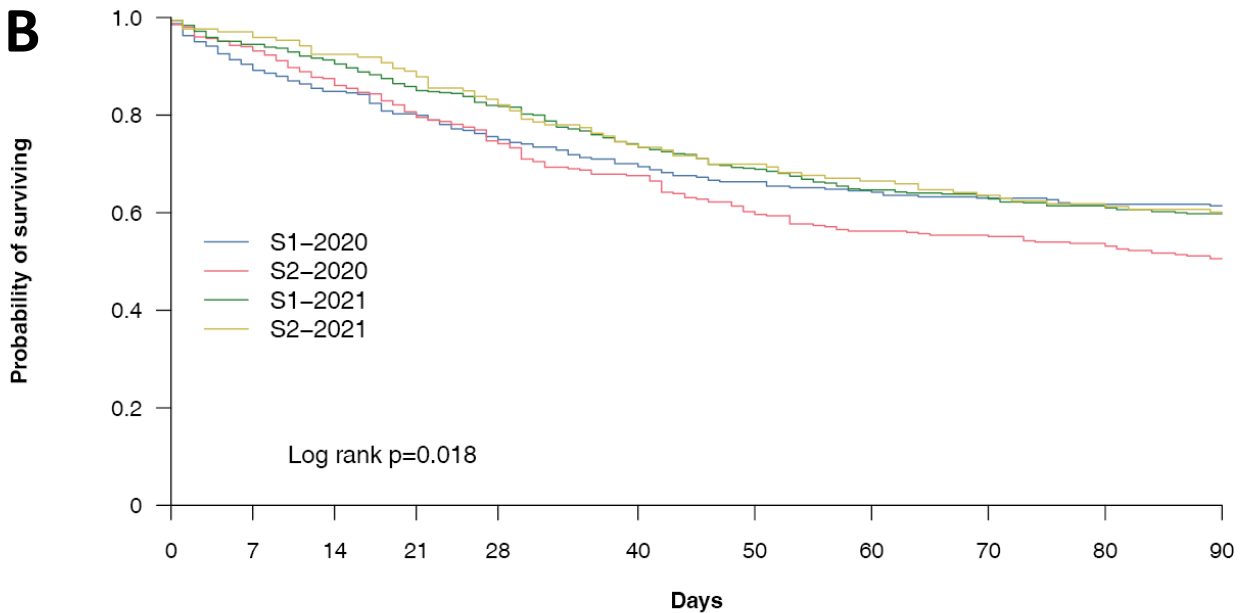
A



Number at risk (number censored)

— Wild type	686 (0)	634 (0)	593 (0)	555 (0)	517 (0)	475 (0)	443 (0)	425 (0)	415 (0)	405 (0)	390 (390)
— Alpha	391 (0)	372 (0)	358 (0)	338 (0)	328 (0)	302 (0)	275 (0)	258 (0)	253 (0)	244 (0)	239 (239)
— Delta	195 (0)	188 (0)	179 (0)	172 (0)	161 (0)	142 (0)	133 (0)	127 (0)	123 (0)	120 (0)	117 (117)
— Other	73 (0)	67 (0)	66 (0)	59 (0)	52 (0)	41 (0)	39 (0)	32 (0)	32 (0)	31 (0)	31 (31)

B

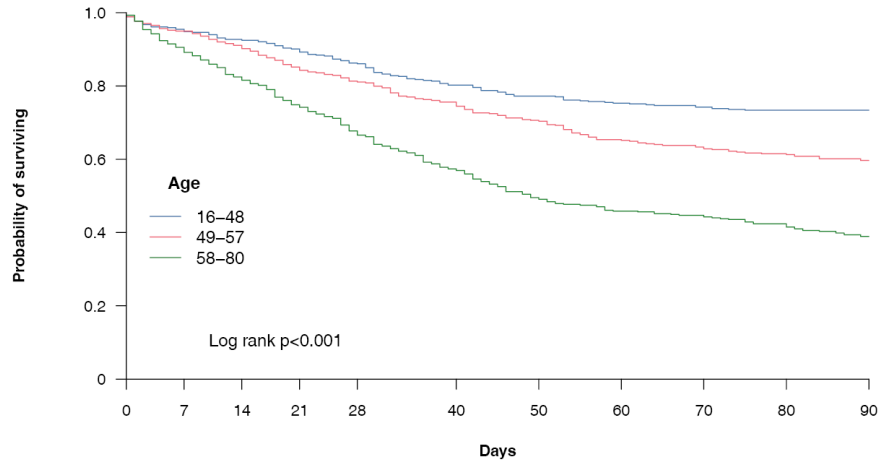


Number at risk (number censored)

— S1-2020	324 (0)	293 (0)	275 (0)	260 (0)	245 (0)	227 (0)	215 (0)	209 (0)	204 (0)	200 (0)	199 (199)
— S2-2020	352 (0)	331 (0)	308 (0)	284 (0)	263 (0)	238 (0)	212 (0)	198 (0)	195 (0)	189 (0)	178 (178)
— S1-2021	495 (0)	468 (0)	452 (0)	425 (0)	406 (0)	367 (0)	342 (0)	320 (0)	314 (0)	304 (0)	296 (296)
— S2-2021	173 (0)	168 (0)	160 (0)	154 (0)	144 (0)	128 (0)	121 (0)	115 (0)	110 (0)	107 (0)	104 (104)

Figure 3.

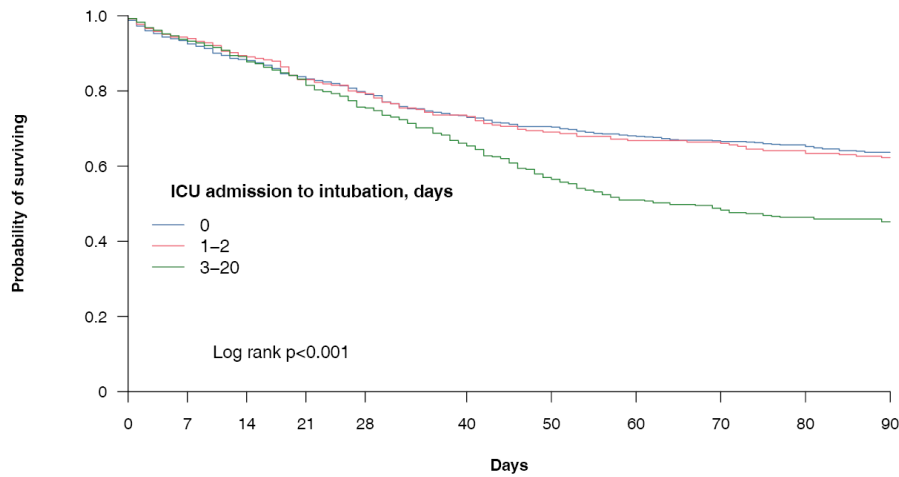
A



Number at risk (number censored)

—	466 (0)	445 (0)	432 (0)	420 (0)	402 (0)	374 (0)	360 (0)	351 (0)	346 (0)	342 (0)	342 (342)
—	439 (0)	417 (0)	400 (0)	374 (0)	357 (0)	332 (0)	310 (0)	287 (0)	278 (0)	270 (0)	262 (262)
—	434 (0)	393 (0)	358 (0)	325 (0)	294 (0)	249 (0)	215 (0)	199 (0)	194 (0)	184 (0)	169 (169)

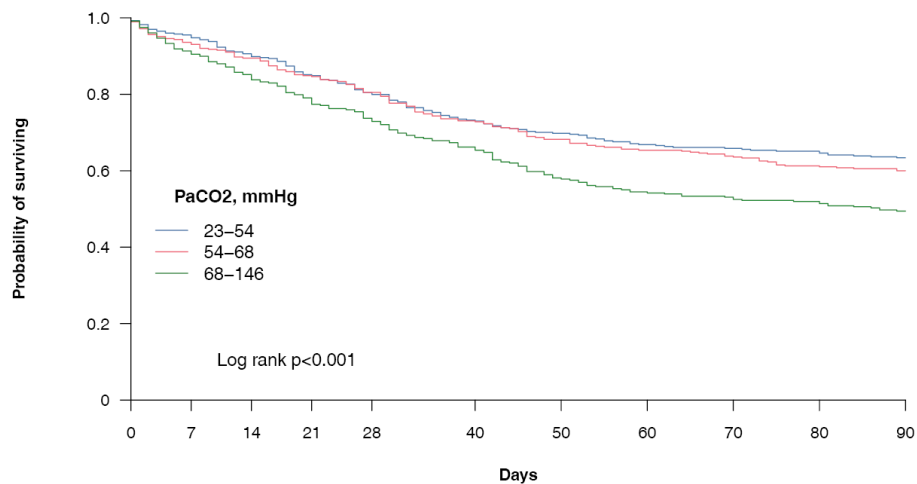
B



Number at risk (number censored)

—	655 (0)	612 (0)	579 (0)	549 (0)	523 (0)	481 (0)	462 (0)	446 (0)	437 (0)	430 (0)	417 (417)
—	265 (0)	250 (0)	237 (0)	220 (0)	211 (0)	195 (0)	183 (0)	177 (0)	176 (0)	170 (0)	165 (165)
—	416 (0)	390 (0)	371 (0)	346 (0)	315 (0)	275 (0)	237 (0)	212 (0)	203 (0)	193 (0)	188 (188)

C



Number at risk (number censored)

—	404 (0)	386 (0)	366 (0)	344 (0)	325 (0)	296 (0)	282 (0)	270 (0)	266 (0)	263 (0)	256 (256)
—	390 (0)	365 (0)	349 (0)	331 (0)	314 (0)	285 (0)	266 (0)	255 (0)	249 (0)	239 (0)	234 (234)
—	358 (0)	327 (0)	305 (0)	283 (0)	264 (0)	237 (0)	208 (0)	195 (0)	190 (0)	186 (0)	177 (177)