Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study

Guillaume Lebreton, Matthieu Schmidt, Maharajah Ponnaiah, Thierry Folliguet, Marylou Para, Julien Guihaire, Emmanuel Lansac, Edouard Sage, Bernard Cholley, Bruno Mégarbane, Pierrick Cronier, Jonathan Zarka, Daniel Da Silva, Sebastien Besset, Tristan Morichau-Beauchant, Igor Lacombat, Nicolas Mongardon, Christian Richard, Jacques Duranteau, Charles Cerf, Gabriel Saiydoun, Romain Sonneville, Jean-Daniel Chiche, Patrick Nataf, Dan Longrois, Alain Combes, Pascal Leprince, and the Paris ECMO-COVID-19 investigators*

Summary

Background In the Île-de-France region (henceforth termed Greater Paris), extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS) was considered early in the COVID-19 pandemic. We report ECMO network organisation and outcomes during the first wave of the pandemic.

Methods In this multicentre cohort study, we present an analysis of all adult patients with laboratory-confirmed SARS-CoV-2 infection and severe ARDS requiring ECMO who were admitted to 17 Greater Paris intensive care units between March 8 and June 3, 2020. Central regulation for ECMO indications and pooling of resources were organised for the Greater Paris intensive care units, with six mobile ECMO teams available for the region. Details of complications (including ECMO-related complications, renal replacement therapy, and pulmonary embolism), clinical outcomes, survival status at 90 days after ECMO initiation, and causes of death are reported. Multivariable analysis was used to identify pre-ECMO variables independently associated with 90-day survival after ECMO.

Findings The 302 patients included who underwent ECMO had a median age of 52 years (IQR 45–58) and Simplified Acute Physiology Score-II of 40 (31–56), and 235 (78%) of whom were men. 165 (55%) were transferred after cannulation by a mobile ECMO team. Before ECMO, 285 (94%) patients were prone positioned, median driving pressure was 18 cm H_2O (14–21), and median ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen was 61 mm Hg (IQR 54–70). During ECMO, 115 (43%) of 270 patients had a major bleeding event, 27 of whom had intracranial haemorrhage; 130 (43%) of 301 patients received renal replacement therapy; and 53 (18%) of 294 had a pulmonary embolism. 138 (46%) patients were alive 90 days after ECMO. The most common causes of death were multiorgan failure (53 [18%] patients) and septic shock (47 [16%] patients). Shorter time between intubation and ECMO (odds ratio 0·91 [95% CI 0·84–0·99] per day decrease), younger age (2·89 [1·41–5·93] for ≤48 years and 2·01 [1·01–3·99] for 49–56 years *vs* ≥57 years), lower pre-ECMO renal component of the Sequential Organ Failure Assessment score (0·67, 0·55–0·83 per point increase), and treatment in centres managing at least 30 venovenous ECMO cases annually (2·98 [1·46–6·04]) were independently associated with improved 90-day survival. There was no significant difference in survival between patients who had mobile and on-site ECMO initiation.

Interpretation Beyond associations with similar factors to those reported on ECMO for non-COVID-19 ARDS, 90-day survival among ECMO-assisted patients with COVID-19 was strongly associated with a centre's experience in venovenous ECMO during the previous year. Early ECMO management in centres with a high venovenous ECMO case volume should be advocated, by applying centralisation and regulation of ECMO indications, which should also help to prevent a shortage of resources.

Funding None.

Introduction

Although COVID-19 can be clinically expressed in several organs, severe acute respiratory distress syndrome (ARDS) is the most common life-threatening condition related to SARS-CoV-2 infection. Along with many other countries, France has been greatly affected by this viral pandemic, with the first resident admitted to intensive care in Paris (Île-de-France region; designated here as Greater Paris) on Feb 25, 2020.

Early reports from China on the use of extracorporeal membrane oxygenation (ECMO) in COVID-19-associated ARDS indicated unfavourable outcomes,[1–4] raising questions about its usefulness in the context of restricted intensive care unit (ICU) beds and resources. Some

(J Guihaire MD); **Department of Cardiac Surgery, Institut Mutualiste Montsouris, Paris, France** (E Lansac MD); **Department of Thoracic Surgery and Lung Transplantation** (Prof E Sage MD) **and Intensive Care Unit** (C Cerf MD), **Hôpital Foch, Suresnes, France; Department of Anesthesiology and Intensive Care, Hôpital Européen Georges Pompidou, AP-HP, Paris, France** (Prof B Cholley MD); **Department of Medical and Toxicological Critical Care, Lariboisière Hospital, AP-HP, Paris University, INSERM UMRS-1144, Paris, France** (Prof B Mégarbane MD); **Intensive Care Unit, Grand Hôpital du Sud Francilien, Corbeil, France** (P Cronier MD); **Intensive Care Unit, Grand Hôpital de l'Est Francilien, Jossigny, France** (J Zarka MD); **Medical Intensive Care Unit, Hôpital Delafontaine, Saint Denis, France** (D Da Silva MD); **Intensive Care Unit, Louis Mourier Hospital, AP-HP, Colombes, France** (S Besset MD); **Intensive Care Unit, Centre Cardiologique du Nord, Saint-Denis, France** (T Morichau-Beauchant MD); **Intensive Care Unit, Jacques Cartier Hospital, Massy, France** (I Lacombat MD); **Intensive Care Unit** (Prof C Richard MD) **and Department of Anesthesiology and Intensive care** (Prof J Duranteau MD), **Bicêtre Hospital, AP-HP, Paris Saclay University, France; University of Paris, UMR 1148, Laboratory of Vascular Translational Science, Paris, France** (Prof R Sonneville, Prof D Longrois MD, M Para); **Medical Intensive Care Unit, Cochin Hospital, AP-HP, Paris, France** (Prof J-D Chiche MD); **Department of Anaesthesia and Intensive Care, Bichat-Claude Bernard Hospital, AP-HP, INSERM U1148, Paris, France** (Prof D Longrois)

Correspondence to:
Guillaume Lebreton, Department of Cardiovascular and Thoracic Surgery, Pitié-Salpêtrière Hospital, Assistance Publique–Hôpitaux de Paris, Sorbonne University, Paris 75013, France
guillaume.lebreton@aphp.fr

See **Online** for appendix

Research in context

Evidence before this study

We searched PubMed for articles published in any language in peer-reviewed journals up to Jan 29, 2021, with the terms "extracorporeal membrane oxygenation" and either "COVID-19" or "severe acute respiratory syndrome coronavirus 2". We identified 215 publications including letters, case reports, and position papers, and only six case series. Very few publications reported patient survival up to 90 days after extracorporeal membrane oxygenation (ECMO) implantation in homogeneous cohorts of patients. Furthermore, extensive use of ECMO during the first wave of the COVID-19 pandemic raised questions about its feasibility (ie, shortage of equipment, bed management, and access). We identified only one article reporting ECMO resource allocation during this pandemic and none reporting the care organisation adopted to face this health crisis.

Added value of this study

This multicentre study reports on ECMO network organisation and outcomes during the COVID-19 pandemic in Greater Paris, one of the first regions in France to be severely affected, and where ECMO has been used to treat refractory acute respiratory distress syndrome (ARDS) related to COVID-19. We developed a dedicated organisation to pool resources and regulate interventions. From March 8 to June 3, 2020, 302 patients with COVID-19 were assisted by ECMO (mainly venovenous ECMO) for refractory ARDS, with a 90-day survival rate of 46% in this homogeneous and extremely severely affected cohort. Most ECMOs were implanted by mobile ECMO teams and the patients were subsequently transferred to an ECMO intensive care unit, with no significant difference in the survival rate compared with initiation of ECMO on site. Earlier ECMO initiation, younger age, no pre-ECMO renal dysfunction, and treatment in centres managing at least 30 venovenous ECMO cases annually were associated with improved 90-day survival. These findings confirm that COVID-19-associated ARDS can be efficiently treated by ECMO, as with other ARDS.

Implications of all the available evidence

With central regulation and pooling of resources on a regional level, venovenous ECMO was an effective extracorporeal technique for managing patients with refractory COVID-19-related ARDS in Greater Paris. As a strong volume–outcome effect was observed, venovenous ECMO should preferably be performed in high-volume expert centres with mobile ECMO teams capable of cannulating patients in remote intensive care units and transporting them to the referral centres.

authors argued that ECMO might not be effective or could even be deleterious (eg, by increasing the release of inflammatory cytokines),[5] whereas various experts[6,7] and the Extracorporeal Life Support Organization (ELSO)[8] were quick to suggest potential interest in ECMO for COVID-19-associated ARDS.

After the report of the first COVID-19 case in Paris, there was an exponential increase in calls for ECMO implantation in patients with COVID-19 over the following weeks. Thus, the need for a regional hub-and-spoke organisation became apparent, but there were many questions and challenges for the development of such a programme. First, the literature was scarce, with conflicting views on the efficacy of ECMO in COVID-19-associated ARDS; the number of potential candidates for ECMO and the availability of consoles and circuits were unknown; the French health system was overwhelmed by an urgent need to increase the number of ICU beds and thus, in that context, ECMO availability was not a high priority for regional agency and hospital decision makers; and finally, the potential for supply of materials from industry in the subsequent months was at least uncertain.

This study reports on the ECMO network organisation developed during the COVID-19 pandemic in Greater Paris, and the characteristics and 90-day clinical outcomes of patients who received ECMO for SARS-CoV-2 infection. We also aimed to identify predictors of 90-day survival.

Methods

Study design

This multicentre cohort study included all adult patients with COVID-19 with severe ARDS requiring ECMO who were admitted to any Greater Paris ICU between March 8 and June 3, 2020. 17 of these ICUs were designated ECMO centres and were supported by six mobile ECMO teams with capability for cannulation of patients at non-ECMO ICUs and subsequent transfer to the ECMO centres. All consecutive patients with laboratory-confirmed SARS-CoV-2 infection, defined as a positive result on real-time RT-PCR assay from nasal or pharyngeal swabs or respiratory tract aspirates,[9] and who received extracorporeal life support (ie, venovenous, venoarterial, or venoarterial–venous ECMO) for severe ARDS were included. All patients or close relatives were informed that their data were included in this ECMO-COVID-19 Île-de-France cohort. Data from 83 patients treated in the Paris–Sorbonne University Hospital Network ICUs, previously reported in a retrospective cohort study,[10] were included. The Sorbonne University Ethics Committee (CER-SU-2020-46) approved this study.

ECMO network organisation

During the pandemic, the ECMO network organisation comprised four steps (appendix p 45). Step 1 was the preparation of an inventory, with the help of the biomedical industry, listing all ECMO supplies available in Greater Paris, an area with a population of 12·21 million

in 2019. This information was not available at an administrative level, and some centres had received consoles in 2009 during the influenza A H1N1 epidemic with no formal follow-up. By contacting colleagues from 30 Greater Paris ICUs considered to have consoles and circuits, a good approximation was made of the resources available. More importantly, direct contact with colleagues had a positive and constructive effect on the networking process. Supplies were scarce, and the need to define rules and control availability early on was clear, with some supplies being reserved for non-COVID-19 indications (ie, cardiogenic shock, post-cardiotomy cardiac failure, paediatrics).

Step 2 involved defining the working processes needed to share equipment and human resources, including an attempt to homogenise the criteria for ECMO indication and management, and initiating systems to obtain rapid feedback on the efficacy or futility of the strategy in place. A task force, including heads of eight of the 17 ECMO centres and the six heads of the ECMO mobile units (appendix p 4), wrote guidelines for ECMO indications and organisation. Centralisation of the indications for ECMO was recommended for several reasons: (1) in view of the anticipated shortage of equipment, the primary aim was to base the decision to use ECMO on expertise and science-based medicine, avoiding compassionate use and futility; (2) to avoid tension between the ICUs requiring ECMO and the mobile unit teams; and (3) to maintain an accurate and up-to-date inventory of the equipment available. The guideline proposal was circulated to the ICUs, proposed to the regional health agency, and was officially approved on March 23, 2020.

Step 3 comprised networking and communications. A central ECMO-COVID-19 hub was established at the Pitié-Salpêtrière Hospital ICU that Greater Paris practitioners could call for advice on ECMO indications. A daily report was emailed to all relevant stakeholders and agencies throughout the first wave of the pandemic, listing the number of new cases and deaths, the ECMO weaning rate, and the real-time availability of equipment. A WhatsApp group was set up to facilitate discussions in the group and to dispatch the mobile ECMO teams. Thus, the centralisation process allowed the dispatching of six mobile ECMO teams, depending on their location and availability, and the allocation of ICU beds and equipment, enabling the pooling of equipment and immediate sharing on demand.

Step 4 concerned dissemination of information. Owing to heterogeneity between centres in terms of experience and numbers of patients on ECMO, a weekly web meeting was organised for the ECMO task force, which involved a growing number of participants (appendix p 4). The goal of these meetings was to summarise ECMO activity and update all centres on special issues, including thrombotic risk and strategy for anticoagulation, cases requiring venoarterial or venoarterial–venous ECMO, associated treatments, and early outcomes. In addition, as our growing regional experience with venovenous ECMO in COVID-19 was unique, it was shared with foreign colleagues, especially from the USA, through regular web meetings.

ECMO indications for COVID-19

Patients considered for ECMO had to fulfil the eligibility criteria used in the ECMO arm of the EOLIA trial.[11] Neuromuscular-blocking drugs and prone positioning before ECMO were highly recommended. Contra-indications for ECMO support in the pandemic context were age greater than 70 years, presence of serious comorbidities (eg, advanced cardiac, respiratory, or liver failure; metastatic cancer; and haematological malignancies), cardiac arrest (except if cardiopulmonary resuscitation was provided immediately and the low-flow time was <15 min), refractory multiple organ failure or Simplified Acute Physiology Score (SAPS)-II greater than 90, irreversible neurological injury, and mechanical ventilation for more than 10 days.

Regulation of cannulation and bed management

Through calls to the ECMO-COVID-19 hub, ECMO indications were evaluated by a medical team that included at least two intensivists. When the indication for ECMO was approved (central triage), and in the event that cannulation was not available on site, the coordination group determined which of the six mobile teams was available (operational regulation) to cannulate and which of the 17 ICUs could admit the patient on ECMO (bed management).

A mobile team, comprising a cardiovascular surgeon and a perfusionist, was sent by car to the patient's bedside. Venovenous ECMO was percutaneously inserted with a 23–29-Fr drainage cannula and an 18–23-Fr return cannula by a cardiovascular surgeon wearing personal protective equipment (ie, respiratory FFP2 or N95 mask, gown, goggles, and gloves; see video). Percutaneous femoro–jugular ultrasonography-guided cannulation with a large drainage cannula was the recommended technique. Pump flow was adjusted to obtain blood oxygen saturation greater than 90%. Adequate position of the cannulas was verified by ultrasonography and chest x-ray. If the patient was initially cannulated in a non-ECMO centre, they were then transported to one of the 17 ICUs able to manage ECMO. After successful ECMO weaning, patients were generally transferred to a different ward or hospital to continue the long process of mechanical ventilation weaning[12] to allow a quicker turnover of ECMO beds.

Recommended management with venovenous ECMO

Given the high risk of thromboembolic events with COVID-19, including massive pulmonary embolism, the task force recommended a target activated partial thromboplastin time for anticoagulation with unfractionated heparin of 60–75 s or anti-Xa activity between 0·3 and 0·5 IU/mL. Daily monitoring of

plasma-free haemoglobin and fibrinogenaemia was highly recommended. The haemoglobin threshold for red cell transfusion was 7–8 g/dL (or up to 10 g/dL when hypoxaemia persisted) and platelet transfusions were discouraged except for severe thrombocytopenia accompanied by bleeding. To enhance protection from ventilator-induced lung injury, ultraprotective lung ventilation combining a reduction of tidal volume, respiratory rate, and airway and driving pressures on ECMO was encouraged.[11,13] Patients were assessed daily for possible ECMO weaning on the basis of the clinical and biological criteria described in the EOLIA trial.[11] Notably, indication and timing of the tracheostomy were left to the physicians' discretion.

Data collection and outcomes

Baseline data were collected on age, sex, body-mass index, SAPS-II score,[14] Sequential Organ Failure Assessment (SOFA)[15] score, and comorbidities. In addition, information was collected on pre-ECMO management, including treatment with rescue therapies, ventilator settings (positive end-expiratory pressure, fraction of inspired oxygen, respiratory rate, tidal volume, plateau pressure, driving pressure), arterial blood-gas parameters, and laboratory values (eg, white blood count, creatinine, bilirubin levels). We also recorded dates of first symptom, hospital admission, intubation, and ECMO initiation, whether patients were transferred on ECMO by a mobile team from another hospital, and the number of ECMOs done by the admitting hospital in the previous year. From ECMO initiation, ECMO and mechanical ventilation characteristics were recorded. Data concerning ECMO resources (consoles and circuits) were continuously collected.

Patient outcomes included ICU-related and ECMO-related complications, length of ECMO and ICU stay, survival status at 90 days after initiation of ECMO, and causes of death. ECMO-related complications and organ dysfunction included major bleeding, ECMO circuit change, severe thrombocytopenia, stroke, renal replacement therapy, proven pulmonary embolism, pneumothorax, ventilator-associated pneumonia, bacteraemia, and cardiac arrest. Major bleeding was defined as bleeding requiring two or more units of packed red blood cells due to an obvious haemorrhagic event, bleeding necessitating a surgical or interventional procedure, an intracranial haemorrhage, or bleeding leading to death.

Statistical analysis

Continuous variables are expressed as mean (SD) or median (IQR) and were compared between groups according to 90-day survival status with the t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Normality was tested with the Shapiro-Wilk test. Categorical variables are expressed as frequency (%) and were compared with the χ^2 test. Age, time from intubation to ECMO, time from symptom onset to ECMO, and pre-ECMO plateau pressure and lactate were divided into tertiles, and venovenous ECMO centre volume was dichotomised (≥30 and <30 cases annually; appendix pp 54–59).[16]

A multivariable logistic regression model was used to identify variables independently associated with 90-day survival after ECMO. Variables entered in the multivariable model were defined a priori on the basis of published literature in the ECMO and COVID-19 fields, regardless of their univariate p value (appendix pp 9–25). Variable selection was done through a backward stepwise conditional method. The results are expressed as odds ratios with 95% CIs, and p values from a Wald test are reported. The goodness of the overall fit of the model was validated by Omnibus tests of model coefficients at the 5% level of significance and receiver operating characteristic curve analysis.

Kaplan-Meier plots were produced for variables that were significantly associated with the survival outcome, as well as for those that seemed relevant based on the literature (eg, transfer by mobile ECMO team). All patients were censored at 90 days after ECMO. Univariable analysis of factors associated with 90-day overall survival was done using log-rank tests.

We did a sensitivity analysis to evaluate the robustness of our findings in terms of missing data by repeating the univariate and multivariable analyses with multiple imputation for variables with missing values used in the multivariable analysis (appendix pp 9–25). We applied the machine-learning algorithm random forest on the dataset to validate the independent prognostic variables obtained by multivariable analysis. The algorithm was set for 5000 random trees. An exhaustive principal component analysis (PCA) to determine the variables that best discriminate the survival outcome (alive or dead at 90 days after ECMO) and the correlation network of the PCA loadings were done on the whole dataset. Further details of analyses are included in the statistical analysis plan (appendix pp 5–8).

All statistical analyses were done using SPSS (version 26.0) and R (version 3.5.3). Random forest, PCA, and correlation networks were made using the corrPlot, randomForest, and MetaboAnalystR packages in R.

Role of the funding source

There was no funding source for this study.

Results

On March 10, 2020, 165 ECMO consoles (appendix p 41) and 389 circuits were available across 30 hospitals in Greater Paris; 19 patients were already on ECMO support. 17 additional pumps were provided by industry or other centres in France and elsewhere in Europe by April 17, leading to the availability of 182 pumps in Greater Paris. 25 consoles were reserved for patients requiring ECMO

unrelated to COVID-19; this number was subsequently reduced to 19 due to the shortage of equipment (figure 1). At the peak of the crisis, 131 patients were assisted with ECMO for COVID-19-associated ARDS (figure 1). A further 32 patients received venoarterial ECMO for isolated cardiogenic shock with or without a positive SARS-CoV-2 PCR result and were not included in this study. The highest number of venovenous ECMO implantations on a single day during this period was 14 (figure 1).

Of the 17 ICUs identified with capability to care for patients with COVID-19 on ECMO, three centres had managed at least 30 patients with venovenous ECMO in the previous year (ie, high case volume), three had managed ten to 30 patients, and 11 had treated fewer than ten patients (appendix p 41). 12 centres had cannulation capability. The number of ICU beds at the 17 ECMO centres increased from a total of 501 in 2019 to 1210 at the peak of the first wave. Although a single mobile ECMO team was initially active in Greater Paris, public and private cardiac surgery centres set up five additional teams, increasing the number of mobile units during the crisis to six.

Of 575 calls to the ECMO-COVID-19 hub for patients with COVID-19-associated severe ARDs, 302 patients met the eligibility criteria and underwent ECMO in 17 ICUs (figure 2); 62 patients were considered not sufficiently sick at the time of the call, and 211 were considered too sick, with a likely poor prognosis (appendix p 47). Of 302 patients, 288 initially received venovenous ECMO (one converted to venoarterial ECMO for pulmonary embolism after 5 days, two to venoarterial–venous ECMO after 3 and 5 days), 11 initially had venoarterial ECMO (two converted to venoarterial–venous ECMO within 24 h), and three patients initially had venoarterial–venous ECMO (one converted to venovenous ECMO after 1 day). The six mobile ECMO teams cannulated 212 patients, of whom 165 were transferred to an ICU with ECMO capability. 90 patients were already at ICUs with capability for cannulation and ECMO care (figure 2; appendix pp 48–49).

The pre-ECMO demographic and clinical characteristics of the 302 included patients, including ventilation parameters and blood-gas values at cannulation, are presented in table 1 for the overall cohort and according to 90-day survival status. Median age was 52 years (IQR 45–58) and the majority were male. Before ECMO, almost all patients had been placed in the prone position or had received continuous neuromuscular blockers, and more than half had received inhaled nitric oxide or prostacyclin (table 1).

Procedural characteristics for ECMO and mechanical ventilation, and complications and clinical outcomes for the overall cohort and according to 90-day survival status are detailed in table 2. Insertion of femoro–jugular cannulas was done in 273 (90%) patients with large drainage cannulas, after a median duration of mechanical
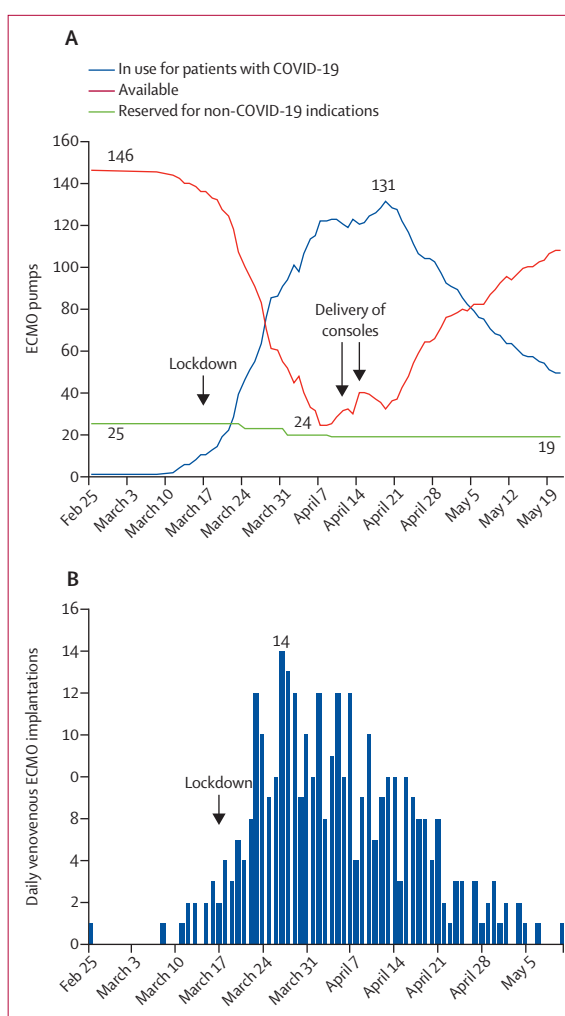

Figure 1: **Inventory of ECMO pumps (A) and daily venovenous ECMO implantations for COVID-19-associated ARDS (B) between March 8 and June 3, 2020, in Greater Paris**
ECMO resources available in 30 Greater Paris ICUs with consoles and circuits. ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome.

ventilation of 5 days (IQR 3–7). ECMO support led to reductions in tidal volume in the 24 h following ECMO initiation and normalisation of arterial blood gases.

Renal failure requiring renal replacement therapy occurred in 130 (43%) of 301 patients, major bleeding requiring transfusion occurred in 115 (43%) of 270 patients, and intracranial haemorrhage occurred in 27 (12%) of 223 patients. 55 (18%) of 302 patients had severe thrombocytopenia (defined as $<50 \times 10^9$ cells per L). Despite guideline-recommended therapeutic anticoagulation, circuit thrombosis (requiring circuit change) occurred in 31 (10%) of 302 patients and pulmonary embolism was diagnosed in 53 (18%) of 294 patients. Median duration of ECMO support was 14 days (IQR 8–26) and median duration of ICU stay was 30 days (17–47; table 2).

Overall, 138 (46%) of the 302 patients were alive 90 days after ECMO. The percentage increased to 60%

(61 of 101 patients) in the three centres with high venovenous ECMO case volume in the previous year (table 1). A comparison of patient characteristics according to 90-day survival status between centres is shown in the appendix (pp 42–44). The most common causes of death were multiorgan failure and septic shock (table 2).

In multivariable analysis, survivors were younger (≤48 vs ≥57 years), had a shorter time between intubation and initiation of ECMO, and had a lower renal component in the pre-ECMO SOFA score (table 3). High case volume for venovenous ECMO (ie, ≥30 ECMOs in the previous year) was also associated with better outcomes (table 3). Receiver
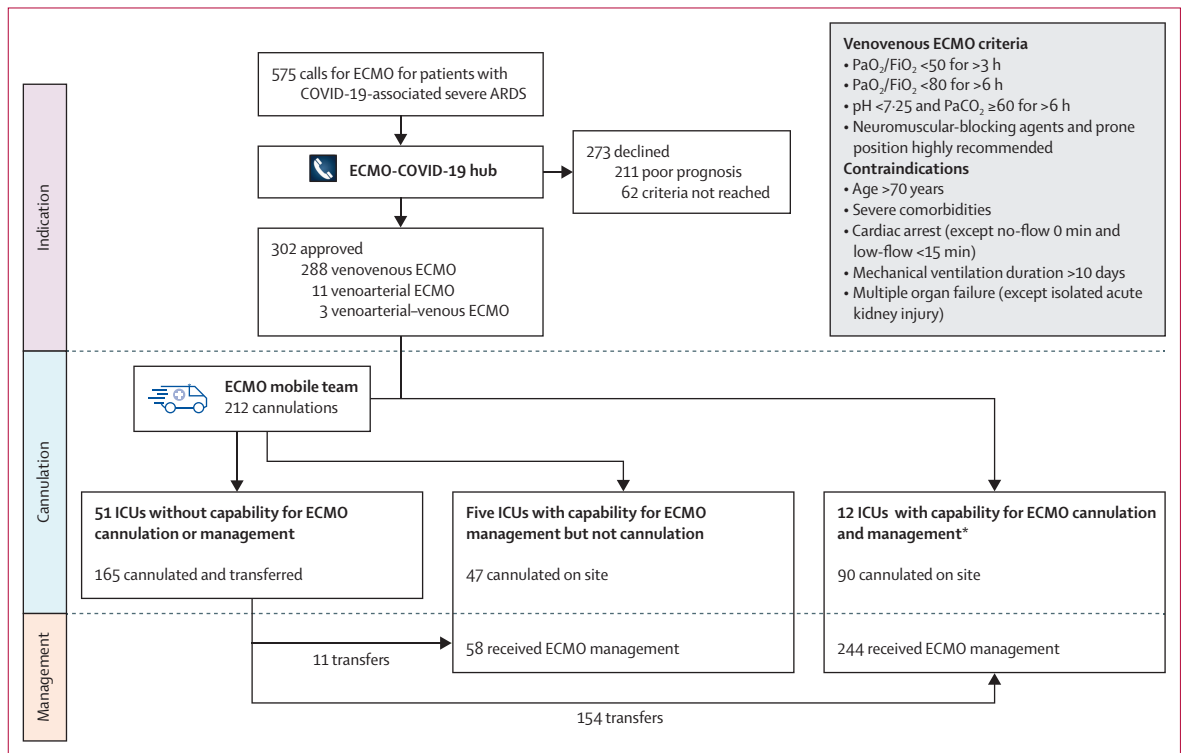

Figure 2: **Organisation of the Greater Paris ECMO network during the COVID-19 pandemic, March 8 to June 3, 2020**
ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. PaCO$_2$=partial pressure of arterial carbon dioxide. PaO$_2$/FiO$_2$=ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen. *Including ten cardiothoracic centres.

	All patients (n=302)	Survival status 90 days after ECMO		p value
		Alive (n=138)	Dead (n=164)	
Age, years	52 (45–58)	49 (42–56)	54 (48–60)	<0·0001
≤48	99 (33%)	59 (43%)	40 (24%)	0·0001*
49–56	100 (33%)	45 (33%)	55 (34%)	..
≥57	103 (34%)	34 (25%)	69 (42%)	..
Sex	..	..	..	0·22
Female	67 (22%)	35 (25%)	32 (20%)	..
Male	235 (78%)	103 (75%)	132 (80%)	..
Body-mass index, kg/cm²	29·7 (26·8–33·5); n=296	30·0 (26·5–33·4); n=136	29·6 (27·1–33·7); n=160	0·85
≤30	153 (52%)	69 (51%)	84 (53%)	0·76*
>30	143 (48%)	67 (49%)	76 (48%)	..
SAPS-II	40 (31–56); n=289	41 (31–55); n=128	39 (31–57); n=161	0·74
≥30	101 (33%)	61 (44%)	40 (24%)	0·0003*
<30	201 (67%)	77 (56%)	124 (76%)	..
				(Table 1 continues on next page)

	All patients (n=302)	Survival status 90 days after ECMO		p value
		Alive (n=138)	Dead (n=164)	
(Continued from previous page)				
Total SOFA score	12 (9–14); n=281	12 (9–13); n=128	12 (10–15); n=153	0·0012
Renal component ≥3	60/285 (21%)	17/129 (13%)	43/156 (28%)	0·0008
Cardiovascular component ≥3	149/284 (52%)	68/128 (53%)	81/156 (52%)	0·69
Comorbid conditions				
Hypertension	103 (34%)	44 (32%)	59 (36%)	0·46
Diabetes	87 (29%)	35 (25%)	52 (32%)	0·23
Ischaemic cardiomyopathy	10 (3%)	2 (1%)	8 (5%)	0·098
Chronic respiratory disease†	34 (11%)	19 (14%)	15 (9%)	0·21
Active smoker	11 (4%)	2 (1%)	9 (5%)	0·062
Immunocompromised‡	18 (6%)	5 (4%)	13 (8%)	0·12
Time to ECMO, days				
First symptoms to ECMO	14 (11–18); n=295	13 (10–17); n=136	14 (11–19); n=159	0·0079
Hospital admission to ECMO	7 (5–10)	6 (4–9)	7 (5–11)	0·0015
Intubation to ECMO	5 (3–7)	4 (2–6)	5 (3–8)	0·0002
Transfer on ECMO by mobile team from another hospital	165 (55%)	79 (57%)	86 (52%)	0·40
Number of ECMOs done in previous year in ECMO centre patient was admitted to	65 (9–172)	74 (5–319)	71 (11–74)	0·0084
Number of venovenous ECMOs done in previous year	13 (3–59)	13 (2–59)	13 (5–15)	0·0013
Ventilation parameters				
FiO_2, mm Hg	100 (100–100); n=295	100 (100–100); n=135	100 (100–100); n=160	0·091
PEEP, cm H_2O	12 (10–14); n=276	12 (10–14); n=126	12 (10–14); n=150	0·20
Tidal volume, mL/kg predicted bodyweight	5·6 (4·9–6·2); n=260	5·8 (5·1–6·3); n=120	5·6 (4·7–6·1); n=140	0·054
Respiratory rate, breaths per min	28 (26–30); n=245	29 (26–30); n=109	28 (26–30); n=136	0·94
Plateau pressure, cm H_2O	30 (27–32); n=252	30 (27–32); n=117	30 (26–34); n=135	0·42
Driving pressure, cm H_2O§	18 (14–21); n=251	18 (15–20); n=116	18 (14–22); n=135	0·31
Last blood-gas values before ECMO				
pH	7·31 (7·23–7·37); n=247	7·32 (7·26–7·38); n=125	7·29 (7·21–7·35); n=122	0·0017
PaO_2/FiO_2, mm Hg	61 (54–70); n=294	61 (53–70); n=136	60 (54–72); n=158	0·59
$PaCO_2$, mm Hg	57 (48–67); n=286	56 (47–66); n=132	58 (50–68); n=154	0·11
Plasma bicarbonate, mmol/L	28 (24–32); n=273	28 (24–32); n=128	28 (24–32); n=145	0·78
SaO_2	88% (83–92); n=262	88% (82–92); n=117	88% (83–92); n=145	0·99
Arterial lactate, mmol/L	1·7 (1·3–2·2); n=276	1·7 (1·2–2·1); n=130	1·7 (1·4–2·3); n=146	0·022
Laboratory values				
White cell count, g/L	12·8 (9·6–16·6); n=281	11·6 (9·3–15·5); n=129	14·1 (10·0–17·2); n=152	0·66
Lymphocytes, g/L	0·9 (0·6–1·3); n=247	0·9 (0·6–1·5); n=109	1·0 (0·6–1·3); n=138	0·22
Serum creatinine, μmol/L	83 (62–155); n=270	69 (56–101); n=128	96 (71–216); n=142	0·0024
Serum bilirubin, μmol/L	13 (8–22); n=268	12 (8–25); n=127	15 (8–21); n=141	0·60
Haematocrit	30% (26–35); n=273	31% (27–36); n=125	30% (25–35); n=148	0·13
Rescue therapy before ECMO				
Neuromuscular blockade	291 (96%)	130 (94%)	161 (98%)	0·067
Prone positioning	285 (94%)	130 (94%)	155 (95%)	0·91
Inhaled nitric oxide or prostacyclin	168 (56%)	68 (49%)	100 (61%)	0·014
Steroids	61 (20%)	30 (22%)	31 (19%)	0·54
Renal replacement therapy	37 (12%)	6 (4%)	31 (19%)	0·0001

Data are median (IQR) or median (IQR); n (where data are not available for all patients), n (%), or n/N (%). ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2=partial pressure of arterial oxygen. PaO_2/FiO_2=ratio of PaO_2 to FiO_2. PEEP=positive end-expiratory pressure. SaO_2=arterial oxygen saturation. SAPS=Simplified Acute Physiology Score. SOFA=Sequential Organ Failure Assessment. *p value for comparison between all listed subcategories. †Chronic obstructive pulmonary disease or asthma. ‡Haematological malignancies, active solid tumour, or having received specific anti-tumour treatment within 1 year, solid-organ transplant, or HIV-infected, or treated with long-term corticosteroids or immunosuppressants. §Plateau pressure minus PEEP.

Table 1: Demographic, clinical, and mechanical ventilation characteristics before ECMO overall and according to 90-day survival status

operating characteristic curve analysis showed that the overall fit of the multivariable model was good (p=0·0004; appendix p 53). Survival rates did not differ significantly between patients transferred by the mobile ECMO team and those managed on site (figure 3).

In a sensitivity analysis, use of multiple imputation for variables with missing values used in multivariable analysis supported the robustness of our findings (appendix pp 9–40). The random forest algorithm accurately classified the independent prognostic variables identified by the multivariable analysis (appendix p 50). The boxplots of the top four features in random forest along with the other features included in the multivariable analysis are presented in the appendix (pp 51–52). PCA discriminated the survival outcome (alive or dead at 90 days after ECMO) with 9·7% variance at component 1. PCA and the correlation network of the PCA loadings (37 significant features) are shown in the appendix (p 46).

	All patients (n=302)	Survival status 90 days after ECMO		p value
		Alive (n=138)	Dead (n=164)	
Venovenous ECMO	288 (95%)	133 (96%)	155 (95%)	0·44
Femoro–jugular	273 (90%)	130 (94%)	143 (87%)	0·43
Femoro–femoral	15 (5%)	3 (2%)	12 (7%)	0·020
Diameter of the admission cannula, Fr	25 (25–29)	29 (25–29)	25 (24–29)	0·017
Diameter of the return cannula, Fr	21 (19–21)	21 (19–21)	21 (19–21)	0·28
Venoarterial or venoarterial–venous ECMO	14 (5%)	5 (4%)	9 (5%)	0·44
Femoro–femoral venoarterial ECMO	10 (3%)	3 (2%)	7 (4%)	0·21
Femoro–subclavian venoarterial ECMO	1 (<1%)	1 (1%)	0	NA
Femoro–femoro–jugular venoarterial–venous ECMO	3 (1%)	1 (1%)	2 (1%)	0·56
ECMO blood flow, L/min	5·0 (4·4–5·5); n=287	5·0 (4·3–5·4); n=134	5·0 (4·5–5·4); n=153	0·38
Sweep gas flow, L/min	6 (4–8); n=285	5 (4–7); n=130	6 (4–8); n=155	0·0098
Membrane FmO_2	100% (89–100); n=294	100% (90–100); n=135	100% (85–100); n=159	0·78
Ventilation parameters on ECMO day 1				
FiO_2, mm Hg	80 (60–100); n=294	60 (50–100); n=136	95 (60–100); n=158	0·0005
PEEP, cm H_2O	12 (10–14); n=286	12 (10–14); n=133	12 (10–14); n=153	0·32
Tidal volume, mL/kg predicted bodyweight	3·3 (2·2–4·5); n=281	2·9 (2·0–4·4); n=133	3·3 (2·2–4·6); n=148	0·46
Respiratory rate, breaths per min	20 (14–22); n=264	20 (15–22); n=123	20 (14–21); n=141	0·088
Plateau pressure, cm H_2O	25 (24–27); n=269	25 (24–28); n=129	25 (24–27); n=140	0·46
Driving pressure, cm H_2O	13 (12–16); n=267	13 (12–15); n=127	14 (12–16); n=140	0·22
Prone positioning on ECMO	193 (64%)	95 (69%)	98 (60%)	0·10
High-dose corticosteroids on ECMO	84/301 (28%)	35/138 (25%)	49/163 (30%)	0·37
Tracheostomy	59 (20%)	51 (37%)	8 (5%)	<0·0001
Complications during ECMO				
Renal replacement therapy	130/301 (43%)	38/137 (28%)	92 (56%)	<0·0001
Pneumothorax	23/270 (9%)	7/133 (5%)	16/137 (12%)	0·059
Cardiac arrest	46/270 (17%)	8/133 (6%)	38/137 (28%)	<0·0001
Thrombosis of ECMO circuit	31 (10%)	12 (9%)	19 (12%)	0·41
ECMO setting or insertion change*	39/301 (13%)	8 (6%)	31/163 (19%)	<0·0001
Repeat ECMO needed after decannulation	16/295 (5%)	5/137 (4%)	11/158 (7%)	0·21
Severe thrombocytopenia (<50 × 10⁹ cells per L)	55 (18%)	17 (12%)	38 (23%)	0·014
Massive haemorrhage requiring transfusion	115/270 (43%)	41/133 (31%)	74/137 (54%)	<0·0001
Intracranial haemorrhage	27/223 (12%)	5/86 (6%)	22/137 (16%)	0·0098
Ischaemic stroke	6/220 (3%)	1/86 (1%)	5/134 (4%)	0·26
Pulmonary embolism	53/294 (18%)	15/132 (11%)	38/162 (23%)	0·0073
Antibiotic-treated ventilator-associated pneumonia	257/301 (85%)	119 (86%)	138/163 (85%)	0·61
Antibiotic-treated cannula infection	45/301 (15%)	27 (20%)	18/163 (11%)	0·038
At least 1 antibiotic-treated bacteraemia episode	148/300 (49%)	65 (47%)	83/162 (51%)	0·78
ECMO duration, days	14 (8–26); n=296	17 (10–27); n=132	12 (6–25); n=164	0·081
Invasive mechanical ventilation duration, days	28 (15–44); n=287	33 (25–50); n=124	20 (12–37); n=163	<0·0001
			(Table 2 continues on next page)	

	All patients (n=302)	Survival status 90 days after ECMO		p value
		Alive (n=138)	Dead (n=164)	
(Continued from previous page)				
ICU length of stay, days	30 (17–47); n=289	39 (29–57); n=127	21 (13–37); n=162	<0·0001
Cause of death				
Multiorgan failure	53 (18%)	..	53 (32%)	..
Septic shock	47 (16%)	..	47 (29%)	..
Intracranial haemorrhage	22 (7%)	..	22 (13%)	..
Haemorrhagic shock	11 (4%)	..	11 (7%)	..
Cardiovascular shock	9 (3%)	..	9 (5%)	..
Pulmonary embolism	9 (3%)	..	9 (5%)	..
Ischaemic stroke	5 (2%)	..	5 (3%)	..
Other	8 (3%)	..	8 (5%)	..

Data are median (IQR) or median (IQR); n (where data are not available for all patients), n (%), or n/N (%). ECMO=extracorporeal membrane oxygenation. FiO₂=fraction of inspired oxygen. FmO₂=membrane fraction of oxygen. Fr=French. ICU=intensive care unit. NA=not applicable. PEEP=positive end-expiratory pressure. *Includes ECMO cannulation switches from venoarterial to venovenous, and venoarterial to venous–arteriovenous.

Table 2: **ECMO and mechanical ventilation characteristics on the first day of ECMO, complications during ECMO, and clinical outcomes overall and according to 90-day survival status**

Discussion

This report describes our adaptive approach to management of ARDS with ECMO during the COVID-19 outbreak in Greater Paris, an area with more than 12 million inhabitants. The overall rate of 90-day survival was 46%, and was better in younger patients, in those who had no pre-ECMO renal dysfunction, and in patients who had a shorter delay between intubation and initiation of ECMO. Venovenous ECMO case volume in the previous year also markedly influenced the outcome, with better 90-day survival associated with more experienced centres.

Within a matter of days and facing so many unknowns—especially the uncertain effectiveness of ECMO in this pathology—the hospitals of Greater Paris rationalised the use of scarce resources in the context of an international shortage of ECMO equipment. The pooling of equipment made it possible to effectively manage the shortage of equipment in a given centre, which did not become a limiting factor during this period. The plan to pool resources, centralise referrals, and regulate beds was initially proposed by the medical teams and was subsequently supported by the local health authorities. This collective initiative was effective for responding to the changing needs during the pandemic.

Managing scarce resources in a crisis involves ethical and practical considerations when guiding the triage of patients. As defined for crisis management in other areas,[17–20] when ECMO needs are high and resources are few, prioritisation of indications is necessary, and preference should be given to those who are more likely to benefit. Our group recommended stopping ECMO activity in indications with a poor prognosis (eg, out-of-hospital cardiac arrest), and the programme for normothermic

	Odds ratio (95% CI)	p value
Age, years	..	0·012
≤48	2·89 (1·41–5·93)	..
49–56	2·01 (1·01–3·99)	..
≥57	1 (ref)	..
Pre-ECMO renal component of the SOFA-II score, per point increase	0·67 (0·55–0·83)	0·0003
Time between intubation and ECMO, per day decrease	0·91 (0·84–0·99)	0·022
Centre with ≥30 venovenous ECMOs in previous year	2·98 (1·46–6·04)	0·0026

ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. SOFA=Sequential Organ Failure Assessment.

Table 3: **Pre-ECMO variables associated in multivariable analysis with 90-day survival in patients with severe COVID-19-associated ARDS supported by ECMO**

regional perfusion for organ donation was interrupted. Additionally, several consoles were reserved in each centre for non-COVID-19 indications. The centralisation of indications as well as pooling of resources made it possible to manage the shortage of equipment and rationalise the use of resources, whereas lack of ICU beds with staff experienced in ECMO appeared to be an important limitation.

In patients with COVID-19 with severe ARDS, our observed 90-day mortality of 54% (40% in centres with a high annual venovenous ECMO case volume) was higher than the 38% estimated cumulative incidence of in-hospital mortality 90 days after the initiation of ECMO reported in the international cohort study of the ELSO registry.[21] However, 27% of the patients included in the international cohort were discharged to a long-term acute care centre or to another hospital, which might have led to an underestimation of the actual 90-day mortality.

Although the patients in our cohort met the EOLIA criteria,[11] the severity of ARDS was greater,[10] as
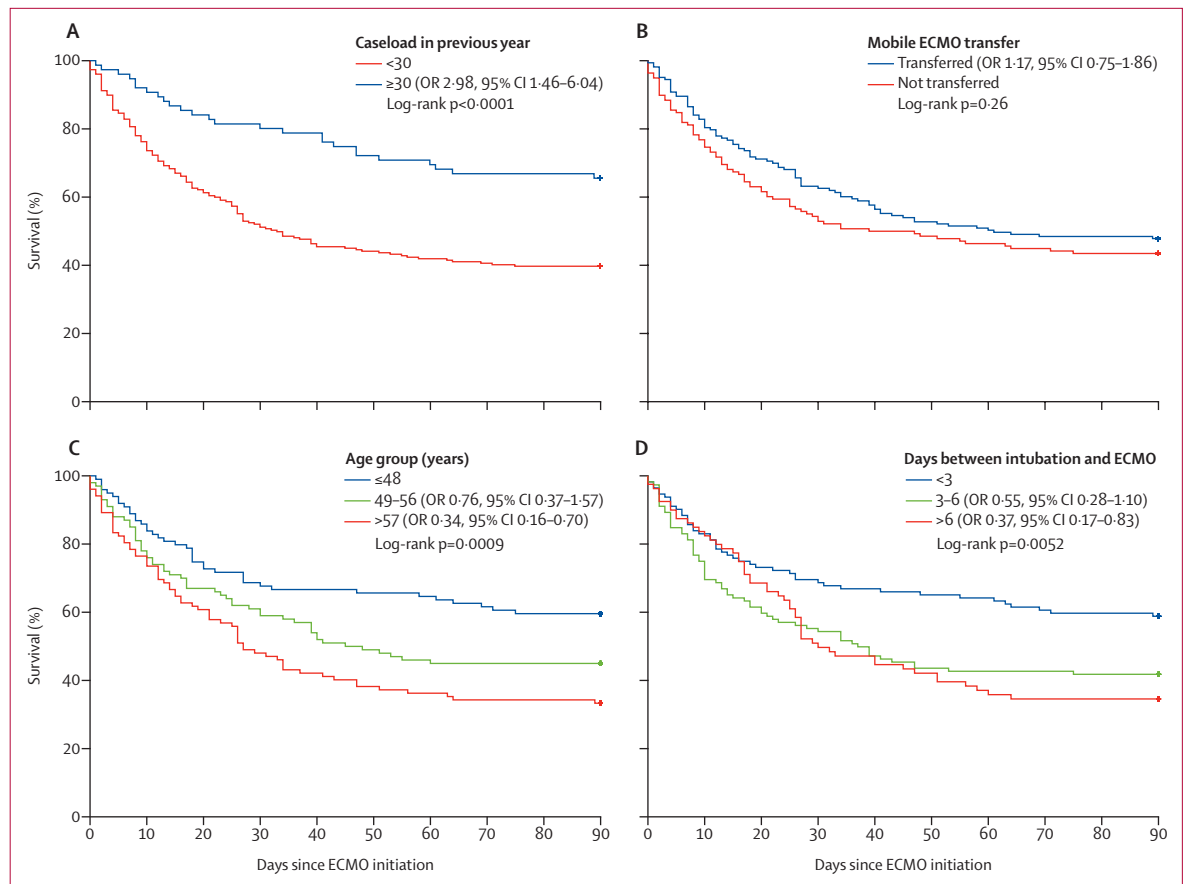
Figure 3: 90-day survival according to venovenous ECMO caseload in the previous year (A), mobile ECMO transfer (B), age group (C), and delay between orotracheal intubation and ECMO implantation (D)
ECMO=extracorporeal membrane oxygenation. OR=odds ratio.

shown by the lower pre-implantation median ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (61 [IQR 54–70]) than that in the EOLIA trial (mean 73 [SD 30]) or LIFEGARD cohort (mean 71 [34]).[11,13] The large proportion of patients cannulated by a mobile ECMO team and then transferred to ECMO centres (55%) might explain this finding. Furthermore, dual-lumen single ECMO cannulas were not used during this first COVID-19 outbreak.

We report high rates of renal failure requiring renal replacement therapy and pulmonary embolism on ECMO, consistent with a previous study.[10] The high rates of pulmonary embolism on ECMO reflect the hyperthrombogenicity associated with COVID-19.[22–25] This might suggest the need for a more intense anticoagulation regimen compared with the approach used for non-COVID-19 patients with severe ARDS on ECMO.[11] However, we also report a high rate of haemorrhagic complications and a greater incidence of intracranial bleeding compared with other ECMO cohorts (eg, 2% in the EOLIA trial and 6% in the recent COVID ELSO registry[21]). Severe bleeding complications on ECMO are multifactorial (circuit-associated

defibrination and thrombocytopenia, disseminated intravascular coagulation, acquired von Willebrand syndrome, or COVID-19-associated endotheliitis) and the more intensive anticoagulation regimen in our cohort of patients with COVID-19 receiving ECMO could have contributed to this finding.[26] The appropriate approach regarding anticoagulation during venovenous ECMO in COVID-19 remains undefined and warrants further investigation.

In our study, younger age, lower pre-ECMO renal dysfunction, and shorter delay between intubation and ECMO were independently associated with better survival, consistent with previous studies,[27] and argue in favour of early implantation in cases of serious ARDS, allowing ultraprotective ventilation to prevent the mechanical damage to the lung parenchyma due to artificial ventilation.[28] From a clinical perspective, these findings indicate the need to identify the correct balance between early ECMO implantation and use of prone positioning.

Despite central regulation of ECMO indications and wide dissemination of ECMO management protocols, our outcomes varied between centres. The positive effect of ECMO case volume on outcome has been reported

previously,[16,29,30] and is reinforced here by the fact that all indications were centralised and met the same criteria. Interestingly, the total number of ECMO procedures done annually (ie, including venovenous and venoarterial ECMOs) was not independently associated with survival, whereas venovenous ECMO case volume in the preceding year was strongly associated with improved outcomes. This finding suggests that venovenous ECMO requires specific expertise that is not naturally obtained in centres with primarily venoarterial ECMO experience. However, the threshold of ECMO cases that defines a high-volume ECMO centre is unknown. A retrospective analysis from an international ECMO registry reported that patients receiving ECMO at hospitals with more than 30 ECMO cases annually had significantly lower odds of mortality than adults receiving ECMO at hospitals with fewer than six cases annually.[16] Conversely, we observed no significant survival difference between patients cannulated and transferred by our mobile teams to an ECMO centre and patients cannulated and managed on site, which validates the concept and effectiveness of mobile ECMO teams.[31]

We acknowledge some limitations of our study. First, it took place during the first wave of the pandemic, before the publication of landmark therapeutic clinical trials.[32,33] Thus, our results could differ with systematic use of dexamethasone or remdesivir. Second, due to its observational design, we cannot assess the benefits of ECMO compared with maximum medical care. In addition, residual confounders that were not taken into account might limit the relevance and generalisability of our results to other ECMO centres. Finally, the high rate of ECMO use in Greater Paris versus other metropolitan areas should be noted. The extremely high incidence of COVID-19 cases in Paris during that time, as well as a well established mobile ECMO programme before the outbreak, could explain this finding, and might further affect the relevance and generalisability of our results to other centres and regions.

In conclusion, among ECMO-assisted patients in Greater Paris with severe COVID-19-related ARDS, the rate of 90-day survival was 46%. Age, delay between orotracheal intubation and ECMO implantation, and renal dysfunction are major factors that should be considered in the decision to proceed with ECMO. During the ongoing worldwide COVID-19 pandemic, early ECMO management in centres with a high venovenous ECMO case volume should be advocated when feasible, while applying the same principle of centralisation and regulation of ECMO indications to prevent a shortage of resources. Whether ECMO provides a better outcome than maximal mechanical ventilation for COVID-19-associated severe ARDS deserves further investigation.

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