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Outcomes of Patients Denied ECMO During the COVID-19 Pandemic in Greater Paris, France

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Abbreviations

ARDS, acute respiratory distress syndrome

COVID-19, coronavirus disease 2019

ICU, intensive care unit

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MV, mechanical ventilation

VV-ECMO, venovenous-extracorporeal membrane oxygenation

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All authors contributed to the revision, read, and approved the final manuscript version of the manuscript.

MS takes responsibility for the integrity of the work as a whole, from inception to published article.

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Matthieu Schmidt reports lecture fees from Getinge, Drager and Xenios outside the submitted work. Charles-Edouard Luyt reports reports having receiving fees from Bayer Healthcare, ThermoFisher Brahms, Biomérieux, Faron, Carmat, Aerogen, Merck Sharp & Dohme, outside the submitted work. Alain Combes reports grants from Getinge, personal fees from Getinge, Baxter and Xenios outside the submitted work. The other authors declare that they have no conflicts of interest related to the purpose of this manuscript.

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Venovenous extracorporeal membrane oxygenation (ECMO) was considered early in the pandemic to rescue the most severe forms of COVID-19-associated acute respiratory distress syndrome (ARDS). The day-90 survival of these patients was 60-64% in the largest cohorts published to date (1, 2). To prevent a shortage of resources and avoid compassionate use and futility, an ECMO hub-and-spoke network organization was created in Greater Paris, France. Guidelines for ECMO indications and management were developed by a Task Force and disseminated by the regional health administration. These criteria did not change during the study period. All ECMO indications were validated by the Pitié-Salpêtrière Hospital ECMO team. Patients considered for ECMO had to fulfill EOLIA trial ARDS severity criteria (3) despite the optimization of mechanical ventilation, a trial of prone positioning and the use of neuromuscular-blocking agents. Contraindications for ECMO were age >70 years (case-by-case discussion for age 65-70), serious comorbidities including immunosuppression, chronic lung diseases and extreme obesity, multiple organ failure, and ongoing mechanical ventilation for >10 days. While our network organization and outcomes after ECMO have been described elsewhere (4), the outcome of patients denied ECMO is still unknown.

In this context, we prospectively collected characteristics of all patients proposed for ECMO at the ECMO-COVID-19 hub between March 8 and June 3, 2020. At least two intensivists discussed each patient's case and decided: “ECMO, yes”, i.e. prompt cannulation by a local or a mobile ECMO team; “ECMO, no, not yet” because criteria for ECMO were not met; or “ECMO, no, never”, because of an anticipated poor prognosis despite ECMO (5). When an “ECMO, no, not yet” decision was made, advices to optimize patients management and mechanical ventilation settings were given, with a possibility to reevaluate later ECMO indication.

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Patients' characteristics between the three groups were compared by ANOVA. Kaplan-Meier survival curves were computed and compared using log-rank tests. Follow-up started from the decision to initiate ECMO or not. The study was approved by the local ethical committee, Comité d'Ethique de la Recherche of Sorbonne University (#CER-SU-2020-69).

Of the 575 cases from 75 centers submitted to the ECMO-COVID-19 hub, 302 (53%) patients met eligibility criteria and received ECMO (4) of whom 12 received ECMO after a first "ECMO, no, not yet" decision. The latter 12 patients were included in the "ECMO, yes" group. ECMO was denied to 273 (48%) patients after a first call, of whom 15 had too many missing data and 12 received ECMO secondarily (i.e included in the "ECMO, yes" group for the analysis). Reasons for ECMO refusals in the 162 (66%) "ECMO, no, never" patients were mechanical ventilation >10 days (n=68), age >65 years (n=53), multiple organ failure (n=32), immunosuppression (n=23), or severe disability due to extreme obesity (n=16). For 35/68 patients, mechanical ventilation > 10 days was the only reason for refusing ECMO whereas 27/53 patients were refused only because of an age >65 years. "ECMO, no, not yet" was advised for 84 (34%) patients. Characteristics and outcomes of patients are provided in Table 1. Briefly, "ECMO, yes" patients were younger, had a shorter time between intubation and ECMO-COVID hub call, and a higher RESP score compared to patients denied ECMO ($p < 0.01$). Compared to the 2 other patients groups, "ECMO, no, not yet" patients had significantly lower driving pressure and higher PaO_2/FiO_2 and lung static compliance (both $p < 0.01$). They also were more frequently on renal replacement therapy. Ninety-day survival (Figure 1) was obtained for 233/246 patients denied ECMO (i.e 83 "ECMO, no, not yet" and 150 "ECMO, no, never" patients), and was not different between "ECMO yes" and "ECMO, no, not yet" patients (49% versus 46%, log-rank test $p = 0.93$). However, the 90-day survival of "ECMO, no, never" patients was significantly lower compared to the two other groups

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(14%, log-rank-test p < 0.001). Compared to "ECMO, no, not yet" and "ECMO, no, never" patients, "ECMO yes" patients had significantly longer stay in the intensive care unit (ICU) (30 [17–47] vs. 24 [15-37] and 16 [10-26] days, p <0.01) and longer duration of mechanical ventilation (28 [15-44] vs. 22 [13-32] and 16 [9-26] days, p <0.01), respectively.

Our study reports the characteristics and outcomes of severe ARDS COVID-19 patients referred for ECMO decision during the first wave of the pandemic in the Greater Paris. Similar 90-day survival was observed for patients who received ECMO and those for whom ECMO was not yet indicated. Alternatively, patients considered not suitable for ECMO had a very low 90-day survival.

The decision to initiate ECMO in severe ARDS patients remains complex, especially in the context of a pandemic with shortage of resources and ICU beds and of a new disease, for which mid-term and long-term outcomes are still unknown. Ideally, the decision should be based on scientific evidence and the ability to identify patients more likely to benefit from ECMO. The similar survival rate observed in "ECMO, yes" and "ECMO, no, not yet" patients is reassuring and validates a-posteriori the restrictive ECMO selection criteria we defined for COVID patients. However, a sizeable proportion of patients in the "not yet" group may have received ECMO before the pandemic (3) and we cannot exclude that early ECMO may have improved their outcomes. The very low survival rate of "ECMO, no, never" patients is in agreement with series evaluating outcome predictors of COVID-19 patients with severe ARDS (6). These patients were older, had more comorbidities, had spent more days on mechanical ventilation, and had signs of more severe lung disease. Although not all of them died, the probability of ECMO saving many lives in this group is obviously lower. The substantial proportion of ECMO refusal only because of mechanical ventilation

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>10 days could advocate for an earlier call to the ECMO center although we cannot ensure that criteria for ECMO initiation had already been met in the days preceding the call.

Our study has some limitations. Data were collected mainly on the day of the call to the ECMO-COVID hub, with no information regarding complications and organ dysfunction occurring during the ICU stay in patients who were denied ECMO. Our study also took place during the first wave of the pandemic in France. The management of COVID patients in later phases of the pandemic, with more frequent use of dexamethasone and tocilizumab, and more frequent and longer recourse to non-invasive ventilation strategies before intubation, may have changed the outcomes of our 3 patients groups (7–9).

In conclusion, the Greater Paris ECMO hub-and-spoke network which first defined criteria for ECMO and then regulated and centralized ECMO indications during the COVID pandemic appropriately selected patients who were more likely to benefit from the technique (10).

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Table 1. Characteristics of the patients discussed for ECMO according to the cannulation decision.

	"ECMO, yes" (n = 302)	"ECMO, no, not yet" (n = 84)	"ECMO, no, never" (n = 162)	*P*
Age, years	52 (45-58)	57 (48-63)	61 (54-66)	< 0.01
Male	235 (78)	57 (68)	118 (73)	0.14
Body mass index, kg/m^2	29.7 (26.8-33.5)	30 (26.6-33.9)	30.2 (26.8-35)	0.28
SAPS-II at ICU admission	40 (31-56)	41 (36-57)	41 (33-56)	0.29
Comorbidities				
Hypertension	103 (34)	32 (38)	70 (43)	0.13
Diabetes	87 (29)	23 (27)	47 (29)	0.96
Ischemic cardiomyopathy	10 (3)	6 (7)	9 (6)	0.25
Chronic respiratory disease	34 (11)	11 (13)	10 (6)	0.13
Immunocompromised	18 (6)	4 (5)	23 (14)	< 0.01
Time, days				
Hospital admission to ECMO-COVID-19 hub call	7 (5-10)	8 (6-12)	11 (7-15)	< 0.01
Intubation to ECMO-COVID-19 hub call	5 (3-7)	7 (4-11)	8 (5-13)	< 0.01
Characteristics at the time of the call				
RESP score	3 (2-5)	2 (1-3)	1 (0-2)	< 0.01
FiO_2, %	100 (100-100)	100 (80-100)	100 (100-100)	< 0.01
PEEP, cmH_2O	12 (10-14)	12 (10–14)	12 (10–14)	0.27
Tidal volume, mL/kg PBW	5.6 (4.9-6.2)	6.4 (5.9-6,8)	6.3 (5.7-6.7)	< 0.01
Respiratory rate, breaths/min	28 (26-30)	28 (26-30)	30 (28-32)	< 0.01
Plateau pressure, cmH_2O	30 (27-32)	28 (26-29)	31 (30-33)	< 0.01
Driving pressure, cmH_2O	18 (14-21)	16 (14-18)	20 (17-22)	< 0.01
Static compliance, mL/cmH_2O	21.0 (16.5-26.9)	25.1 (22.2-31.3)	20 (16.2-23.3)	< 0.01
pH	7.31 (7.23-7.37)	7.35 (7.29-7.38)	7.29 (7.22-7.35)	< 0.01
PaO_2/FiO_2, mmHg	61 (54-70)	80 (69-96)	65 (56-78)	< 0.01
$PaCO_2$, mmHg	57 (48-67)	55 (48-61)	60 (52-71)	< 0.01
Prone positioning	285 (94)	78 (94)	145 (98)	0.17
Neuromuscular blockades	291 (96)	71 (86)	162 (100)	< 0.01
Renal replacement therapy	37 (12)	22 (27)	47 (30)	< 0.01

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Figure 1. Kaplan-Meier survival analysis at 90 days from the ECMO-COVID hub call according to the decision of cannulation

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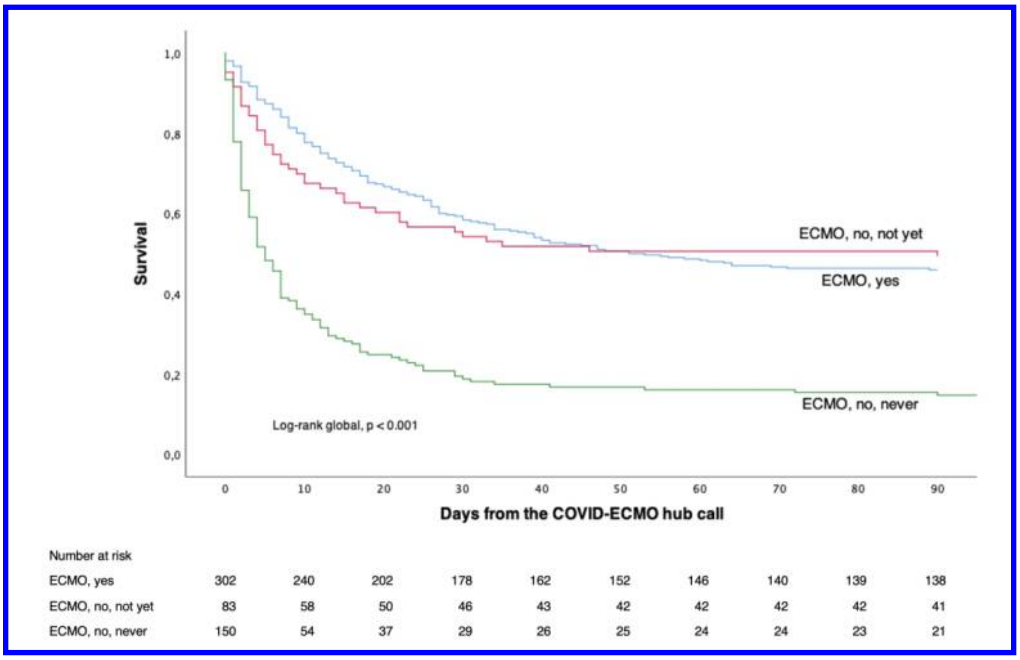

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