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Extracorporeal life support in COVID-19-related acute respiratory distress syndrome: A EuroELSO international survey

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Abstract

Extracorporeal life support (ECLS) is a means to support patients with acute respiratory failure. Initially, recommendations to treat severe cases of pandemic coronavirus disease 2019 (COVID-19) with ECLS have been restrained. In the meantime, ECLS has been shown to produce similar outcomes in patients with severe COVID-19 compared to existing data on ARDS mortality. We performed an international email survey to assess how ECLS providers worldwide have previously used ECLS during the treatment of critically ill patients with COVID-19. A questionnaire with 45 questions (covering, e.g., indication, technical aspects, benefit, and reasons for treatment discontinuation), mostly multiple choice, was distributed by email to ECLS centers. The survey

Members of the study group are listed in the appendix.

was approved by the European branch of the Extracorporeal Life Support Organization (ELSO); 276 ECMO professionals from 98 centers in 30 different countries on four continents reported that they employed ECMO for very severe COVID-19 cases, mostly in veno-venous configuration (87%). The most common reason to establish ECLS was isolated hypoxemic respiratory failure (50%), followed by a combination of hypoxemia and hypercapnia (39%). Only a small fraction of patients required veno-arterial cannulation due to heart failure (3%). Time on ECLS varied between less than 2 and more than 4 weeks. The main reason to discontinue ECLS treatment prior to patient's recovery was lack of clinical improvement (53%), followed by major bleeding, mostly intracranially (13%). Only 4% of respondents reported that triage situations, lack of staff or lack of oxygenators, were responsible for discontinuation of ECLS support. Most ECLS physicians (51%, IQR 30%) agreed that patients with COVID-19-induced ARDS (CARDS) benefitted from ECLS. Overall mortality of COVID-19 patients on ECLS was estimated to be about 55%. ECLS has been utilized successfully during the COVID-19 pandemic to stabilize CARDS patients in hypoxemic or hypercapnic lung failure. Age and multimorbidity limited the use of ECLS. Triage situations were rarely a concern. ECLS providers stated that patients with severe COVID-19 benefitted from ECLS.

KEYWORDS

COVID-19, COVID-19-induced acute respiratory distress syndrome, extracorporeal membrane oxygenation, extracorporeal life support, SARS-CoV-2, survey

1 | INTRODUCTION

Early in 2020, countries worldwide have been facing a surge of patients with acute respiratory distress syndrome (ARDS) due to pandemic Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) disease 2019 (COVID-19). Survival of those most severely affected by COVID-19-related ARDS (CARDS) might depend on extracorporeal membrane oxygenation (ECLS) as bridge to recovery.¹⁻³

In this global pandemic, hospitals and healthcare systems have been pushed to the verge of collapse. During the first phase of the COVID-19 pandemic, the number of critically ill patients requiring invasive ventilation often exceeded ventilator capacities, creating a need for intensive care unit (ICU) triage.⁴ In this scenario, it was highly unlikely that ECLS would be broadly recommended to critical care providers to treat COVID-19, given its high demands on personnel and resources.⁵ In its initial guidance document, ELSO considered to offer ECLS only to specific patients not responding to maximal conventional therapy, including proning and neuromuscular blockade.⁶ Additionally, early reports suggested mortality rates could be higher than 90% in COVID-19 patients supported with ECLS.⁷

A recent trial reported that veno-venous (VV-)ECLS reduced 60-day mortality in non-COVID-19-related ARDS to 35% in the ECLS group versus 46% in the conventional management group (relative risk 0.76, 95% CI 0.55–1.04; $P = .09$).⁸ The study highlighted that VV-ECLS can facilitate

protective ventilation of ARDS patients with reduced tidal volumes, plateau, and driving pressures,⁹ mostly due to effective extracorporeal CO₂ removal. CARDS might not differ as much from non-COVID ARDS as was previously expected.¹⁰ Physiological considerations make it thus reasonable to think about ECLS as a bail-out strategy in critically ill patients with CARDS. A recently published retrospective data suggested that mortality of patients with CARDS receiving VV-ECLS might be comparable to past ARDS cohorts.¹¹ Given that COVID-19 pathophysiology is still poorly understood, little is currently known about how to tailor ECLS treatment to meet COVID-19 specific challenges, for example, hypercoagulable state¹² or how long ECLS should be continued when patients fail to improve. We therefore designed an online survey to elicit how ECLS providers worldwide have previously employed ECLS to treat critically ill COVID-19 patients. Our survey was approved by the European branch of the Extracorporeal Life Support Organization (EuroELSO).

2 | METHODS

We created a questionnaire consisting of 45 questions and distributed it to 4193 physicians that had published on an ECLS-related topic since the year 2000 in a PubMed-listed journal with an available e-mail using a commercially available internet survey platform (SurveyMonkey Inc., San Mateo, CA, USA).

The ethical committee (Ärztchamber des Saarlandes) waived the need for a formal approval since the questionnaire did not retrieve actual patient data.

3 | QUESTIONNAIRE

The questionnaire was composed of two sections: The first dealt with general questions regarding contact information, details on hospital and ICU capacity, as well as years of ECLS experience. The second part was designed to elicit most common indications for ECLS use in COVID-19, details about ECLS circuit configuration as well as complications and reasons for possible treatment discontinuation. We did not ask for any patient-specific data. For conformity reasons and to facilitate participation in the survey, most of the questions were multiple choice with two to nine possible answers per question. The last eight items requested the participant to express his extent of agreement with a specific statement about ECLS therapy in the context of COVID-19 on a visual analog scale. The survey is partly available in the Supporting Information.

The survey questions and multiple-choice responses with their respective organization in the different sections were circulated and consented between a group of 23 very experienced physicians in this field. When consensus of all questions and answers was reached, the survey was transferred to an online platform (SurveyMonkey Inc.). Automatic data retrieval and descriptive statistics were retrieved through this platform. More than one answer from centers was possible. This was allowed, as many centers comprise several departments with physicians from different backgrounds (e.g., anesthesiology and surgery).

Results from multiple-choice questions are expressed in median, participants' extent of agreement or disagreement in mean, and standard deviation in percent. The survey was launched on June 8, 2020; deadline for return was June 20, 2020. Final analysis of results was performed using an extrapolation tool provided by SurveyMonkey as well as SPSS.

Participants were given the opportunity to be listed as collaborators. Those participants who did not supply hospital or contact information or who did not complete the survey could not be included in the list of collaborators.

4 | RESULTS

4.1 | General data on ECLS centers and treatment capacities

Two hundred seventy-six ECLS professionals from 98 centers in 30 different countries on five continents (North America, South America, Europe, Asia, and Australia) responded to the survey. The overall response rate of individual

ECLS physicians was 9.0%. Sixty-four percent of responding centers were ELSO members. Response rate was heavily skewed depending on geography. Seventy-one percent of the largest participating ECLS centers (more than one hundred COVID-19 patients treated on the ICU) were located in Europe, 21% in North America. As it was possible to skip questions, sometimes the denominator is less than 276. In this case, the number of respondents is given in brackets.

Centers' median number of years with ECLS experience was 14, mainly in ECLS treatment of adults or adult and pediatric patients (85%). Only 1.3% of participants were exclusively specialized in neonatal ECLS. Most common numbers of patients supported with ECLS per year prior to COVID-19 in the participants' centers ranged from 21 to 50, 13% of centers having even supported more the 100 patients on VV-ECLS per year prior to the pandemic.

4.2 | Numbers of patients with COVID-19 with or without ECLS

The majority of ECLS providers (30%) stated that 2–6 patients with COVID-19 had received ECLS in their center, with 85% of all centers having supported a maximum of 15 patients on ECLS by survey deadline. ECLS treatment had mostly been initiated in the participants' hospitals (63%), only a minority of patients was retrieved on ECLS by mobile ECLS retrieval teams from other hospitals.

4.3 | Indication for ECLS and circuit configuration

The most common reason to initiate ECLS for COVID-19 was isolated hypoxemia (50%), followed by a combination of hypoxemia and hypercapnia (39%). Isolated hypercapnia was rarely a reason to cannulate a patient (3%). Only 6% stated that ECLS was started to facilitate lung-protective ventilation ($n = 105$). The majority of ECLS cannulations (88%) were performed in VV configuration. Eight percent of centers used veno-arterial configuration (VA-ECLS) in one or more patients, and 3% had to extend to a V-AV circuit in at least one case (one venous draining cannula, one arterial returning cannula, and one venous returning cannula). In those cases, where an arterial cannulation was required, the indications were specified as biventricular failure ($n = 2$) and, in one case, right heart failure due to pulmonary embolism ($n = 1$). See also Figure 1A,B.

4.4 | Anticoagulation management

Targeting anticoagulation therapy in patients with COVID-19 on ECLS, 60% of participants ($n = 110$) stated that they did

not change their standard anticoagulation strategy compared to cases of ARDS due to other causes. Forty percent used higher doses of anticoagulants than usual, monitored by higher prothrombin time or higher activated clotting time. Only one of 110 ECLS providers stated that they deliberately used lower doses of anticoagulants than usual for ECLS in COVID-19. Antiplatelet therapy was also rarely used (1%) to prevent clotting. The details of the anticoagulants or antiplatelet agents administered were not part of the survey. See also Figure 1C.

4.5 | Reasons to abstain from ECLS

The two main reasons to refrain from ECLS initiation were patient age (74%) and comorbidities (85%, not further specified). Twenty-eight percent of participants stated that ECLS was withdrawn due to a patient's known or suspected wishes. Nine percent decided against ECLS because it was not actively recommended for COVID-19-induced ARDS by responsible scientific societies at that time. Seven percent reported that a surge of COVID-19 patients and overwhelming

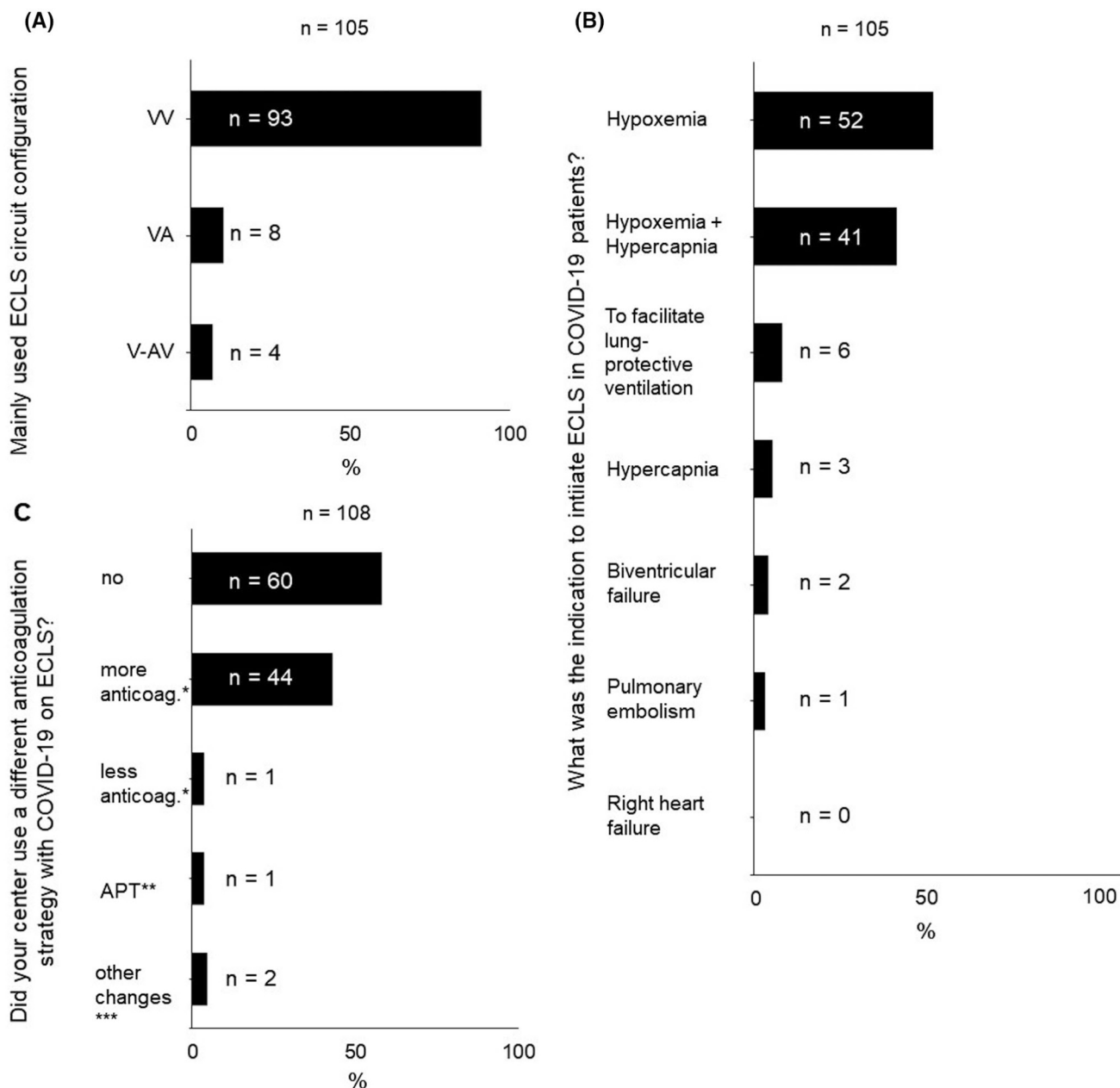


FIGURE 1 A–C, Extracorporeal life support (ECLS) circuit configuration, indication, and anticoagulation strategy. *measured in higher or reduced prothrombin time (PTT) or **activated clotting time (ACT); ***were specified as direct thrombin inhibition ($n = 1$) and Anti-Xa-activity ($n = 1$). (D,E) Duration of ECLS therapy and reasons for treatment discontinuation. *were specified as futility ($n = 2$), intractable septic shock ($n = 1$), multi-organ failure ($n = 3$), and bleeding other than intracranial ($n = 1$)

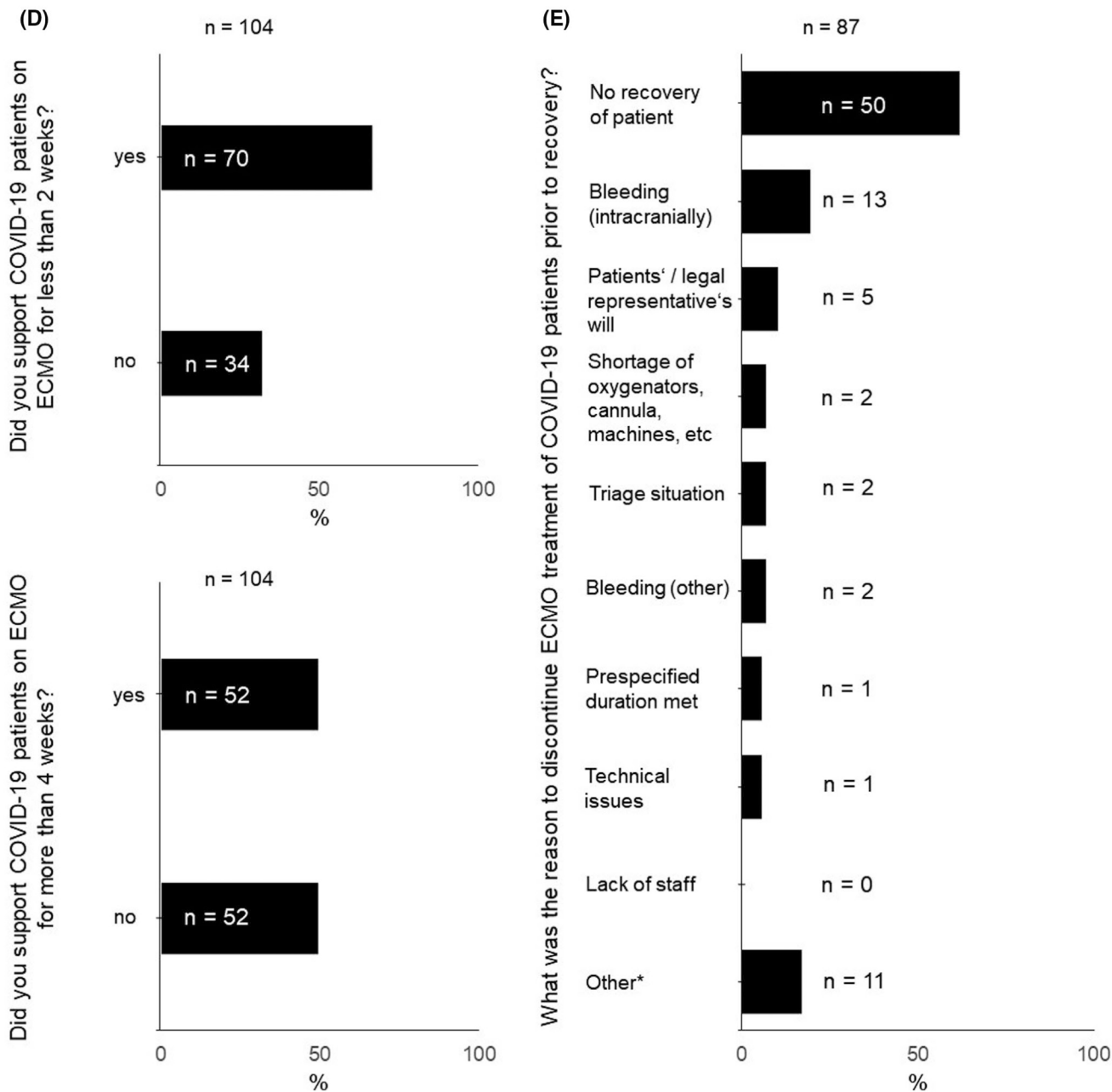


FIGURE 1 (Continued)

workload made ECLS impracticable. Only 5% of participants reported that they had to abstain from ECLS initiation due to a shortage of oxygenators, machines, or ECLS cannulas.

4.6 | Duration of ECLS support

Most patients were supported with ECLS for less than 2 weeks. However, 50% of all participants stated that they had also treated patients with ECLS for more than 4 weeks (Figure 1D).

4.7 | Reasons for ECLS discontinuation

Seventy-two percent of participants confirmed that their center would withdraw ECLS if there was no perspective for a COVID-19 patient to recover. If ECLS treatment was discontinued prior to recovery, futility was mostly stated as the reason ($n = 50$ from 94 responses, 53%). ECLS-related complications were the second most important reason for treatment discontinuation. Fourteen percent of ECLS providers stated that they had terminated ECLS due to major bleeding ($n = 15$), mainly intracranial hemorrhage ($n = 13$) and, less frequently, extracranially.

In 1% of cases, further unspecified technical issues led to ECLS withdrawal. The question also offered “lack of staff” as a possible answer, which was not chosen. However, 2% of participants

($n = 2$, Germany and France) stated that a triage situation forced physicians to discontinue ECLS prior to the patient’s possible recovery. Two percent of respondents named lack of ECLS

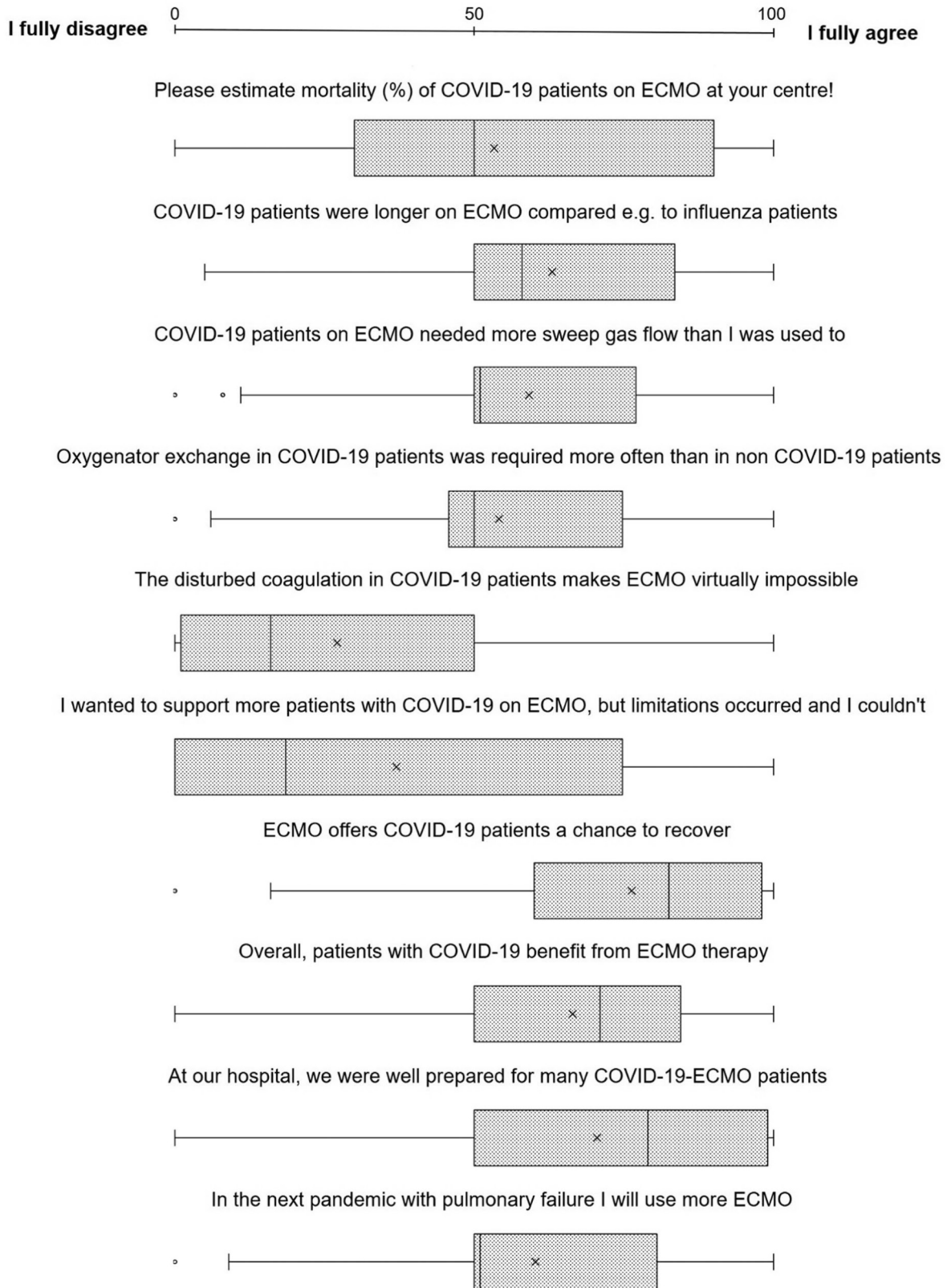


FIGURE 2 Participants’ extent of agreement to statements about COVID-19 and extracorporeal life support (ECLS) therapy; 0 = full disagreement, 100% = full agreement. Results are expressed in box plots. The left box barrier equals the 25th percentile, and the right barrier equals the 75th percentile. Median is expressed by the full line inside the box, and mean is marked as an “x”

oxygenators, ECLS machines, or consumables as the reason for ECLS discontinuation. See also Figure 1E.

4.8 | Estimation of patients' outcome

When asked to estimate the percentage of patients who died while on ECLS due to COVID-19, average mortality was estimated to be 55%, meaning that 45% of patients had survived on ECLS at least until the end of the survey.

4.9 | ECLS providers' opinions on COVID-19 and ECLS

The last eight questions were designed to investigate a participant's opinion on certain statements about ECLS and COVID-19, measured in percentage of agreement. Participants agreed to 58% (IQR 33%) on median that patients were longer on ECLS due to COVID-19 compared to other causes of ARDS. The claim that CARDS patients on ECLS required more sweep gas flow than what the individual ECLS physician was used to was accepted by 58% (IQR 26.8%). The statement that oxygenator change was more frequently required in CARDS patients on ECLS had an acceptance rate of 50% on average (IQR 27%). The claim that disturbed coagulation in COVID-19 patients would make ECLS impossible was mostly rejected (16% agreement, IQR 48%). The assumption that ECLS offers patients with COVID-19-induced ARDS a chance to recover found relatively strong acceptance (agreement extent of 82%, IQR 38%), with 71% (IQR 34%) agreement with the claim that CARDS patients benefitted from ECLS therapy. Box plots are displayed in Figure 2.

For results not outlined here, see Supporting Information.

5 | DISCUSSION AND CONCLUSIONS

Survey results prove that critical care providers worldwide have repeatedly successfully used ECLS to support patients in COVID-19-related respiratory failure despite official recommendations and were limited to carefully singled-out patients. At the time the survey was launched, data regarding the outcome of COVID-19 patients treated with ECLS were limited to case reports and small case series. Recent retrospective cohort studies on COVID-19 patients receiving ECLS have produced encouraging results¹¹ but were unpublished at that time. Critical care providers hence had to rely on what was already known about ARDS from different causes. Both clinical experience and pathophysiology of CARDS made ECLS appealing to treat COVID-19, even when data on mortality or complication rate were missing.

Several groups have reported evidence that COVID-19 might be associated with a hypercoagulable state, resulting in an increased risk of thromboembolic complications.^{12,13} Exposing hypercoagulable blood to the artificial surface of an ECLS circuit could therefore come with a considerable risk of thromboembolism. Interestingly, when asked about ECLS-related complications in COVID-19, 13% of ECLS providers stated that ECLS had to be terminated due to major bleeding, but only one case of relevant pulmonary embolism on VV-ECLS was reported. It should be noted though that minor thrombosis or thromboembolism could have remained undetected during ECLS therapy; hence, a reliable incidence of all thrombotic events cannot be provided or was underestimated by the ECLS providers. Nevertheless, given that 50% of all participants had treated patients on ECLS for more than 4 weeks, the overall occurrence of lethal thromboembolism on ECLS in COVID-19 was surprisingly low. Only a minority of ECLS physicians said that they increased the dosage of anticoagulants to prevent clotting on ECLS. There was also no general agreement that oxygenator change was required more frequently compared to patients with ARDS from other causes. Although increased rate of oxygenator pump head thrombosis in COVID-19 has been reported,¹⁴ suspected hypercoagulation in COVID-19 did not seem to translate to a higher incidence of life-threatening pulmonary or systemic thromboembolism in patients with COVID-19 on ECLS. Prospective studies should address how much anticoagulation for ECLS in COVID-19 is needed so that both the risk of thrombosis and hemorrhage can be minimized.

Although predominantly affecting the lungs, multiple organ involvement of COVID-19 has been reported. Cardiac complications in COVID-19 have recently gathered broad attention. Acute myocardial injury in the absence of macroscopic coronary artery disease is suspected to occur in up to 10% of patients especially in the critically ill.¹⁵⁻¹⁸ In a recent retrospective analysis, Zayat et al found that, among others, increased levels of amino-terminal pro-brain natriuretic peptide (NT-pro-BNP) predict worse survival in COVID-19 patients on extracorporeal life support.¹⁹ While 11% of our participants reported that they employed also veno-arterial ECLS for COVID-19, only 3% of participants specified that arterial cannulation was required because of acute heart or circulatory failure, in one case caused by fulminant pulmonary embolism. So far, our survey results do not support the hypothesis that severe cardiac involvement in COVID-19 translated to an increased need for cardiac support (e.g., with VA-ECLS) in patients with CARDS.

A recently published study investigating outcomes of all adult patients with CARDS treated with ECLS using a EuroELSO registry estimated overall 90-day mortality to be less than 40%.¹¹ When asked about the mortality of COVID-19 patients on ECLS, the mean estimation in our survey was 55%, meaning that roughly 45% could be weaned

off extracorporeal support at survey deadline. If these data translate to real-life mortality, survival of COVID-19 patients on ECLS could be comparable to non-COVID-19-induced ARDS. At the time of report, no prospective data on the outcome nor complication rate of ECLS therapy in COVID-19 are available. For the time being, our survey suggests that ECLS for COVID-19 is practicable, effective, and does not lead to higher complication rates in COVID-19 if it is utilized in experienced ECLS centers. Most participants agreed that their patients benefitted from ECLS therapy and stated that, in a hypothetical scenario of a future respiratory pandemic, they would use it more readily to treat acute respiratory failure.

Our survey has several limitations. Firstly, while it reflects opinions of a fairly large cohort of physicians providing ECLS services, we nevertheless did not ask for patient-specific data outcome. Hence, we cannot provide statistical evidence on ECLS-related end points, for example, overall survival, 28-day mortality, or discharge from ICU. Secondly, the survey was addressed mainly to tertiary care centers who have repeatedly published on ECLS, leading to a skewness of representation, possibly to the disadvantage of primary and secondary care hospitals with less ECLS experience.

Critical care providers need to know not only whether to use ECLS but also how to manage ECLS therapy in a disease as poorly understood as COVID-19. Currently, this knowledge is expanding.¹¹ Across Europe, more than 2100 patients in 180 centers were already treated on ECLS for respiratory and/or circulatory failure due to COVID-19 (<https://www.euroelso.net/covid-19/covid-19-survey/>; last accessed on November 23). The data from this survey (theoretical considerations early in the pandemic) and the EuroELSO (real-world data with weekly updates) data are in line, suggesting that ECLS is a useful adjunctive tool in COVID-19-related respiratory failure. As the survey was conducted in June, a follow-up survey may be indicated at the appropriate time.

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CONFLICT OF INTEREST

Robert Bals declares funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Novartis, CLS Behring, the German Federal Ministry of Education and Research (BMBF) Competence Network Asthma and COPD (ASCONET), Sander-Stiftung, Schwiete-Stiftung, Krebshilfe and Mukoviszidose eV. Conflicts that the editors consider relevant to the content of the

manuscript have been disclosed. All other authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

S.M., A.K., A.B., G.D., S.H., T.M., and P.L. drafted the survey. L.M.B., J.S., H.B., F.S.T., O.M., R.L., J.B., and R.M. revised the survey for important content. P.L. launched the survey and oversaw collection of data. R.K. provided IT tools for survey preparation. S.M. drafted the manuscript. A.K., L.M.B., A.S., J.S., G.D., S.H., F.S., R.B., F.S.T., O.M., R.L., J.B., R.M., and P.L. revised the manuscript for important intellectual content. All authors have seen and approved the final version of the manuscript.

CONSENT TO BE LISTED AS COLLABORATOR

All colleagues who participated in the survey and agreed to be named publicly were included as collaborators.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

APPENDIX

The COVID-19 ECLS (COVEC) study group

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