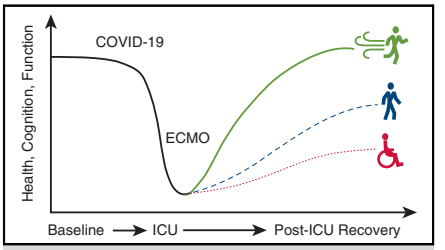
Long-term recovery of survivors of coronavirus disease (COVID-19) treated with extracorporeal membrane oxygenation: The next imperative

Check for updates

Kirby P. Mayer, DPT, PhD,[a] Sarah E. Jolley, MD, MSc,[b] Eric W. Etchill, MD,[c] Shoaib Fakhri, MD,[b] Jordan Hoffman, MD,[d] Carla M. Sevin, MD,[e] Joseph B. Zwischenberger, MD,[f] and Jessica Y. Rove, MD,[g] the Outcomes and Recovery After COVID-19 Leading to ECMO (ORACLE) Group*

The novel pathogen severe acute respiratory syndrome coronavirus 2 triggering coronavirus disease 2019 (COVID-19) leads to invasive mechanical ventilation in an estimated 20% of hospitalized patients with an associated mortality as high as 80%.[1] According to the international Extracorporeal Life Support Organization (ELSO), more than 2200 patients with COVID-19–associated acute respiratory distress syndrome (ARDS) have been treated with extracorporeal membrane oxygenation (ECMO).[2,3] ELSO members report a 55% survival rate for patients with COVID-19 treated with ECMO, and factors affecting survival are being investigated at several centers.[3] As the clinical response to COVID-19 evolves, cardiothoracic surgeons and the critical care community have a responsibility to understand the recovery trajectory of patients with COVID-19 who were treated with ECMO (Figure 1). The authors have formed the Outcomes and Recovery After COVID-19 Leading to ECMO (ORACLE) Group, a broadly multidisciplinary collaboration between 5 academic medical centers who incorporate protocolized outpatient postintensive care unit (post-ICU) follow-up of survivors of COVID-19–associated ARDS who were supported with ECMO (Figure 2). The goal of this collaborative is to characterize the recovery of these patients and target future investigations aimed at optimizing their survivorship.



Back to baseline (*green*), some deficits (*blue*), significant disability (*red*).

CENTRAL MESSAGE

This review introduces a multicenter initiative to track the long-term physical, cognitive, and emotional recovery of survivors of COVID-19 treated with ECMO.

PERSPECTIVE

Survivors of COVID-19 treated with ECMO are at risk for long-term physical, cognitive, and emotional deficits related to their critical illness. Multicenter, protocolized, outpatient, post-ICU follow-up of these patients aims to characterize their survivorship and target subsequent investigations at optimizing their recovery.

See Commentaries on pages 169 and 171.

COVID-19 CRITICAL ILLNESS, ECMO, AND POSTINTENSIVE CARE SYNDROME (PICS)

PICS is a term used to describe the collective impairments in physical function, mental health, and cognition observed in survivors of the ICU. Follow-up of ARDS survivors, including those who had influenza A subtype H1N1 or severe acute respiratory syndrome, shows these deficits can persist for years and negatively impact meaningful recovery.[4-12] For example, at 1 year from hospitalization, one-third of previously employed survivors of the ICU remain jobless.[13] Thousands of survivors of COVID-19–associated ARDS, including those treated with ECMO, are at risk for long-lasting sequelae of their critical illness.[14,15]

From the [a]Department of Physical Therapy, College of Health Sciences, and [f]Division of Cardiothoracic Surgery, Department of Surgery, College of Medicine, University of Kentucky, Lexington, Ky; [b]Division of Pulmonary Sciences and Critical Care, Department of Medicine, and [g]Division of Cardiothoracic Surgery, Department of Surgery, University of Colorado, Anschutz Medical Campus, Aurora, Colo; [c]Division of Cardiothoracic Surgery, Department of Surgery, Johns Hopkins University, Baltimore, Md; [d]Division of Cardiothoracic Surgery, Department of Surgery, and [e]Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University, Nashville, Tenn.

* Additional ORACLE Group authors: Glenn J. R. Whitman, MD, Ann M. Parker, MD, Matthew F. Mart, MD, Joseph A. Hippensteel, MD, Karsten Bartels, MD, PhD, Ashley A. Montgomery-Yates, MD, Sung-Min Cho, DO, MHS, Bo Soo Kim, MD, Chintan Ramani, MBBS, Alexandra Kadl, MD, MS, and Kyle Enfield, MD

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Address for reprints: Jessica Y. Rove, MD, 12631 E 17th Ave, Mailstop C310, Aurora, CO 80045 (E-mail: Jessica.Rove@cuanschutz.edu).

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Abbreviations and Acronyms

ARDS = acute respiratory distress syndrome
COVID-19 = coronavirus disease 2019
ECMO = extracorporeal membrane oxygenation
ELSO = Extracoporeal Life Support Organization
ICU = intensive care unit
ORACLE = Outcomes and Recovery After COVID-19 Leading to ECMO
PICS = postintensive care syndrome
PTSD = post-traumatic stress disorder

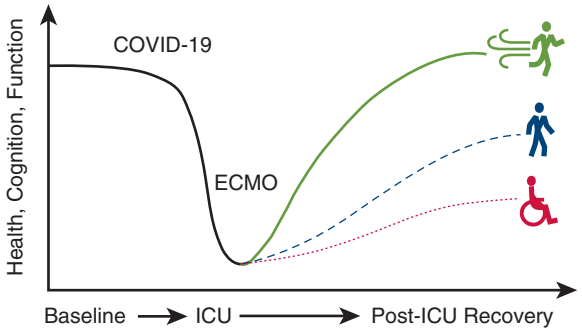

FIGURE 1. Survivors of COVID-19 treated with ECMO are at risk for long-term physical, cognitive, and emotional deficits related to their critical illness. The illustration depicts 3 potential post-ICU recovery trajectories: back to baseline health, cognition, and physical function (*green*, *solid line*); survival with some deficits (*blue*, *long dashed line*); and survival with significant disability (*red*, *short dashed line*). *COVID-19*, Coronavirus disease 2019; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit.

Specific physical impairments of survivors of the ICU include neuromuscular weakness, ICU-acquired weakness, and musculoskeletal pain.[16-20] Nearly 56% of patients recovering from COVID-19 at rehabilitation centers in Italy are unable to walk in the very early stage of recovery.[21] Patients repeatedly alternating between prone and supine positions may experience brachial plexus or upper-extremity sequelae. In the setting of COVID-19, infection precautions have essentially eliminated early rehabilitation interventions in the ICU, further increasing the risk of long-term physical impairments.

Regarding emotional health, one-quarter to one-third of survivors of the ICU are reported to experience depression, anxiety, and post-traumatic stress disorder (PTSD), with a large percentage experiencing multiple mental health conditions.[22-25] The morbidity of this burden can persist for several years.[4] Patients in the ICU with COVID-19 may be at additional risk for impaired emotional health due to social isolation, limited family visitation, intense (often confusing) media coverage during the pandemic, fear of spreading the disease to close contacts, death of close family members, and stigma due to contracting or spreading the virus.[26,27]

Cognitive impairments in survivors of the ICU include deficits in language, memory, attention, and visual–spatial abilities.[22,28] At 1-year follow-up of patients with ARDS, one-third of survivors demonstrated cognitive impairment with neuropsychological test scores consistent with moderate traumatic brain injury.[14] ICU delirium can contribute to long-term cognitive dysfunction.[29] At 1-month follow-up of survivors of COVID-19 critical illness, 42% who experienced delirium during hospitalization have ongoing impairments in cognitive function.[30] Stroke also increases the risk of long-term cognitive deficits, and the risk of stroke is increased in patients with COVID-19 and in patients treated with ECMO.[31,32]

In comparison with the extensive literature on PICS after critical illness from ARDS, there are limited data on the specific long-term outcomes of ECMO survivors. Other than the 6-month follow-up in the United Kingdom–based multicenter CESAR (Conventional ventilatory support vs ECMO for severe adult respiratory failure) trial, conclusions are largely limited to single-center investigations, small numbers of patients, and incomplete follow-up.[33] Survivors of ECMO have been reported to experience decreased return to usual activity and worse chronic pain, in addition to depression, anxiety, and PTSD that can persist up to 3 years after hospitalization.[7,9,34,35] A single-center study from France reported 2-year follow-up demonstrating no difference in cognitive function, anxiety, depression, and PTSD between patients with ARDS treated with ECMO compared with those who were not.[36]

Although evidence-based critical care interventions can optimize survival and survivorship of critically ill patients, including those requiring ECMO, infection control precautions during the COVID-19 pandemic have disrupted these best practices, with a yet-unknown impact on the recovery of survivors of the ICU. Reducing sedation and paralytic requirements and encouraging early mobilization and cognitive exercises while in the ICU have been shown to improve physical function and reduce cognitive impairment and PTSD.[37-44] Unfortunately, in the setting of COVID-19 precautions, a fully masked, gowned, and gloved critical care nurse is the only provider going in and out of an isolation room in the ICU. Family and familiar visitors are not allowed or severely restricted, and at best, similarly covered beyond recognition. Patients in isolation are not ambulating around the ICU extubated on ECMO as previously encouraged. Although decreasing sedation requirements for patients receiving ECMO may reduce their risk of physical and cognitive deficits, accidental ECMO decannulation can be lethal and cause unintended viral exposure of

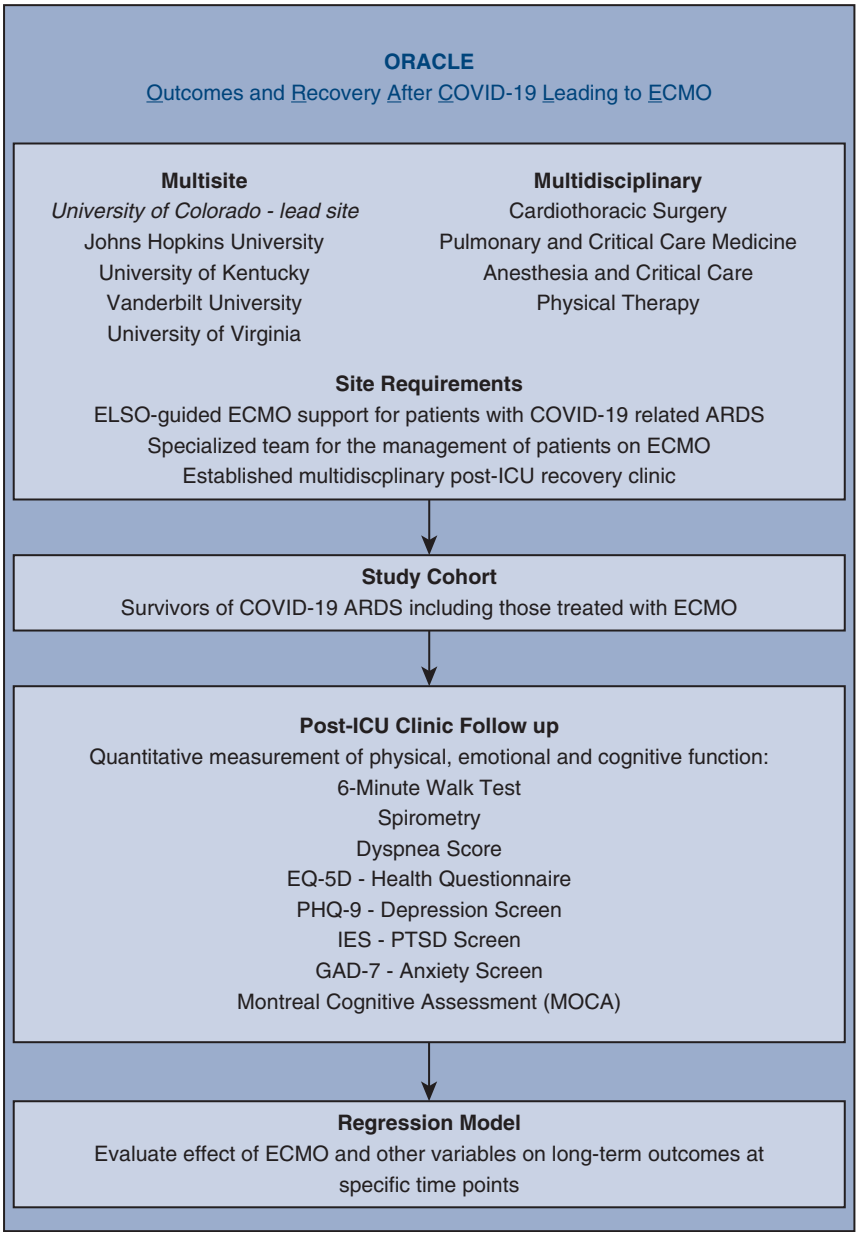

FIGURE 2. The Outcomes and Recovery After COVID-19 Leading to ECMO (ORACLE) Group is a broadly multidisciplinary collaboration between 5 academic medical centers who incorporate protocolized post-ICU follow up of patients with COVID-19–associated ARDS who were treated with ECMO. The ORACLE study cohort includes survivors of COVID-19 ARDS including those supported with ECMO. Follow-up includes collection of quantitative measurements of physical, emotional, and cognitive function including a 6-minute walk test, spirometry, dyspnea score, the EQ-5D general health questionnaire, PHQ-9 depression screen, IES PTSD screen, GAD-7 screen, and the MOCA. Data analysis will use a regression model to evaluate the effect of ECMO and other variables on the long-term outcomes of this cohort. *ELSO*, Extracoporeal Life Support Organization; *ECMO*, extracorporeal membrane oxygenation; *COVID-19*, coronavirus disease 2019; *ICU*, intensive care unit; *ARDS*, acute respiratory distress syndrome; *EQ-5D*, EuroQol 5-Dimension; *PHQ-9*, Patient Health Questionnaire-9; *IES*, Impact of Event Scale; *PTSD*, post-traumatic stress disorder; *GAD-7*, Generalized Anxiety Disorder 7-item; *MOCA*, Montreal Cognitive Assessment.

caregivers. Unintended self-extubation of a patient with COVID-19 would require a subsequent reintubation, creating an additional high-risk exposure. Only follow-up of these patients with COVID-19–associated ARDS treated with ECMO will determine the long-term impact of these disrupted critical care practices.

COVID-19 AND ECMO RECOVERY

Since the majority of survivors are at high risk for more than 1 impairment in cognitive, physical, or emotional health, protocolized follow-up is our best mechanism to define the needs and optimize the recovery of survivors of COVID-19–associated ARDS treated with ECMO.[15,45] In

the last several years, the number of ICU recovery clinics has been increasing. The COVID-19 pandemic has only accelerated this trend due to an unprecedented spike in the incidence of ARDS and critical illness. ICU recovery clinics consist of a multidisciplinary team of providers who identify deficits associated with PICS. Intensivists, pharmacists, and rehabilitation specialists, including physical and occupational therapists, speech language pathologists, psychologists, and physiatrists, assess and tailor care to individual critical illness survivors.[46-49] In patients who followed up in the Vanderbilt ICU Recovery clinic, there was a high prevalence of problems warranting intervention, from cognitive impairment, anxiety, and depression to physical debility and medication-related problems.[47] These clinics provide (1) timely access and longitudinal treatment for the multifaceted recovery of critically ill patients with COVID-19–associated ARDS and (2) an opportunity to characterize the unique recovery needs of patients with COVID-19–associated ARDS who were supported with ECMO.

The ORACLE Group is a broadly multidisciplinary and multisite collaboration of providers with mutual interest in studying long-term outcomes in patients with COVID-19–associated ARDS treated with ECMO (Figure 2). Requirements for participating sites include (1) use of ELSO recommendations for ECMO support in patients with COVID-19 as a guideline for when and which patients to support with ECMO, (2) a specialized team for the management of ECMO patients, and (3) an established multidisciplinary post-ICU recovery clinic. ORACLE is evaluating survivors of COVID-19–related ARDS who required mechanical ventilation, including those who were supported with ECMO. The institutional review board waived the need for Informed Written Consent (University of Colorado and all other sites [COMIRB#20-0731], approved April 4, 2020).

Deidentified demographic, clinical, and laboratory data associated with the inpatient stay and ECMO course are being collected. All patients are referred for post-ICU recovery clinic follow-up during which period additional data collection includes objective quantitative measures of neuropsychiatric changes with the EuroQol 5-Dimension health questionnaire, anxiety, depression and PTSD screening, cognitive impairment with the Montreal Cognitive Assessment, and physical function with a 6-minute walk test, spirometry, and dyspnea score. These metrics were guided by the Core ICU Outcome Measurement Set for evaluating patients who recover from acute respiratory failure by an International Modified Delphi Consensus Study.[50] A regression model will evaluate the effect of ECMO and other chosen variables on long-term outcomes at specific time points. To the best of our knowledge, no previous study has looked at the association between ECMO and PICS-related outcomes in patients with COVID-19. While we recognize there are likely inherent differences (eg, age and severity of illness) between patients who receive ECMO and those who do not, it is well known that PICS occurs in all types of patients in the ICU across the spectrum of disease severity. Further, the hallmark features of PICS were described in cohorts of patients with ARDS, the primary disease process observed in patients with COVID-19 and respiratory failure.[6] Based on the previous literature around ICU survivorship, it is likely that patients surviving ECMO experience some, if not all, of the deficits observed in non-ECMO respiratory failure survivors.

Although there are analyses supporting the cost-effectiveness of ECMO in select populations, as well as data showing multidisciplinary post-ICU recovery clinic interventions reduce rehospitalizations, there are not yet any data on the cost-effectiveness of combined critical care interventions with post-ICU recovery care.[33,51-53] Although characterizing the recovery needs of post-ICU ECMO survivors can expand our existing paradigm of evaluating cost-effectiveness of ECMO based on survival alone, cost analysis in this particular case is limited by the fact that the circumstances of the COVID-19 pandemic are substantially different from the circumstances used to generate the cost-effectiveness data in CESAR.[33] The demands on the health care system generated by the pandemic, particularly acute at the outset, were unanticipated and unbudgeted and thus health care systems were understaffed, underspaced, and underequipped—all exceptions to usual cost-based modeling. Post-ICU recovery clinics across the United States have opened out of necessity to treat the rapid increase in critical illness survivors suffering from diagnoses related to PICS. These clinics remain under-resourced. Furthermore, the sudden rapid increase in virtual health visits in combination with in-person clinic visits has a cost-funding structure that continues to evolve.

In the span of several months, there are suddenly thousands of critical illness survivors of COVID-19, including hundreds recovering from ECMO. Understanding risk factors for short- and long-term outcomes unique to COVID-19–associated respiratory failure, and ECMO survivors in particular, is of paramount importance. In addition, characterizing the recovery needs of these post-ICU survivors expands our existing paradigm of evaluating cost-effectiveness of ECMO based on survival alone. The pressing needs of this growing population require a multisite and multidisciplinary collaboration to provide timely investigation and inform subsequent studies aimed at improving the recovery of survivors of this unprecedented global pandemic.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or

reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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