

## ***Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults***

**Effective:** December 1, 2023

**Next Review:** September 2024

**Last Review:** October 2023

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Extracorporeal Membrane Oxygenation (ECMO) is a complex treatment which utilizes a modified cardiopulmonary bypass circuit for temporary life support as a treatment for reversible cardiac and/or respiratory failure.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy does not address the use of ECMO in children or neonates, which may be considered medically necessary. In addition, this policy does not address the use of short-term extracorporeal support, including ECMO, such as during surgical procedures. The Policy Guidelines section below includes information regarding weaning and/or discontinuation of ECMO.

- I. Extracorporeal Membrane Oxygenation (ECMO) in adults (18 years or older) may be considered **medically necessary** as a treatment of respiratory or cardiac failure that is potentially reversible when both of the following Criteria (A. and B.) are met:
  - A. At least one of the following criteria is met:

1. Hypoxic respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one or more of the following:
    - a. Murray Lung Injury Score three or higher (see Policy Guidelines for Murray Lung Injury Score); or
    - b. PaO<sub>2</sub>/FiO<sub>2</sub> of less than 100 mm Hg on fraction of inspired oxygen (FiO<sub>2</sub>) greater than 90%; or
    - c. Inability to maintain airway plateau pressure (P<sub>plat</sub>) less than 30 cm H<sub>2</sub>O despite a tidal volume of four to six mL/kg ideal body weight (IBW); or
    - d. Oxygenation Index greater than 30: Oxygenation Index equals FiO<sub>2</sub> times 100 times MAP divided by PaO<sub>2</sub> mm Hg. [FiO<sub>2</sub> times 100 equals FiO<sub>2</sub> as percentage; MAP equals mean airway pressure in cm H<sub>2</sub>O; PaO<sub>2</sub> equals partial pressure oxygen in arterial blood].
  2. Respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one of the following:
    - a. Significant hypercapnea despite high P<sub>plat</sub> (greater than 30 cm H<sub>2</sub>O); or
    - b. A pH of less than 7.20 due to significant uncompensated hypercapnia
  3. Severe air leak syndromes including, but not limited to:
    - a. Significant tracheal airway injuries; or
    - b. An air-leak or broncho-pleural fistula that prevents adequate ventilation with lung-protective ventilation (see Policy Guidelines) strategies.
  4. Refractory cardiogenic shock as demonstrated by one of the following:
    - a. Inadequate tissue perfusion manifested as hypotension and low cardiac output despite adequate intravascular volume; or
    - b. Shock which persists despite volume administration, inotropes and vasoconstrictors, and intra-aortic balloon counterpulsation.
  5. Hypothermia with a core temperature of less than 28 degrees centigrade.
  6. As a bridge to heart, lung, or heart-lung transplantation.
- B. None of the following contraindications are present:
1. Ventilation with high ventilator pressure (P<sub>plat</sub> greater than 30 cm H<sub>2</sub>O) sustained throughout a seven-day period and/or high FiO<sub>2</sub> (greater than 80%) sustained throughout a seven-day period; or
  2. Signs of intracranial bleeding, or other major central nervous system injury without the potential to recover meaningful function; or
  3. Presence of an irreversible, terminal illness; or
  4. Cardiac decompensation and not meeting medical necessity criteria for heart transplant or ventricular assist device; or
  5. Chronic organ failure without the potential to recover meaningful function; or
  6. Prolonged CPR without adequate tissue perfusion; or

7. Patient choice to decline extraordinary life support interventions. (see Policy Guidelines)
- II. The continued use of Extracorporeal Membrane Oxygenation (ECMO) in adult patients meeting Criterion I., is considered **not medically necessary** if any one or more of the following conditions are present for five or more days:
  - A. Neurologic devastation determined by at least two physicians agreeing after evaluation, (including neurologic examination, head CT, and EEG), that the patient has sustained irreversible cessation of all functioning of the brain, including the brain stem and an outcome better than “persistent vegetative state” at six months is unlikely. At least one of these physicians should be a neurologist, neurosurgeon, and/or neuro-intensivist.
  - B. Hypotension and/or hypoxemia recalcitrant to all maneuvers which causes inadequate aerobic metabolism demonstrated by evidence of profound tissue ischemia [creatinine phosphokinase (CPK), lactate, lactate to pyruvate (L/P) ratio, near-infrared spectroscopy (NIRS)].
  - C. End-stage cardiac or lung failure without alternative long-term plan (i.e., ineligible for assist device and/or transplant), and the patient is unable to wean from ECMO.
- III. The use of Extracorporeal Membrane Oxygenation (ECMO) as a treatment of respiratory or cardiac failure in adult patients is considered **not medically necessary** if Criterion I.A. is not met OR if any of the contraindications listed in Criterion I.B. are present.
- IV. The use of Extracorporeal Membrane Oxygenation (ECMO) in adult patients is considered **investigational** in all other situations, including but not limited to use for indications other than respiratory or cardiac failure.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

### RESPIRATORY FAILURE REVERSIBILITY

The reversibility of the underlying respiratory failure is best determined by the treating physicians, ideally physicians with expertise in pulmonary medicine and/or critical care. Some of the underlying causes of respiratory failure which are commonly considered reversible are as follows:

- Acute respiratory distress syndrome (ARDS)
- Acute pulmonary edema
- Acute chest trauma
- Infectious and noninfectious pneumonia
- Pulmonary hemorrhage
- Pulmonary embolism
- Asthma exacerbation
- Aspiration pneumonitis.

## MAXIMAL LUNG-PROTECTIVE VENTILATION

The American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline made the following recommendations regarding lung-protective ARDS ventilation management:<sup>[1]</sup>

- Low tidal volume ventilation (4 to 8 mL/kg of predicted body weight)
- Plateau pressure (pPlat) less than 30 cm H<sub>2</sub>O

Additional lung protective options include prone positioning<sup>[2]</sup> and neuromuscular blockade<sup>[3]</sup>.

## MURRAY LUNG INJURY SCORE

The Murray Lung Injury Score is a system for classifying the severity of respiratory failure. It was developed for use in ARDS, but has been applied to other indications.<sup>[4]</sup> This score includes four subscales, each of which is scored from 0 to 4. The final score is obtained by dividing the collective score by the number of subscales used. A score of 0 indicates no lung injury; a score of 1 to 2.5 indicates mild or moderate lung injury; and a score of 2.5 indicates severe lung injury, e.g. ARDS. Table 1 shows the components of the Murray scoring system.

**Table 1: Murray Lung Injury Score**

Subscale	Criteria	Score
Chest x-ray score	No alveolar consolidation	0
	Alveolar consolidation confined to 1 quadrant	1
	Alveolar consolidation confined to 2 quadrants	2
	Alveolar consolidation confined to 3 quadrants	3
	Alveolar consolidation in all 4 quadrants	4
Hypoxemia score	PaO <sub>2</sub> /FiO <sub>2</sub> >300	0
	PaO <sub>2</sub> /FiO <sub>2</sub> 225-299	1
	PaO <sub>2</sub> /FiO <sub>2</sub> 175-224	2
	PaO <sub>2</sub> /FiO <sub>2</sub> 100-174	3
	PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 100	4
PEEP score (when ventilated)	PEEP ≤ 5 cm H <sub>2</sub> O	0
	PEEP 6-8 cm H <sub>2</sub> O	1
	PEEP 9-11 cm H <sub>2</sub> O	2
	PEEP 12-14 cm H <sub>2</sub> O	3
	PEEP ≥ 15 cm H <sub>2</sub> O	4
Respiratory system compliance score (when available)	Compliance >80 mL/cm H <sub>2</sub> O	0
	Compliance 60-79 mL/cm H <sub>2</sub> O	1
	Compliance 40-59 mL/cm H <sub>2</sub> O	2
	Compliance 20-39 mL/cm H <sub>2</sub> O	3
	Compliance ≤ 19 mL/cm H <sub>2</sub> O	4

CPAP – continuous positive airway pressure; FiO<sub>2</sub> – fraction of inspired oxygen; PaO<sub>2</sub> – partial pressure of oxygen in arterial blood; PEEP – peak end expiratory pressure.

In addition to the Murray Lung Injury Score, the Berlin Definition is gaining acceptance for classifying ARDS.<sup>[5]</sup>

## PATIENT CHOICE TO DECLINE EXTRAORDINARY LIFE SUPPORT INTERVENTIONS

Choices to decline extraordinary life support interventions may include, but is not limited to, the presence of an advanced directive, healthcare directive, Physician Orders for Life Sustaining

Treatment (POLST), or Physician Orders for Scope of Treatment (POST) to indicate the patient or the patient's health care representative or agent has selected any of the following upon which life-sustaining support would be withheld or withdrawn:

- A Do Not Resuscitate (DNR, DNAR, No Code) order; or
- Allow Natural Death; or
- No CPR or advanced cardiac life support interventions; or
- An equivalent choice.

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Indication for the requested service
- Documentation of symptoms, associated diagnoses, and treatments

## CROSS REFERENCES

1. [Ventricular Assist Devices and Total Artificial Hearts](#), Surgery, Policy No. 52
2. [Treatment of Adult Sepsis](#), Medicine, Policy No. 172

## BACKGROUND

Extracorporeal Membrane Oxygenation (ECMO), also referred to as extracorporeal life support (ECLS), or extracorporeal lung assist (ELA), has been proposed as an alternative treatment for cardiac and respiratory failure in adult patients and is described by the Extracorporeal Life Support Organization (ELSO) as, “the use of mechanical devices to temporarily (days to months) support heart or lung function (partially or totally) during cardiopulmonary failure, leading to organ recovery or replacement.”<sup>[6]</sup> ECMO is used for prolonged time periods (days to weeks) and involves removing a portion of the patient's blood, pumping it through a membrane oxygenator, removing carbon dioxide, rewarming the blood, and returning it to the patient. ECMO is a complex treatment requiring a specialized staff and specific equipment. The ELSO specialty group maintains a registry of detailed data from a voluntary international consortium of health care centers which utilize ECMO.<sup>[6]</sup>

Historically, ECMO has been used in neonatal and pediatric populations to treat respiratory failure related to a variety of respiratory diseases. The treatment may be used in newborn infants with neonatal respiratory distress due to congenital diaphragmatic hernia, meconium aspiration, hyaline membrane disease, pulmonary hypertension and pulmonary hypoplasia, and pneumonia with sepsis. ECMO is associated with a 55% survival rate in this subgroup and has become an accepted treatment for respiratory failure in pediatric and neonatal patients, despite the lack the randomized trials.<sup>[7-9]</sup>

With improvements in ECMO circuit technology and methods of supportive care, ECMO has been proposed as salvage therapy to prevent irreversible neurologic damage in adults with acute, reversible respiratory or cardiac failure. In critically ill adult patients, ECMO also may be considered a non-ventilatory treatment by which to avoid ventilator induced lung injury (VILI)

associated with mechanical ventilation. In these situations, death would be imminent unless medical interventions can immediately reverse the underlying disease process or physiologic functions can be supported for long enough that normal reparative processes or treatment can occur (e.g., resolution of ARDS or treatment of infection) or other life-saving intervention can be delivered (e.g., provision of a lung transplant).

## **DISEASE-SPECIFIC INDICATIONS FOR ECMO**

Venoarterial (VA) and venovenous (VV) ECMO have been investigated for a wide range of adult conditions that can lead to respiratory or cardiorespiratory failure, some of which overlap clinical categories (e.g., H1N1 influenza infection leading to ARDS and cardiovascular collapse), which makes categorization difficult. ARDS has been defined by consensus in the Berlin definition, which includes criteria for the timing of symptoms, imaging findings, exclusion of other causes, and degree of oxygenation.<sup>[5]</sup> However, in general, indications for ECMO can be categorized as follows:

- Acute respiratory failure due to potentially reversible causes. Acute respiratory failure refers to the failure of either oxygenation, removal of carbon dioxide, or both, and may be due to a wide range of causes. In these cases, ECMO is most often used as a bridge to recovery. Specific potentially reversible or treatable indications for ECMO may include ARDS, acute pneumonias, and a variety of other pulmonary disorders.
- Bridge to lung transplant. Lung transplant is used for management of chronic respiratory failure, most frequently in the setting of advanced chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, emphysema due to alpha-1-antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. In the end stages of these diseases, patients may require additional respiratory support while awaiting an appropriate donor. In addition, patients who have undergone a transplant may require retransplantation due to graft dysfunction after the primary transplant.
- Acute-onset cardiogenic or obstructive shock is defined as shock that is due to cardiac pump failure or vascular obstruction, refractory to inotropes and/or other mechanical circulatory support. Examples of this category include postcardiotomy syndrome (ie, failure to wean from bypass), acute coronary syndrome, myocarditis, cardiomyopathy, massive pulmonary embolism, and prolonged arrhythmias.
- ECMO-assisted cardiopulmonary resuscitation (ECPR). ECMO can be used as an adjunct to CPR in patients who do not respond to initial resuscitation measures.

## **TECHNOLOGY DESCRIPTION**

The basic components of ECMO include a pump, an oxygenator, sometimes referred to as a “membrane lung,” and some form of vascular access. Based on the vascular access type, ECMO can be described as VV or VA. VA ECMO has the potential to provide cardiac and ventilatory support.

More recently, these include ventilation support devices that provide oxygenation and removal of CO<sub>2</sub> without the use of a pump system or interventional lung assist devices (e.g., iLA® Membrane Ventilator, Novalung GmbH). These technologies are not the focus of this evidence review but are described briefly because there is overlap in patient populations treated with extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) and those treated with ECMO, and some

studies have reported on both technologies.

In contrast to VA and VV ECMO, which use large-bore catheters and generally high flow through the ECMO circuits, other systems use pumpless systems to remove CO<sub>2</sub>. These pumpless devices achieve ECCO<sub>2</sub>R via a thin double-lumen central venous catheter and relatively low extracorporeal blood flow. They have been investigated as a means to allow low tidal volume ventilator strategies, which may have benefit in ARDS and other conditions where lung compliance is affected. Although ECMO systems can effect CO<sub>2</sub> removal, dedicated ECCO<sub>2</sub>R systems are differentiated by simpler mechanics and the fact that they do not require dedicated staff.<sup>[10]</sup>

## **Venovenous ECMO**

### Technique

In venovenous extracorporeal membrane oxygenation (VV ECMO), the ECMO oxygenator is in series with the native lungs, and the ECMO circuit provides respiratory support. Venous blood is withdrawn through a large-bore intravenous line, oxygen is added and CO<sub>2</sub> removed, and oxygenated blood is returned to the venous circulation near the right atrium. Venous access for VV ECMO can be configured through two single lumen catheters (typically in the right internal jugular and femoral veins), or through one dual lumen catheter in the right internal jugular vein. In the femoro-jugular approach, a single large multiperforated drainage cannula is inserted in the femoral vein and advanced to the cavo-atrial junction, and the return cannula is inserted into the superior vena cava via the right internal jugular vein. Alternatively, in the bi-femoral-jugular approach, drainage cannulae are placed in both the superior vena cava and the inferior vena cava via the jugular and femoral veins, and a femoral return cannula is advanced to the right atrium. In the dual-lumen catheter approach, a single bicaval cannula is inserted via the right jugular vein and positioned to allow drainage from the inferior vena cava and superior vena cava and return via the right atrium.

### Indications

VV ECMO provides only respiratory support, and therefore is used for conditions in which there is progressive loss in ability to provide adequate gas exchange due to abnormalities in the lung parenchyma, airways, or chest wall. Right ventricular (RV) dysfunction due to pulmonary hypertension that is secondary to parenchymal lung disease may sometimes be effectively treated by VV ECMO.

However, acute or chronic obstruction of the pulmonary vasculature (e.g., saddle pulmonary embolism) may require VA ECMO. There may be cases in which RV dysfunction due to pulmonary hypertension caused by severe parenchymal lung disease may be severe enough to require VA ECMO. In adults, VV ECMO is generally used only in situations in which all other reasonable avenues of respiratory support have been exhausted, including mechanical ventilation with lung protective strategies, pharmacologic therapy, and prone positioning.

## **Venoarterial ECMO**

### Technique

In venoarterial extracorporeal membrane oxygenation (VA ECMO), the ECMO oxygenator is in parallel with the native lungs and the ECMO circuit provides both cardiac and respiratory support. In VA ECMO, venous blood is withdrawn, oxygen is added, and CO<sub>2</sub> removed similar

to VV ECMO, but blood is returned to the arterial circulation. Cannulation for VA ECMO can be done peripherally, with withdrawal of blood from a cannula in the femoral or internal jugular vein and return of blood through a cannula in the femoral or subclavian artery. Alternatively, it can be done centrally, with withdrawal of blood directly from a cannula in the right atrium and return of blood through a cannula in the aorta. VA ECMO typically requires a high blood flow extracorporeal circuit.

### Indications

VA ECMO provides both cardiac and respiratory support. Thus, it is used in situations of significant cardiac dysfunction that is refractory to other therapies, when significant respiratory involvement is suspected or demonstrated, such as treatment-resistant cardiogenic shock, pulmonary embolism, or primary parenchymal lung disease severe enough to compromise right heart function. Echocardiography should be used before ECMO is considered or started to identify severe left ventricular dysfunction which might necessitate the use of VA ECMO. The use of peripheral VA ECMO in the presence of adequate cardiac function may cause severe hypoxia in the upper part of the body (brain and heart) in the setting of a severe pulmonary shunt.

### **MEDICAL MANAGEMENT DURING ECMO**

During ECMO, patients require supportive care and treatment for their underlying medical condition, including ventilator management, fluid management, and systemic anticoagulation to prevent circuit clotting, nutritional management, and appropriate antimicrobials. Maintenance of the ECMO circuit requires frequent monitoring by medical and nursing staff and evaluation at least once per 24 hours by a perfusion expert.

ECMO may be associated with significant complications, which can be related to the vascular access required to the need for systemic anticoagulation, including hemorrhage, limb ischemia, compartment syndrome, cannula thrombosis, and limb amputation. Patients are also at risk of progression of their underlying disease process.

## **EVIDENCE SUMMARY**

The ideal study design to evaluate the specific therapeutic effects of VA ECMO or VV ECMO for adult respiratory and cardiorespiratory conditions would be multicenter randomized controlled trials (RCTs) that compare ECMO with best standard therapy, such as mechanical ventilation. RCTs are needed to adequately control for confounding factors, evaluate adverse effects, safety, effectiveness, and individual patient differences (age, condition, and severity of illness) compared to standard therapy. The RCT is the most rigorous and reliable study design for demonstrating a causal relationship between the therapy under investigation and the health outcomes of interest. Specifically, questions regarding appropriate patient selection, standardization, and duration of ECMO treatment and complication and survival rates, would be addressed. However, there are challenges in conducting RCTs to evaluate ECMO due to several factors, such as small patient populations and the urgent and emergent setting in which ECMO is typically utilized. Given these confounding factors, data from large randomized controlled trials are not expected in the near future.

Current guidelines for establishing causality require direct evidence which demonstrates that the effect of utilizing ECMO as a treatment of respiratory or cardiac failure in adults is greater than the combined influence of all confounding factors for the given condition.<sup>[11]</sup> Given that



RCTs are unlikely, evidence from non-randomized trials may be considered when treatment with ECMO results in an improvement of symptoms which is so sizable that the health improvement rules out the combined effect of all other possible concurrent treatments or natural progression of the disease. Currently, there is limited evidence of this magnitude regarding patient selection, timing and therapeutic strategies in adult patients with respiratory or cardiac failure.<sup>[12, 13]</sup> Therefore large studies with adequate follow-up are needed in order to validate appropriate patient selection criteria, treatment strategies and timing of ECMO use.

## **ECMO IN ADULTS WITH ACUTE RESPIRATORY FAILURE**

The current evidence regarding ECMO in adult patients is primarily limited to nonrandomized studies with heterogenous patient populations, treated at various healthcare institutions with differing ECMO treatment protocols. In addition, ECMO technology and treatment protocols have evolved over the past several decades with the use of lung-protective ventilation systems.<sup>[12, 13]</sup> Therefore, the following literature review focuses on systematic reviews and meta-analyses regarding the use of ECMO in adults in the past two decades.

### **Systematic Reviews and Technology Assessments**

Shrestha (2022) performed a systematic review and meta-analysis of trials conducted after 2000 comparing ECMO to standard mechanical ventilation in patients with ARDS.<sup>[14]</sup> 12 studies, two of which were RCTs, were included in the meta-analysis. ECMO did not significantly improve in-hospital mortality (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.40 to 1.41) or hospital length of stay (mean deviation, 3.92; 95% CI, -6.26 to 14.11). However, 30-day (OR, 0.56; 95% CI, 0.37 to 0.84) and 90-day (OR, 0.59; 95% CI, 0.41 to 0.85) mortality improved in patients treated with ECMO compared with those managed with standard mechanical ventilation.

The systematic review by Chong (2022) analyzed the use of ECMO in coronavirus disease 2019 (COVID-19) and compared the clinical characteristics between COVID-19 survivors and non-survivors.<sup>[15]</sup> 16 cohort studies with 706 COVID-19 patients who required ECMO were included in this study. The survivors of COVID-19 who required ECMO were younger than the non survivors (51 vs. 55 years old), had fewer comorbidities, less renal replacement therapy, and vasopressor requirement. The duration of mechanical ventilation before ECMO support initiation and total ECMO support duration was similar among survivors and non-survivors. Another systematic review and meta-analysis by Ling (2022) comments on the extensive use of ECMO for COVID-19 from December 2019 to January 2022 in adults.<sup>[16]</sup> This analysis included 52 studies comprising 18,211 patients in the meta-analysis. The authors concluded that the mortality rate for patients receiving ECMO for COVID-19-related ARDS has increased as the pandemic has progressed. Mortality could be predicted based on age, time of final patient enrollment, administration of corticosteroids, and reduced duration of ECMO run.

A systematic review and meta-analysis by Ramanathan (2021) evaluated the use of ECMO in patients with COVID-19 on patient survival.<sup>[17]</sup> The meta-analysis included 22 retrospective observational studies with a total of 1,896 patients. Of the 19 studies that reported ECMO modality, VV ECMO was predominately used (98.6%). The pooled in-hospital mortality of COVID-19 ECMO patients was 37.1% (95% CI 32.3 to 42.0%). However, this analysis included patients that were still hospitalized (including 68 patients still on ECMO), so the calculated mortality is likely an underestimate of the true value. For the 18 studies that reported complications (n=1,721), there were 1,583 reported complications. Renal complications were the most common (559), followed by mechanical complications (429) and

infection (171).

Combes (2020) performed an individual patient data meta-analysis of the two most recent RCTs that compared VV ECMO to standard mechanical ventilation in severe ARDS. The two RCTs included a total of 429 patients.<sup>[18]</sup> The primary outcome of the meta-analysis was 90-day mortality. Mortality rates at 90 days were 36% in the ECMO group and 48% in the standard mechanical ventilation group (relative risk [RR] 0.75, 95% CI 0.6 to 0.94,  $p=0.013$ ,  $I^2=0\%$ ). The risk of 90-day treatment failure, defined as death for the ECMO group and death or crossover to ECMO for the mechanical ventilation group, was also lower in the ECMO group (RR 0.65, 95% CI 0.52 to 0.8,  $I^2=0\%$ ).

Aoyama (2019) reported results of a systematic review and meta-analysis analyzing mortality in ARDS patients following different lung protective ventilation strategies.<sup>[19]</sup> Included studies were limited to RCTs of interventions for adults with moderate to severe ARDS that used lung protective ventilation. A total of 25 RCTs were included evaluating nine interventions. Prone positioning and VV ECMO were found to have a statistically significant association with lower 28-day mortality compared with lung protective ventilation alone (prone positioning: RR 0.69, 95% credible interval 0.48 to 0.99, low quality of evidence; VV ECMO RR 0.60, 95% CI 0.38 to 0.93, moderate quality of evidence).

Vaquer (2017) performed a systematic review and meta-analysis analyzing complications and hospital mortality associated with ARDS patients who underwent VV ECMO.<sup>[20]</sup> Twelve studies were included that comprised 1,042 patients with refractory ARDS. The pooled mortality at hospital discharge was 37.7% ( $z = -3.73$ ; CI 95% = 31.8 to 44.1;  $I^2 = 74.2\%$ ;  $p<0.001$ ). This review included some H1N1 populations. H1N1 as the underlying cause of ARDS was determined to be an independent moderator of mortality.

In 2015, the Washington State Health Care Authority published a health technology assessment (HTA) for ECMO in adults.<sup>[21]</sup> Evidence of clinical efficacy of ECMO compared to conventional treatment included RCTs, good-quality comparative cohort studies, and good-quality systematic reviews. The review identified two RCTs, both of good quality. Among the 41 comparative cohort studies identified, 16 were of good quality, eight of fair quality and 17 of poor quality. The bulk of the good quality evidence was for pulmonary support, including two randomized control trials<sup>[22, 23]</sup> and six observational studies. Based on the evidence, which was admitted to have significant limitations for some indications, and expert consensus, the committee determined that ECMO is effective for patients with severe life-threatening respiratory or cardiac dysfunction that is not responding to conventional management but is potentially reversible; as a bridging therapy for patients in pulmonary and/or cardiac failure for transplantation.

Tramm (2015) published a Cochrane review on the use of ECMO for critically ill adults. The reviewers included RCTs, quasi-RCTs, and cluster RCTs that evaluated VV or VA ECMO compared with conventional respiratory and cardiac support.<sup>[24]</sup> Four RCTs were identified (Peek [2009]<sup>[23]</sup>, Morris [1994]<sup>[25]</sup>, Bein [2013]<sup>[22]</sup>, Zapol [1979]<sup>[26]</sup>), which are described below. Combined, the trials included 389 subjects. Inclusion criteria (acute respiratory failure with specific criteria for arterial oxygen saturation and ventilator support) were generally similar across studies. Risk of bias was assessed as low for the trials by Peek, Bein, and Zapol, and high for the trial by Morris. The reviewers were unable to perform a meta-analysis due to clinical heterogeneity across studies. The Morris and Zapol trials were not considered to represent current standards of care. The reviewers summarized the outcomes from these

studies (findings described individually above). They concluded: “We recommend combining results of ongoing RCTs with results of trials conducted after the year 2000 if no significant shifts in technology or treatment occur. Until these new results become available, data on use of ECMO in patients with acute respiratory failure remain inconclusive.”

Schmidt (2015) conducted a systematic review of studies reporting outcomes for extracorporeal gas exchange, including both ECMO and ECCO<sub>2</sub>R, in adults with acute respiratory failure.<sup>[27]</sup> The review identified 56 studies, of which four were RCTs, seven were case-control studies, and 45 were case series. Two of the RCTs evaluated ECCO<sub>2</sub>R in ARDS patients, while the other two evaluated ECMO in ARDS. One RCT evaluating ECMO in ARDS was from the 1970s and was noted to have significant methodologic issues. The second RCT evaluating ECMO in ARDS was the CESAR trial (described above). The reviewers have reported that retrospective cohort studies of ECMO using more updated technology reported high rates (approximately 60% to 80%) of short-term survival. The RCTs reporting on ECCO<sub>2</sub>R in ARDS patients included those by Morris (1994) and Bein (2013). As noted in the Randomized Controlled Trials section below, the Morris trial was stopped early due to futility. In the second RCT of ECCO<sub>2</sub>R in ARDS (Bein), the number of ventilator-free days did not differ significantly between groups.

Zampieri (2013), reported the results of a systematic review and meta-analysis evaluating the role of VV ECMO for severe acute respiratory failure in adults.<sup>[28]</sup> The authors searched for RCTs and observational case-control studies with severity-matched patients that evaluated the use of ECMO in severe acute respiratory failure in adults. Three studies were included in the meta-analysis that comprised a total of 353 patients of whom 179 received ECMO, one RCT (CESAR trial,<sup>[29]</sup> described below) and two case control studies<sup>[30, 31]</sup> with severity-matched patients. For the primary analysis, the pooled in-hospital mortality in the ECMO-treated group was not significantly different from the control group (OR, 0.71; 95% CI, 0.34 to 1.47; p=0.358). Both nonrandomized studies included only patients treated for H1N1 influenza A infection, which may limit their generalizability to other patient populations.

Zangrillo (2013), reported the results of a systematic review and meta-analysis that evaluated the role of ECMO for respiratory failure due to H1N1 influenza A infection in adults.<sup>[32]</sup> The meta-analysis included eight studies, all observational cohort studies, that included 1357 patients with confirmed or suspected H1N1 infection requiring ICU admission, 266 (20%) of whom were treated with ECMO. The median age of those receiving ECMO was 36 years, with 43% men. In 94% of cases, VV ECMO was used, with VA ECMO used only in patients presenting with respiratory and systolic cardiac failure or unresponsive to VV ECMO. The median ECMO use time was 10 days. Reported outcomes were variable across the studies, but in a random-effects pooled model, the overall in-hospital mortality was 27.5% (95% CI, 18.4% to 36.7%), with a median ICU stay of 25 days and an overall median length of stay of 37 days.

Hirshberg (2013) conducted a review of evidence regarding ECMO use in critically ill adults with ARDS.<sup>[33]</sup> Studies included in the review were limited to the two most recent years' publications. A total of 12 case series and 12 review articles were considered in the assessment. Successful ECMO treatment of ARDS secondary to H1N1 was reported within the literature; however, studies were limited in the discussion of alternative modes of ventilation or other interventions. In addition, two national registry reports published conflicting conclusions regarding H1N1-related ARDS and ECMO treatment.<sup>[30, 31]</sup> The authors made key observations, concluding:

- Increase in ARDS survival over time makes historical controls and comparisons to determine the efficacy of ECMO challenging and likely unreliable.
- Scientifically credible evidence to support the use of ECMO in the routine management of patients with ARDS is lacking.
- The use of ECMO as a salvage therapy in practice biases the interpretation of case series results.

Additional systematic reviews<sup>[34, 35]</sup> were identified which also noted the heterogeneous nature of patients studied as well as a lack of well-designed randomized trials comparing ECMO to other therapies.

There are some older systematic reviews on H1N1-related respiratory distress/failure published prior to 2013 that will not be described in detail here.<sup>[36-38]</sup>

### **Randomized Controlled Trials**

Combes (2018) reported the results of an RCT comparing the use of ECMO to conventional treatment for severe ARDS.<sup>[39]</sup> The ECMO group included 124 patients and the control group included 125. Sixty-day mortality was 35% and 46% in the ECMO and control groups, respectively, and the relative risk was 0.76 (95% CI 0.55 to 1.04,  $p=0.09$ ). From the control group, 35 patients who had refractory hypoxemia crossed over to the ECMO group. Of these, 20 (57%) died. Differences in frequency of complications between groups included a greater number of bleeding events leading to transfusions, more cases of severe thrombocytopenia, and fewer cases of ischemic stroke in the ECMO group. One limitation of this study involves the risk of bias due to crossover, such as carryover, period effects, and missing data. Another limitation of this study was the possible confounding factors associated with non-standardized treatment protocols between the two groups. The ECMO group underwent percutaneous venovenous cannulation and was given heparin in varying doses to achieve a targeted activated PTT time; the control group was not exposed to these variables. In contrast, the control group was exposed to ventilatory treatment, neuromuscular blocking agents, and prone positioning that differed from the comparative group, limiting the generalizability of any findings.

The Xtravent study, reported by Bein (2013), randomized patients with ARDS to a strategy of low tidal volume ventilation combined with ECCO<sub>2</sub>R ( $n=40$ ) or a conventional ventilation strategy ( $n=39$ ).<sup>[22]</sup> For the study's primary end point (28 and 60 ventilator-free days), there was no significant difference between treatment groups. However, the interventions evaluated are better characterized as pumpless extracorporeal lung assist devices (CO<sub>2</sub> removal only), making them less relevant to the evaluation of ECMO.

Peek (2010) conducted an RCT and economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation in adults with severe respiratory failure (CESAR trial).<sup>[29]</sup> Patients were 18 to 65 years old with severe, but reversible, respiratory failure (defined as a Murray score  $\geq 3.0$ ), or uncompensated hypercapnia with a pH  $<7.20$ . The primary study outcome was death or severe disability at six-month follow-up. Secondary outcomes included: duration of ventilation, use of high frequency/oscillation/jet ventilation, use of nitric oxide, prone positioning, use of steroids, length of intensive care unit stay, and length of hospital stay - and (for ECMO patients only) mode (VV or VA), duration of ECMO, blood flow and sweep flow. Exclusion criteria were: high pressure ( $>30$  cm H<sub>2</sub>O for peak inspiratory pressure) or high FIO<sub>2</sub> ( $>0.8$ ) ventilation for more than seven days; intracranial bleeding; other contraindication to limited heparinization; or any contraindication to continuation of active treatment. A total of 180

patients (90 in each arm) were randomized from 68 centers. Data from 87 patients in the conventional management (CM) group and 68 patients from the ECMO group were available at six-month follow-up. Authors reported significantly better mortality and disability rates in the ECMO arm compared to the CM arm six months after randomization, (33/90 [36.7%] versus 46/87 [52.9%] respectively). However, these outcomes included the 22 patients who were randomized to the ECMO treatment arm, but who never received ECMO due to death or improvement with conventional treatment. A comparison of patients actually treated with ECMO to those treated with CM did not result in a significant difference between groups [33/68 (49%) versus 46/87 (52.9%) respectively] at six-month follow-up. The study is further limited by a lack of standardized mechanical ventilation management in the CM group.

Two early small RCTs were identified that compared some form of extracorporeal support with standard care. They are described here briefly. Morris (1994) reported the results of an RCT comparing a ventilator strategy of low-frequency positive-pressure ventilation (LFPPV) ECCO<sub>2</sub>R (ECCO<sub>2</sub>R; n=21) to standard care (n=19) in adults with ARDS.<sup>[25]</sup> In this trial, there was no significant difference in 30-day survival between groups (33% for LFPPV-ECCO<sub>2</sub>R patients vs 42% for conventional ventilation patients; p=0.8), although the trial was stopped early due to futility. The clinical practices in this trial are likely not representative of current practice. In a very early RCT, Zapol (1979)<sup>[26]</sup> compared mechanical ventilation with partial VA bypass (n=42) to conventional ventilation (n=48) in individuals with severe hypoxemic respiratory failure.

## Nonrandomized Studies

Numerous nonrandomized comparative and non-comparative studies have been published regarding outcomes in patients treated with ECMO for cardiac or respiratory failure due to a variety of conditions. Several key nonrandomized comparative studies are reviewed below:

Shaefi (2021) published a multicenter retrospective cohort study examining ECMO receipt versus no ECMO receipt within seven days of ICU admission in mechanically ventilated patients with severe respiratory failure due to COVID-19.<sup>[40]</sup> The study used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID) and performed a target trial emulation that included 130 ECMO-treated patients and 1,167 patients who did not receive ECMO. During a median follow-up of 38 days, 45 (34.6%) patients who received ECMO and 553 (47.4%) patients who did not die (adjusted HR 0.55, 95% CI 0.41 to 0.74).

Davies (2009), published an observational series to characterize patients with influenza A (H1N1)-associated ARDS treated with ECMO.<sup>[41]</sup> A total of 61 patients with confirmed H1N1 influenza (n=53) or influenza A, not otherwise subtyped (n=8) and an additional 133 influenza patients treated with mechanical ventilation were included in the study. Compared to the 133 patients who improved with conventional care, median days of mechanical ventilation were longer in patients treated with ECMO (18 [9 to 27] vs. 8 [4 to 14] days, p=0.001), median ICU days were higher (22 [13 to 32] vs. 12 [7 to 18] days, p=0.001) and ICU mortality was higher (23% vs. 9%, p=0.01). At the point of data assessment, 48 (71%) of the ECMO patients had survived to ICU discharge, 14 (21% mortality) had died, and six remained in the ICU. Of the 22 patients still remaining in the hospital, 16 had survived to ICU discharge. By comparison, the non-ECMO cohort had 13% mortality at the time of reporting, suggesting no observable benefit with ECMO treatment.

Additional nonrandomized studies regarding the use of ECMO for a variety of conditions have

been published<sup>[42-51]</sup>, with a majority of studies reporting an overall survival to discharge ranging from 50% to 68%<sup>[45, 46, 52-54]</sup> in patients with severe respiratory failure. Overall, these publications suggest some survival benefit with ECMO treatment; however, these studies should be interpreted with caution due to the following limitations:

- Results from small sample sizes ( $n < 100$ ), limit the ability to rule out the role of chance as an explanation of study findings.
- Results from studies with short-term follow-up (hospital discharge) are not adequate to determine the durability of the treatment effect.
- A lack of comparison group, without which it is not possible to account for the many types of bias that can affect study outcomes.

### **Section Summary: Acute Respiratory Failure**

Although evidence to establish standardized protocols regarding patient selection and treatment strategies is lacking, there is sufficient evidence to suggest the use of ECMO in patients with severe acute respiratory or cardiac failure may provide some survival benefit when the risks associated with mechanical ventilation are very high. Questions remain about the generalizability of findings from the CESAR trial and nonrandomized study results to other patient populations, and further clinical trials in more specific patient populations are needed.

### **ECMO IN ADULTS AS A BRIDGE TO TRANSPLANTATION**

The evidence related to the use of ECMO as a bridge to transplantation consists of three large nonrandomized comparative studies and small case series ranging from 13 to 46 patients.<sup>[47, 52, 55-65]</sup> Some retrospective studies have compared outcomes for patients treated with and without ECMO preoperatively. Overall, these studies report success rates of 81 to 87%, and one-year survival rates of 74 to 100%. Adverse events reported in these series include: renal failure requiring temporary dialysis, pulmonary infections, sepsis, tracheostomy required, and distal digital ischemia. Since ECMO is generally determined to be medically necessary as a bridge to transplant, the published studies are not described in detail. Of note, three large studies are described below.

Fukuhara (2018) performed a retrospective analysis of the use of ECMO as a bridge to heart transplant in patients whose data were collected by the United Network of Organ Sharing (UNOS).<sup>[66]</sup> Of 25,168 recipients identified between 2003 and 2016, 104 were bridged with ECMO and 6,148 were bridged with a continuous-flow left ventricular assist device (CF-LVAD). Differences between the groups at baseline included younger age, more likely to have severely disabled functional status, shorter waitlist time, higher model for end-stage liver disease excluding international normalized ration (MELD-XI) score, and more frequent mechanical ventilation in the ECMO group as compared to the CF-LVAD group. Kaplan-Meier calculated estimated posttransplant survival was 73.1% and 93.1% in the ECMO and CF-LVAD groups, respectively at 90 days ( $p < 0.001$ ) and 67.4% and 82.4% in the ECMO and CF-LVAD groups, respectively at three years ( $p < 0.001$ ). Multivariable logistic and Cox regression analyses showed that for ECMO patients, the only contributor to both 90-day and three-year mortality was MELD-XI score. Limitations of this study include a difference in cohort size between the groups and a high rate of missing data.

Moonsamy (2020) also performed a retrospective analysis of ECMO as a bridge to heart transplant in patients in the UNOS database, but for procedures conducted between 2005 and 2017.<sup>[67]</sup> Of 24,905 recipients identified, 177 were bridged with ECMO, 203 were bridged with

temporary circulatory support-ventricular assist devices (TCS-VAD), and 7,904 were bridged with a left ventricular assist device (LVAD). Unadjusted posttransplant survival at one and five years was  $90 \pm 0.4\%$  and  $77 \pm 0.7\%$  for durable LVAD,  $84 \pm 3\%$  and  $71 \pm 4\%$  for all TCS-VAD types,  $79 \pm 9\%$  and  $73 \pm 14\%$  for biventricular TCS-VAD, and  $68 \pm 3\%$  and  $61 \pm 8\%$  for ECMO. According to the propensity-matched pairwise comparisons, ECMO had significantly poorer outcomes ( $p=0.019$ ) than all TCS-VAD, which had similar outcomes to LVAD ( $p=0.380$ ). According to the Cox analysis, ECMO was a predictor of posttransplant mortality compared with TCS-VAD (hazard ratio [HR] 2.4, 95% CI 1.44 to 4.01,  $p=0.001$ ).

Schechter (2016) published a survival analysis comparing types of preoperative support prior to lung transplantation, using data from UNOS.<sup>[68]</sup> Included in the analysis were 12,403 adult lung transplantations from 2005 through 2013: 11,607 (94.6%) did not receive invasive support prior to transplantation, 612 (4.9%) received invasive mechanical ventilation (iMV) only, 119 (1%) received iMV plus ECMO, and 65 (0.5%) received ECMO only. Table 2 shows the cumulative survival for patients at six months, one year, and three years, by support prior to transplantation. Compared to patients with no invasive support, patients receiving iMV with or without ECMO had an increased mortality risk. The mortality of patients receiving ECMO alone was not significantly different from patients receiving no support at three years. A limitation of the study is related to the use of registry data, in that complications due to the bridge strategy and certain details, such as equipment and technique of ECMO, are not available. In addition, underlying demographic differences are not represented in the comparisons.

**Table 2. Cumulative Survival among Patients Undergoing Lung Transplantation, by Type of Support (Schechter 2016)**

Support	N	6 Months	1 Year	3 Years
No support	11,607	89.4%	84.2%	67.0%
Invasive mechanical ventilation only	612	79.9%	72.0%	57.0%
Invasive mechanical ventilation plus ECMO	119	68.1%	61.0%	45.1%
ECMO only	65	75.2%	70.4%	64.5%

ECMO: extracorporeal membrane oxygenation.

Jayarajan (2014) evaluated survival rates of ECMO and mechanical ventilation (MV) treatment as a bridge to heart-lung transplantation (HLT).<sup>[69]</sup> The primary study outcome was risk-adjusted all-cause mortality. Of 542 adult patients who received HLT between 1995 and 2011, 15 (2.8%) received ECMO and 22 (4.1%) received MV as a bridge to transplantation. At 30-day survival, the ECMO group had worse survival than the control group (patients who did not receive either ECMO or MV) (20% vs. 83.5%, respectively). Similar results were reported at 5-year survival (20% vs. 47.4%, respectively;  $p<0.001$ ). Both ECMO (HR 3.820,  $p=0.003$ ) and MV (HR 2.011,  $p=0.030$ ) were independently associated with mortality. The authors concluded that HLT recipients receiving ECMO or MV as a bridge to transplantation had increased short and long-term mortality and that additional studies were needed in order to establish optimal treatment protocols and patient selection criteria for ECMO as a bridge to HLT.

## ECMO IN ADULTS WITH REFRACTORY CARDIOGENIC SHOCK

### Systematic Reviews

Zavalichi (2020) performed a systematic review of studies of VA ECMO for patients with cardiogenic shock due to myocardial infarction.<sup>[70]</sup> Nine observational studies with a total of

1,998 adult patients were included. The quality scores of the included studies ranged from 5 to 9, with a mean quality score of 7 (medium-to-high quality). The survival rate at discharge ranged from 30.0% to 79.2%. Rates of acute kidney failure were reported in only three studies and ranged from 24% to 47%. Other reported complications included hypoxic ischemic encephalopathy (75% and 45.7% in the two reporting studies), gastrointestinal bleeding (3.6% in one study) and multiple organ failure (48.8% and 39.1% in the two reporting studies).

Biancari (2018) performed a systematic review and meta-analysis of patients requiring postcardiotomy VA-ECMO.<sup>[71]</sup> A total of 31 studies, 25 of which were considered good quality, were included in the analysis and with a total of 2,986 patients. The mean age of patients was 58.1 years. Hospital survival was 36.1%, which was not influenced by study quality. The mean duration of ECMO was not associated with hospital survival. The weaning rate from VA-ECMO, pooled rate of reoperation for bleeding, and major neurological event were 59.5%, 42.9%, and 11.3%, respectively. Rates of lower limb ischemia, deep sternal wound infection/mediastinitis, and renal replacement therapy were reported as 10.8%, 14.7%, and 47.1%, respectively. Patients stayed in the intensive care unit for a mean of 13.3 days. From the 11 studies that reported Kaplan-Meier estimates of one-year survival including operative deaths, the pooled one-year survival rate after postcardiotomy VA-ECMO was 30.9%. Limitations of this analysis include that many of the included studies were small and retrospective and used heterogeneous procedures.

Wang (2018) reported the results of a meta-analysis of 20 observational studies of ECMO for postcardiotomy cardiogenic shock.<sup>[72]</sup> A total of 2,877 patients were included in the analysis. The pooled rates of one-year survival and midterm survival were 34.0% and 24.0%, respectively. Leg ischemia, redo surgery, renal failure, neurologic complications, and infection were reported in 18.0%, 14.0%, 50.0%, 57.0%, 16.0%, and 31.0% of patients, respectively. Commonly reported risk factors of in-hospital mortality were age greater than 65 years, pre-ECMO or post-ECMO blood lactate, renal insufficiency, a longer duration of ECMO, and neurologic complications.

Xie (2015) reported on a meta-analysis evaluating VA ECMO for cardiogenic shock and cardiac arrest that included observational studies and clinical trials with at least 10 adult patients.<sup>[35]</sup> Twenty-two studies, all observational, with a total of 1199 patients (12 studies [n=659 patients] with cardiogenic shock; five studies [n=277 patients] with cardiac arrest; five studies [n=263 patients] with both patient types) met inclusion criteria. Across the 16 studies (n=841 patients) that reported survival to discharge, the weighted average survival was 40.2% (95% CI 33.9% to 46.7%). Across the 14 studies that reported 30-day survival, the weighted average survival was 52.8% (95% CI 43.9% to 61.6%), with similar survival rates at three, six, and 12 months across studies that reported those outcomes. Across studies that reported on cardiogenic shock only, the weighted average survival to discharge was 42.1% (95% CI 32.2% to 52.4%,  $I^2=79%$ ). Across all studies, complications were common, most frequently acute kidney injury (pooled incidence 47.4%, 95% CI 30.2% to 64.9%,  $I^2=92%$ ), followed by renal dialysis (pooled incidence 35.2%, 95% CI 23% to 47.4%,  $I^2=95%$ ) and reoperation for bleeding (pooled incidence 30.3%, 95% CI 1.8% to 72.2%,  $I^2=98%$ ). However, the authors noted that it is uncertain that the complications were entirely due to ECMO, given the underlying illness in patients who receive ECMO.

### **Randomized Controlled Trials**

Ostadal (2023) published results of a multicenter RCT that compared immediate



implementation of VA-ECMO (n=58) to an initially conservative therapy that permitted downstream use of VA-ECMO (n=59), in patients with either rapidly deteriorating or severe cardiogenic shock.<sup>[73]</sup> The composite primary end point was death from any cause, resuscitated circulatory arrest, and implementation of another mechanical circulatory support device at 30 days. The composite primary end point was similar between the two treatment groups and occurred in 37 (63.8%) and 42 (71.2%) patients in the immediate VA-ECMO and the no early VA-ECMO groups, respectively (HR, 0.72; 95% CI, 0.46 to 1.12; p=0.21). VA-ECMO was used in 23 (39%) of the no early VA-ECMO patients. 30-day incidence of resuscitated cardiac arrest, all-cause mortality, and serious adverse events (sepsis, pneumonia, stroke, leg ischemia, and bleeding) were not significantly different between the two treatment groups. The authors concluded that immediate implementation of VA-ECMO in patients with cardiogenic shock did not improve clinical outcomes compared to an early conservative treatment that allowed downstream use of VA-ECMO in cases of worsening hemodynamic status.

### **Nonrandomized Studies**

Numerous nonrandomized comparative and non-comparative studies have been published regarding outcomes in patients treated with ECMO for refractory cardiogenic shock. Several key nonrandomized studies that are either large or comparative are reviewed below:

Kowalewski (2021) published a retrospective case review of 7,185 adults included in the Extracorporeal Life Support Organization registry who received VA ECMO for PCCS between January 2010 and December 2018.<sup>[74]</sup> Successful weaning from ECMO was achieved in 56.4%, and survival to hospital discharge occurred in 41.7%. Complications included kidney failure (48.9%), surgical site bleeding (26.4%), cardiac arrhythmias (15.9%), sepsis (12.1%), metabolic disorders (26.9%), and neurologic complications (9.1%).

Biancari (2021) reported survival rates among 665 patients who received VA ECMO for postcardiotomy cardiogenic shock between January 2010 and March 2018 at 17 cardiac surgery centers.<sup>[75]</sup> Of the 665 patients in the study, only 240 (36.1%) survived to hospital discharge. With a mean follow-up of 1.7 years for the overall cohort and 4.6 years for the patients who survived to hospital discharge, the five-year survival rate was 27.7% for the overall cohort and 76.9% for the cohort of patients surviving to hospital discharge. The five-year survival rate was lower in patients greater than 70 years of age (12.2% vs 34.4% in younger patients; HR, 1.84; 95% CI, 1.522 to 2.224).

Hernandez-Montfort (2020) published a report of longitudinal outcomes of patients with advanced heart failure and cardiogenic shock treated with temporary circulatory support.<sup>[76]</sup> Patients registered into the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support with continuous flow left ventricular assist devices or biventricular assist devices were analyzed. Of the 5,632 patients treated with pre-operative temporary circulatory support, ECMO was used in 1,138 cases and intra-aortic balloon pumps (IABP) were used in 3,901 cases. Patients treated with ECMO had greater need of biventricular support after durable ventricular assist devices (22% ECMO, 5% IABP, and 7% other TCS; p<0.001) and longer post-implant intensive care stays (ECMO 24 days, IABP 14 days, and other TCS 12 days; p<0.001). Propensity score matching analysis indicated ECMO was associated with a higher hazard impacting early phase survival vs. other temporary circulatory support (hazard ratio, 1.80; p<0.01) and IABP (hazard ratio, 1.65; p<0.01).

Lemor (2020) reported a retrospective comparison between ECMO and Impella placement in 6,290 patients with cardiogenic shock secondary to acute myocardial infarction.<sup>[77]</sup> Study data was derived from the National Inpatient Sample, a publicly available database of all-payer hospital inpatient stays developed by the Agency for Healthcare Research and Quality. After propensity score matching (n=450 propensity score-matched patients per treatment), in-hospital mortality was higher among patients who received ECMO (43.4% vs 26.7%, OR 2.10; 95% CI 1.12 to 3.95, p=0.021). Before propensity score matching, the incidence of acute ischemic stroke was greater in the ECMO group (OR 3.28, 95% CI 1.04 to 10.31, p=0.042), but this difference was not significant after propensity score matching (OR 5.24, 95% CI 0.60 to 45.68, p=0.134). Vascular complications were greater in ECMO-treated patients (propensity score-matched cohort OR 2.87, 95% CI 1.01 to 8.28, p=0.05).

A retrospective case series reported by El Sibai (2018) reported outcomes of patients undergoing ECMO for cardiogenic shock. Of the 922 patients included in the study, 51.0% survived to hospital discharge. Mean length of stay was 21.8 days. An association was reported between increased mortality and respiratory diseases, genitourinary diseases, undergoing an echocardiogram, and presenting during seasons other than Fall. A decrease in mortality was associated with injury and poisoning, certain vascular procedures, and increased length of stay.

Aso (2016) analyzed 5,263 patients from the Japanese Diagnosis Procedure Combination database who received VA ECMO during hospitalization.<sup>[78]</sup> Reasons for receiving VA ECMO included: cardiogenic shock (88%), pulmonary embolism (7%), hypothermia (2%), trauma (2%), and poisoning (1%). Among patients in the cardiogenic shock group, 33% died during VA ECMO, 40% died after weaning from VA ECMO, and 25% were discharged following weaning from VA ECMO. Multivariate logistic regression for in-hospital mortality showed an increased risk among patients 60 years of age and older, a BMI less than 18.5 kg, a BMI of 25 kg or more, ischemic heart disease, myocarditis, use of intra-aortic balloon pumping, use of continuous serial replacement therapy, and cardiac arrest.

Diddle (2015) reported on 147 patients (150 ECMO runs), treated with ECMO for acute myocarditis, who were identified from the Extracorporeal Life Support Organization database.<sup>[79]</sup> Patients in this group were relatively young (median age, 31 years) and were most often treated with VA ECMO (91%). Of the cohort, 101 (69%) were decannulated from ECMO and 90 (61%) survived to discharge. In multivariable analysis, the occurrence of pre-ECMO cardiac arrest and the need for higher ECMO support at four hours were significantly associated with in-hospital mortality (OR 2.4, 95% CI 1.1 to 5.0, p=0.02 for pre-ECMO arrest; OR 2.8, 95% CI 1.1 to 7.3, p=0.03 for increased ECMO support at four hours).

Chamogeorgakis (2013) conducted a retrospective chart review of patients with cardiogenic shock at a single center, comparing outcomes of 18 patients treated with a temporary miniaturized percutaneous ventricular assist device (mpVAD) with 61 patients who underwent ECMO.<sup>[80]</sup> The patient population was mostly male adults who had had myocardial infarction documented during the same hospital admission. Mean follow-up time was 14.3 months. No benefit from use of ECMO was found on in-hospital survival (ECMO 50.0% mp-VAD 49.2%), successful weaning off mechanical support (ECMO 33.3%, mp-VAD 19.7%), or bridging to long-term support or transplant (ECMO 27.8%, mp-VAD 31.1%).

## **Section Summary: Refractory Cardiogenic Shock**

The evidence on ECMO for adults with refractory cardiogenic shock includes meta-analyses, case series, and several observational studies. For the use of ECMO in the failure to wean from bypass population, retrospective studies and case series found some successful cases of weaning patients from ECMO in the setting of very high expected morbidity and mortality rates. However, without comparative studies, it is difficult to assess whether rates of weaning from bypass are better with ECMO than with standard care. When used for refractory cardiogenic shock, ECMO is accompanied by high mortality and complication rates. A propensity score-matched retrospective cohort study found higher rates of in-hospital mortality with ECMO compared to Impella among patients with cardiogenic shock secondary to acute myocardial infarction.

## **ECMO-ASSISTED CARDIOPULMONARY RESUSCITATION**

### **Systematic Reviews**

Scquizzato (2022) published a systematic review and meta-analysis of two RCTs and four propensity score-matched studies of patients with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation with those treated with conventional cardiopulmonary resuscitation.<sup>[81]</sup> Patients treated with extracorporeal cardiopulmonary resuscitation had higher rates of survival with favorable neurological outcome (81 of 584 patients [14%] vs. 46 of 593 patients [7.8%]; OR = 2.11; 95% CI, 1.41 to 3.15;  $p < 0.001$ ) and of survival at the longest follow-up available compared with conventional cardiopulmonary resuscitation (131 of 584 patients [22%] vs. 102 of 593 patients [17%]; OR = 1.40; 95% CI, 1.05-1.87;  $p = 0.02$ ). Survival at hospital discharge or 30 days was similar among the two treatment groups (142 of 584 patients [24%] vs. 122 of 593 patients [21%]; OR = 1.26; 95% CI, 0.95 to 1.66;  $p = 0.10$ ).

Twohig (2019) reported a systematic review and meta-analysis of the effectiveness of ECMO-assisted cardiopulmonary resuscitation (ECPR) versus conventional CPR in patients in cardiac arrest.<sup>[82]</sup> 17 papers were included, six papers compared ECPR to CPR, three papers evaluated parameters of patients that survived ECPR, and three papers evaluated both. 11 papers were graded as being at moderate risk of bias and the remainder were considered to be at either serious or critical risk of bias. One comparative study was prospective and six used propensity scoring. ECPR showed a survival benefit (OR 0.40,  $p < 0.001$ ), and a greater likelihood of being neurologically intact (OR 0.10,  $p < 0.001$ ) compared to conventional CPR. Having an initial shockable rhythm was associated with survival (OR 0.38) as was the arrest to ECPR time (mean difference -10.17 min, 95% CI -19.22 to -1.13), but high heterogeneity limits confidence in this finding.

Debaty (2017) published a systematic review and meta-analysis on prognostic factors for patients receiving ECPR following out-of-hospital refractory cardiac arrest, to inform the decision of which patients benefit most from ECPR.<sup>[83]</sup> The search included literature through September 2016. Fifteen retrospective and prospective cohort studies were included (total  $n = 841$  patients). The overall rate of a favorable outcome following ECPR was 15%, though the range among the studies was wide (0% to 50%) due to heterogeneity of inclusion criteria, outcome definition, and compliance with protocol. Favorable outcomes occurred more frequently among patients with initial shockable cardiac rhythms, shorter low-flow duration, higher arterial pH, and lower serum lactate concentration on hospital admission. No significant differences were found when age, gender, and bystander CPR attempt were evaluated.

### **Randomized Controlled Trials**

Two RCTs evaluated the use of ECPR in out-of-hospital cardiac arrest. Yannopoulos (2020) reported the results of the Advanced REperfusion STRategies for Refractory Cardiac Arrest (ARREST) trial, a small (n=30) phase 2 adaptive RCT comparing early ECPR to standard emergency department-based advanced cardiac life support (ACLS) for out-of-hospital cardiac arrest.<sup>[84]</sup> Patients were randomized to treatment groups upon arrival to the hospital. Patients without pulses who were assigned to standard ACLS were treated for at least 15 minutes after emergency department arrival or for at least 60 minutes after the 911 call; after that, declaration of death or continuation of CPR was at the discretion of the treating emergency physician. Only two patients in the standard ACLS group achieved return of spontaneous circulation in the emergency department and were admitted to the hospital. In the early ECPR group, two patients were declared dead prior to starting ECMO due to severe metabolic derangement and hypoxemia on presentation. The trial was terminated early after a planned interim analysis showed that the posterior probability of ECMO superiority exceeded the prespecified monitoring boundary. Members of the data safety and monitoring board indicated given that the primary endpoint was survival to hospital discharge, that there were ethical concerns with continuing the trial in the presence of strong evidence for efficacy. The primary outcome, survival to hospital discharge, occurred in 6 of 14 (43%) patients treated with early ECPR and 1 patient of 15 (7%) treated with standard ACLS (risk difference 36.2%, 95% CI 3.7 to 59.2, posterior probability of ECMO superiority 0.9861). One patient in the early ECPR group withdrew from the study prior to discharge and was not included in the primary endpoint analysis. Cumulative survival over six months was significantly better with early ECPR than with standard ACLS treatment (HR 0.16, 95% CI 0.06 to 0.41, log-rank test  $p < 0.0001$ ). No unanticipated serious adverse events occurred during the trial; however, the small sample size of the trial limits its ability to detect differences in safety.

Behlolavek (2022) conducted a RCT at a single-center in the Czech Republic (the Prague OHCA [out-of-hospital cardiac arrest] study) comparing an early invasive approach including ECPR to a standard ACLS approach in adults experiencing refractory out-of-hospital cardiac arrest (n=264).<sup>[85]</sup> The participants were adults aged 18 to 65 years receiving ongoing resuscitation for a witnessed out-of-hospital cardiac arrest of presumed cardiac etiology. The trial was terminated early at the recommendations of the data safety and monitoring board because the standardized test statistics for results of the primary end point (survival with minimal or no neurologic impairment at 180 day) intersected a prespecified stopping rule for futility. The authors concluded that an invasive strategy of intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcomes at 180 days as compared to standard resuscitation. The authors reanalyzed the data of the Prague OHCA trial dividing all participants into three cohorts: those who achieved prehospital spontaneous circulation (n=83), those who did not achieve prehospital spontaneous circulation and received conventional CPR (n=81), and those who did not achieve prehospital spontaneous circulation and received ECPR (n=92).<sup>[86]</sup> 180-day survival was longest in patients who achieved spontaneous circulation (61.5%) and lower in those who did not achieve spontaneous circulation (1.2% in patients with CPR and 23.9% in patients with ECPR). ECPR was associated with a lower risk of 180-day death (HR, 0.21; 95% CI, 0.14 to 0.31;  $p < .001$ ).

## **Nonrandomized Studies**

Numerous nonrandomized comparative and non-comparative studies have been published regarding outcomes in patients treated with ECMO for cardiopulmonary resuscitation. Several key nonrandomized studies that are large or comparative are reviewed below:

Park (2014) developed a predictive score for survival to discharge using a series of 152 consecutive patients who received ECPR for in-hospital cardiac arrest.<sup>[87]</sup> In this series, in-hospital death occurred in 104 (68.4%) patients. Factors significantly associated with improved survival were an age of 66 years or less, the presence of an arrest rhythm of pulseless electrical activity or ventricular fibrillation or pulseless ventricular tachycardia, shorter CPR to ECMO time, higher initial mean arterial pressure, and higher Sequential Organ Failure Assessment scores. A score developed from these factors and evaluated in a test set generated from the initial sample using a bootstrap method was associated with a sensitivity and specificity of 89.6% and 75.0%, respectively, for predicting survival to discharge. This score may help select patients for ECMO, but further validation is needed.

Maekawa (2013) reported results from a prospective observational cohort of adult patients who underwent ECPR after prolonged conventional CPR after out-of-hospital cardiac arrest.<sup>[88]</sup> The study included 162 patients, 53 in the ECPR group and 109 in the conventional CPR group. After propensity score matching, 24 patients in each group were analyzed. The survival rate was higher in the matched ECPR group (29.2%) than in the matched conventional CPR group (8.3%,  $p=0.018$ ).

Shin (2011) compared ECPR with conventional CPR in adult patients who had undergone CPR for more than 10 minutes after witnessed in-hospital cardiac arrest.<sup>[89]</sup> 406 patients were included, 85 who underwent ECPR and 321 who underwent conventional CPR. The cause of arrest was considered cardiac in most cases ( $n=340$  [83.7%]) and noncardiac (secondary to respiratory failure or hypovolemia) in the remainder ( $n=66$  [16.3%]). The decision to initiate ECPR was made by the CPR team leader. Typically, the ECMO device was available in the catheterization laboratory, coronary care unit, and operating room, and an ECMO cart was transported to the CPR site within 5 to 10 minutes during the day and within 10 to 20 minutes at night. After propensity score matching, 120 patient pairs were included; in the matched group, ECPR was associated with significantly higher rates of survival to discharge with minimal neurologic impairment (OR for mortality or significant neurologic deficit, 0.17, 95% CI 0.04 to 0.68,  $p=0.012$ ) and survival at six months with minimal neurologic impairment (HR 0.48, 95% CI 0.29 to 0.77,  $p=0.003$ ).

In contrast, in a single institution cohort of 122 patients with in-hospital cardiac arrest of cardiac origin with prolonged (greater than 10 minutes) conventional CPR, Lin demonstrated no survival difference between patients who had return of spontaneous breathing after ECMO and those who had return of spontaneous circulation after conventional CPR.<sup>[90]</sup> After propensity score matching, 59 patients experienced return of spontaneous breathing after ECPR and 63 patients experienced sustained return of spontaneous circulation after conventional CPR. Acute coronary syndrome was the most common etiology of cardiac arrest, occurring in 73% of the ECPR patients and 50.9% of the conventional CPR patients. In the 27 ECPR response group, eight (29.6%) patients survived to discharge, while in the conventional CPR response group, five (18.5%) patients survived to discharge. In a multivariable model, ECPR was not associated with reduced mortality (adjusted HR 0.618, 95% CI 0.325 to 1.176  $p=0.413$ ).

In an earlier prospective study, Chen (2008) compared ECPR with conventional CPR in adult patients who had undergone prolonged (>10 minutes) conventional CPR after in-hospital cardiac arrest of cardiac origin.<sup>[91]</sup> 172 patients were included, 59 in the ECPR group and 113 in the conventional CPR group. The decision to call the extracorporeal life-support team was made by the physician in charge. The average duration from the call to team arrival was five to seven minutes during the day and 15 to 30 minutes overnight. Survival to discharge occurred

in 17 (28.8%) patients in the ECPR group and in 14 (12.3%) patients in the conventional CPR group. In a multivariable logistic regression model to predict survival at discharge, use of ECPR was associated with reduce risk of death before discharge (adjusted HR 0.50, 95% CI 0.33 to 0.74,  $p=0.001$ ).

Other noncomparative case series have described the use of ECPR for refractory cardiac arrest.<sup>[90, 92-102]</sup> Overall, these studies suggest that ECPR is feasible, particularly for in-hospital cardiac arrests, although mortality rates are high.

### **Section Summary: Cardiopulmonary Resuscitation**

Evidence for the use of ECPR in cardiac arrest consists of a single RCT and meta-analyses of nonrandomized comparative studies, most of which demonstrated a survival benefit with ECPR. The ARREST trial enrolled 30 patients and found a significant difference in survival to discharge favoring early ECPR in the cardiac catheterization laboratory over standard ACLS management in the ED. However, only one patient in the standard ACLS group survived to discharge, so further studies are required to examine comparative effects on long-term survival and functional outcomes. In the other RCT, a strategy of intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcomes at 180 days as compared to standard resuscitation; however, the authors stated that "the trial was possibly underpowered to detect a clinically relevant difference." Nearly all of the nonrandomized comparative studies were retrospective and at risk of bias, limiting conclusions. Selection for ECMO in these studies was at the discretion of treating physicians, and although propensity matching was used in some studies, selection bias in the small studies may remain. Multiple unanswered questions remain about the role of ECPR in refractory cardiac arrest, including appropriate patient populations, duration of conventional CPR, and assessment of futility. Studies have begun to address the question of appropriate patient population, with results indicating that patients with an initial shockable cardiac rhythm, shorter low-flow duration, higher arterial pH, and lower serum lactate concentrations on hospital admission experienced favorable outcomes. Further study is needed to evaluate efficacy and define the population that may benefit from this treatment.

## **ECMO IN ADULTS WITH OTHER CONDITIONS**

### **Systematic Reviews**

Lazzeri (2013) evaluated the use of ECMO to improve outcomes after refractory cardiac arrest (CA).<sup>[103]</sup> Authors concluded that analyses of the available observational studies were characterized by heterogeneity and controversial results. In addition authors noted, "the impact of ECMO implantation in CA patients can be considered a clinical challenge, since it is strictly linked to the 'clinical selection of patients'", as well as the technical skills and experience of the team. The study concluded that improved outcomes from the use of ECMO, in patients with refractory CA, could not be established but that, "...optimal utilization requires a dedicated local health-care organization and expertise in the field (both for the technical implementation of the device and for the intensive care management of these patients). A careful selection of patients guarantees optimal utilization of resources and a better outcome."

In 2009, Cardarelli conducted a meta-analysis regarding the use of ECMO in adult patients in cardiac arrest or immediately after cardiopulmonary resuscitation (CPR).<sup>[38]</sup> Data was collected from observational studies published between: 1990-2007, and included 11 case series and nine case reports. A total of 135 patients were included in the analysis with a median age of 56

years (18 to 83). Overall survival to discharge in patients receiving ECMO was 40% (54 of 135 patients). Survival was notably improved in younger patients (17 to 41 years) and in patients where ECMO was used for short periods of time (0.875 to 2.3 days, odds ratio 0.2). Authors noted that major complications such as neurologic sequelae were not well described in the pooled studies.

### **Nonrandomized Studies**

Myers (2020) reported results of a retrospective analysis of adult patients treated with ECMO who had septic shock at the time of cannulation.<sup>[104]</sup> A total of 32 patients met the inclusion criteria during the seven-year study period. Median ejection fraction was 51% and median time on ECMO was 5.8 days. 13 patients (41%) survived to discharge and median survival was 14.5 days. No statistically significant subgroup differences were reported.

Ro (2018) reported the outcomes of venoarterial ECMO in 71 adult patients with septic shock.<sup>[105]</sup> Of the 11 patients (15.5% of the total) that were successfully weaned from ECMO, five survived to discharge. This was compared to the rate of successful weaning in 253 cardiogenic shock patients receiving ECMO, which was 45.5% ( $p < 0.001$ ). Lactate levels, both pre- and six-hours-post-procedure, were significantly higher in the nonsurvivors ( $p = 0.002$ ).

Huesch (2018) published a retrospective chart review of outcomes, length of stay, and discharge destination of adult patients treated with ECMO between 2007 and 2015.<sup>[106]</sup> From a review of Pennsylvania state-regulated hospitals, 2,948 consecutive patients admitted for respiratory, cardiac, cardiac arrest, or uncategorized based on administrative data were treated with ECMO. The average observed death rate was 51.7%. Of patients who survived, 14.6% went home to self-care and 15.2% went to home health care. Readmission was reported for 43.8% within one month and 60.6% within one year.

Sauneuf (2017) evaluated patients admitted to the ICU for pheochromocytoma crisis. A total of 34 patients were included, 14 of whom received ECMO.<sup>[107]</sup> 90-day mortality was not significantly different between patients who were or were not treated with ECMO, despite the ECMO group having higher severity scores at admission.

Ramanathan (2017) analyzed data from the Extracorporeal Life Support Organization Registry database of patients treated with ECMO for community-acquired pneumonia and in 2019 of patients treated with ECMO for adenoviral pneumonia.<sup>[108, 109]</sup> Their data came from a greater than 10-year period, over which the number of patients treated with ECMO increased. Of the community-acquired pneumonia patients (a total of 1,055 patients), 66% survived. Duration of mechanical ventilation prior to extracorporeal membrane oxygenation, lower arterial pressure, fungal pneumonia, and advancing age were all factors indicated as predictors of mortality via a multiple regression analysis. Of the adenoviral pneumonia patients (a total of 542 patients), overall mortality was 58% overall (307/529 patients), and when divided by age, 86.4% for neonates (108 of 125), 49% for children (158 of 327), and 49% for adults (41 of 83).

Dangers (2017) reported the outcomes from 105 patients implanted with VA ECMO for acute decompensated heart failure at one ICU.<sup>[110]</sup> One-year survival was 42%. Independent predictors of one-year mortality were determined with multivariable analyses to be pre-extracorporeal membrane oxygenation Sequential Organ Failure Assessment score of more than 11, idiopathic cardiomyopathy, cardiac disease duration greater than two-years pre-ECMO, pre-ECMO blood lactate greater than 4 mmol/L.

Other nonrandomized studies reported outcomes following ECMO for trauma<sup>[111]</sup>, as a bridge to long-term left ventricular assist device or durable mechanical circulatory support <sup>[112, 113]</sup>, as post-cardiovascular surgery support<sup>[114]</sup>, ischemic heart disease<sup>[115]</sup>, COVID-19<sup>[116]</sup>, and others<sup>[117]</sup>.

## ADVERSE EFFECTS OF ECMO IN ADULTS

### Systematic Reviews

Abruzzo (2022) performed a systematic review of venous thromboembolic events in adults receiving ECMO support in patients with cardiac and respiratory dysfunction.<sup>[118]</sup> This review included studies that were published over the past 15 years, primary or original research publications, full text articles, and relevance to the research topic. This study reported that ECMO-supported patients not only experienced high rates of venous thrombosis (VT) and venous thromboembolism (VTE), ECMO was also a positive predictor for VTE. The study found that anticoagulation is critical for prevention and treatment of thromboses in patients on ECMO but can also increase complications including bleeding risk. Severe bleeding is a very common complication that is seen in patients supported by ECMO and can require multiple blood transfusions. Due to the lack of knowledge and literature centered on this topic area, currently there are no official guidelines for prompt diagnosis by screening or to optimize prevention and treatment of VTE in this specific population.

Thongprayoon (2019) performed a systematic review and meta-analysis on the incidence and mortality risk of acute kidney injury in patients receiving ECMO.<sup>[119]</sup> A total of 41 studies met the inclusion criteria, including 10,282 patients receiving ECMO. Studies were only included if they reported acute kidney injury using standard definitions including RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease: Improving Global Outcomes) classifications, severe acute kidney injury requiring renal replacement therapy (RRT), and mortality risk of AKI among adult patients (age  $\geq 18$  years old) on ECMO. The pooled estimated incidence of acute kidney failure and severe acute kidney failure requiring RRT while on ECMO were 62.8% (95%CI: 52.1% to 72.4%) and 44.9% (95%CI: 40.8% to 49.0%), respectively. In patients receiving RRT for acute kidney injury, the pooled OR was 3.73 (95% CI, 2.21 to 4.99).

A systematic review by Fletcher-Sandersjö (2018) analyzed the incidence, outcome, and predictors of ECMO-associated intracranial hemorrhage in adult patients. 25 articles met inclusion criteria. In the included studies, the incidence of intracranial hemorrhage was between 1.8 and 21%. For patients who developed intracerebral hemorrhage, relative risk of mortality was 1.27 to 4.43 compared to those that did not.

Zangrillo (2013) conducted a systematic review and meta-analysis regarding outcomes and complications related to ECMO.<sup>[120]</sup> Studies reporting complications and mortality in 100 or more patients were included in the analysis. The primary outcome was mortality at the longest follow-up date, while secondary outcomes were fatal and non-fatal complications. A total of 12 studies were included (1763 patients) with ECMO treatment utilized for acute respiratory failure, cardiogenic shock, or both. The most common ECMO-associated complications were as follows:

- renal failure requiring continuous venovenous hemofiltration (52%)
- bacterial pneumonia (33%)
- any bleeding (33%)



- oxygenator dysfunction requiring replacement (29%)
- sepsis (26%)
- hemolysis (18%)
- liver dysfunction (16%)
- leg ischemia (10%)
- venous thrombosis (10%)
- central nervous system complications (8%)
- gastrointestinal bleeding (7%)
- aspiration pneumonia (5%)
- disseminated intravascular coagulation (5%).

The overall mortality at 30-day follow-up was 54%, with 45% of fatal events occurring during ECMO and 13% occurring after ECMO.

Cheng (2013) conducted a systematic review and meta-analysis evaluating complications related to ECMO treatment of cardiogenic shock or cardiac arrest in adult patients.<sup>[121]</sup> Studies reporting complication rates and including at least 10 patients were included for a total of 20 studies (1,866 patients). The pooled estimated complication rates with 95% confidence were as follows:

Complication	Pooled Estimated Complication Rate (%)	95% Confidence Interval
Acute kidney injury	55.6	35.5% to 74.0%
Renal replacement therapy	46.0	36.7% to 55.5%
Rethoracotomy for bleeding or tamponade in postcardiotomy patients	41.9	24.3% to 61.8%
Major or significant bleeding	40.8	26.8% to 56.6%
Significant infection	30.4	19.5% to 44.0%
Lower extremity ischemia	16.9	12.5% to 22.6%
Neurologic complications	13.3	9.9% to 17.7%
Fasciotomy or compartment syndrome	10.3	7.3% to 14.5%
Stroke	5.9	4.2% to 8.3%
Lower extremity amputation	4.7	2.3% to 9.3%

In addition, 17 studies reported survival to discharge with a pooled survival rate of 534 of 1,529 patients, ranging from 20.8% to 65.4%. The authors concluded that, “although ECMO can improve survival of patients with advanced heart disease, there is significant associated morbidity with performance of this intervention.” Similar complication rates were reported in a 2014 review by Xie.<sup>[35]</sup>

Given the significant complications associated with ECMO, additional studies are needed which compare ECMO to other standard treatments, such as mechanical ventilation (MV), in order to better define appropriate patient selection criteria and treatment strategies in these high-risk patients.

### Nonrandomized Studies

Numerous nonrandomized studies were identified which demonstrated that ECMO was associated with other serious complications<sup>[7, 122]</sup>, including, but not limited to: brachial plexus injury<sup>[123]</sup>, thoracic complications (including bleeding and pneumothorax)<sup>[124-126]</sup>, infection<sup>[127-130]</sup>

(e.g., systemic, surgical site, respiratory tract, urinary tract), limb ischemia<sup>[131]</sup>, neurological injury<sup>[132, 133]</sup>, abdominal compartment syndrome<sup>[134]</sup>, groin lymphocele<sup>[135]</sup>, chronic kidney failure<sup>[136]</sup>, and major vascular complications<sup>[133, 137]</sup>. Furthermore, a recent analysis of ELSO database indicated that ECMO-related infections were higher in adults compared to children and neonates (30.6 vs. 20.8 vs. 10.1 infections per 1,000 ECMO days, respectively).<sup>[138]</sup>

## PRACTICE GUIDELINE SUMMARY

### AMERICAN THORACIC SOCIETY-LED INTERNATIONAL TASK FORCE

An International Task Force consisting of clinicians from academic centers active in COVID-19 patient care developed consensus suggestions on management of COVID-19 using the electronic decision-making portion of the Convergence of Opinion on Recommendations and Evidence (CORE) process.<sup>[139]</sup> The task force suggestions are based upon scarce direct evidence, indirect evidence, and clinical experience. Regarding ECMO, the Task Force made the following recommendation:

For patients with refractory hypoxemia due to progressive COVID-19 pneumonia (i.e., ARDS), we suggest that extracorporeal membrane oxygenation (ECMO) be considered if prone ventilation fails.

### AMERICAN THORACIC SOCIETY/EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE/SOCIETY OF CRITICAL CARE MEDICINE

In 2017, the American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline made recommendations on the use of mechanical ventilation in adult patients with acute respiratory distress syndrome (ARDS).<sup>[1]</sup> The guideline stated “Additional evidence is necessary to make a definitive recommendation for or against the use of extracorporeal membrane oxygenation in patients with severe ARDS.” It went on to state “we recommend evidence-based use of lung-protective ventilation and early medical management for patients with severe ARDS before use of ECMO.”

### EXTRACORPOREAL LIFE SUPPORT ORGANIZATION

The ELSO guidelines for the use of ECMO for adult respiratory failure has been replaced by the ELSO Guideline for Adult Respiratory Failure Managed with Venovenous ECMO (VV ECMO) in June 2021.<sup>[140]</sup>

#### Adult Respiratory Failure

ELSO indicated VV ECMO could be considered in patients who met one or more of the following criteria:

1. Hypoxemic respiratory failure ( $\text{PaO}_2/\text{FiO}_2 < 80$  mm Hg)\*, after optimal medical management, including, in the absence of contraindications, a trial of prone positioning.
2. Hypercapnic respiratory failure ( $\text{pH} < 7.25$ ), despite optimal conventional mechanical ventilation (respiratory rate 35 bpm and plateau pressure  $[\text{Pplat}] \leq 30$  cm H<sub>2</sub>O).
3. Ventilatory support as a bridge to lung transplantation or primary graft dysfunction following lung transplant.

Specific clinical conditions:

- Acute respiratory distress syndrome (e.g., viral/bacterial pneumonia and aspiration)
- Acute eosinophilic pneumonia
- Diffuse alveolar hemorrhage or pulmonary hemorrhage
- Severe asthma
- Thoracic trauma (e.g., traumatic lung injury and severe pulmonary contusion)
- Severe inhalational injury
- Large bronchopleural fistula
- Peri-lung transplant (e.g., primary lung graft dysfunction and bridge to transplant)

Relative contraindications for venovenous extracorporeal membrane oxygenation

- Central nervous system hemorrhage
- Significant central nervous system injury
- Irreversible and incapacitating central nervous system pathology
- Systemic bleeding
- Contraindications to anticoagulation
- Immunosuppression
- Older age (increasing risk of death with increasing age, but no threshold is established)
- Mechanical ventilation for more than seven days with Pplat > 30 cm H<sub>2</sub>O and FiO<sub>2</sub> > 90%

### Adult Cardiac Failure

ELSO, along with other organizations published guidelines regarding the use of ECMO for adults postcardiotomy, which included the following statements/recommendations:<sup>[141]</sup>

- There is no consensus regarding when to initiate ECLS in this setting. The decision to start ECLS is based on the risks and benefits of high-dose inotropes and low cardiac output compared to ECLS with its associated complications and challenges.
- It is recommended that postcardiotomy support be initiated prior to end-organ injury or onset of anaerobic metabolism (lactate level <4 mmol/L) in patients with likelihood of myocardial recovery and in the absence of uncontrollable bleeding not amenable to surgical repair (class I, level B).
- When the likelihood of native myocardial recovery is low, postcardiotomy ECLS is recommended in patients who are eligible for long-term mechanical circulatory support or a heart transplant (class I, level C).
- The early use of ECLS after cardiac surgery in a patient with an intra-aortic balloon pump and optimal medical therapy and failure to wean from bypass or marginal hemodynamics is recommended (class I, level B).

The guidelines also listed contraindications for ECMO in this setting:

- The only absolute contraindication is uncontrollable bleeding.
- Significant comorbidities, advanced age, elevated lactate level, and renal injury are risk factors associated with death and should be considered prior to ECLS initiation (class IIa, level B).
- Other relative contraindications:
  - Known cerebrovascular disease
  - Aortic valve insufficiency
  - or anticoagulation, advanced age, obesity

## Coronavirus Disease 2019 (COVID-19)

ELSO published guidelines in 2021 regarding the use of ECMO for COVID-19, which stated that:<sup>[142]</sup>

During the pandemic, indications for ECMO should remain unchanged. Conventional therapies for ARDS should be applied according to the standard algorithm, leading to use of ECMO after other measures, including prone positioning, have been attempted unless contraindicated. There is no evidence to support delaying ECMO when it is indicated. ECMO is recommended if the following are met:

- $\text{PaO}_2/\text{FiO}_2 \geq 150$  mm Hg and  $\text{pH} < 7.2$  with  $\text{PaCO}_2 \geq 60$  mmHg for  $>6$  hours
- $\text{PaO}_2/\text{FiO}_2 < 150$  mm Hg plus 1 of the following despite recommended measures (eg, prone positioning, neuromuscular blockade, high PEEP strategy):
- $\text{PaO}_2/\text{FiO}_2 < 80$  mm Hg for  $>6$  hours
- $\text{PaO}_2/\text{FiO}_2 < 50$  mm Hg for  $>3$  hours
- $\text{pH} < 7.25$  with  $\text{PaCO}_2 \geq 60$  mmHg for  $>6$  hours with respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep  $\text{Pplat} < 32$  cm  $\text{H}_2\text{O}$

ECMO centers should establish descriptions for levels of diminishing ECMO capacity; when capacity diminishes, selection criteria should become more stringent based on likelihood of survival. Exclusion criteria include:

- End-stage chronic organ failure without anticipated recovery and not a candidate for durable device or transplant
- Severe acute multiple organ failure with anticipated death despite ECMO support
- Severe acute neurologic injury with poor prognosis for recovery
- Additional potential contraindications:
  - Long invasive mechanical ventilation duration  $>10$  days
  - Patient/surrogate declines blood products
  - Inability to receive systemic anticoagulation
  - Ongoing CPR
  - Significant underlying comorbidities
  - Advanced age
  - Immunocompromise

## INTERNATIONAL EXTRACORPOREAL MEMBRANE OXYGENATION NETWORK

In 2014, the International ECMO Network, with endorsement by ELSO, published a position paper detailing institutional, staffing, and reporting requirements for facilities providing ECMO.<sup>[143]</sup>

## AMERICAN HEART ASSOCIATION

In 2020, the American Heart Association (AHA) issued updated guidelines on cardiopulmonary resuscitation (CPR) and emergency cardiovascular care, which included a new systematic review of the evidence for ECPR and recommendations about the use of ECPR for adults with in- or out-of-hospital cardiac arrest.<sup>[144]</sup> The systematic review identified no RCTs evaluating ECPR for cardiac arrest and variability in the inclusion and exclusion criteria of the studies was

noted, which potentially affects generalizability. The guidelines make the following recommendations related to ECPR:

“There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. In settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support” (Class IIb, level of evidence C—limited data).”

## SUMMARY

The research for extracorporeal membrane oxygenation (ECMO) for adult respiratory or cardiac failure has limitations. Despite these limitations, the research shows that ECMO for adult respiratory or cardiac failure improves health outcomes, including survival rates, compared to conventional therapy. Therefore, ECMO may be considered medically necessary as a treatment of respiratory or cardiac failure in adults when policy criteria are met.

The continuation of extracorporeal membrane oxygenation (ECMO) in adults is not clinically indicated when continued use criteria are not met. Therefore, ECMO continued use is considered not medically necessary when criteria are not met.

The use of extracorporeal membrane oxygenation (ECMO) in adults is not clinically indicated for cardiac or pulmonary failure when policy criteria are not met, or when contraindications are present. Therefore, ECMO is considered not medically necessary in these circumstances.

Due to a lack of research and clinical practice guidelines, the use of ECMO is considered investigational in all other situations.

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## CODES

Codes	Number	Description
CPT	33946	Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-venous
	33947	;initiation, veno-arterial
	33948	;daily management, each day, veno-venous
	33949	;daily management, each day, veno-arterial
	33952	;insertion of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)
	33954	;insertion of peripheral (arterial and/or venous) cannula(e), open, 6 years and older
	33956	;insertion of central cannula(e) by sternotomy or thoracotomy, 6 years and older
	33958	;reposition peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)
	33962	;reposition peripheral (arterial and/or venous) cannula(e), open, 6 years and older (includes fluoroscopic guidance, when performed)
	33964	;reposition central cannula(e) by sternotomy or thoracotomy, 6 years and older (includes fluoroscopic guidance, when performed)
	33966	;removal of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older

	33984	;removal of peripheral (arterial and/or venous) cannula(e), open, 6 years and older
	33986	;removal of central cannula(e) by sternotomy or thoracotomy, 6 years and older
	33987	Arterial exposure with creation of graft conduit (eg, chimney graft) to facilitate arterial perfusion for ECMO/ECLS (List separately in addition to code for primary procedure)
	33988	Insertion of left heart vent by thoracici incision (eg, sternotomy, thoracotomy) for ECMO/ECLS
	33989	Removal of left heart vent by thoracic incision (eg, sternotomy, thoracotomy) for ECMO/ECLS
ICD-9 PCS	39.65	Extracorporeal membrane oxygenation [ECMO]
ICD-10 PCS	5A15223	Extracorporeal Membrane Oxygenation, continuous
HCPCS	None	

**Date of Origin:** July 2014