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REVIEW

Extracorporeal membrane oxygenation in nontraumatic critical care: new horizons in resuscitation

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Abstract

Extracorporeal membrane oxygenation (ECMO) transfers blood from a large vein into a machine, oxygenates it, and then reinfuses the oxygenated blood back to the patient through a large vascular catheter. Resuscitation procedures using ECMO are known as extracorporeal cardiopulmonary resuscitation or extracorporeal life support. On one hand, the procedure is suitable for selected patients with severe respiratory diseases, cardiogenic or septic shock, intoxications, thyrotoxicosis, trauma, or cardiac arrest. On the other hand, geriatric persons with multiple diseases, end-stage malignancies, those with cardiopulmonary diseases, or dementia are not candidates for extracorporeal cardiopulmonary resuscitation (ECPR). The potential indications for ECMO are still expanding, but well-designed, multicentric studies are needed to assess benefit and harms.

Keywords

Extracorporeal membrane oxygenation; Extracorporeal cardiopulmonary resuscitation; Extracorporeal life support; Resuscitation; Survival; Cardiac arrest

1. Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) is the term used to define the treatment of a patient with venoarterial extracorporeal membrane oxygenation (VA-ECMO) in the context of refractory cardiac arrest resuscitation to institute blood circulation and tissue oxygenation following failure of conventional cardiopulmonary resuscitation (CPR) [1]. On the other hand, ECMO defines the device and application that takes on the function of these organs in life-threatening conditions of heart and lung failure. The aim is to transfer the blood from a large vein into the machine through cannulation, to oxygenate it, and then to infuse the blood into the patient through a large vascular catheter. The mechanism is similar to the procedure performed in coronary bypass surgery. Although ECMO is not capable of curing the underlying disease, it can save a patient's life temporarily [2]. Recently, the International Liaison Committee on Resuscitation recommended implementing ECPR as a rescue treatment for certain situations, both outside and within healthcare institutions, when conventional CPR fails to provide spontaneous circulation and under conditions where this approach is feasible [3]. Refractory arrest is characterized by the absence of the return of spontaneous circulation (ROSC) in five to 30 minutes after the commencement of appropriate interventions, namely, CPR and advanced cardiac life support [4, 5].

Resuscitation procedures using ECMO are known as ECPR or extracorporeal life support (ECLS) in the literature. The term ECLS is mostly used to describe VA-ECMO [6]. The main objective of ECPR encompasses the individual's complete relief, although transitions to permanent ventricular assist devices or transplanted hearts may represent potential alternatives in a subset of patients to lengthen life expectancy [7]. Despite the persistence of significant barriers to evidence following the emergence of ECMO in 1950s, the range of potential indications expanded, and the outcomes improved remarkably in the emergency setting. Likewise, there is an apparent enthusiasm for the commencement of ECMO within the earlier phases of life-threatening conditions. Nevertheless, the complexity of the application and adverse effects prevent its widespread use as a routine procedure.

Swedzky *et al.* [8] pointed out the conditions to consider a patient as a candidate for ECPR. These suggested criteria are composed of age below 65 years, shockable initial rhythm, witnessed circulatory arrest, CPR started within 5 minutes following arrest, no ROSC in 15 minutes of CPR, and serum lactate measurements lower than 12 mmol/L. Although pediatric considerations are beyond the scope of this article, many studies have provided robust data on the beneficial effects of the use of ECMO in children with critical illness such as refractory septic shock [9].

2. Technical aspects and mechanisms of ECMO, ECLS, and ECPR

The technique of VA-ECMO is well known and employed in resistant cardiogenic shock following cardiac surgery, acute coronary syndromes, myocarditis, or pulmonary embolism, and particularly, during cardiac arrest [10, 11]. Native blood circulates into the aorta from the heart and lungs, interacting with retrograde flow from the device during VA-ECMO, which creates two distinct circulations [12]. This is defined as "dual circulation" and is known to have varying contents of O_2 and CO_2 through these blood flows.

Percutaneous cannulation is associated with a lower risk of serious neurologic sequelae and less local infections compared to cut-down procedure [13, 14].

Recent advances supported the earliest intervention, including pre-hospital cannulation if possible, and emphasized that patients eligible for ECPR should be transported early (*i.e.*, load and go) for in-centre initiation ($\leq$60 minutes after collapse) [7]. Bilateral femoral cannulation appears to be associated with lower risks for peripheral limb complications, such as lower limb ischemia, thrombotic occlusion, and rupture [15]. For experienced providers, the femoral cannulation procedure can be completed in less than 10–15 minutes [4]. Limb perfusion should be monitored very carefully: clinically and using Doppler ultrasound [16]. Timing of the intervention is critical; therefore, novel standby ECMO strategies during high-risk valve replacement operations have been proposed recently [17]. Using this method, the median (IQR) cannulation time was 8 (range: 6–11) minutes, and the median (IQR) ECMO duration was 35 (range: 24–48) hours. Despite the advances in the technique used, the results of ECPR are still unclear and debated. Meanwhile, the success rates of conventional CPR are not very high, around one-sixth in-hospital and one-tenth out-of-hospital. ECPR appeared to be superior to conventional CPR for improved neurological outcomes and survival in cardiac arrest patients, although bleeding was increased [18].

The initiation of ECPR in the early period can positively affect survival in selected patients. ECMO was associated with a reduction in 90-day to one-year mortality compared to conventional treatment (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.70 to 0.92; p = 0.002, I^2 = 11%) [19]. A meta-analysis in 2023 that included 36 reviews revealed that veno-venous (VV) ECMO showed a survival rate of 64.7% compared with the use of conventional mechanical ventilation, which showed a survival rate of 23.5% in patients with hypoxic respiratory failure [20].

If the time between arrest and the start of the ECMO flow can be shortened, 15–20% survival rate can be a reasonable estimate. Reducing the time between arrest and starting ECPR can positively contribute to the improvement of cerebral perfusion. In witnessed out-of-hospital arrests, ECPR has been shown to have increased neurological survival rate (29% ECPR–8.9% CPR) [21]. Large population-based studies involving this condition have not been conducted so far.

Coordination of the ECLS team and mobile device utilization in line with established protocols is necessary to yield the most effective healthcare possible to patients admitted to the hospital [6]. Recently, Cho *et al*. [22] issued Extracorporeal Life Support Organization (ELSO) consensus guidelines which pointed out five key clinical areas needing guidance:

(1) neurological monitoring,

(2) post-cannulation early physiological targets and acute brain injury,

(3) neurological therapy, including medical and surgical intervention,

(4) neurological prognostication,

(5) neurological follow-up.

A promising algorithm was offered in 2015, proposing a protocol including mechanical CPR, early percutaneous coronary intervention (PCI), peri-arrest therapeutic temperature management (TTM), and ECMO for refractory cardiac arrest (The CHEER Trial) [23]. This protocol was accompanied by a higher survival, so that discharge from hospital without sequelae was recorded in 54% of the patients. Five years later, the "2CHEER" study has validated the previous findings, ECMO used for resistant circulatory arrest demonstrates favorable survival if protocolized healthcare is provided in line with preset criteria [24].

Discharge rates with favorable neurological recovery reached 44% of the target population. After adjusting for lactate, time from collapse to ECMO flow was found to be significantly predictive of survival.

2.1 Which to use? Veno-arterial (VA) and veno-venous (VV) ECMO

Characteristics of veno-arterial (VA) and veno-venous (VV) ECMO practices are summarized in Table 1. VV-ECMO is employed to treat acute respiratory failure, while VA-ECMO is used for interventions covered by hemodynamic or cardiovascular support, such as in patients with cardiogenic shock refractory to optimal conventional treatment, and has had mixed results [25, 26]. A more complex configuration of ECMO is central ECMO, which involves a sternotomy and direct surgical cannulation of the right atrium and aorta. It is remarkable that more than 90% of the patients with respiratory failure attributed to COVID-19 underwent VV-ECMO [27].

TABLE 1. Characteristics of veno-arterial (VA) and veno-venous (VV) ECMO practices.

Veno-arterial (VA) ECMO	Veno-venous (VV) ECMO
Cardiac + respiratory support	Respiratory support
Better oxygenation capacity High afterload Considerable rate of systemic embolism Non-pulsatile circulation	Easy cannulation (double lumen catheters) Less systemic embolism Pulsatile, physiological circulation Limited oxygenation capacity (recirculation, mixing) Right ventricular volume load

ECMO, extracorporeal membrane oxygenation.

2.2 ECMO anticoagulation and antibiotics

Although routine anticoagulant use is controversial for ECMO, most centers view this practice as a prerequisite for a successful procedure [28]. Decision making for anticoagulation in ECMO patients should be pursued, balancing the thrombotic and hemorrhagic processes. An individual patient's age, comorbid diseases, and underlying medical conditions should be taken into account. Anticoagulation protocols should be tailored for each patient and monitored via activated partial thromboplastin time (aPTT) or activated clotting time (ACT), and if necessary, alternative tools like anti-Xa and viscoelastic assays (VEA) [29].

Anticoagulation is reported to be used more frequently in non-traumatic cases than in trauma. Wood *et al*. [30] found that significantly fewer patients in the no-anticoagulation cohort experienced complications, especially hemorrhagic and thrombotic events, when compared to those in the anticoagulation cohort. Zhang *et al*. [31] also reported that bleeding and thrombosis occurred commonly during the procedure, and optimal anticoagulation strategies have not been elaborated yet. Recent reports have also pointed out that the usage of anti-factor Xa activity to adjust the efficacy of unfractionated heparin (UFH) is necessary, since it has significant correlation with the UFH administration, which plays a role in preventing thromboembolic events [32].

Since clot formation in arterial cannulas may lead to microembolism, certain monitoring tests are used to monitor hemostasis once patients are initiated on anticoagulation; tests include but are not limited to prothrombin time, activated partial thromboplastin time, D-dimer, platelet count, and antithrombin plasma-free hemoglobin test—the latter only to monitor hemolysis [33, 34]. The anticoagulation is usually initiated after 24 h in patients with a high risk of bleeding or those undergoing surgery; otherwise, it is started at the initiation of ECMO [35]. UFH is the most used anticoagulation agent, although low molecular weight heparin (LMWH) can be used since its pharmacokinetic properties are more predictable [29]. Supplementation with antithrombin can be proposed if levels are lower than 50% to 70% to optimize heparin efficacy. During ECMO support, heparin or nafamostat mesilate is used for anticoagulation with a target activated partial thromboplastin time (aPTT) of 60–80 s Direct thrombin inhibitors (*e.g.*, bivalirudin) are important regimens to consider, particularly for patients with heparin-induced thrombocytopenia. Prophylactic treatment with antibiotics has not showed any effect on the short-term mortality of patients receiving ECMO [36]. Nosocomial infection rates, however, appeared to have declined with antibiotics.

3. Use of ECMO in various conditions

3.1 ECMO algorithm integrated into standard CPR

In the current situation, the American Heart Association (AHA) does not support ECPR applications. Nonetheless, it can be employed in cardiac arrest patients with short-term and potentially reversible causes. Of course, studies to clarify this may involve serious ethical problems. Here, the CPR is carried out per the standard guideline recommendations. However, during CPR, the patient is very difficult to cannulate for ECMO. The targeted vein may not be available for intervention in hypotensive conditions. Ultrasound can be used, or a cut-down can be opened. Fig. 1 (Ref. [37]) illustrates an exemplary flow chart of patient selection and choice of device for patients with cardiogenic shock (CS).

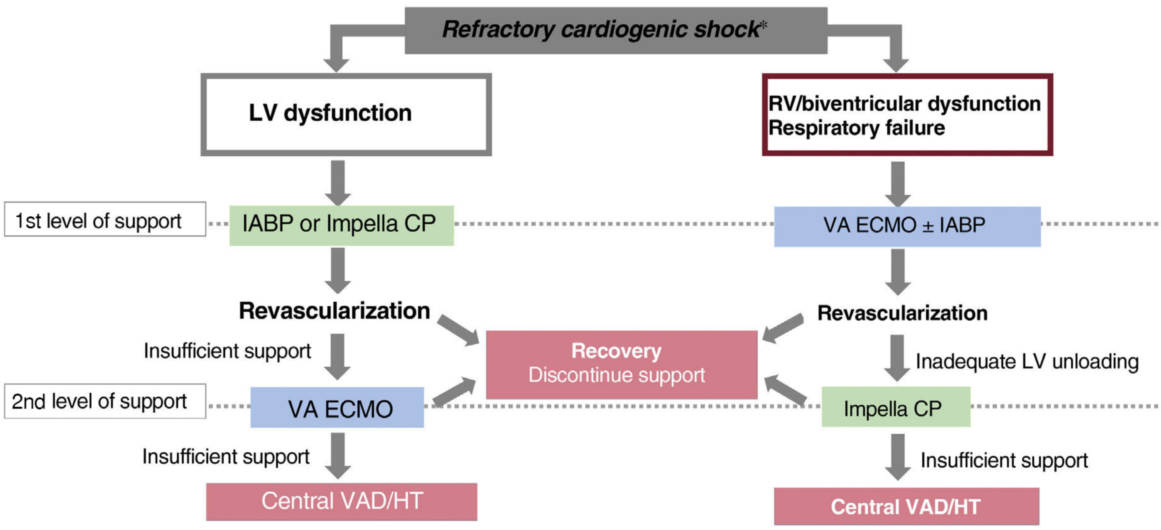

FIGURE 1. Patient selection and choice of device for patients with cardiogenic shock (CS). HT, heart transplant; IABP, intra-aortic counterpulsation balloon pump; LV, left ventricle; RV, right ventricle; VA, venoarterial; VAD, ventricular assist device (Adapted from Martínez-Sellés 2023, with permission [37]). ECMO, extracorporeal membrane oxygenation; CP, Cardiac Pump. *Systolic blood pressure (SBP) <90 mmHg for more than 30 min or inotropes to get SBP >90 mmHg, signs of pulmonary congestion and poor perfusion, and at least one of the following: altered mental state, cold clammy skin, oliguria <30 mL/h or arterial lactate >2.0 mmol/L. Refractory cardiogenic shock (CS) is CS despite vasopressors/inotropes and appropriate volume replacement.

3.2 Use of ECMO in acute respiratory distress syndrome (ARDS)

The use of ECMO in acute respiratory distress syndrome (ARDS) is known to convey a substantial morbidity and mortality. Interestingly, only insignificant changes in the mortality rate were recorded following posttraumatic ARDS since the 1980s, no geographical difference in the industrialized countries, no dependence on the ARDS definition used, and no association with injury severity, respectively (range between 20% and 25%) [38].

The working mechanism of ECMO for resting the lungs is much less damaging to the lungs compared with the traditional ventilator support. Although initial studies on respiratory failure did not achieve satisfactory results compared to conventional ventilation, survival rates were found to be around 52–75% in the 1990s and 2000s with the development of ECMO technology. Hemmila *et al*. [39] cited a survival of 52% in adults who had received ECMO between 1989 and 2003. The benefit of ECMO may have stemmed from the correction of blood gas abnormalities and the prevention of ventilator-induced lung injury (VILI). However, the nonselective utilization of this strategy is immature and deficient unless a critical assessment of attributed risks and benefits is carried out [40].

Especially in those with ARDS induced by the H1N1 outbreak, ECMO has increased survival rates of up to four-fifths in patients with advanced resistant hypoxemia, where conventional ventilator treatment has failed. These ratios in the "*Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure*" (CESAR) study made ECMO popular again as a treatment alternative, despite the methodological deficiencies in the study [41]. Expedient initiation of VV-ECMO in severe ARDS patients may be associated with a substantial reduction in VILI and improve patients with severe hypoxia. Nevertheless, more studies are required to assess the effectiveness of the procedure on the clinical course compared to traditional approaches, including prone positioning [42].

The 2020s have witnessed a surge of demand for ECMO due to the overwhelming emergence of COVID-19-related acute respiratory distress syndrome (CARDS). Between March 2020 and March 2025, almost 18.000 COVID-19 patients treated with VV-ECMO have been reported in the Extracorporeal Life Support Organization (ELSO) Registry, with a mortality rate for these patients reaching 48% [43].

Patients with COVID-19 undergoing ECMO have a high death rate, around 39% in a meta-analytic study, which is greater than that reported in influenza patients treated with ECMO [44, 45]. Patients with COVID-19 pneumonia had a higher risk of death than did patients with non-COVID-19 pneumonia (odds ratio, 1.98) [27].

Compared to survivors of non-COVID-19 ARDS treated with ECMO, the survivors in a published cohort of COVID-19 ARDS scored significantly lower on social functioning, physical functioning, and general health ($p < 0.01$, $p = 0.02$, $p < 0.01$) [46]. Patients who have recovered from intensive care treatment for COVID-19-related ARDS and have received ECMO therapy continue to experience more severe impairments in their physical, mental, and cognitive health-related quality of life. A longer ECMO duration may improve outcomes in this selected patient population.

A German study evaluated quality of life and mental health status in survivors after VV-ECMO for COVID-19-related ARDS between 2020 and 2022 and reported that during the study period, 44.3% survived after VV-ECMO for COVID-19 ARDS [47]. Quality of life and mental health status after VV-ECMO in the course of COVID-19 was significantly lower than the non-COVID-19 population who had also undergone VV-ECMO. In a multicentric Australia study between February 2020 and May 2024, use of ECMO was highest during the Delta wave (3.6%, median duration 18 days) [48].

Sklienka *et al*. [49] abstracted data and published findings on the uses of ECMO in CARDS. They found that "full-awake" VV-ECMO was preferred over mechanical ventilation, with concerns over barotrauma and patient refusal of intubation and mechanical ventilation. The mortality rate for CARDS patients treated with full-awake VV-ECMO (including only patients from cohort studies) reached 33.0%, notably lower than the 48% reported for CARDS patients treated with VV-ECMO in the ELSO registry.

3.3 Use of ECMO in poisoning

ECMO can be utilized as an adjunctive supportive therapy, like other most treatment modalities in intoxications. Hemodynamics and oxygenation can be achieved with ECMO until the toxin is excreted or metabolized from the body. ECMO does not neutralize or eliminate the toxin. Nonetheless, it supports the healing of the affected end-organ and saves time. It has been used as a primary remedy in case series with tricyclic antidepressant poisoning and other cardiovascular drugs, including antiarrhythmics. Not every poisoned patient is a candidate for ECMO, since it is not a risk-free application [50]. In many cases, ECMO has been administered just before cardiac arrest, which contributes to high survival rates. For example, analysis of a large international data registry (Toxicology Investigators Consortium Core Registry) revealed that ventricular dysrhythmia following severe prolongation of the corrected QT interval (QTc) associated with acute drug overdose is prevented with ECMO [51].

Earlier reports disclosed that most reported drug-intoxicated cases had cardiovascular problems, and the resultant cardiac failures were effectively treated by ECMO [52]. Cardiogenic shock and arrhythmias can arise from cardiovascular toxins, including β-blockers, calcium channel blockers, and tricyclic antidepressants, while severe respiratory failure can result from respiratory toxins, such as opioids and paraquat. ECMO is used as a bridge to recovery, transplantation, or adjunctive therapies, and the survival rates vary widely. Severe acidosis (pH $<$7.1) and the need for dialysis before ECMO predict mortality [53]. It is reasonable to utilize ECLS techniques such as VA-ECMO for life-threatening β-blocker poisoning with cardiogenic shock refractory to pharmacological interventions and refractory cases with calcium channel blockers and local anesthetics [54]. An analysis of adult cases in the Extracorporeal Life Support Organization (ELSO) registry demonstrated that opioids (45.3%) were most commonly implicated, followed by neurologic drugs (*e.g.*, antidepressants, antiepileptics) (14.5%) and smoke inhalation (13.7%) [55]. Almost one-fifth of the patients (19.7%) had a pre-ECMO cardiac arrest. Of note, survivors were cannulated significantly earlier than non-survivors (25 h versus 123 h; p = 0.02). Importantly, most patients (71.2%) survived to hospital discharge. These findings also implied that ECMO may be a viable treatment for severe poisoning when it is administered before cardiovascular collapse. Accordingly, guidelines recommend VA-ECMO and ECPR as a rescue therapy for intoxication [54]. The use of VA-ECMO for poisoning is increasing [56]. There is scarce data to compare VA-ECMO with supportive care in patients with poisoning. Observational studies showed that patients with cardiac arrest or refractory shock due to poisoning who are managed with VA-ECMO have lower mortality than other patients treated with VA-ECMO and lower mortality compared with poisoned patients treated with standard critical care and antidotal therapy alone [57]. Of note, patients with hematological and metabolic poisons had higher mortality on VA-ECMO compared with patients with other poisonings [56]. In addition, the use of VV-ECMO for refractory respiratory failure due to poisoning was associated with a clinically significant survival benefit compared to other respiratory diagnoses requiring the procedure.

ECMO is used as a bridge to recovery, transplantation, or adjunctive therapies, and the survival rates vary widely [53]. Recently, awake ECMO has been employed as a successful method to provide an optimum physical status before lung transplantation in patients with paraquat and diquat poisoning [58, 59]. Likewise, ECMO is also among the armamentarium against acute liver failure, in conjunction with renal replacement therapy, therapeutic plasma exchange, and vasopressors [55].

3.4 ECMO bridging to lung transplantation (LTx)

ECMO bridging to lung transplantation (LTx) is suitable for patients awaiting this procedure when other measures of respiratory support fail or when hemodynamic instability occurs, the disease is severe, and the donor organ is readily available [31]. Elderly patients (>65 years) or reversible multiple organ failure are not contraindications for this phenomenon, ECMO bridging LTx. ECMO functions as a bridge to LTx by maintaining pulmonary and circulatory stability in critically ill patients awaiting donor organs [60]. It also aids in evaluating marginal donor organs and supports patients through acute complications after the procedure.

3.5 Use of ECMO in pulmonary embolism (PE)

PE is among the most common causes of death all over the world, for which emergency thrombolysis, surgical interventions, and other treatment modalities are employed with varying success rates. In the last decades, many case series and meta-analyses have underlined the critical role of ECMO in the management of PE [61, 62]. VA-ECMO has been particularly beneficial to restore hemodynamic stabilization, thereby serving as a bridge to definitive treatments (*e.g.*, thrombectomy) in these patients.

4. Reservations and drawbacks of ECMO

Reservations and drawbacks of ECMO include methodological errors and bias in publications, costly application, the need for competent staff, and unclear effect on in-hospital mortality. Potentially, while ECMO is expected to reduce short-term death rate in those with acute respiratory failure, weaknesses of the data prevent us from achieving this result [63]. Conditions in which ECMO proved unsuccessful in acute respiratory failure include advanced age, long-term ventilator treatment before ECMO, multiple organ failure, low compliance of pre-ECMO respiratory system, and immunosuppression.

Bleeding, acute renal failure, infection, vessel obstruction-leg ischemia, and ischemic stroke are among the complications of ECMO [2]. Limb ischemia result from various mechanisms, including arterial obstruction, cannulation injury, loss of pulsatile flow, thromboembolism, venous stasis from compressive obstruction with large venous cannulas, and systemic vasoconstriction due to shock and pharmacologic vasoconstriction [64]. A recent report from a large series study indicated that combined hemostatic complications (both bleeding and thrombosis) were reported in 13.7% [49]. Indications, contraindications, and complications of ECMO in clinical practice are provided in Table 2 [65].

There are several limitations in the present study. The search strategy, selection of the database, keywords, and period of literature data may have limited the retrieved findings and approaches. This search may not include studies available in other databases and journals, and unpublished studies. In addition, technological advances have changed the availability of ECMO procedures, alternative approaches in the pre-hospital field and hospital emergency departments, and intensive care units, which may have skewed the results in a different direction.

5. Conclusions

Available data suggest that ECPR might restore circulation and facilitate tissue oxygenation in various cardiac arrest situations. In this context, ECMO acts as a time-saver between the failed organ/system and the healing process, or in decision-making. Nonetheless, it shows promising survival rates with protocolized care in patients with refractory cardiac arrest. Recent data support the use of ECMO in acute respiratory failure, cardiac arrest, and cardiogenic shock, while the potential indications for ECMO continue to expand. VV-ECMO is mostly preferred to manage acute respiratory failure, while VA-ECMO is used for interventions to treat hemodynamic or cardiovascular failure, such as in patients with cardiogenic shock refractory to optimal conventional treatment. Differences in hospital policies and national regulations may result in variations in ECMO application and results. Nonetheless, staff training is essential to ensure the high-quality performance of ECMO and ECPR.

TABLE 2. Indications, contraindications, and complications of ECMO.

ECMO Criteria	Clinical conditions and diagnoses
Indications	
	Cardiovascular arrest/collapse
	Cardiogenic shock
	Resistant hypotension
	Inadequate ventilation/ARDS
ECMO Contraindications (mostly relative)	
	Situations that are incompatible with normal life, even if the patient recovers.
	Very low weight patients (<2 kg); prematurity (<34 weeks), also be cautious if body mass index >30 kg/m^2.
	Presence of diseases that will impair quality of life (central nervous system diseases, malignancy, risk of systemic bleeding with anticoagulation).
	Patient being "too sick" even for ECMO (prolonged conventional treatment, fatal diagnosis).
	Sepsis (Be cautious for patients with The Sepsis-Related/Sequential Organ Failure Assessment Score (SOFA) >12 points.
	Lack of family consent.
Complications	
	Extremity ischemia
	Compartment syndrome
	Stroke
	Acute renal failure
	Vascular rupture
	Bleeding/coagulopathy/hemolysis
	Infection

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.

AVAILABILITY OF DATA AND MATERIALS

Data and materials are not publicly available but are available to corresponding or first authors upon reasonable request.

AUTHOR CONTRIBUTIONS

FSA and OK—conceptualization. FSA, BAO, GAO—methodology; supervision. BO, BAO—software. BO, GAO and OK—validation. FSA, OK, BO—formal analysis. BAO, OK—investigation; visualization. FSA—data curation. GAO, BO—writing–original draft preparation. GAO, BAO, OK—writing–review and editing. BAO, FSA, BO, OK—project administration. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Ozgur Karcioglu is serving as one of the Editorial Board members of this journal. We declare that Ozgur Karcioglu had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to NB.

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