Special Article

Bridging Life: The Science and Practice of ECMO in Severe Cardiopulmonary Failure

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Abstract

Extracorporeal Membrane Oxygenation (ECMO) is a life-saving intervention for patients with severe cardiopulmonary failure, providing critical support when conventional therapies are inadequate. This review aims to offer a concise, comprehensive overview of ECMO, covering its theoretical foundations, clinical applications, and recent advancements. Designed as a practical resource for medical professionals involved in ECMO care, this review also serves as a guide for those interested in exploring ECMO's role in managing respiratory and heart failure, including post-ECMO care. The review discusses the physiological mechanisms of ECMO, key clinical indications, patient selection criteria, and its evolving role in modern critical care. Common ECMO-related complications, such as thrombosis, bleeding, and mechanical failure, are highlighted, along with strategies for management and troubleshooting. Ethical considerations, including resource allocation and end-of-life decisions, are explored, as well as the psychosocial impacts on patients and their families. This review also contextualizes ECMO within current clinical practices, identifying global disparities in access to ECMO services. Looking ahead, it discusses the future of ECMO, including technological innovations and the potential for personalized treatments. By bridging theoretical principles with practical applications, this article aims to enhance understanding of ECMO's pivotal role in saving lives and improving patient outcomes.

Keywords: extracorporeal membrane oxygenation, ECMO, severe cardiopulmonary failure, cardiogenic shock

Extracorporeal membrane oxygenation (ECMO) has emerged as a critical lifesaving therapy for patients suffering from severe cardiopulmonary failure who do not respond to conventional management. Originally developed for neonatal support, ECMO technology has rapidly evolved over the past few decades, broadening its applications across multiple critical care settings for both adult and pediatric populations. The process of ECMO involves bypassing the heart and lungs, allowing the device to oxygenate blood and remove carbon dioxide outside of the body, which provides temporary support while underlying pathologies are addressed. Studies have shown that ECMO, when implemented under carefully monitored conditions, can significantly improve survival rates among patients with acute respiratory distress syndrome (ARDS) and cardiogenic shock.[1-4] However, the procedure is not without risk, as complications such as bleeding, infection, and thromboembolism remain significant challenges. This article provides an in-depth review of the science and clinical practice of ECMO, including indications, management strategies, recent advancements, and the challenges associated with its use in critical care.

A. Physiology of ECMO

ECMO operates by diverting blood from the patient's circulatory system, oxygenating it extracorporeally, and removing carbon dioxide before reinfusing it into circulation (Figure 1). This procedure alleviates strain on the patient's heart and lungs, allowing these organs to recover from conditions such as acute respiratory distress syndrome (ARDS), cardiogenic shock, or cardiac arrest.[5] There are two main ECMO modalities:

Veno-Arterial (VA) ECMO: Used primarily for cardiac failure or combined heart-lung failure. VA ECMO bypasses the heart, providing circulatory support in addition to gas exchange.[6] This modality is essential for patients experiencing cardiac shock, as it temporarily replaces cardiac function, buying time for potential recovery or additional interventions.

Veno-Venous (VV) ECMO: Primarily indicated for severe respiratory failure when the heart's function is still relatively preserved. VV ECMO diverts blood from one vein, oxygenates it, and reinfuses it through another vein. This modality addresses gas exchange while preserving the natural cardiac output, making it suitable for ARDS and other severe respiratory conditions where the heart's function remains relatively stable.[2] However, the main contraindications for VV ECMO include the inability to accept blood products, irreversible lung disease, and end-stage disease without lung transplant candidacy. These contraindications are critical in patient selection to ensure the efficacy of the treatment and avoid inappropriate use in cases where ECMO would not improve outcomes.[7]

In cases where basic ECMO configurations provide inadequate support, more complex setups, such as hybrid and parallel configurations8, can be considered. Additionally, various cannulation sites may be utilized depending on the clinical situation.9 Selecting the most appropriate configuration is critical and requires a thorough understanding of the patient's underlying pathophysiology. Customizing the ECMO setup based on the patient's specific clinical status not only helps optimize outcomes but also minimizes potential risks.

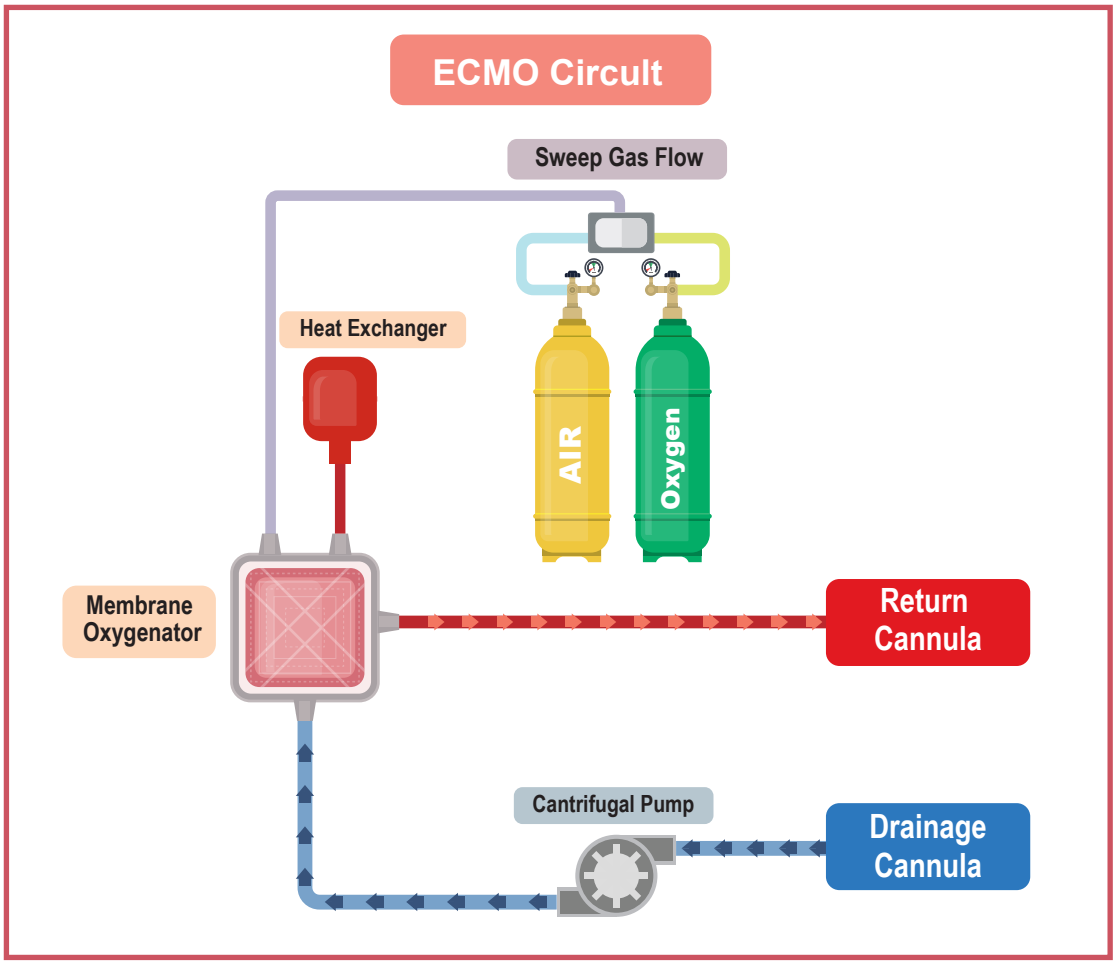

Figure 1: Extracorporeal membrane oxygenation (ECMO) Circuit

B. Indications and Patient Selection Criteria

ECMO indications have expanded over the years, but optimal patient selection remains crucial. The decision to initiate ECMO is complex and must be based on stringent criteria, as its benefits must outweigh potential risks. Common indications for ECMO include:

Acute Respiratory Distress Syndrome (ARDS): ECMO is increasingly utilized as a bridge to recovery in cases of ARDS when conventional ventilator management proves insufficient. The multicenter randomized controlled trial CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) demonstrated a significant improvement in survival without severe disability at 6 months for patients transferred to a specialized center for ECMO consideration,

compared to those who continued with conventional ventilation. Adult patients with severe but potentially reversible respiratory failure—especially those with a Murray score greater than 3.0 or a pH of less than 7.20 despite optimal conventional management—should be transferred to a center with an ECMO-based protocol. This transfer can substantially improve survival without severe disability.[10] Additionally, the landmark EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial confirmed that ECMO can enhance survival rates in severe ARDS cases, although careful patient selection remains essential for achieving the best outcomes.[1,11] Volutrauma, atelectrauma, and barotrauma are all forms of ventilator-induced lung injury that can worsen the condition of patients with ARDS.[12] To mitigate these risks, prone positioning and lung-protective ventilation are essential ARDS therapies that have consistently improved survival outcomes by reducing ventilator-induced damage and optimizing oxygenation in affected patients.[13]

Cardiogenic Shock and Post-Cardiotomy Shock: Cardiogenic shock is a critical condition characterized by insufficient cardiac output, leading to inadequate perfusion of vital organs despite adequate filling pressures. It is commonly defined by a cardiac index of less than 2, even when filling pressures such as central venous pressure (CVP > 10 mmHg) or pulmonary capillary wedge pressure (PCWP > 18 mmHg) are within normal limits. In these cases, the heart is unable to meet the body's metabolic demands, resulting in end-organ hypoperfusion. Indications for VA ECMO include cardiogenic shock that is refractory to optimal medical management, even in the presence of biventricular failure, concomitant respiratory failure, inadequate support from other devices, and refractory cardiac arrest. The primary goals of VA ECMO are to provide a bridge to recovery of native cardiac function, offer durable mechanical circulatory support (such as with a left ventricular assist device), or serve as a bridge to cardiac transplantation. VA ECMO is particularly valuable due to its ease of bedside implementation, its ability to support both the left and right ventricles, and its capacity to provide respiratory support. VA ECMO can be used to stabilize circulation and has been shown to improve survival rates in patients suffering from severe heart failure or myocardial infarction. By providing temporary circulatory and respiratory support, ECMO allows time for the patient to stabilize, enabling additional interventions such as coronary artery interventions or implantation of a ventricular assist device (VAD) that may be necessary for long-term recovery.[3,4] However, while VA ECMO is a powerful tool in managing cardiogenic shock, certain contraindications must be considered. These include irreversible cardiac injury, end-stage disease, and mechanical limitations such as severe peripheral vascular disease, moderate to severe aortic regurgitation, or aortic dissection. Other contraindications include factors that pose a high risk of poor outcomes, such as advanced age, prolonged shock, septic shock, and the inability to effectively anticoagulate the patient. In such cases, ECMO may not offer the expected benefits, and the risks of complications may outweigh the potential for recovery.

Acute Pulmonary Embolism and Cardiac Arrest: ECMO's rapid application can support circulatory function and oxygenation in cases of massive pulmonary embolism or during refractory cardiac arrest. Early deployment in these situations has been associated with improved neurological outcomes, emphasizing the importance of prompt patient selection.[14,15]

Other emerging uses include ECMO for COVID-19-related respiratory failure, highlighting its value during the pandemic.[16,17] Since ECMO involves invasive techniques and high costs, patient selection must consider comorbidities, prognosis, overall goals of care and balance risks and benefits, as complications, including bleeding, thromboembolism, and infection, remain significant concerns. Recent guidelines stress the importance of a multidisciplinary approach to ECMO candidacy, ensuring that the intervention aligns with the patient's clinical trajectory and anticipated recovery potential.

C. ECMO Circuit, Current Clinical Protocols and Guidelines in ECMO Implementation

In clinical practice, ECMO usage is guided by strict protocols designed to maximize patient safety and outcomes. The Extracorporeal Life Support Organization (ELSO) has established standardized guidelines to assist healthcare providers in deciding when and how ECMO should be implemented. Key factors include:

Timing of Initiation: Optimal timing is crucial; studies suggest that early ECMO initiation in cases of severe ARDS or cardiogenic shock can lead to better outcomes than delayed interventions.[1,18]

Cannulation Techniques and Management: Proper cannulation is essential for ECMO effectiveness. There are three main cannulation techniques: percutaneous, open, and hybrid, each with its own set of advantages and challenges, depending on the patient's condition and the experience of the ECMO team. The choice of cannulation site (femoral vs. jugular) and cannula size depends on the patient's size, vessel size/condition, and the level of support required. For VA ECMO, larger cannulas may be necessary for higher flow rates, and femoral artery and vein cannulation is often preferred for ease of access and support of higher flow. On the other hand, for VV ECMO, jugular vein access is more commonly used to optimize drainage and blood return, with smaller cannulas typically required. Selecting the correct cannula size ensures adequate flow and reduces the risk of complications such as inadequate patient support, hemolysis, vascular injury, distal artery ischemia, and venous congestion. Larger cannulas may cause distal artery ischemia by increasing resistance, while smaller cannulas may fail to provide adequate flow, leading to insufficient oxygenation or perfusion. Additionally, improper venous cannulation can result in venous congestion, leading to complications like increased pressure in the venous system. The common configurations for VV and VA ECMO involve jugular vein to femoral vein cannulation for VV, and

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femoral artery to femoral vein or central cannulation for VA, depending on the support required and patient condition. In central VA ECMO, while the configuration offers stable flow, it carries risks such as increased difficulty in cannulation, higher risk of bleeding, and a need for surgical expertise. Furthermore, during VA ECMO, limb ischemia can be a concern due to reduced perfusion distal to the arterial cannula. To address this, a distal perfusion cannula is often placed to ensure blood flow to the lower limbs, reducing the risk of ischemia and improving overall circulation. The cannula length, cannula radius, and blood viscosity all affect cannula flow. Among these, the cannula radius has the greatest impact on flow, as described by Poiseuille's Law, which states that flow is proportional to the fourth power of the radius. A small change in the radius can significantly affect the flow rate, while changes in length and blood viscosity have a lesser impact. Therefore, careful consideration of cannula dimensions is critical to optimizing flow and minimizing risks. Specialized training, including ultrasound guidance, is key to optimizing cannula selection and placement, minimizing these risks, and ensuring effective ECMO support.[6]

Centrifugal pump: The working principle of a centrifugal pump is based on the rotation of an impeller, which generates centrifugal force to move fluid. Its performance is influenced by factors such as *preload* and *afterload*; high preload ensures adequate fluid intake, while the afterload affects the ease of expelling fluid. Centrifugal pumps are limited in their ability to generate *excessive positive pressures*, as they focus more on maintaining steady flow rather than achieving high pressure. However, they can create *damaging negative pressures*, which may cause cavitation or fluid damage if excessive suction occurs. Despite this, centrifugal pumps are more tolerant of small amounts of *microair* compared to other pump types, but air removal remains critical to prevent air embolism and ensure patient safety in ECMO systems.[19] Finally, *centrifugal pumps do not use occlusive movement of fluid like peristaltic* or roller pumps, as they rely on the impeller's rotation to move fluid smoothly, avoiding any direct trapping or squeezing of the fluid. This results in a continuous, non-interrupted flow.[20] Contemporary centrifugal pumps are magnetically actuated, which is associated with lower hemolysis compared to earlier models. Consequently, there has been a notable shift over the past decade from roller pumps to centrifugal pumps in clinical applications.[21,22]

Membrane Oxygenator: The membrane oxygenator is a critical component of the ECMO circuit, responsible for gas exchange—specifically, oxygen uptake and carbon dioxide clearance. It mimics the function of the lungs by facilitating the diffusion of oxygen into the blood and the removal of carbon dioxide from the blood, essentially performing the role of the lungs when they are not functioning adequately. In modern ECMO systems, the membrane oxygenator is often paired with a heat exchanger to regulate the temperature of the blood, preventing hypothermia or hyperthermia, which could complicate patient management. The oxygenator itself typically consists of a set of microporous membranes that allow for the efficient transfer of gases between the blood and the gas flowing through the oxygenator. Oxygen is added to the blood through these membranes, while carbon dioxide is diffused out, with the membranes acting as a selective barrier. The performance of the membrane oxygenator is continuously monitored through parameters such as gas exchange efficiency, pre- and post-oxygenator pressures, and blood gases. Expected ECMO pressure region findings include the following: negative drainage pressure, positive pre-membrane lung pressure, and positive post-membrane pressure (lower than the pre-membrane lung pressure). The pre-membrane lung pressures rise due to factors such as thrombus formation, increased blood viscosity, or clotting within the oxygenator, all of which can create higher resistance to blood flow. Additionally, any damage to the membrane, microair presence, or improper blood flow dynamics can also contribute to the pressure drop. These factors compromise oxygenation efficiency and can result in complications, making regular monitoring essential. In line with current guidelines, the duration of use of the membrane oxygenator is also a key consideration, as prolonged use can increase the risk of hemolysis, clot formation, and biocompatibility issues. ECMO teams are advised to routinely assess the oxygenator's performance and consider replacement if necessary, especially in long-term ECMO runs. Thus, the membrane oxygenator serves as the cornerstone for ensuring effective gas exchange in ECMO, with proper maintenance, monitoring, and appropriate selection of the oxygenator being critical in achieving optimal patient outcomes in ECMO therapy.[23]

Initiation and Monitoring: Key components of the pre-initiation checklist before starting ECMO blood flow include ensuring the patient's anticoagulant status, setting the rotations per minute (RPM) to 1500, and checking the circuit for air. The sweep gas flow should be titrated based on the patient's PCO2 and pH levels, while ECMO flow should be adjusted according to the arterial oxygen concentration. Ideally, the target pH should be between 7.35 and 7.45, achieved by adjusting the sweep gas flow rate. However, patient-specific factors may require deviations from this ideal range. For patients on VV ECMO, an acceptable PaO2 target range is 65-90 mmHg, which can be adjusted by titrating the circuit blood flow, aiming for approximately 60% of the patient's native cardiac output. Again, patient-specific factors may necessitate deviations from this goal.

Cardiac output is the primary determinant of arterial oxygen content (CaO2) as it directly affects the oxygen delivery to tissues. During ECMO, it is essential to measure circuit blood flow, as pump speed alone does not provide accurate information regarding actual blood flow. Tissue oxygenation depends critically on the DO2 (oxygen delivery) to VO2 (oxygen consumption) ratio, which should be maintained at 2:1 to prevent tissue hypoxia. The majority of oxygen in the blood is bound to hemoglobin, which plays a vital role in ensuring adequate tissue perfusion.

Carbon dioxide (CO2) removal during ECMO is mainly influenced by sweep gas flow, the partial pressure of CO2 in the patient, and the surface area of the membrane lung. The membrane lung's surface area is crucial for efficient gas exchange, as larger surface areas enhance both oxygen uptake and CO2 clearance. Oxygen uptake is most directly impacted by the rate of blood flow through the oxygenator; thus, maintaining adequate flow is essential for optimizing performance.

For patients on VV ECMO, improving right ventricular (RV) function can be achieved by reducing ventilator settings, which alleviates pulmonary vasoconstriction. However, aggressive ventilator settings that cause hypoxia, hypercarbia, or increased mean airway pressure can exacerbate RV failure by increasing afterload. In VV ECMO, pulmonary arterial catheter measurements may be skewed due to the return of oxygenated blood to the right ventricle, which artificially elevates central venous oxygen saturation (ScvO2). Additionally, saline uptake from the drainage cannula can reduce thermodilution, while the return of oxygenated blood affects the Fick equation for cardiac output. In contrast, VA ECMO improves both systemic and pulmonary perfusion, although right ventricular preload is typically reduced and left ventricular afterload is increased upon VA ECMO initiation.

For VA ECMO, safe initiation requires a thoughtful approach, incorporating patient preparation, a pre-initiation checklist, and a structured initiation process. When calculating an initial flow goal, a common practice is to use a flow index of 2.4 L/min/m². ECMO blood flow should be primarily titrated to achieve a mean arterial pressure (MAP) of 60-70 mmHg. The goal is to improve organ perfusion, which can be assessed by improvements in mixed venous oxygen saturation (SvO2) and/or central venous oxygen saturation (ScvO2), lactate clearance, mental status, liver function, and renal function. Sweep gas flow should be titrated based on the patient's arterial PCO2 and pH levels to facilitate heart rest and reduce systemic vascular resistance. Anticoagulant infusion should be started if no contraindications exist, and chest X-ray should be performed to verify the position of the cannulas. An echocardiogram should be conducted to guide further titration and assess the need for left ventricular decompression.

Left ventricular distension occurs when aortic pressure exceeds left ventricular systolic pressure, leading to myocardial ischemia, pulmonary edema, and potential thrombosis. To manage this complication, the key principles involve reducing left ventricular afterload, supporting contractility, and ensuring adequate but not excessive preload. Inotropes can be added to increase left ventricular contractility and enhance ejection. Intravenous vasodilators can also be used to optimize left ventricular ejection by reducing afterload created by high ECMO flow. Other techniques for left ventricular decompression include intra-aortic balloon pump (IABP) insertion, Impella insertion, septostomy, and direct left ventricular venting.

Systemic anticoagulation is crucial in ECMO therapy, as it reduces the prothrombin interaction between blood and the ECMO circuit, ensuring adequate blood flow and preventing clot formation. Laboratory monitoring plays a crucial role in evaluating the anticoagulant effect of heparin and ensuring that the dose is adjusted to maintain therapeutic levels within the desired range. The activated partial thromboplastin time (aPTT) is the most commonly used test to monitor heparin therapy. However, Anti-Xa is a more specific test for the anticoagulant effect of heparin, while protamine sulfate serves as the reversal agent when necessary. In managing ECMO patients, best-practice guidelines recommend using short-acting sedatives, such as propofol or dexmedetomidine, to maintain light sedation.[24] This approach, in combination with sedation targets that focus on lighter levels, helps optimize patient care and minimize complications. Notably, awake ECMO offers several benefits for select patients, including reduced risks of delirium, ventilator-induced lung injury, ventilator-associated pneumonia, and improved patient mobility.[25,26] Furthermore, approximately 50% of ECMO patients will require renal replacement therapy (RRT) after ECMO initiation.27 The "safe zone" for circuit access for RRT is located post-pump and pre-oxygenator, ensuring the proper functioning of both the ECMO and renal support systems.

Mechanical Complications of ECMO

Four common mechanical complications associated with ECMO configurations are drainage insufficiency, return obstruction, recirculation and dual circulation (differential oxygenation). The causes and management of each complication are outlined below:

- **Drainage Insufficiency:** This can lead to hypoxemia and hypotension, often due to reduced circuit blood flow. Indicators of drainage insufficiency include flow chatter or intermittent drops, which can be caused by factors such as patient agitation, hypovolemia, tension pneumothorax, dynamic hyperinflation, cardiac tamponade, intra-abdominal hypertension, high ventilator PEEP, excessive pump speed, or malpositioning of the drainage cannula. The first step in management is to reduce pump speed until blood flow stabilizes, then address the underlying cause. In some cases, additional drainage cannulas may be required.

- **Return Obstruction:** This can result from clotted membrane lungs obstructing the return flow in VA ECMO with femoro-femoral cannulation, or from cardiac tamponade in VV ECMO with femoro-jugular cannulation. Obstructions such as kinking, clamping, or compression of the return cannula can also contribute. To manage return obstruction, the circuit should be inspected from the membrane lung to the return cannula, and the obstruction should be identified and relieved.

- **Recirculation:** Recirculation is a common complication in VV ECMO, particularly when the drainage cannula is positioned in the femoral vein and the return cannula is

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placed in the internal jugular vein. The main factors influencing recirculation in VV ECMO include pump flow, cannula position, and cardiac output. One potential drawback of VV ECMO, when compared to VA ECMO, is the recirculation of oxygenated blood. Modifiable factors, such as ECMO pump speed and the distance between the drainage and return cannulas, significantly impact the extent of recirculation. Higher pump speeds and shorter distances between the cannulas lead to a greater recirculation fraction. As more oxygenated blood is drawn back into the drainage cannula, pre-membrane oxygen saturation increases, resulting in a decrease in overall patient oxygen saturation. To manage recirculation, the pump speed should be reduced, and the cannulas should be repositioned to increase the distance between the drainage and return cannulas. Additionally, any malpositioning of dual-lumen cannulas should be corrected to minimize the occurrence of recirculation.

- **Dual circulation (Differential oxygenation):** This complication occurs in patients on peripheral VA ECMO when the native lung supplies oxygen to the upper body while the ECMO circuit provides oxygen to the lower body, leading to differential oxygenation and carbon dioxide removal. In most cases, the native lungs are diseased, but the left ventricle begins to recover its function. As a result, the upper body experiences hypoxemia while the lower body experiences hyperoxemia. This discrepancy can cause hypoxemic blood to perfuse the heart and brain. The mixing point between oxygenated (red) and deoxygenated (dark) blood is influenced by heart function. The earliest signs of differential oxygenation can be detected by monitoring the oxygenation of the right upper extremity, typically through a right radial artery line or a pulse oximeter. Treatment involves addressing the underlying lung disease, providing respiratory support, and considering the potential for discontinuing VA ECMO. Diuresis may also be beneficial. If the patient is not a candidate for VA ECMO decannulation and continues to experience hypoxia, there are three potential treatment options: increasing ECMO blood flow (as a temporary measure), converting to a hybrid V-VA ECMO configuration (by placing an additional return cannula in the internal jugular vein and adjusting blood flow with partial limb occlusion clamps), or switching to a more central return configuration.

Weaning Protocols: Weaning from ECMO should be a gradual process, based on careful monitoring of oxygenation, cardiac function, and hemodynamic stability. For patients on VV ECMO, weaning involves reducing ECMO support while allowing the native lungs to take over the respiratory load. Key indicators of lung recovery in VV ECMO patients include improvements in lung imaging, respiratory compliance, and stable blood gas values under ECMO settings. In patients with irreversible lung injury, alternative exit strategies should be considered.

A commonly performed "trial-off" procedure on VV ECMO involves reducing the sweep gas flow to zero, effectively halting the circuit's involvement in gas exchange while relying on the native lungs for oxygenation and ventilation. The circuit blood flow is maintained to prevent thrombosis but no longer supports gas exchange.

Weaning from VA ECMO requires careful evaluation of heart recovery indicators, including end-organ perfusion, adequate mean arterial pressure, and a pulse pressure of at least 15 mmHg. Echocardiography plays a critical role in assessing the patient's tolerance to weaning. Key echocardiographic parameters associated with successful weaning include a left ventricular ejection fraction (LVEF) greater than 25%, an aortic velocity-time integral (VTI) greater than 10 cm, and a tissue Doppler lateral mitral annulus peak systolic velocity (TDSA) greater than 6 cm/sec.[28] One approach involves optimizing inotropic support, followed by a gradual reduction in ECMO blood flow to 50%, and then to 25% of the adequate cardiac output every 5-10 minutes, down to a flow rate of 0.5 or 1 liter per minute. Ideally, the patient should be adequately anticoagulated prior to weaning, with a bolus of heparin or direct thrombin inhibitor if necessary. Weaning is considered successful when mean arterial pressure and cardiac output remain stable while filling pressures stay consistent. For patients with irreversible cardiac injury, alternative exit strategies should be considered.

Multidisciplinary coordination is essential throughout the weaning process to avoid sudden hemodynamic shifts and ensure optimal patient outcomes.[29,30]

The implementation of standardized protocols has led to improved survival rates and decreased complications in ECMO-supported patients, underlining the importance of adherence to evidence-based practices.

D. Complications and Management Strategies

Despite its life-saving potential in critical situations, Extracorporeal Membrane Oxygenation (ECMO) is associated with a range of complications that require constant vigilance and meticulous management. These complications can significantly affect patient outcomes and are typically categorized into two main types: medical and mechanical. Both categories, if not promptly addressed, can lead to worsened prognoses. Medical complications associated with ECMO include stroke, bleeding, thrombosis, hemolysis, limb ischemia, cardiac arrest, and infection. These are often a result of the patient's underlying condition or the body's response to ECMO support. In contrast, mechanical complications are typically related to the ECMO system itself and include pump failure, gas failure, membrane lung failure, air embolism, circuit disruption, and accidental decannulation. These issues generally require immediate intervention to prevent further deterioration of the patient's condition. For patients on VV ECMO, the survival rate drops to approximately 40% in the event of a mechanical complication, compared to a baseline survival rate of 60% for standard VV ECMO cases. The following sections will explore the primary risks associated

with ECMO therapy in greater detail, as well as the management strategies that should be implemented to mitigate these complications.

Brain: Neurological complications associated with ECMO include seizures (occurring in 0.4-1.9% of cases), central nervous system (CNS) infarction (1.2-6.3%), CNS hemorrhage (2.2-5.7%), and brain death (0.9-3%).[31] These complications are linked to a reduced survival rate, which ranges from 0% to 37%. Extracorporeal cardiopulmonary resuscitation (ECPR)—the emergency use of VA ECMO in patients experiencing cardiac arrest—has the highest incidence of ischemic neurological injury. Patients requiring ECPR often present with acute cardiopulmonary failure, which can progress to cardiac arrest. Several factors contribute to the risk of neurological complications, which can be categorized into pre-ECMO and ECMO-related management factors. Pre-ECMO factors include conditions such as hypoxemia, hypotension, and acidemia, all of which can increase the likelihood of neurological injury. ECMO-related factors include anticoagulation therapy, loss of pulsatile blood flow, ischemia/reperfusion injury, fluctuations in cerebral blood flow, and the use of large neck cannulas for drainage.[32] To mitigate these risks, it is essential to minimize sedation levels, regularly review anticoagulation therapy, and conduct serial neurological assessments. Multidisciplinary evaluations should also be performed to ensure comprehensive care. Imaging studies should be considered if there are concerns regarding neurological function, particularly after the initiation of ECMO therapy.

Hemorrhage: Bleeding is a common complication in patients on ECMO. The incidence of bleeding complications varies, with bleeding occurring at the cannulation site in 10.5% of cases, in the gastrointestinal system in 4.2%, in the central nervous system in 4.8%, and due to circuit coagulopathy in 0.7%.[31] To reduce the risk of bleeding complications, several proactive measures can be implemented. These include the use of peripheral cannulation rather than central cannulation, strict management of anticoagulation to ensure that the patient's anticoagulation levels remain within the therapeutic range without exceeding it, and minimizing invasive procedures while the patient is on ECMO. When bleeding complications do occur, management strategies include mechanical compression (such as compression of the bleeding site or removal of extraneous material), surgical intervention (such as suturing or replacing an ECMO cannula), the local application of hemostyptics (agents that promote hemostasis, or the cessation of bleeding, due to their astringent properties), and the correction of coagulation factors. The decision to either continue or temporarily withhold anticoagulation therapy in such cases is a complex and challenging one, requiring careful assessment of the patient's clinical condition and ongoing bleeding risk.[33-37]

Thromboembolic Events: Circuit thrombosis and embolic events can significantly compromise ECMO effectiveness and elevate the risk of stroke. The incidence of thrombosis-related complications includes circuit thrombosis (5.6%), membrane oxygenator failure (4.4%), circuit exchange (5.1%), deep vein thrombosis (18-85%), and central nervous system infarction (3%).[31,38] An integrated, proactive approach involving regular screening for circuit thrombosis and continuous monitoring of the circuit is essential for mitigating these risks. Strict adherence to established anticoagulation protocols is crucial to prevent time spent below the therapeutic range, which can increase the likelihood of thrombus formation. Additionally, minimizing procedural complexity, using simple circuits with fewer connections, and selecting biocompatible or coated surface circuits are vital strategies in reducing the risk of life-threatening complications. Management of circuit thrombosis and related complications should include escalating anticoagulant intensity or switching to alternative anticoagulants, clot removal, and replacing affected circuit components. These interventions should be considered promptly, ideally before embolization occurs.[38-41] Furthermore, emerging technologies, such as continuous real-time monitoring systems, are being integrated into ECMO practice to improve early detection of thrombus formation, thus enhancing patient outcomes.

Hemolysis: Although there have been significant technological advancements over the past two decades, hemolysis continues to pose a challenge in ECMO therapy. The primary cause of hemolysis is shear stress induced by the ECMO circuit. This stress leads to the release of free hemoglobin, which can bind to nitric oxide, causing vasoconstriction and increasing both systemic and pulmonary vascular resistance. These changes can further impair right ventricular function. Additionally, depletion of nitric oxide may disrupt platelet and endothelial cell function, thereby facilitating the formation of microthrombi and microclots. Free hemoglobin is nephrotoxic, capable of causing tubular necrosis or precipitating within renal tubules, leading to renal injury. Plasma-free hemoglobin (pFHb) serves as an important marker for hemolysis, indicating the release of hemoglobin from red blood cells into the plasma. As hemolysis progresses, the body's ability to clear free hemoglobin via scavenger proteins like haptoglobin becomes overwhelmed, resulting in elevated pFHb levels. Moderate hemolysis is defined by a pFHb level of 50-100 mg/dL, while severe hemolysis is characterized by levels greater than 100 mg/dL. The overall incidence of significant hemolysis (pFHb >50 mg/dL) is 2.1%. Additional markers of hemolysis include elevated lactate dehydrogenase (LDH) and hemoglobinuria.[42] To prevent hemolysis, it is crucial to minimize shear stress within the ECMO circuit and ensure proper circuit function. Strategies to achieve this include preventing thrombosis, particularly at the pump head and membrane oxygenator, where reduced blood flow can damage red blood cells. The use of heparin-coated cannulas and circuits, avoiding areas of low or stagnant blood flow, and optimizing anticoagulation management are all key components of prevention. It is also essential to avoid drainage insufficiency, which can expose blood to extremely negative pressures, potentially leading to cavitation or air formation. Additionally, RPM should be

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carefully controlled to prevent excessive flow rates, and unnecessary connectors and circuit manipulation should be minimized to reduce turbulence. If hemolysis is suspected, a thorough check of the circuit should be conducted to identify any clots or malfunction in the pump or membrane oxygenator. Management may involve identifying the underlying cause, performing plasmapheresis, or replacing the ECMO circuit if hemolysis occurs without a clear etiology.

Limb Ischemia: Limb ischemia is most commonly associated with peripheral VA ECMO, with an overall incidence of approximately 3.6%.[31] It typically occurs in patients undergoing peripheral VA ECMO, where obstruction of blood flow may result from cannulation of the femoral or axillary arteries. The causes of limb ischemia include obstruction at the cannulation site, external compression, arterial trauma (such as dissection), embolization, vasospasm, and pre-existing peripheral vascular disease. Preventive strategies for limb ischemia focus on ensuring adequate perfusion to the affected limb. These strategies include the placement of a distal perfusion catheter, using a smaller return cannula, and promptly weaning off vasopressors after ECMO initiation. Diagnosis and monitoring should include regular observation for mottling, assessing regional tissue oxygen saturation using Near-Infrared Spectroscopy (NIRS), and performing ultrasonography to evaluate blood flow and detect abnormalities. In cases where ischemia persists, placement of a distal perfusion catheter distal to the cannulation site, connected to the return cannula, can help restore limb perfusion. If compartment syndrome develops, fasciotomy may be required to relieve pressure and prevent further tissue damage.[43]

Cardiac Arrest: The management of cardiac arrest in patients on ECMO depends on the type of ECMO circuit and its functionality. The first two critical steps in managing any cardiac arrest while on VV or VA ECMO are to call for help and assess the ECMO circuit. It is important to ensure that blood flow, gas flow, and the color of the blood are all appropriately maintained. For patients on VV ECMO experiencing cardiac arrest, Advanced Cardiovascular Life Support (ACLS) should be administered without additional respiratory support, while simultaneously troubleshooting the cause of the arrest. If resources and expertise permit, conversion to VA ECMO may be considered. If the underlying problem is related to the circuit, both respiratory and hemodynamic support will be necessary to stabilize the patient. In cases of cardiac arrest with VA ECMO, even in the presence of cardiac standstill, the patient may still be adequately supported depending on their overall condition and tolerance of the event. The next step is to troubleshoot the cause of the cardiac arrest, which may involve evaluating circuit function, assessing oxygenation, and reviewing the patient's clinical status.

Infections: The invasive nature of ECMO cannulation and prolonged ECMO support and ICU stay elevate the risk of infection. Data from large registry studies indicate that nosocomial infections remain a leading cause of morbidity in ECMO patients.[44,45] Infection control practices, including sterile cannulation techniques and stringent aseptic procedures, play a vital role in minimizing infection rates.[46]

Effective management of these complications is essential, as they directly impact patient outcomes. The involvement of multidisciplinary teams, including intensivists, cardiologists, and infection control specialists, is critical to achieving optimal ECMO care.

Pump failure: Pump failure in ECMO typically presents as an abrupt cessation of blood flow within the circuit, resulting in a loss of ECMO support. This failure can occur at various points: the console, the driver, or the pump head itself. Signs of pump head thrombosis include unusual noises emanating from the pump, along with palpable vibrations, and progressive hemolysis, which is indicated by elevated serum free hemoglobin levels and D-dimers.[47] Management involves discontinuing ECMO support, stabilizing the patient, and addressing the pump issue. If thrombosis or an airlock is suspected, replacement or de-airing of the pump head may be necessary. It is crucial to immediately call for assistance to ensure sufficient personnel are available to manage both the patient and the ECMO circuit. In some cases, temporarily moving the pump head to manual operation (hand cranking) can allow ECMO support to resume. Before attempting hand cranking, be sure to remove the rerun clamp. In the event of an airlock, thrombosis, or pump head disengagement, however, hand cranking is not appropriate, and other interventions should be considered. At this point, the underlying cause of the pump failure must be addressed. If there is an electrical or mechanical failure of the pump console or driver, it is important to arrange for a replacement. If the pump head is disengaged, it should be carefully removed and properly re-engaged to restore function.

Gas Failure and Membrane lung failure: The membrane lung (ML), being a foreign body with a large surface area, can activate both inflammatory and coagulation pathways in the blood. This can result in fibrin and clot deposition within the membrane lung.[48] Additionally, moisture buildup in the gas phase or debris accumulation in the blood phase can impair gas exchange and increase resistance to blood flow within the membrane lung. Flashlight examination of the membrane lung may help identify fibrin and clot deposition.

Monitoring the function of the membrane lung is critical and involves several key parameters:

1) Pre- and post-membrane lung pressures.
2) Hematologic profile, which includes DIC labs (platelet count, PT, aPTT, D-dimer, fibrinogen) and hemolysis markers (Hb, free Hb, LDH, haptoglobin).
3) Gas exchange, including oxygen uptake and CO2 removal.

Signs of membrane lung dysfunction include increased membrane pressure drop (Δ P),49 elevated pre-membrane pressure, and decreased circuit blood flow (BF). To evaluate the internal resistance of the membrane lung, the following formula is used:

ΔP = Ppre−Ppost
Normalized ΔP = (Ppre−Ppost)/ BF
where Ppre = pre-ML pressure, Ppost = post-ML pressure.

As a clot develops in the membrane lung (ML), an increase in membrane lung resistance leads to higher ΔP. To account for variations in blood flow rate (BF), monitoring ΔP adjusted for the BF rate (ΔP/BF) provides a more accurate reflection of the membrane lung resistance.

A decrease in oxygen content (VO_2) to less than 100-150 ml/min, despite maximal effective blood flow, suggests membrane lung failure. The formula for VO_2 is:
$VO_2 = BF \times (CpostO_2 - CpreO_2)$
where $CpostO_2$ = O2 content of post membrane and $CpreO_2$ = O2 content of pre membrane.

Furthermore, persistent $P_{Post\text{-}ML}CO2$ greater than 40 mmHg and a reduction in the $PpreCO_2$ - $PpostCO_2$ gradient to less than 10 mmHg (clearance of less than 10 mmHg PCO2 between pre- and post-ML blood gases), despite a maximal sweep gas flow rate, is another indicator of membrane lung failure,[50] and membrane lung exchange should be considered.

The primary causes of gas exchange issues in ECMO are membrane lung failure and gas failure. Identifying and addressing the underlying cause of dysfunction is crucial for effective management. One approach to address moisture buildup in the hollow fibers of the membrane lung is a technique called "sighing". This involves temporarily increasing the sweep gas flow rate to 10-15 liters per minute for 10 seconds to attempt to clear moisture from the system. If successful, this may improve gas exchange. However, if sighing does not resolve the issue, the membrane lung or the entire ECMO circuit may need to be exchanged. Exchanging the membrane lung or circuit requires temporarily clamping the ECMO circuit. As this procedure may compromise circulatory support, enhanced cardiopulmonary support is necessary to maintain patient stability during the exchange.[51]

Air embolism: Air embolism during ECMO support can arise from several sources, including improper ECMO priming or connection, displacement of the drainage cannula out of the vascular bed, circuit breaches allowing air entrainment, excessively negative pressures in the ECMO circuit, or a stopcock left open on a central venous line (51). The severity of the air embolism depends on the volume and location of the entrained air, ranging from mild to catastrophic consequences. When air passes through the pump head, a distinctive sound may be heard, which can serve as the first indication of air in the system. Additionally, air bubbles can interfere with blood flow monitoring, triggering low-flow alarms or activating the bubble sensor. If air accumulates in large volumes, it may cause pump stoppage and loss of ECMO support. If a significant amount of air enters the centrifugal pump head, the pump may become "deprimed," leading to an airlock that results in the loss of blood flow and places the patient at risk for cardiopulmonary decompensation. The management of air embolism involves several key actions. First, an attempt should be made to aspirate the air without interrupting blood flow. If a large volume of air is detected in the ECMO circuit, the return line should be clamped as close to the patient as possible to prevent air from entering the patient's circulation. An urgent call for assistance is necessary to ensure adequate staffing and support, as the patient will require respiratory and/or cardiac support through conventional methods. If de-airing is unsuccessful, a circuit exchange may be required. Throughout this process, it is essential to identify and address the source of the air embolism to prevent further complications.[52]

Circuit disruption: Circuit disruption refers to a break in the continuity of the extracorporeal circuit. The most common cause of noise and vibrations within the centrifugal pump is improper seating of the pump head within its housing. The correct procedure for properly inserting the pump head involves clamping the arterial line, stopping the flow, opening the securement system, properly inserting and securing the pump head, gradually increasing the rotations per minute (RPM), removing the clamp, and then increasing the RPM to the target rate. Another form of circuit disruption can occur if there is a break in the drainage or return side of the system. Negative pressure can lead to air entrainment, while positive pressure can result in blood loss. The management of circuit disruption includes several steps: the initial response should be to clamp both sides of the disruption to prevent further blood loss. An immediate call for assistance should be made to ensure sufficient staffing and support. During this time, the patient may require respiratory and/or cardiac support through conventional methods. Following stabilization, the next steps involve repairing or replacing the disrupted section of the circuit to restore ECMO function.

In conclusion, air embolism, circuit breach, console failure, and accidental decannulation are critical situations that necessitate the emergent cessation of ECMO support. The management of these issues follows similar steps as described earlier. Once the underlying problem has been addressed, ECMO support should be resumed, unless the patient is deemed ready for weaning off ECMO.[53]

E. Psychosocial Impacts and Rehabilitation Post-ECMO

Surviving ECMO treatment often entails a prolonged and intensive rehabilitation process. The psychosocial impact of ECMO, which includes both the psychological toll on patients and families and the physical rehabilitation required post-treatment, is an area gaining increased attention in recent research.

- **Psychological Effects:** Studies indicate that patients who survive ECMO support often experience post-traumatic stress disorder (PTSD), depression, and anxiety related to their ICU experience. Specialized mental health support, including cognitive-behavioral therapy, has proven effective in addressing these challenges and aiding in psychological recovery.[54-56]

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- **Physical Rehabilitation:** After intensive care for ARDS, physical limitations can persist for up to five years.57 One study found that the predicted walking distance at five years was only 66% of the expected distance for the patient's age.58 Physical therapy during ECMO support is both safe and feasible and can be performed during both VV ECMO and VA ECMO. It has also been shown to reduce the incidence of delirium. Effective rehabilitation requires coordination from a multidisciplinary team and adherence to a stepwise rehabilitation protocol. Patients typically need comprehensive rehabilitation to restore muscle strength, respiratory function, and overall physical mobility. Early mobilization programs during ECMO support have been implemented to counteract ICU-acquired weakness, ultimately shortening recovery time and improving long-term outcomes.[58,59]

- **Support for Families:** ECMO therapy can be mentally taxing for patients' families, who experience high levels of stress and uncertainty during treatment. Family-centered care programs, including regular updates and counseling, have been shown to alleviate some of this burden and improve overall satisfaction with ECMO care.[60]

Addressing psychosocial aspects of ECMO care has become a key component in holistic ECMO management, as it significantly affects both patient outcomes and family wellbeing.

F. Ethical Considerations in ECMO Utilization

The use of ECMO presents significant ethical challenges, especially due to its resource-intensive nature, high cost, and associated risks. The decision-making process surrounding ECMO involves balancing the potential benefits of life-sustaining intervention with concerns about patient quality of life, autonomy, and resource allocation. This section discusses four primary ethical considerations related to ECMO: *patient autonomy and informed consent, allocation of limited resources, quality of life and end-of-life care, and healthcare team responsibilities and moral distress.*

1. Patient Autonomy and Informed Consent

ECMO is a complex and invasive intervention that involves substantial risks, and the decision to initiate or discontinue it raises important questions about patient autonomy. In many cases, ECMO candidates are critically ill and unable to participate in decision-making, which places the responsibility on healthcare proxies or family members.

- **Challenges in Informed Consent:** ECMO is often an emergency intervention, making it difficult to achieve fully informed consent. Families may struggle to understand the implications of ECMO due to the technical nature of the therapy, and medical teams may lack the time for comprehensive discussions in acute scenarios. In such cases, providers must balance the need for urgent intervention with the ethical imperative of ensuring that families comprehend the potential outcomes and limitations of ECMO.[61,62]

- **Balancing Autonomy and Best Interests:** When patients have clear advance directives or prior preferences regarding life-support measures, these should guide ECMO-related decisions. However, the lack of prior directives is common, and in such cases, families and healthcare providers must navigate the difficult terrain of choosing ECMO based on the patient's best interests and their perceived quality of life preferences.[63-65]

2. Allocation of Limited Resources

ECMO requires substantial resources, including specialized equipment, skilled personnel, and ICU space. These limitations raise questions about how best to allocate ECMO support, particularly during crises like the COVID-19 pandemic when demand exceeds availability.

- **Prioritizing Patients During Resource Scarcity:** In times of high demand, determining which patients should receive ECMO support is ethically complex. Some institutions use criteria based on severity of illness, prognosis, or likelihood of benefit, often leading to decisions that exclude patients with comorbid conditions or those deemed to have lower chances of survival. While these criteria aim to maximize positive outcomes, they can unintentionally discriminate against vulnerable populations, raising questions of equity and justice.[66]

- **Resource Allocation Policies:** National and international guidelines, such as those from ELSO, provide frameworks for equitable ECMO resource allocation. However, these policies often need adaptation to the local healthcare context and resource availability. An ethically sound allocation policy should be transparent, consider community values, and ensure fair access to ECMO, particularly when demand outstrips capacity.[66-68]

- **Economic Implications:** ECMO is costly, and its high expense can strain healthcare budgets, especially in public healthcare systems. Decisions regarding ECMO must account for the ethical considerations of resource stewardship, balancing the potential life-saving benefits of ECMO with the financial implications for the healthcare system and society.[69,70]

3. Quality of Life and End-of-Life Care

While ECMO can extend life in critical situations, it does not guarantee a meaningful recovery. Quality of life after ECMO is variable, with some survivors experiencing long-term physical and cognitive impairments. This raises ethical questions about the appropriateness of ECMO when prognosis for recovery is poor.

- **Determining Prognosis and the Role of Palliative Care:** Predicting outcomes in ECMO patients is challenging. In cases where recovery appears unlikely or the patient may face severe post-ECMO disabilities, initiating or continuing ECMO can be ethically questionable. Integrating palliative care early in ECMO cases can offer support to families in making value-aligned decisions, helping them to weigh the benefits and burdens of continued support.[71,72]

- **End-of-Life Decisions and Withdrawal of ECMO:** Deciding to withdraw ECMO, particularly when the patient cannot participate, is one of the most ethically challenging aspects of ECMO care. These decisions often involve extensive discussions among family members and healthcare providers, with considerations of patient dignity, suffering, and the perceived quality of life post-intervention. Research suggests that clear guidelines and regular communication can aid families in coping with withdrawal decisions and the grief associated with end-of-life care.[71,73,74]

- **Avoiding 'Futile' Care:** Futility in ECMO refers to cases where the therapy is unlikely to achieve the desired therapeutic benefit. Clinicians must carefully assess whether ECMO can genuinely offer a meaningful chance for recovery, especially in patients with multiple comorbidities or progressive terminal illnesses. Providing ECMO in these situations may inadvertently prolong suffering, raising ethical concerns about non-maleficence.

4. Healthcare Team Responsibilities and Moral Distress

The high-stakes environment of ECMO can impose a significant emotional and ethical burden on healthcare providers. Moral distress arises when team members feel that they are unable to act according to their ethical beliefs, often due to institutional policies, family requests, or other constraints.

- **Moral Distress Among Healthcare Providers:** ECMO teams frequently face morally complex situations, such as providing care they perceive as futile or extending life at the request of family members when recovery appears unlikely. This distress can impact provider wellbeing and compromise their ability to deliver empathetic, patient-centered care. Regular ethical debriefings, mental health support, and a culture that respects provider perspectives can mitigate moral distress in ECMO teams.[75]

- **Ethics Consultation Services:** In difficult ECMO cases, ethics consultations provide a structured platform for discussing complex decisions, particularly those involving prolonged or potentially non-beneficial ECMO support. Ethics consultations foster interdisciplinary dialogue, allowing healthcare teams, patients, and families to explore the values and goals that should guide care. This collaborative approach is shown to reduce moral distress and enhance decision-making quality in critical care.[76]

G. Global Perspectives on ECMO Utilization

The adoption and accessibility of ECMO differ significantly across regions due to factors such as healthcare infrastructure, availability of specialized equipment, and trained personnel. ECMO usage during the COVID-19 pandemic highlighted these disparities, with some countries expanding ECMO capacity, while others faced resource limitations.

- **ECMO in High-Income vs. Low-Income Settings:** High-income countries, such as the U.S., Japan, and Germany, have dedicated ECMO centers and well-trained personnel, allowing for widespread ECMO availability. In contrast, low-income settings often face challenges related to equipment costs, limited intensive care resources, and staff shortages. Efforts are being made to develop cost-effective ECMO systems and training programs to address these disparities.[77]

- **International Collaboration and Knowledge Exchange:** Organizations like ELSO play a pivotal role in sharing ECMO expertise across borders, particularly during global health emergencies. Through webinars, training programs, and collaborative research, ELSO aims to standardize ECMO protocols internationally and improve access in resource-limited areas.[78]

- **Cultural Perceptions and Ethical Considerations:** In some regions, ECMO utilization is influenced by cultural attitudes toward end-of-life care, quality of life considerations, and ethical concerns related to resource allocation. The high costs and potential risks associated with ECMO often necessitate thorough discussions with patients and families regarding treatment goals and expectations.[79-81]

The globalization of ECMO requires an understanding of these diverse perspectives to develop equitable and culturally sensitive policies for its deployment, especially in crisis situations.

H. Technological Advancements and Future Directions in ECMO

The outcomes of ECMO treatment can vary based on the underlying cause of cardiac and/or respiratory failure, the specific indications (including ECPR), the type of ECMO used, timing, and the patient's condition. A recent meta-analysis of randomized controlled trials (RCTs) by Burrell A et al.,(2023) [82] included RCTs, quasi-RCTs, and cluster-RCTs that compared VV ECMO, VA ECMO, or ECPR with conventional support in critically ill adults. The analysis involved five RCTs with a total of 757 participants: two studies of VV ECMO (429 participants),[1,69] one of VA ECMO (41 participants),[83] and two of ECPR (285 participants).[84,85] The findings indicated that ECMO was associated with a reduction in mortality from 90

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days to one year compared to conventional treatment (risk ratio [RR] 0.80, 95% confidence interval [CI] 0.70 to 0.92; $p = 0.002$, $I^2 = 11\%$). This result remained consistent after sensitivity analysis, excluding a trial with uncertain risk of bias. Subgroup analysis showed no significant difference in outcomes across VV, VA, or ECPR modes ($p = 0.73$). Four studies reported an increased risk of major hemorrhage with ECMO (RR 3.32, 95% CI 1.90 to 5.82; $p < 0.001$), while two studies found no significant difference in favorable neurological outcomes (RR 2.83, 95% CI 0.36 to 22.42; $p = 0.32$).

In the context of cardiogenic shock, the use of a percutaneous ventricular assist device (pVAD or Impella), a catheter-based axial flow pump that directs blood from the left ventricle into the circulation, may improve outcomes.[86-89] This is especially relevant as ECMO alone can cause left ventricular overload.[90]

Technological advancements in ECMO have significantly improved patient outcomes and expanded its applications. Future developments will focus on enhancing device safety, efficiency, and adaptability to meet the growing demand in critical care. The future of ECMO lies in personalization and precision, with advancements enabling tailored care that adjusts ECMO parameters to each patient's unique physiology and condition. Personalized ECMO therapy aims to maximize efficacy, minimize risks, and improve patient outcomes. Key areas of development include *miniaturization and portability, precision in cannulation techniques, biocompatibility improvements, development of non-invasive monitoring and integrating artificial intelligence (AI) application in ECMO.*

1. Miniaturization and Portability

The first step in intrahospital ECMO transport is identifying the need for ECMO support. When assigning roles to staff members on the ECMO transport teams, roles should be allocated based on the appropriate skill set of each individual. An effective 'hub and spoke' ECMO referral model offers significant benefits, including the optimal use of limited ECMO resources, development of specialized experience and expertise, and the overall improvement of patient outcomes. The 'hub and spoke' model refers to a system where a central hospital or facility (the 'hub') provides advanced care and coordination, while smaller hospitals or satellite locations (the 'spokes') refer patients in need of specialized care to the hub. This approach allows for efficient distribution of resources and expertise across multiple facilities, ensuring that patients receive the right level of care promptly.

Advancements in miniaturization have led to the development of portable ECMO devices, making ECMO support more efficient, compact, and feasible outside of traditional ICU settings. These portable ECMO systems are particularly beneficial in transport and emergency settings, offering increased flexibility and expanding the reach of life-saving ECMO support. Portable ECMO also improves patient mobility, enabling them to be transferred between facilities without compromising the quality of care.

- **ECMO on the Move:** Transport ECMO allows patients to be stabilized and moved to specialized centers without interruption in life support. For instance, helicopter and ambulance ECMO services have been introduced in some high-resource settings, enabling timely interventions for critically ill patients and reducing mortality in transit.[91,92]

- **Wearable ECMO Prototypes:** Research is underway on wearable ECMO devices, which, though still experimental, hold promise for supporting long-term patients with reversible conditions. A wearable ECMO system could allow for early mobilization, facilitating rehabilitation and potentially reducing the length of ICU stays.[93]

Developing ECMO systems that are both cost-effective and easy to operate will be crucial in expanding access in low- and middle-income countries. Simplified, durable, and affordable ECMO devices could play a pivotal role in making life-saving ECMO technology more widely available, reducing global disparities in critical care.

2. Precision in Cannulation Techniques

Cannulation is a critical procedure in ECMO, and future directions focus on imaging and navigation technologies that will allow for more precise cannulation, reducing risks and optimizing blood flow dynamics. Augmented reality (AR)-guided cannulation systems are under investigation to improve success rates in cannulation.[94]

3. Biocompatibility improvements

One of the major challenges in ECMO therapy is the risk of complications, such as clotting, bleeding, and infection, due to the artificial surfaces of the circuit components. Advances in biomaterials and surface modifications aim to improve biocompatibility and reduce adverse events associated with ECMO circuits.

- **Advanced Coatings:** New materials with heparin-like or anti-thrombogenic coatings reduce clotting risk, thereby decreasing the need for anticoagulation, which often complicates ECMO therapy. These coatings create a less reactive surface, minimizing blood activation and improving patient safety.[95-97]

- **Hybrid Oxygenators and Membranes:** Next-generation oxygenators integrate hybrid materials that better mimic human endothelial surfaces, promoting a natural blood flow and reducing shear stress. This approach aims to extend the lifespan of oxygenators, making ECMO safer and more efficient for prolonged use.[98,99]

- **Antimicrobial Coatings and Infection Control:** ECMO circuits are prone to microbial colonization, which can lead

to bloodstream infections. Antimicrobial surface modifications and the use of silver or antibiotic coatings on cannulas are under investigation to mitigate this risk, enhancing patient safety during extended ECMO therapy.[100-103]

4. Development of non-invasive monitoring

Developments in non-invasive monitoring technologies offer promising avenues to enhance ECMO safety, particularly in reducing the need for frequent blood sampling and minimizing the risk of infection and other complications.

- **Near-Infrared Spectroscopy (NIRS):** NIRS is a non-invasive monitoring tool used to assess tissue oxygenation levels. Its integration with ECMO systems allows real-time monitoring of cerebral and peripheral oxygenation, helping clinicians quickly detect issues related to oxygen delivery and perfusion.[104,105]

- **Continuous Glucose Monitoring and Metabolic Sensors:** Patients on ECMO are at high risk of metabolic dysregulation, making glucose management crucial. Continuous glucose monitoring sensors integrated into ECMO systems can provide real-time data, enabling timely interventions to maintain optimal metabolic balance.[106]

- **Wireless and Remote Monitoring:** Advances in wireless sensors allow for remote monitoring of ECMO patients, enabling continuous oversight and early intervention in case of adverse events. This technology is particularly valuable in resource-limited settings, where it may allow fewer staff to monitor more patients effectively, improving resource efficiency.[107]

5. Integrating artificial intelligence (AI) application in ECMO

Artificial Intelligence (AI) is transforming the landscape of healthcare, and ECMO is no exception. AI's potential to enhance decision-making, improve patient monitoring, and predict outcomes is gradually reshaping ECMO management. Key areas where AI is making a difference in ECMO include **predictive analytics, clinical decision support systems (CDSS), automated monitoring and control, personalized patient management and reducing cognitive load/ moral distress.** These applications of AI help to increase the precision, safety, and efficiency of ECMO, ensuring that interventions align with patient needs and minimize risks.

5.1 Predictive Analytics for Patient Outcomes

AI-driven predictive analytics leverage vast amounts of patient data to forecast outcomes, identifying early signs of improvement or deterioration. This capability is critical in ECMO, where timely intervention can greatly impact patient survival and recovery.

- **Mortality and Morbidity Predictions:** Predictive algorithms analyze historical patient data to provide estimates of mortality and morbidity risks, supporting clinicians in setting realistic expectations and making informed decisions. By training on patient data such as vital signs, laboratory results, and ECMO-specific parameters, machine learning models can predict adverse events, such as multi-organ failure or cardiac complications, allowing for proactive interventions.[108-111]

- **ECMO Duration Forecasting:** Predicting the necessary duration of ECMO therapy can improve resource allocation and patient management. AI models trained to evaluate factors influencing ECMO duration help clinicians anticipate how long a patient might require support, informing decisions about weaning and optimizing ICU resources.[112-114]

5.2 Clinical Decision Support Systems (CDSS)

AI-based CDSS provide real-time recommendations based on data analysis, making ECMO management more efficient and accurate. These systems aim to bridge knowledge gaps and reduce variability in ECMO practices across different clinicians and institutions.

- **Weaning and Withdrawal Decision-Making:** One of the most challenging aspects of ECMO care is determining the optimal time for weaning or withdrawal. AI-driven CDSS can assess patient stability and trends, offering evidence-based recommendations for ECMO discontinuation. These systems incorporate physiological data and clinical outcomes to assist clinicians in balancing the benefits and risks of continued ECMO support and readmissions after ECMO hospitalization.[115,116]

- **Personalized Treatment Adjustments:** CDSS can tailor ECMO parameters to individual patient needs. For instance, AI algorithms can optimize blood flow rates and oxygenation levels, ensuring that each patient receives appropriate support based on their unique physiological profile. By continuously adjusting parameters, CDSS can reduce complications and improve patient outcomes.[117]

5.3 Automated Monitoring and Control

Real-time monitoring and automatic adjustments are essential in ECMO, where patient stability can fluctuate rapidly. AI enables the automation of these processes, relieving clinicians of continuous manual monitoring and increasing response speed.

- **Anomaly Detection:** AI-driven monitoring systems can detect abnormalities in real-time by analyzing trends in vital signs, blood gas levels, and ECMO circuit parameters. For example, these systems can alert clinicians to issues

such as cannula malposition, air embolisms, or impending clot formation, enabling prompt action to prevent complications.[118]

- **Closed-Loop Control Systems:** In advanced ECMO systems, AI can provide closed-loop control, adjusting parameters such as pump speed and oxygenation automatically based on continuous feedback from patient monitoring data. This reduces the need for constant manual adjustments and can stabilize patient physiology more effectively. Closed-loop systems help manage patient status during times of fluctuation, promoting safer and more consistent ECMO delivery.[119,120]

5.4 Personalized Patient Management

Personalization is a critical goal in ECMO, as each patient's response to treatment can vary widely. AI is advancing ECMO by allowing treatment to be adapted to each individual's unique needs and risk profile.

- **Stratifying Risk and Customizing Protocols:** AI can help stratify ECMO patients based on risk profiles and personalize treatment protocols. For example, patients with specific comorbidities may benefit from unique anticoagulation strategies, which can be adjusted by AI-driven algorithms to minimize bleeding or thrombotic complications. This precision medicine approach ensures that each patient receives optimal care that aligns with their specific risks and needs.[121]

- **Genomics and Biomarker Integration:** In the future, AI may enhance ECMO therapy by integrating genomics and biomarkers to personalize treatment. Genetic factors that influence blood clotting or inflammation could help predict individual risks, guiding tailored anticoagulation or anti-inflammatory strategies. Researchers are exploring genetic and biomarker indicators to predict a patient's response to ECMO. This personalized approach could enable clinicians to identify patients who are likely to benefit from ECMO, allowing for customized intervention plans based on individual susceptibility to complications.[122-125] By combining biomarker data with AI models, clinicians may soon optimize ECMO interventions to improve patient outcomes.[126,127]

5.5. Reducing Cognitive Load and Moral Distress

AI can reduce the cognitive burden on ECMO teams by automating routine tasks and providing structured, data-driven guidance. This, in turn, can alleviate moral distress associated with difficult decisions, such as those related to end-of-life care.

- **Supporting Clinical Judgment in Complex Cases:** AI-based tools can serve as adjuncts to clinical judgment in high-stakes ECMO cases. By providing data-driven recommendations, these tools can offer additional confidence to healthcare providers, especially in cases involving ethical dilemmas or resource constraints. This helps teams feel more supported in making challenging decisions, improving overall team morale and patient care quality.[118]

- **Enhancing Training and Simulation:** AI can play a role in training new ECMO specialists through simulation programs that use real patient data to create realistic ECMO scenarios. AI-driven simulations can prepare clinicians for high-stress situations, improving their response accuracy and decision-making speed when faced with real-life ECMO emergencies.[128,129]

Challenges and Future Directions in AI for ECMO

While AI offers significant potential, challenges remain in integrating AI seamlessly into ECMO workflows. Issues related to data privacy, algorithm transparency, and the need for large, high-quality datasets are critical to address.

- **Data Privacy and Security:** The use of AI in ECMO relies on extensive patient data, which raises concerns regarding privacy and security. Ensuring that AI models comply with privacy regulations is crucial, especially given the sensitive nature of patient health information.

- **Algorithm Transparency and Trust:** Clinicians may be hesitant to rely on AI without understanding how algorithms reach their conclusions. Therefore, creating transparent AI systems that clinicians can interpret and trust is essential for widespread adoption in ECMO.

- **Building Comprehensive Datasets:** Effective AI models require large datasets that represent diverse patient populations. Creating robust, comprehensive datasets that include patients from varied backgrounds will be crucial to developing generalizable AI models that can be applied in ECMO centers worldwide.

I. Conclusion

ECMO has become an indispensable intervention in the management of severe cardiopulmonary failure, offering a life-sustaining bridge for patients unresponsive to conventional therapies. As its technology has evolved, ECMO is now widely applied across diverse critical care settings worldwide. However, its successful implementation requires skilled personnel, careful patient selection, and diligent management of potential complications.

Looking ahead, ECMO's role in critical care is poised to expand with ongoing technological advancements, such as AI integration, wearable ECMO systems, and precision medicine. These innovations hold the promise of transforming ECMO into a more personalized and accessible therapy, with the potential to improve patient outcomes and broaden its global reach. Nevertheless, addressing the ethical and logistical

challenges associated with ECMO remains paramount. It is essential to ensure equitable access, mitigate disparities, and consider the psychosocial impacts on both patients and their families.

Ethical considerations surrounding ECMO demand a nuanced approach, balancing patient autonomy, fair resource allocation, and the prioritization of quality of life. As the technology continues to advance, healthcare providers must navigate these complexities with compassion and transparency, fostering open dialogue with patients and families. Additionally, emerging decision-support tools, such as predictive analytics, could help improve the ethical alignment of ECMO care by guiding informed, patient-centered decisions.

The integration of AI into ECMO represents a significant leap forward, with the potential to enhance decision-making, optimize patient monitoring, and refine ECMO delivery. While challenges remain, continued research and innovation will likely improve the precision and accessibility of ECMO, making this life-saving therapy more effective and widely available. As the field evolves, international collaboration and ongoing advancements will ensure ECMO continues to provide hope, better survival rates, and improved quality of life for the most critically ill patients.

References

1. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378(21):1965-75. doi: 10.1056/NEJMoa1800385.
2. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. 2011;365(20):1905-14. doi: 10.1056/NEJMct1103720.
3. Benenati S, Toma M, Canale C, et al. Mechanical circulatory support in patients with cardiogenic shock not secondary to cardiotomy: a network meta-analysis. *Heart Fail Rev.* 2022;27(3):927-34. doi: 10.1007/s10741-021-10092-y.
4. Megaly M, Buda K, Alaswad K, et al. Comparative analysis of patient characteristics in cardiogenic shock studies: differences between trials and registries. *JACC Cardiovasc Interv.* 2022;15(3):297-304. doi: 10.1016/j.jcin.2021.11.036.
5. Lim H. The physiology of extracorporeal membrane oxygenation: The Fick principle. *Perfusion*. 2023;38(2):236-44. doi: 10.1177/02676591211055971.
6. Makdisi G, Wang IW. Extra corporeal membrane oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis.* 2015;7(7):E166-76. doi: 10.3978/j.issn.2072-1439.2015.07.17.
7. Harnisch LO, Moerer O. Contraindications to the initiation of veno-venous ECMO for severe acute respiratory failure in adults: a systematic review and practical approach based on the current literature. *Membranes (Basel).* 2021;11(8):584. doi: 10.3390/membranes11080584.
8. Shah A, Dave S, Goerlich CE, et al. Hybrid and parallel extracorporeal membrane oxygenation circuits. *JTCVS Tech.* 2021;8:77-85. doi: 10.1016/j.xjtc.2021.02.024.
9. Sorokin V, MacLaren G, Vidanapathirana PC, et al. Choosing the appropriate configuration and cannulation strategies for extracorporeal membrane oxygenation: the potential dynamic process of organ support and importance of hybrid modes. *Eur J Heart Fail*. 2017;19 (Suppl 2):75-83. doi: 10.1002/ejhf.849.
10. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009;374(9698):1351-63. doi: 10.1016/S0140-6736(09)61069-2.
11. Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive *Care Med.* 2023;49(7):727-59. doi: 10.1007/s00134-023-07050-7.
12. Gattinoni L, Quintel M, Marini JJ. Volutrauma and atelectrauma: which is worse? *Crit Care*. 2018;22(1):264. doi: 10.1186/s13054-018-2199-2.
13. Qadir N, Sahetya S, Munshi L, et al. An update on management of adult patients with acute respiratory distress syndrome: an official american thoracic society clinical practice guideline. *Am J Respir Crit Care Med*. 2024;209(1):24-36. doi: 10.1164/rccm.202311-2011ST.
14. Farmakis IT, Sagoschen I, Barco S, et al. Extracorporeal membrane oxygenation and reperfusion strategies in high-risk pulmonary embolism hospitalizations. *Crit Care Med*. 2024;52(10):e512-e21. doi: 10.1097/CCM.0000000000006361.
15. Davies MG, Hart JP. Current status of ECMO for massive pulmonary embolism. *Front Cardiovasc Med*. 2023;10:1298686. doi: 10.3389/fcvm.2023.1298686.
16. Bertini P, Guarracino F, Falcone M, et al. ECMO in COVID-19 patients: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth.* 2022;36(8 Pt A):2700-6. doi: 10.1053/j.jvca.2021.11.006.
17. Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med.* 2020;8(5):518-26. doi: 10.1016/S2213-2600(20)30121-1.
18. Morisson L, Duceau B, Do Rego H, et al. A new machine learning algorithm to predict veno-arterial ECMO implantation after post-cardiotomy low cardiac output syndrome. *Anaesth Crit Care Pain Med.* 2023;42(1):101172. doi: 10.1016/j.accpm.2022.101172.
19. Chan KM, Wan WTP, Ling L, et al. Management of circuit air in extracorporeal membrane oxygenation: a single center experience. *ASAIO J.* 2022;68(3):e39-e43. doi: 10.1097/MAT.0000000000001494.

20. Han D, Leibowitz JL, Han L, et al. Computational fluid dynamics analysis and experimental hemolytic performance of three clinical centrifugal blood pumps: Revolution, Rotaflow and CentriMag. *Med Nov Technol Devices*. 2022;15:100153. doi: 10.1016/j.medntd.2022.100153.
21. Nakazawa T, Makinouchi K, Takami Y, et al. The effect of the impeller-driver magnetic coupling distance on hemolysis in a compact centrifugal pump. *Artif Organs.* 1996;20(3):252-7. doi: 10.1111/j.1525-1594.1996.tb04434.x.
22. Puentener P, Schuck M, Kolar JW. The Influence of impeller geometries on hemolysis in bearingless centrifugal pumps. *IEEE Open J Eng Med Biol.* 2020;1:316-23. doi: 10.1109/OJEMB.2020.3037507.
23. Mouzakis FL, Kashefi A, Hima F, et al. Has Extracorporeal Gas Exchange Performance Reached Its Peak? Membranes (Basel). 2024;14(3):68. doi: 10.3390/membranes14030068.
24. Devlin JW, Skrobik Y, Gélinas C, et al. Executive summary: clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* 2018;46(9):1532-48. doi: 10.1097/CCM.0000000000003259.
25. Xia J, Gu S, Li M, et al. Spontaneous breathing in patients with severe acute respiratory distress syndrome receiving prolonged extracorporeal membrane oxygenation. *BMC Pulm Med.* 2019;19(1):237. doi: 10.1186/s12890-019-1016-2.
26. Deng L, Xia Q, Chi C, et al. Awake veno-arterial extracorporeal membrane oxygenation in patients with perioperative period acute heart failure in cardiac surgery. *J Thorac Dis.* 2020;12(5):2179-87. doi: 10.21037/jtd.2020.04.38.
27. Gao X, Ninan J, Bohman JK, et al. Extracorporeal membrane oxygenation and acute kidney injury: a single-center retrospective cohort. *Sci Rep*. 2023;13(1):15112. doi: 10.1038/s41598-023-42325-5.
28. Ortuno S, Delmas C, Diehl JL, et al. Weaning from veno-arterial extra-corporeal membrane oxygenation: which strategy to use? *Ann Cardiothorac Surg*. 2019;8(1):E1-E8. doi: 10.21037/acs.2018.08.05.
29. Lüsebrink E, Stremmel C, Stark K, et al. Update on Weaning from Veno-Arterial Extracorporeal Membrane Oxygenation. *J Clin Med.* 2020;9(4):992. doi: 10.3390/jcm9040992.
30. Tsiouris A, Protos AN, Saikus CE, et al. Fundamentals of weaning veno-arterial and veno-venous extracorporeal membrane oxygenation. *Indian J Thorac Cardiovasc Surg.* 2023;39(Suppl 1):1-11. doi: 10.1007/s12055-023-01474-y.
31. Tonna JE, Boonstra PS, MacLaren G, et al. Extracorporeal life support organization registry international report 2022: 100,000 Survivors. *ASAIO J*. 2024;70(2):131-43. doi: 10.1097/MAT.0000000000002128.
32. Pisano DV, Ortoleva JP, Wieruszewski PM. Short-term neurologic complications in patients undergoing extracorporeal membrane oxygenation support: areview on pathophysiology, incidence, risk factors, and outcomes. *Pulm Ther.* 2024;10(3):267-78. doi: 10.1007/s41030-024-00265-z.
33. Helms J, Frere C, Thiele T, et al. Anticoagulation in adult patients supported with extracorporeal membrane oxygenation: guidance from the scientific and standardization committees on perioperative and critical care haemostasis and thrombosis of the international society on thrombosis and haemostasis. *J Thromb Haemost.* 2023;21(2):373-96. doi: 10.1016/j.jtha.2022.11.014.
34. Liu Y, Yuan Z, Han X, et al. A Comparison of cctivated partial thromboplastin time and activated coagulation time for anticoagulation monitoring during extracorporeal membrane oxygenation therapy. Hamostaseologie. 2023;43(3):171-8. doi: 10.1055/a-1796-8652.
35. Rajsic S, Breitkopf R, Oezpeker UC, et al. The role of excessive anticoagulation and missing hyperinflammation in ECMO-associated bleeding. *J Clin Med*. 2022;11(9):2314. doi: 10.3390/jcm11092314.
36. Murphy DA, Hockings LE, Andrews RK, et al. Extracorporeal membrane oxygenation-hemostatic complications. Transfus *Med Rev.* 2015;29(2):90-101. doi: 10.1016/j.tmrv.2014.12.001.
37. Lotz C, Streiber N, Roewer N, et al. Therapeutic interventions and risk factors of bleeding during extracorporeal membrane oxygenation. *ASAIO J.* 2017;63(5):624-30. doi: 10.1097/MAT.0000000000000525.
38. Abruzzo A, Gorantla V, Thomas SE. Venous thromboembolic events in the setting of extracorporeal membrane oxygenation support in adults: A systematic review. *Thrombosis Res.* 2022;212:58-71. doi: 10.1016/j.thromres.2022.02.015.
39. Rajsic S, Breitkopf R, Jadzic D, et al. Anticoagulation Strategies during Extracorporeal Membrane Oxygenation: A Narrative Review. *J Clin Med.* 2022;11(17):5147. doi: 10.3390/jcm11175147.
40. Rajsic S, Breitkopf R, Rugg C, et al. Thrombotic Events Develop in 1 Out of 5 Patients Receiving ECMO Support: An 11-Year Referral Centre Experience. *J Clin Med.* 2023;12(3):1082. doi: 10.3390/jcm12031082.
41. Zeibi Shirejini S, Carberry J, et al. Current and future strategies to monitor and manage coagulation in ECMO patients. *Thromb J.* 2023;21(1):11. doi: 10.1186/s12959-023-00452-z.
42. Dufour N, Radjou A, Thuong M. Hemolysis and plasma free hemoglobin during extracorporeal membrane oxygenation support: from clinical implications to laboratory details. *ASAIO J*. 2020;66(3):239-46. doi: 10.1097/MAT.0000000000000974.
43. Bonicolini E, Martucci G, Simons J, et al. Limb ischemia in peripheral veno-arterial extracorporeal membrane oxygenation: a narrative review of incidence, prevention, monitoring, and treatment. *Crit Care*. 2019;23(1):266. doi: 10.1186/s13054-019-2541-3.
44. Ait Hssain A, Vahedian-Azimi A, Ibrahim AS, et al. Incidence, risk factors and outcomes of nosocomial infection in adult patients supported by extracorporeal membrane oxygenation: a systematic review and meta-analysis. *Crit Care.* 2024;28(1):158. doi: 10.1186/s13054-024-04946-8.
45. Li X, Wang L, Wang H, Hou X. Outcome and clinical characteristics of nosocomial infection in adult patients undergoing extracorporeal membrane oxygenation: a systematic review and meta-analysis. *Front Public Health.* 2022;10:857873. doi: 10.3389/fpubh.2022.857873.
46. Peña-López Y, Machado MC, Rello J. Infection in ECMO patients: Changes in epidemiology, diagnosis and prevention. *Anaesth Crit Care Pain Med*. 2024;43(1):101319. doi: 10.1016/j.accpm.2023.101319.
47. Diehl A, Gantner D. Pump head thrombosis in extracorporeal membrane oxygenation (ECMO). *Intensive Care Med.* 2018;44(3):376-7. doi: 10.1007/s00134-017-4976-9.

48. Lehle K, Philipp A, Gleich O, et al. Efficiency in extracorporeal membrane oxygenation-cellular deposits on polymethylpentene membranes increase resistance to blood flow and reduce gas exchange capacity. *ASAIO J.* 2008;54(6):612-7. doi: 10.1097/MAT.0b013e318186a807.
49. Patel B, Arcaro M, Chatterjee S. Bedside troubleshooting during venovenous extracorporeal membrane oxygenation (ECMO). *J Thorac Dis*. 2019;11(Suppl 14):S1698-S707. doi: 10.21037/jtd.2019.04.81.
50. Zakhary B, Vercaemst L, Mason P, et al. How I approach membrane lung dysfunction in patients receiving ECMO. *Crit Care.* 2020;24(1):671. doi: 10.1186/s13054-020-03388-2.
51. Butt SP, Razzaq N, Saleem Y, et al. Improving ECMO therapy: Monitoring oxygenator functionality and identifying key indicators, factors, and considerations for changeout. *J Extra Corpor Technol*. 2024;56(1):20-9. doi: 10.1051/ject/2023047.
52. Yan S, Lou S, Zhao Y, et al. Air in extracorporeal membrane oxygenation: can never be overemphasized. Perfusion. 2021;36(1):97-9. doi: 10.1177/0267659120918471.
53. Kim DH, Cho WH, Son J, Lee SK, Yeo HJ. Catastrophic mechanical complications of extracorporeal membrane oxygenation. *ASAIO J.* 2021;67(9):1000-5. doi: 10.1097/MAT.0000000000001354.
54. Kurniawati ER, Rutjens VGH, Vranken NPA, et al. Quality of life following adult veno-venous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review. *Qual Life Res*. 2021;30(8):2123-35. doi: 10.1007/s11136-021-02834-0.
55. Kolle A, Irgens EC, Moi AL, et al. The psychological and HRQoL related aftermaths of extra corporeal membrane oxygenation treatment: a cross-sectional study. *Intensive Crit Care Nurs.* 2021;65:103058. doi: 10.1016/j.iccn.2021.103058.
56. Kalra A, Kang JK, Khanduja S, et al. Long-term neuropsychiatric, beurocognitive, and functional outcomes of patients receiving ECMO: a systematic review and meta-analysis. *Neurology*. 2024;102(3):e208081. doi: 10.1212/WNL.0000000000208081.
57. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-304. doi: 10.1056/NEJMoa1011802.
58. Kourek C, Nanas S, Kotanidou A, et al. Modalities of exercise training in patients with extracorporeal membrane oxygenation support. *J Cardiovasc Dev Dis.* 2022;9(2):34. doi: 10.3390/jcdd9020034.
59. Rivera JD, Fox ES, Fernando SM, et al. Physical rehabilitation and mobilization in patients receiving extracorporeal life support: a systematic review. *Crit Care Explor.* 2024;6(6):e1095. doi: 10.1097/CCE.0000000000001095.
60. Onrust M, Lansink-Hartgring AO, van der Meulen I, et al. Coping strategies, anxiety and depressive symptoms in family members of patients treated with extracorporeal membrane oxygenation: a prospective cohort study. *Heart Lung.* 2022;52:146-51. doi: 10.1016/j.hrtlng.2022.01.002.
61. Peetz AB, Sadovnikoff N, O'Connor MF. Is informed consent for extracorporeal life support even possible? *AMA J Ethics.* 2015;17(3):236-42. doi: 10.1001/journalofethics.2015.17.3.stas1-1503.
62. Lin PJ. Some ethical legal issues in heart disease surgery. Acta *Cardiol Sin.* 2014;30(6):529-37. doi: 10.6515/acs20140929b.
63. Paris JJ, Schreiber MD, Statter M, et al. Beyond autonomy—physicians' refusal to use life-prolonging extracorporeal membrane oxygenation. *N Engl J Med*. 1993;329(5):354-7. doi: 10.1056/NEJM199307293290512.
64. Moynihan KM, Taylor LS, Siegel B, et al. "Death as the One Great Certainty": ethical implications of children with irreversible cardiorespiratory failure and dependence on extracorporeal membrane oxygenation. *Front Pediatr.* 2023;11:1325207. doi: 10.3389/fped.2023.1325207.
65. Enumah ZO, Carrese J, Choi CW. The ethics of extracorporeal membrane oxygenation: revisiting the principles of clinical bioethics. *Ann Thorac Surg*. 2021;112(1):61-6. doi: 10.1016/j.athoracsur.2020.08.045.
66. Han JJ, Shin M, Patrick WL, et al. How should ECMO be used under conditions of severe scarcity? A population study of public perception. *J Cardiothorac Vasc Anesth*. 2022;36(6):1662-9. doi: 10.1053/j.jvca.2021.05.058.
67. Gerall C, Cheung EW, Klein-Cloud R, et al. Allocation of resources and development of guidelines for extracorporeal membrane oxygenation (ECMO): experience from a pediatric center in the epicenter of the COVID-19 pandemic. *J Pediatr Surg*. 2020;55(12):2548-54. doi: 10.1016/j.jpedsurg.2020.08.015.
68. Xue B, Shah N, Yang H, et al. Multi-horizon predictive models for guiding extracorporeal resource allocation in critically ill COVID-19 patients. *J Am Med Inform Assoc.* 2023;30(4):656-67. doi: 10.1093/jamia/ocac256.
69. Peek GJ, Elbourne D, Mugford M, et al. Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). *Health Technol Assess.* 2010;14(35):1-46. doi: 10.3310/hta14350.
70. Abrams D, MacLaren G, Lorusso R, et al. Extracorporeal cardiopulmonary resuscitation in adults: evidence and implications. *Intensive Care Med.* 2022;48(1):1-15. doi: 10.1007/s00134-021-06514-y.
71. DeMartino ES, Braus NA, Sulmasy DP, et al. Decisions to withdraw extracorporeal membrane oxygenation support: patient characteristics and ethical considerations. *Mayo Clin Proc*. 2019;94(4):620-7. doi: 10.1016/j.mayocp.2018.09.020.
72. Sade RM, Gibney BC, Hawkins RB. When life support is pointless, stop it. J Thorac Cardiovasc Surg. 2023;165(6):2165-8. doi: 10.1016/j.jtcvs.2022.09.027.
73. Williams SB, Dahnke MD. Clarification and Mitigation of Ethical Problems Surrounding Withdrawal of Extracorporeal Membrane Oxygenation. *Crit Care Nurse.* 2016;36(5):56-65. doi: 10.4037/ccn2016504.
74. Siegel MD. End-of-life decision making in the ICU. Clin Chest Med. 2009;30(1):181-94, x. doi: 10.1016/j.ccm.2008.11.002.
75. Griggs S, Hampton D, Edward J, et al. Impact of case review debriefings on moral distress of extracorporeal membrane oxygenation nurses. *Crit Care Nurse.* 2023;43(3):12-8. doi: 10.4037/ccn2023870.
76. Au SS, Couillard P, Roze des Ordons A, et al. Outcomes of ethics consultations in adult ICUs: a systematic review and meta-analysis. *Crit Care Med.* 2018;46(5):799-808. doi: 10.1097/CCM.0000000000002999.

77. Bartlett ES, Lim A, Kivlehan S, et al. Critical care delivery across health care systems in low-income and low-middle-income country settings: A systematic review. *J Glob Health.* 2023;13:04141. doi: 10.7189/jogh.13.04141.
78. Zakhary B, Shekar K, Diaz R, et al. Position paper on global extracorporeal membrane oxygenation education and educational agenda for the future: a statement from the extracorporeal life support organization ECMOed taskforce. *Crit Care Med*. 2020;48(3):406-14. doi: 10.1097/CCM.0000000000004158.
79. Tukacs M, Cato KD. Extubation during extracorporeal membrane oxygenation in adults: An international qualitative study on experts' opinions. *Heart Lung.* 2021;50(2):299-306. doi: 10.1016/j.hrtlng.2021.01.010.
80. Akdeniz M, Yardımcı B, Kavukcu E. Ethical considerations at the end-of-life care. *SAGE Open Med.* 2021;9:20503121211000918. doi: 10.1177/20503121211000918.
81. Ramanathan K. Ethical challenges of adult ECMO. Indian J *Thorac Cardiovasc Surg*. 2021;37(Suppl 2):303-8. doi: 10.1007/s12055-020-00922-3.
82. Burrell A, Kim J, Alliegro P, et al. Extracorporeal membrane oxygenation for critically ill adults. *Cochrane Database Syst Rev*. 2023;9(9):CD010381. doi: 10.1002/14651858.CD010381.pub3.
83. Lackermair K, Brunner S, Orban M, et al. Outcome of patients treated with extracorporeal life support in cardiogenic shock complicating acute myocardial infarction: 1-year result from the ECLS-Shock study. *Clin Res Cardiol.* 2021;110(9):1412-20. doi: 10.1007/s00392-020-01778-8.
84. Belohlavek J, Smalcova J, Rob D, et al. Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA.* 2022;327(8):737-47. doi: 10.1001/jama.2022.1025.
85. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet.* 2020;396(10265):1807-16. doi: 10.1016/S0140-6736(20)32338-2.
86. Mondellini GM, van den Enden AJM, Van Mieghem NM. Perspectives on why DanGer shock is the first positive trial on mechanical circulatory support in cardiogenic shock. *Heart Fail Rev.* 2025;30(2):381-5. doi: 10.1007/s10741-024-10470-2.
87. Frye J, Tao M, Gupta S, et al. Safety and utility of mechanical circulatory support in patients with acute myocardial infarction complicated by cardiogenic shock: A systematic review and meta-analysis. *Cardiovasc Revasc Med.* 2025;70:23-33. doi: 10.1016/j.carrev.2024.06.016.
88. Udesen NLJ, Beske RP, Hassager C, et al. Microaxial flow pump hemodynamic and metabolic effects in infarct-related cardiogenic shock: a substudy of the DanGer shock randomized clinical trial. *JAMA Cardiol.* 2025;10(1):9-16. doi: 10.1001/jamacardio.2024.4197.
89. Patel B, Davis RP, Saatee S. Mechanical circulatory support devices in the older adults. *Clin Geriatr Med.* 2025;41(1):51-63. doi: 10.1016/j.cger.2024.03.006.
90. Tarantini G, Panza A, Lorenzoni G, et al. Breaking down cardiogenic shock: an analytical reflection on the DanGer-SHOCK and ECLS-SHOCK trials. *Am J Cardiol.* 2025;236:30-3. doi: 10.1016/j.amjcard.2024.10.032.
91. Strudthoff LJ, Lüken H, Jansen SV, et al. In Vitro and In Vivo feasibility study for a portable VV-ECMO and ECCO(2)R system. *Membranes (Basel).* 2022;12(2):133. doi: 10.3390/membranes12020133.
92. Fuchs A, Schmucki R, Meuli L, et al. Helicopter inter-hospital transfer for patients undergoing extracorporeal membrane oxygenation: a retrospective 12-year analysis of a service system. *Scand J Trauma Resusc Emerg Med.* 2022;30(1):33. doi: 10.1186/s13049-022-01018-0.
93. Schmack B, Hanke JS, Schmitto JD, et al. ECMO-TO-GO: application of a portable on the body veno-arterial ECMO device in a bridge-to-transplantation setting. *JHLT Open.* 2024;4:100069. doi: 10.1016/j.jhlto.2024.100069.
94. Wolf J, Wolfer V, Halbe M, et al. Comparing the effectiveness of augmented reality-based and conventional instructions during single ECMO cannulation training. *Int J Comput Assist Radiol Surg.* 2021;16(7):1171-80. doi: 10.1007/s11548-021-02408-y.
95. Willers A, Arens J, Mariani S, et al. New trends, advantages and disadvantages in anticoagulation and coating methods used in extracorporeal life support devices. *Membranes (Basel).* 2021;11(8):617. doi: 10.3390/membranes11080617.
96. Ashcraft M, Garren M, Lautner-Csorba O, et al. Surface engineering for endothelium-mimicking functions to combat infection and thrombosis in extracorporeal life support technologies. *Adv Healthc Mater.* 2024;13(22):e2400492. doi: 10.1002/adhm.202400492.
97. Luu CH, Nguyen NT, Ta HT. Unravelling surface modification strategies for preventing medical device-induced thrombosis. *Adv Healthc Mater.* 2024;13(1):e2301039. doi: 10.1002/adhm.202301039.
98. He T, He J, Wang Z, Cui Z. Modification strategies to improve the membrane hemocompatibility in extracorporeal membrane oxygenator (ECMO). *Adv Compos Hybrid Mater.* 2021;4(4):847-64. doi: 10.1007/s42114-021-00244-x.
99. Alabdullh HA, Pflaum M, Mälzer M, et al. Biohybrid lung development: towards complete endothelialization of an assembled extracorporeal membrane oxygenator. *Bioengineering (Basel).* 2023;10(1):72. doi: 10.3390/bioengineering10010072.
100. Pearse I, Corley A, Qu Y, Fraser J. Tissue adhesives for bacterial inhibition in extracorporeal membrane oxygenation cannulae. *Intensive Care Med Exp*. 2021;9(1):25. doi: 10.1186/s40635-021-00388-6.
101. Allou N, Lo Pinto H, Persichini R, et al. Cannula-related infection in patients supported by peripheral ECMO: clinical and microbiological characteristics. *ASAIO J.* 2019;65(2):180-6. doi: 10.1097/MAT.0000000000000771.
102. Sheng K, Gao Y, Bao T, Wang S. Covalent coating strategy for enhancing the biocompatibility and hemocompatibility of blood-contacting medical materials. *Pharmaceutical Science Advances.* 2023;1(1):100001. doi: :10.1016/j.pscia.2022.100001.
103. Walz JM, Avelar RL, Longtine KJ, et al. Anti-infective external coating of central venous catheters: A randomized, noninferiority trial comparing 5-fluorouracil with chlorhexidine/silver sulfadiazine in preventing catheter colonization. *Critical Care Medicine*. 2010;38(11):2095-102. doi: 10.1097/CCM.0b013e3181f265ba.

104. Chang HH, Hou KH, Chiang TW, et al. Using signal features of functional near-infrared spectroscopy for acute physiological score estimation in ECMO patients. *Bioengineering (Basel)*. 2023;11(1):26. doi: 10.3390/bioengineering11010026.
105. Ali J, Cody J, Maldonado Y, et al. Near-infrared spectroscopy (NIRS) for cerebral and tissue oximetry: analysis of evolving applications. J Cardiothorac *Vasc Anesth.* 2022;36(8 Pt A):2758-66. doi: 10.1053/j.jvca.2021.07.015.
106. Phongmekhin T, Wang R. Continuous glucose monitor accuracy during extracorporeal membrane oxygenation. *Crit Care Resusc.* 2024;26(1):58-9. doi: 10.1016/j.ccrj.2023.11.003.
107. Aguirre AD, Shelton KT. Remote monitoring in the use of extracorporeal membrane oxygenation and acute mechanical circulatory support. *Curr Opin Crit Care.* 2022;28(3):308-14. doi: 10.1097/MCC.0000000000000949.
108. Stephens AF, Šeman M, Diehl A, et al. ECMO PAL: using deep neural networks for survival prediction in venoarterial extracorporeal membrane oxygenation. *Intensive Care Med.* 2023;49(9):1090-9. doi: 10.1007/s00134-023-07157-x.
109. Kalra A, Bachina P, Shou BL, et al. Using machine learning to predict neurologic injury in venovenous extracorporeal membrane oxygenation recipients: an ELSO Registry analysis. *JTCVS Open.* 2024;21:140-67. doi: 10.1016/j.xjon.2024.06.013.
110. Kalra A, Bachina P, Shou BL, et al. Acute brain injury risk prediction models in venoarterial extracorporeal membrane oxygenation patients with tree-based machine learning: An Extracorporeal Life Support Organization Registry analysis. *JTCVS Open*. 2024;20:64-88. doi: 10.1016/j.xjon.2024.06.001.
111. Lee H, Song MJ, Cho YJ, et al. Supervised machine learning model to predict mortality in patients undergoing venovenous extracorporeal membrane oxygenation from a nationwide multicentre registry. *BMJ Open Respir Res*. 2023;10(1):e002025. doi: 10.1136/bmjresp-2023-002025.
112. Roberts JA, Bellomo R, Cotta MO, et al. Machines that help machines to help patients: optimising antimicrobial dosing in patients receiving extracorporeal membrane oxygenation and renal replacement therapy using dosing software. *Intensive Care Med.* 2022;48(10):1338-51. doi: 10.1007/s00134-022-06847-2.
113. Fuller J, Abramov A, Mullin D, et al. A deep learning framework for predicting patient decannulation on extracorporeal membrane oxygenation devices: development and model analysis study. *JMIR Biomed Eng.* 2024;9:e48497. doi: 10.2196/48497.
114. Thiara S, Serpa Neto A, Burrell AJC, et al. Association of respiratory parameters at venovenous extracorporeal membrane oxygenation liberation with duration of mechanical ventilation and ICU length of stay: a prospective cohort study. *Crit Care Explor.* 2022;4(5):e0689. doi: 10.1097/CCE.0000000000000689.
115. Suzuki S, Teraoka N, Ito K, et al. A novel predictive score model for successful weaning from mechanical circulatory support in patients with cardiogenic shock. *J Card Fail.* 2024:1071-9164(24)00314-2. doi: 10.1016/j.cardfail.2024.07.023.
116. Balian J, Sakowitz S, Verma A, et al. Machine learning based predictive modeling of readmissions following extracorporeal membrane oxygenation hospitalizations. *Surg Open Sci.* 2024;19:125-30. doi: 10.1016/j.sopen.2024.04.003.
117. Kalra A, Bachina P, Shou BL, et al. Utilizing machine learning to predict neurological injury in venovenous extracorporeal membrane oxygenation patients: an extracorporeal life support organization registry analysis. *Res Sq.* 2023 :rs.3.rs-3779429. doi: 10.21203/rs.3.rs-3779429/v1.
118. Pladet L, Luijken K, Fresiello L, et al. Clinical decision support for ExtraCorporeal Membrane Oxygenation: Will we fly by wire? *Perfusion.* 2023;38(1_suppl):68-81. doi: 10.1177/02676591231163688.
119. Unoki T, Uemura K, Yokota S, et al. Closed-Loop automated control system of extracorporeal membrane oxygenation and left ventricular assist device support in cardiogenic shock. *ASAIO J.* 2024. doi: 10.1097/MAT.0000000000002359.
120. Brendle C, Hackmack KF, Kühn J, et al. Closed-loop control of extracorporeal oxygen and carbon dioxide gas transfer. *Control Engineer Practice.* 2017;59:173-82. doi: 10.1016/j.conengprac.2016.09.016.
121. Abbasi A, Karasu Y, Li C, et al. Machine learning to predict hemorrhage and thrombosis during extracorporeal membrane oxygenation. *Crit Care.* 2020;24(1):689. doi: 10.1186/s13054-020-03403-6.
122. Hsiao YJ, Chiang SC, Wang CH, et al. Epigenomic biomarkers insights in PBMCs for prognostic assessment of ECMO-treated cardiogenic shock patients. *Clin Epigenetics.* 2024;16(1):137. doi: 10.1186/s13148-024-01751-6.
123. Beaini H, Chunawala Z, Cheeran D, et al. Cardiogenic Shock: Focus on Non-Cardiac Biomarkers. *Curr Heart Fail Rep.* 2024;21(6):604-14. doi: 10.1007/s11897-024-00676-8.
124. Senoner T, Treml B, Breitkopf R, et al. ECMO in myocardial infarction-associated cardiogenic shock: blood biomarkers as predictors of mortality. *Diagnostics (Basel).* 2023;13(24):3683. doi: 10.3390/diagnostics13243683.
125. Thiara S, Stukas S, Hoiland R, et al. Characterizing the relationship between arterial carbon dioxide trajectory and serial brain biomarkers with central nervous system injury during veno-venous extracorporeal membrane oxygenation: a prospective cohort study. *Neurocrit Care.* 2024;41(1):20-8. doi: 10.1007/s12028-023-01923-x.
126. Battaglini D, Al-Husinat L, Normando AG, et al. Personalized medicine using omics approaches in acute respiratory distress syndrome to identify biological phenotypes. *Respir Res.* 2022;23(1):318. doi: 10.1186/s12931-022-02233-0.
127. Martucci G, Arcadipane A, Tuzzolino F, et al. Circulating miRNAs as promising biomarkers to evaluate ECMO treatment responses in ARDS patients. *Membranes (Basel).* 2021;11(8):551. doi: 10.3390/membranes11080551.
128. Samant S, Bakhos JJ, Wu W, et al. Artificial intelligence, computational simulations, and extended reality in cardiovascular interventions. *JACC Cardiovasc Interv.* 2023;16(20):2479-97. doi: 10.1016/j.jcin.2023.07.022.
129. Gu K, Guan Z, Lin X, et al. Numerical analysis of aortic hemodynamics under the support of venoarterial extracorporeal membrane oxygenation and intra-aortic balloon pump. *Comput Methods Programs Biomed.* 2019;182:105041. doi: 10.1016/j.cmpb.2019.105041.