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Determining The End of Life in Extracorporeal Membrane Oxygenation Patients: Concept Analysis

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Abstract

Introduction: Extracorporeal membrane oxygenation (ECMO) has emerged as a major advancement in the treatment of critically ill patients, and has shown to be truly life-saving in otherwise hopeless situations. Over-utilization of this technology in end-stage patients, often referred to as "bridge to nowhere" is emerging as a medical and ethical dilemma. Determining "end of life" in ECMO patients, in other words, when to "call it quits", is a controversial and unclear concept, and to date this phenomenon has not been defined or clarified in a systematic method. This study aimed to clarify and define the "end of life" point to help in decision-making for withdrawal or termination of treatment for patients undergoing ECMO treatment.

Methods: Relevant studies from Pubmed, Scopus, Web of Science, and Google Scholar were extracted from 1980 to 2021 using predesigned keywords. Two authors separately screened the titles, abstracts, and the methodological validity of the articles utilizing a valid extraction form. Discussions with the third author were utilized to resolve the disagreements during the review step. Also, two authors independently assessed the quality of the studies.

Results: Fourteen studies were selected: three cross-sectional and eleven retrospective or prospective cohort studies. Four key attributes were identified: brain death, failure to bridge from ECMO to transplantation, myocardial failure, and multi-organ failure. Several antecedents were identified, including age, lactate levels (pre-ECMO), creatinine and bilirubin levels, hematocrit level, mechanical ventilation parameters (pre-ECMO), arterial blood gas (pre-ECMO PaO2<70mmHg), renal function (need for continuous renal replacement therapy – CRRT - during ECMO), SOFA score before ECMO, multi-organ failure, complications on ECMO, duration of ECMO and time of weaning from ECMO, lower annual hospital volume of ECMO and experience with ECMO.

Conclusion: The main concepts for describing the end of life in ECMO patients are brain death and multi-organ failure. However, there are scientific and ethical limitations with any medical recommendations to determine the end of life for ECMO patients precisely.

Keywords: ECMO patients, end of life, concept analysis.

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Background

Significant advances in medicine, biology, and technology over the past 50 years have helped us better understand the biology of death and save lives [1-3]. ICU-based life support, extracorporeal circulatory support, and extracorporeal membrane oxygenation (ECMO) are some of the main advances in technology, care, and treatment that have genuinely impacted modern-day results in saving the lives of critical patients [1, 4-5].

ECMO is a modified form of cardiopulmonary bypass (CPB) that supports patients with life-threatening cardiac, respiratory or combined cardiac and respiratory failure for days or weeks. ECMO may be considered when the patient's condition starts deteriorates and fails to respond or is refractory to conventional therapy [2,6-8]. This

condition can be due to reversible or irreversible organ injury and is usually associated with 50 to 70% mortality rates. If the patient is supported well with ECMO therapy, the mortality risk can be decreased [2, 9-12].

The history of ECMO can be traced back to 1929 in Russia, with a dog's first successfully reported extracorporeal perfusion. The first successful report of ECMO in man was by Gibbon, performed in 1953 [3]. In combat medicine, ECMO can be used in some critically-ill war casualties and pre-hospital emergencies in cases of severe penetrating and non-penetrating chest trauma with acute pulmonary injuries. After being placed on ECMO and stabilized, the dead are transported by specially equipped ambulance to the ECMO reference hospital. There is evidence of the use of ECMO by American and German armies in military medicine [4-18]. Thus, ECMO is being developed as a last resort to salvage patients with severe disorders of the vital cardiovascular system, and new indications of ECMO are emerging in the world's medical systems [5, 18-25].

This new technology has its drawbacks, however. ECMO is associated with about 50% survival up to discharge. The most frequent complications are bleeding, renal failure, pneumonia, and sepsis [6, 26-28]. According to Extracorporeal Life Support Organization (ELSO) guidelines, in cardiac or respiratory failure, ECMO should be considered when there is a 50% risk for death, and it is indicated when the death risk exceeds 80%. In practice, however, individual, institutional experience often determines the indications [2-5].

ECMO has a global mortality rate of about 45%, and the issue of determining when to cease treatment and announce "end of life" in patients on ECMO is a significant challenge for ECMO centers [7]. In general, the process of death or end of life that is sequential and predictable can be induced by one of three physiological mechanisms: 1) cessation of breathing induced by primary respiratory failure or event resulting in a drop in blood oxygen levels, which finally lead to cardiac arrest, 2) cessation of heartbeat and cardiac arrest or pump failure by primary heart diseases such as a heart attack or severe trauma, and 3) cessation of brain function by catastrophic brain injury that leads to loss of brain control on vital functions such as breathing and induces apnea, drop in oxygenation and cardiac arrest [8]. There have been and continue to be scientific and ethical limitations for medical guidelines or recommendations to determine the end of life for ECMO patients. No precise method has been devised or proposed to help medical specialists deal with this challenging situation.

This concept analysis has been performed with the Walker and Avant methods (2013) to develop an operational definition of "end of life in ECMO patients," identify its applications to ECMO team practice and enhance understanding of this concept in the care of ECMO patients.

Methods

Using the Walker and Avant methods (2013)[10], we propose a clear outline of the antecedents and attributes of "end of life in ECMO patients" and suggest empirical references for how the phenomenon can be applicable and transferable in daily practice.

Search strategy

The preferred reporting methods for systematic reviews and meta-analyses (PRISMA) guidelines were followed [9]. We searched the *PUBMED, SCOPUS, Web of Science, and Google Scholar* databases for relevant studies (1980-2021). The databases were searched using both controlled vocabulary words and synonymous free text words that covered the topic of interest: "extracorporeal membrane oxygenation" AND "end-of-life decision" OR "end-of-life decision" OR "terminal phase decision" OR "determination of death" OR "near-death" OR "death" OR "making end of life decisions" OR "final decision" OR "end of life in ECMO patients" OR "death criteria in ECMO patients."

Two authors separately screened the titles, abstracts, and the methodological validity of the articles utilizing a valid extraction form. Discussions with the third author were utilized to resolve the disagreements during the review step. Also, two authors independently assessed the quality of the studies.

Results

Description of included studies

Fifteen studies were finally included: three were cross-sectional, and eleven were retrospective or prospective cohort studies. Cross-sectional studies described 543 ECMO patients for antecedents and attributes for end-of-life, with an extreme quality appraisal level. Prospective and retrospective cohort studies analyzed 61,514 patients for antecedents and characteristics of end-of-life in ECMO patients. These studies also displayed an extreme quality appraisal level.

Attributes

When the concept is evident, attributes or characteristics of the idea are always present and are at the heart of concept analysis (Walker and Avant, 2013)[10]. Four key attributes which were always evident in the "end of life in ECMO patients" identified in the literature reviewed are "brain death," "failure to bridge from ECMO to transplantation," "myocardial failure," and "multi-organ failure."

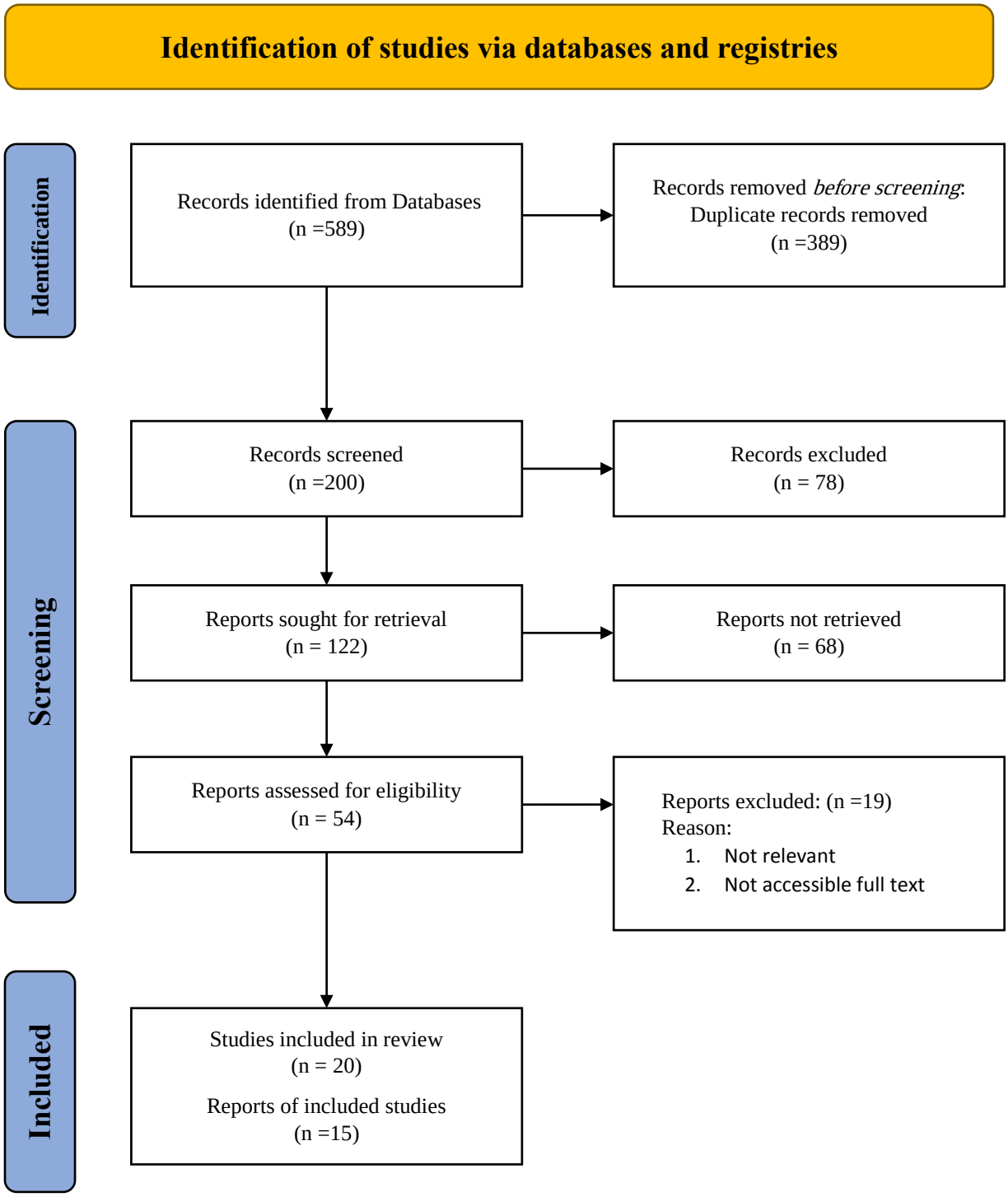

Diagram 1. PRISMA flow chart.

Table 1. Summary of search results

Authors (years)	Aim	Design	Sample size	Key results	Quality score
Smedira et al. 2001 (3)	predictors of survival and logistic regression identified the determinants of bridging or weaning	Prospective cohort	202 patients	Attributes: Failure to bridge or wean included renal and hepatic failure on ECMO, occurrence of a neurologic event. The dominant modes of death were cardiac failure and multisystem organ failure.	Strong
Doll, et al. (2004) (20)	Evaluate the early and long-term outcome as well as predictors of survival when using	Prospectively cohort	219 patients	Attribute: The main cause of death was myocardial failure	Very Strong
Wagner et al. 2008 (21)	analyze pre-operative risk factors of early mortality in patients who underwent either VA-ECMO or VV-ECMO for pulmonary failure	Retrospective cohort	72 patients	Antecedent: serum creatinine and poor renal function prior to ECMO was significantly associated with mortality	Strong
Brogan et al. 2009 (22)	evaluate clinical and treatment factors and survival of adult ECMO in respiratory failure patients	Retrospective cohort	1473 patients	Antecedent: advanced patient age, increased pre-ECMO ventilation duration, diagnosis category and complications while on ECMO were associated with mortality	Very Strong
Thiagarajan .et al… (2009) (23)	Describe outcomes after the use of ECMO to support CPR (E-CPR) in adults	Cross-sectional	295 patients that E-CPR was used for them	Antecedents: lower pre –ECMO PaO2 < 70 mmHg and need for renal replacement therapy during ECMO increased odds of mortality	Very Strong
Roch et al. (2010) (28)	compare characteristics, clinical evolution and outcome in adult patients with ARDS treated with or without ECMO	Prospective observational cohort	18 patients	Antecedents: early improvement of PaO2 to FiO2 ratio was greater in ECMO survivors than non-survivors after ECMO	Strong
Patroniti (2011) (5)	Describe organization and results of ECMO net network	Cross Sectional	153 patients	Antecedents: length of mechanical ventilation prior to ECMO was an independent predictor of mortality	Strong
Ta`i Pham, et al (2012) (7)	analyze factors associated with death in ECMO-treated patients and the influence of ECMO on ICU mortality	Prospective cohort	123 patients	Attribute: increasing values of age, lactate, and plateau pressure under ECMO were associated with death.	Very Strong
Antoine Roch et al (2013) (4)	Identify early factors associated with hospital mortality in ARDS patients treated with ECMO	Cohort	85 patients	Antecedents: patient age >45 and SOFA score > 12 before ECMO was associated with mortality	Very Strong
Pappalardo (2013) (6)	identify predictors of mortality and develop a score allowing better stratification of patients at the time of VV ECMO	Cohort	60 patients	Antecedents: predictors of death before ECMO were hospital length of stay before ECMO, bilirubin, creatinine and hematocrit values and mean arterial pressure.	Very Strong
Barbaro et al. 2015 (2)	determine association between annual ECMO patient volume and hospital mortality rate	Retrospective cohort	56,222 patients	Antecedent: lower annual hospital ECMO volume was associated with mortality	Very Strong
Myles Smith, 2017 (13)	Determine relationship between VA ECMO duration and in-hospital mortality	Retrospective cohort	2699 patients	Antecedent: survival increases per day such that 4 days or less on VA ECMO is associated with a significantly higher mortality rate, most likely reflecting early treatment failure. Survival was observed to be highest when weaned on the fourth day of ECMO but it likely decreases into the second week.	Very Strong
Banjas, 2018 (18)	mortality- associated prognostic variables in lung failure, cardiogenic, septic shock undergoing ECMO	Cross- sectional	131 patients	Antecedents: age, pre-ECMO lactate, and experience with the procedure.	Very Strong
Deatric et al. 2021 (1)	evaluate the incidence of continuous renal replacement therapy (CRRT) in patients supported with ECMO	Retrospective cohort	187 patients	Attribute: Renal failure (CRRT) was associated with higher in-hospital mortality	Very Strong

Attributes

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Antecedents

Walker and Avant (2013) cautioned that too many attributes might overlap with antecedents and consequences. Indeed, some degree of overlap is apparent in the antecedents derived from the literature, as displayed in Table 1. However, in contrast to attributes, the events that must occur before the concept can take place (named antecedents, Walker and Avant, 2013), evident in the literature reviewed are age, lactate level (pre-ECMO), creatinine level, bilirubin level, hematocrit level, mechanical ventilation parameters (duration under ventilator before ECMO), arterial blood gas (pre-ECMO paO2<70 mmHg), renal function (need for CRRT during ECMO), SOFA score before ECMO, multi-organ failure, complications on ECMO, duration of ECMO and time of weaning from ECMO, lower annual hospital ECMO volume and low experience with ECMO [10].

Discussion

Some attributes and antecedents were synthesized from this analysis, including Our results in two categories that consist of the four points and some ancestors of end-of-life in ECMO patients.

Brain death

Brain death is defined as the irreversible cessation of all brain activity. Before the 1940s, death was determined by the end of blood circulation. In the 1950s, death from circulatory stasis became "reversible" with the development of ventilators and cardiopulmonary resuscitation. Physicians started treating patients in permanent comatose states, unable to be liberated from life support machines [11]. Based on ELSO statistics, 21% of 295 adults treated with ECMO–cardiopulmonary resuscitation (ECPR) experienced brain death. Diagnosis of brain death in ECMO patients is essential in guiding decision-making for earlier withdrawal of ECMO support[7].

Hemodynamic stability is required to determine brain death in ECMO patients correctly. Also, for brain death determination in ECMO patients, electroencephalography (EEG) or transcranial Doppler (TCD) sonography can be readily and easily used, and angio-computer tomography (angio-CT) or cerebral scintigraphy may also be utilized[12]. According to the American Academy of Neurology (AAN), the absence of brain stem reflexes and apnea constitute a diagnosis of brain death known as irreversible coma. In the presence of medullary dysfunction, apnea testing can be done as a critical component of brain death testing[13, 14]. Apnea testing for diagnosing death by neurologic criteria is feasible during ECMO. However, there is often concern that apnea testing may lead to oxygen desaturation and hemodynamic instability[15, 16].

Failure to bridge from ECMO to transplantation

ECMO can be used for temporary, complete circulatory support while awaiting myocardial recovery or determining suitability for heart transplantation. Failure to bridge from ECMO to transplantation is one of the main attributes of death in ECMO patients.

ECMO is the first choice for patients with circulatory collapse due to myocardial infarction or myocarditis if they are not candidates for heart transplantation. If no suitable donor heart becomes available and the patient can not be weaned from ECMO, a bridge from ECMO to a device such as VAD will be required [17].

Multi-organ failure

The most common cause of death in ECMO patients is a multi-organ failure [18]. Multi-organ failure is defined as the simultaneous disorder of several main organs of the body: i.e., renal, lung, liver, and cardiac failure. A review of the literature showed that patients undergoing ECMO treatment with renal failure requiring CRRT, acute lung failure, and cardiogenic or septic shock were associated with hospital mortality. Different studies demonstrate that most often, patients that were supported simultaneously with CRRT and ECMO died [7, 19, 20]. Luo, et al demonstrate that combining CRRT with ECMO support was associated with a significantly higher mortality rate. However, multi-system organ failure is the most important cause of death [21]. In patients with severe multi-organ failure not resolving after a few days of ECMO support, VAD implantation may not be indicated and should not be done [22].

Myocardial failure

It has been shown that ECMO can be partially effective in treating cardiopulmonary arrest. On the other hand, E-CPR survival, based on reports in the literature, was associated with 27% survival to hospital discharge [23]. Using ECMO for cardiac failure, however, has limitations. One primary concern is the limited duration of support and the poor outcome associated with the long-term backing in adults. Patients cannot be mobilized with

cannulas implanted in femoral vessels. Furthermore, patients with these devices in place are at risk for complications such as bleeding, infection and sepsis, severe neurologic injury, limb ischemia, and technical problems such as pump malfunction or failure [22].

According to the Yun Imm Lee et al, retrospective single-center cohort study, the SOFA score was a significant prognostic factor in ECMO patients. A SOFA score of 12 was the optimal cutoff score for hospital survival in ECMO patients. A high SOFA score suggests a high degree of multiple-organ failure caused by cardiogenic shock in patients with myocarditis [24]. Also, based on Kaestner et al., bilirubin and lactate levels were associated with mortality during ECMO treatment [25].

The patient's condition before the ECMO treatment can be evaluated with SOFA score, such that the median SOFA score of 12 has been proposed as indicative of poor prognosis of patients before ECMO [19, 26]. Some studies have clearly shown that the survival rate decreases as the duration of mechanical ventilation increases before the institution of ECMO. ECMO initiated early in patients with severe lung injury is expected to be of greatest benefit. A possible reason for this is the inability to apply adequate and safe ventilation without ECMO in the most severe cases, which could result in ventilator-associated lung injury and initiation of multi-system damage. Moreover, ECMO non-survivors required higher doses of inotropes and had higher lactate levels before starting the ECMO [27, 28]. Based on 2013 and 2017 ELSO guidelines, increased age without any cutoff age is a relative contraindication for ECMO [29]. Banja's study showed that three major variables were associated with hospital mortality: age, pre-ECMO lactate, and experience with the procedure in patients with septic and cardiogenic shock and acute lung failure undergoing septic and cardiogenic shock and acute lung failure ECMO treatment[18].

Model case

In line with Rodger's (1989) suggestions, it has not been necessary to invent borderline, contrary, or other related cases to illustrate the concept of end-of-life in ECMO patients. The model case described, a case report from Mayo Clinic in Rochester, Minnesota, has been created from the perspective of the end of life in ECMO patients.

"A 37-year-old female with cardiomyopathy presented with acute exacerbation of chronic bi-systolic failure and hypotension refractory to multiple vasopressors and inotropes. VA-ECMO cannulation was listed as status 1A for a heart transplant. During the patient's long hospital course, multiple hemorrhagic complications developed. She underwent 15 operative procedures and had difficulty with refractory ventricular arrhythmias, recurrent pneumonia, and severe deconditioning. At times in her hospital course, she was alert, ambulatory, and able to eat solid food. Unfortunately, after more than four months of support, the patient had a sudden neurologic deterioration. In a multidisciplinary family meeting, the decision was made to withdraw ECMO support because she was no longer deemed a suitable heart transplant candidate. At her spouse's request, with her durable power of attorney for health care, she was separated from ECMO in the operating room to allow the donation of salvageable organs. This study supported ECMO for 138 days" [30].

In this case, the separation of the patient from ECMO has been done based on a multidisciplinary family meeting. Thus, when neurologic deterioration and brain death are diagnosed, the ECMO team may remove the patient from ECMO. This complex decision-making can be done primarily with multidisciplinary family discussion and based on guidelines.

Empirical referents

Empirical referents can be confused with attributes, also existing when the phenomenon is present (Walker and Avant, 2013). End of life in ECMO patients is different from other patients because in ECMO patients, the extracorporeal circulation supports the cardiac and pulmonary function and thus the life of the patients [1]. In recent years, the number of patients treated with ECMO has grown dramatically, and the in-hospital mortality rate of ECMO patients has remained high. An essential criterion for death determination in ECMO patients is brain death. Consequentlyture, the number of ECMO patients diagnosed with brain dein the future ath will rise[12].

ECMO centers should formulate guidelines or protocols highlighting indications, maintenance, and termination of ECMO (end-of-life) based on available evidence to manage limited healthcare resources better. Information such as ECMO contraindications and the expected approximate costs of ECMO in each institution would also be valuable additions to such documents. If, despite ECMO, the cardiopulmonary function does not recover, we should seek patient preferences if they are awake. Psychiatric counsel, ethics committees, palliative care workers, and social workers should be consulted if the patient agrees to continue palliation. Furthermore, all healthcare staff should participate in counseling and debriefing sessions because they may involve withdrawing support from an awake patient [31].

Consequences

The consequences of determining the end of life in ECMO patients are two-fold: first, ethical considerations

for decisions to withdraw ECMO, and second, organ donation.

Terminal discontinuation of ECMO or withdrawal at the end of life may be the only option for physicians and the ECMO team when ECMO patients are neurologically devastated and brain death is diagnosed for these patients. Such decision-making may be challenging and debatable between physicians, family members, and ECMO team staff. Thus to de-escalate this challenge and improve shared decision-making, following the guidelines and obtaining written consent from the patient's family members for any adverse consequences of ECMO before placing the patient on ECMO is recommended [32, 33].

The second consideration after the determination of circulatory death and confirmed brain death of the ECMO patient is the decision-making for organ donation for transplantation. Thus, because obtaining the family's consent is time-consuming, we may consider organ-preserving ECMO (OP-ECMO). Organ-preserving ECMO can save organs that would otherwise be lost but not salvage the patient's own life. The leader of ECMO should discuss this option with the patient's family and solve conflicts for continuing ECMO. Suppose the brain death of the patient has not been diagnosed and the family has not consented to organ donation. In that case, OP-ECMO is not recommended unless the patient's family agrees to both OP-ECMO and organ donation. Decision-making for these patients to be withdrawn from ECMO is based on the futility of care [34, 35].

End-of-life definition in ECMO patients

In this review and concept analysis, three main concepts that can be suitably used to clarify the end of life in ECMO patients with four attributes and several antecedents, as mentioned above, have been determined.

There are different definitions of death that all human beings inevitably encounter. As a birth, death is one of life's most accurate and universal events. Death is an inevitable end in human life [36]. The American Medical Association defines death as the irreversible cessation of all circulatory, respiratory, and brain functions. As can be seen from these definitions, while death is a natural process that should be regarded positively, for some people, it means destruction [36].

End-of-life issues relate to someone's death and the time just before it, when it is known that they are likely to die soon from an illness or condition [37]. End of life is the synonym of "death" in that it is the permanent, irreversible cessation of all biological functions that sustain a living organism. Brain death is sometimes used as a legal definition [38].

Conclusion

Families should be aware of significantly higher mortality rates for their loved ones on ECMO. With consideration of the concept of end-of-life in ECMO patients, decision-making for these patients can be challenging. It may be pursued when a lack of recovery of cardiopulmonary function or generalized multi-organ dysfunction evidences the futility of treatment. The concept may be difficult for the family, and they may not consent to palliation for the same reason. The main ideas for describing end-of-life in ECMO patients are brain death, multi-organ failure, and failure to bridge to other treatments. Also, some antecedents portend a poor prognosis for ECMO patients and predict mortality. Organ donation is one of the best strategies for brain-dead patients on ECMO. Organ preserving-ECMO can be used in hemodynamically unstable brain-dead patients but requires specific consent from relatives in preparation for organ donation.

Limitations and strengths

The novelty of the present study, based on the aim of this study, is employing the concept analysis approach to define and determine the attributes and antecedents of end-of-life in ECMO patients. However, our study does not include scoring each factor or differentiating the roles of each member of the multidisciplinary ECMO team in decision-making to stop the ECMO machine. It is suggested that future studies score and determine the weight and effect sizes of each item of attributes and antecedents separately to determine the end of life in ECMO patients.

Review Highlights

What Is Already Known?

ECMO has proven to be an indeed life-saving treatment for critically ill patients. Overusing this technology in terminally ill patients, also known as the "bridge to nowhere," is becoming a moral and medical problem.

What Does This Study Add?

Future research should score, weigh, and calculate the effect sizes of each attribute and antecedent individually to predict when ECMO patients will reach the end of their lives.

Conflict of interest

None

Ethical Approval

Not applicable

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