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# Predictors of complications associated with extracorporeal membrane oxygenation

*Preditores de complicações da oxigenação por membrana extracorpórea*

*Predictores de complicaciones de la oxigenación por membrana extracorporea*

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## ABSTRACT

**Objectives:** to identify in the literature, the predictors of ECMO complications in adult patients. **Methods:** integrative review of literature, including articles in Portuguese, English and Spanish published from 2014 to 2018 in five databases. Included articles which analyzed the predictive factors of ECMO complications in adult patients using multivariate analysis. **Results:** a total of 1629 articles were identified, of which 19 were included. Nineteen predictors were identified for neurological complications (e.g., post-ECMO hypoglycemia), seven for bleeding complications (e.g., fungal pneumonia), four for infections complications (e.g., preoperative creatinine level), three for kidney complications (e.g., the length of ICU stay> 20 days) and a combination of factors for mechanical complications (e.g., median flow). **Conclusions:** different predictors were identified to ECMO complications. The knowledge of these predictors enables the individualized targeting of preventive interventions by multidisciplinary team for modifiable factors, as well as intensification of monitoring for early recognition of non-modifiable factors.

**Descriptors:** Adults; Critical Care; Risk Factors; Extracorporeal Membrane Oxygenation; Forecasting.

## RESUMO

**Objetivos:** identificar na literatura os preditores de complicações da oxigenação por membrana extracorpórea (ECMO) em pacientes adultos. **Métodos:** revisão integrativa de literatura, incluindo artigos em português, inglês ou espanhol publicados de 2014 a 2018 publicados em cinco banco/bases de dados. Incluíram-se estudos que investigaram os preditores de complicações da ECMO em adultos por análise múltipla. **Resultados:** recuperaram-se 1629 artigos, dos quais 19 foram incluídos. Identificaram-se 19 preditores para complicações neurológicas (p.ex., hipoglicemia pós-ECMO), sete para complicações hemorrágicas (p.ex., pneumonia fúngica), quatro para complicações infecciosas (p.ex., creatinina pré-operatória), três para complicações renais (p.ex., tempo em UTI>20 dias) e uma combinação de três fatores para complicações mecânicas (p.ex., fluxo da ECMO). **Conclusões:** diferentes preditores foram identificados para complicações da ECMO. O conhecimento desses preditores possibilita o direcionamento individualizado de intervenções preventivas pela equipe multidisciplinar para aqueles que são modificáveis e a intensificação de monitoramento para reconhecimento precoce daqueles não modificáveis.

**Descritores:** Adultos; Cuidados Críticos; Fatores de Risco; Oxigenação por Membrana Extracorpórea; Previsões.

## RESUMEN

**Objetivos:** identificar en la literatura los predictores de complicaciones de la oxigenación por membrana extracorpórea (ECMO) en pacientes adultos. **Métodos:** revisión integradora de la literatura, incluyendo artículos en portugués, inglés o español publicados de 2014-2018 en cinco bancos/bases de datos. Se incluyeron estudios que investigaron los predictores de complicaciones de la ECMO en adultos por análisis múltiple. **Resultados:** se recuperaron 1,629 artículos, de los cuales se incluyeron 19. Se identificaron 19 predictores para complicaciones neurológicas (por ejemplo, hipoglucemia post-ECMO), siete para complicaciones hemorrágicas (por ejemplo., neumonía fúngica), cuatro para complicaciones infecciosas (por ejemplo, creatinina preoperatoria), tres para complicaciones renales (por ejemplo, tiempo en UTI> 20 días) y una combinación de tres factores para complicaciones mecánicas (por ejemplo, flujo de ECMO). **Conclusiones:** se identificaron diferentes predictores para las complicaciones de la ECMO. Conocer estos predictores posibilita el direccionamiento individualizado de intervenciones preventivas por el equipo multidisciplinario para aquellos que son modificables y la intensificación de monitoreo para reconocimiento precoz de aquellos no modificables.

**Descriptores:** Adultos; Cuidados Críticos; Factores de Riesgo; Oxigenación por Membrana Extracorpórea; Predicción.

## INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) involves a heparinized system, percutaneously installed in a blood vessel, from where the patient's blood is drained and pumped - via a centrifugal pump or roller - to an oxygenator membrane. Exchange of oxygen and carbon dioxide occurs in this membrane, and oxygenated blood is returned to the patient through a venous or arterial system[1-2].

ECMO is used in clinical situations that are potentially reversible, but refractory to conventional treatment, such as cardiogenic shock, cardiorespiratory arrest, and respiratory failure[3], in order to maintain the target-organ perfusion until recovery of the affected organ, or until a definitive therapy is determined, acting as a bridge for transplantation, or for another form of ventricular device[2].

The venovenous mode (VV) is used in situations in which only respiratory support is required, while venoarterial mode (VA) is chosen when additional cardiovascular and respiratory support are necessary [2-3].

Even though there are advantages of ECMO when compared to other types of ventricular devices, such as biventricular support and rapid percutaneous implantation[4], the treatment has an elevated rate of in-hospital morbidity and mortality, due to length of hospital stay and complications associated with the therapy[4-5]. The mortality rate may reach 59% and 44% of the patients on cardiovascular and respiratory support, respectively[5]. As the patient remains on ECMO, complications secondary to treatment may be related to the patient's clinical picture, anticoagulation, or the device[6].

The most prevalent complications are: renal (38-75%), hemorrhagic (13-39%), infectious (11-33%), neurological (5.9-21%), and vascular (3.9-12%)[7-9].

Hemorrhagic complications related to anticoagulation are associated with hemodilution of the patient and the consumption of coagulation factors, as well as heparin-induced thrombocytopenia. Determining the optimal level of anticoagulation is still a challenge for many ECMO centers, due to the risk of excessive bleeding, or the risk of thrombocytopenia[6].

Complications related to the device occur in up to 11% of patients[8], and the most important are mechanical failures, such as: rupture or disconnection of the tube, failure of the oxygenator membrane or pump, circuit or membrane exchange with consequent entry of air into the system, causing a gas embolism[6,10].

Considering the complexity of treatment with ECMO, and its potential complications, the Extracorporeal Life Support Organization recommends that patients undergoing the procedure be cared for by a multidisciplinary team[11]. In fact, mortality rates, incidence of problems with cannulation, and cardiovascular events are reduced in intensive care, in-hospital, and after one year, when patients receiving ECMO for respiratory support receive care from multidisciplinary teams. Multidisciplinary teamwork also increases the proportion of patients who are successfully withdrawn from ECMO[12].

To obtain such results, it is essential that members of the multidisciplinary team, responsible for providing care to patients with ECMO, know the predictive factors of the main complications related to the procedure. This will enable them to recognize the individual risks for each individual, and to drive specific plans of care.

## OBJECTIVES

To identify, in the literature, the predictors of ECMO complications in adult patients.

## METHODS

This was an integrative review of literature, conducted based on the steps proposed by Whittemore & Knafl: problem identification, literature search, data evaluation, data analysis, and presentation of results[13].

Problem identification: The problem was represented by a research question, developed using the acronym PEO: P(Patient): adults on ECMO; E(exposure): predictors; O (outcome): complications: "What are the predictors of complications in adults receiving ECMO?"

Literature search: The search was conducted in June of 2018, in the MEDLINE database via Pubmed, and in the Scopus, Latin American Literature in Health Sciences (Lilacs), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science databases.

Controlled descriptors (Descriptors in Health Sciences, Medical Subject Headings, and CINAHL terms), and non-standard terms with different combinations, were used in each of the databases, as seen in Chart 1.

**Chart 1** - Search strategies in each database

| Database | Keywords/descriptors |
|---|---|
| MedLine/ Pubmed | (risk factors[MeSH Terms]) OR "risk factor") OR "risk factor/ predictor") OR "predictor") OR "predictor/determinant/factors") OR "predictor factor") OR "predictors") OR "predictors factors") OR "predictors of complication rate") AND complications[MeSH Terms]) OR "complication") AND ecmo[MeSH Terms]) OR "extracorporeal membrane oxygenation complications") OR "extracorporeal membrane oxygenation support") AND complications[MeSH Subheading]; Filter: >18years; language: English, Spanish and Portuguese; last 5 years (2014-2018); |
| Scopus | TITLE-ABS-KEY (risk AND factors) OR ALL (risk AND factor) OR ALL (predictors) OR ALL (predictor) OR ALL (predictor AND factor) OR ALL (predictors AND factors) AND TITLE-ABS-KEY (ecmo) OR TITLE-ABS (extracorporeal AND membrane AND oxygenation) AND TITLE-ABS (complications) OR ALL (complication); Filter: >18years; language: English, Spanish and Portuguese; last 5 years (2014-2018); |
| Lilacs | (mh:(fatores de risco)) OR (mh:(risk factors)) OR (tw:(fatores preditores)) OR (tw:(risk factor)) OR (tw:(preditores)) OR (tw:(predictors)) OR (tw:(predictors factors)) AND (tw:(ecmo)) OR (mh:(extracorporeal membrane oxygenation)) OR (tw:(extracorporeal membrame oxygenation support)) OR (tw:(extracorporeal life support)) AND (tw:(complicações)) OR (tw:(complication)) OR (tw:(complications)); Filter: >18years; language: English, Spanish and Portuguese; last 5 years (2014-2018); |
| Cinahl (EBSCO) | MH complications OR TI complications AND TI risk factors OR TI (predictors or risk factors) AND MJ extracorporeal membrane oxygenation OR SU ecmo OR SU extracorporeal membrane oxygenation OR TI extracorporeal membrane oxygenation; Filter: >18years; language: English, Spanish and Portuguese; last 5 years (2014-2018); |
| Web of Science | TS= ((((((risk factors OR risk factor) OR predictor) OR predictor factor) OR predictors))) AND TS= ((complications OR complication)) AND TS= (((extracorporeal membrane oxygenation OR ECMO) OR extracorporeal life support)) Filter: >18years; language: English; last 5 years (2014-2018); |

A preliminary search was performed in PUBMED to verify the trend of general publications on ECMO per year, in order to limitation year of publication. The strategy used was: ((ecmo) OR Extracorporeal Membrane Oxygenation [MeSH Terms]) OR Extracorporeal Membrane Oxygenation. In this preliminary search, more than 4800 publications were identified in the years 2014 to 2018, almost twice as many as what was found from 2009 to 2013 (approximately 2700 publications).

Articles published from 2014 to 2018 in English, Spanish or Portuguese, which analyzed the predictive factors of ECMO complications in adult patients using multivariate analysis (e.g., logistic regression or multiple linear regression) were included in the study. Narrative literature reviews, case studies, descriptive studies, congressional records, editorials, and studies that included pregnant women, children, or other associated ventricular devices were excluded.

After reading the titles and abstracts, the articles that met the eligibility criteria of the study were read in full to reapply the inclusion criteria. The identification and screening processes were performed by a single researcher. The eligibility and inclusion processes of the studies were verified by two researchers independently, who then later arrived at a consensus.

Data evaluation: The quality of the studies was evaluated using the Downs & Black scale, developed and validated to estimate methodological quality of observational and experimental studies. It is recognized as methodologically strong, and consists of 27 evaluation items, divided into 5 domains: 1) reporting; 2) external validity; 3) bias; 4) confounding variables; 5) power. The answers are punctuated according to the values: 1 - if the criterion is present, 0 - if it is absent; only one item has a score ranging from 0 to 2, in which each criterion is punctuated differently[14-15].

As this review was composed entirely of observational studies, the Downs & Black scale was adapted as suggested by the Cochrane collaboration, because some issues are not applicable to these studies[15]. Therefore, question 8 was excluded from evaluation, as it analyzed potential adverse events in randomized trials; questions 14 and 15 were excluded because they analyzed blinding of both the patients and the outcome evaluators, related to exposure/intervention knowledge; and, finally, questions 19, 23 and 24 were also excluded, as they assessed the patient's adherence to the intervention and the randomization of studies, and also assessed whether there was clarity and confidentiality in the description of these data. The score for question 27, regarding the power of the study, was modified, maintaining the same scoring criteria as the other questions on the scale, ranging from 0 to 1.

The total possible score of the scale equaled 22. Therefore, high quality studies were those that reached a score greater than or equal to 15 points.

Data analysis: The predictors found were categorized according to the types of complications secondary to ECMO treatment:

- Neurological complications, such as intracranial hemorrhage, brain death, ischemic stroke, and seizure.
- Infectious complications, such as bloodstream infection and urinary tract infection.
- Kidney complications, such as acute renal failure with or without need for hemodialysis.
- Mechanical complications, such as the presence of fibrin or thrombi, whether or not these required the replacement of the circuit or oxygenator.
- Hemorrhagic complications, such as cardiac tamponade, hemothorax, and bleeding at the cannulation site.
- Other complications: those not included in the complications noted above, such as formation of a lymphocele, and severe thrombocytopenia.

Presentation of the results: The results are presented in a descriptive way, using a synoptic table, whose main function was to highlight the information considered relevant for the analysis of the data of each study. This information was recorded according to: author; year of publication; country; periodical; Qualis classification of nursing periodicals, 2013-2016; impact factor according to Journal Citation Reports; study quality evaluation; type of study; sample; ECMO modality; objective; multivariate analysis results per regression models, so that odds ratios, R2 confidence interval and/or p values were considered in the studies; and, predictors of ECMO complications.

Because this was an integrative review, approval of an ethics committee was not required.

## RESULTS

A total of 1629 articles were identified and, after eliminating the duplicates, 1510 articles were eligible based on titles and abstracts. After applying the exclusion criteria, 19 articles were included in the review (Figure 1).

Most articles were of the cohort type (n=18; 94.73%), and were conducted mainly in the USA (n=5; 26.31%). The journals in which the articles were published were stratified into Qualis A1 to B2 for the nursing area, nine of which presented higher strata (A1 and A2), six in B1 and B2, and four had no classification in the nursing area. The impact factor ranged from 0.55 to 4.82, and only one journal did not have this type of evaluation. Samples ranged from ten to 4988 subjects (Chart 2).

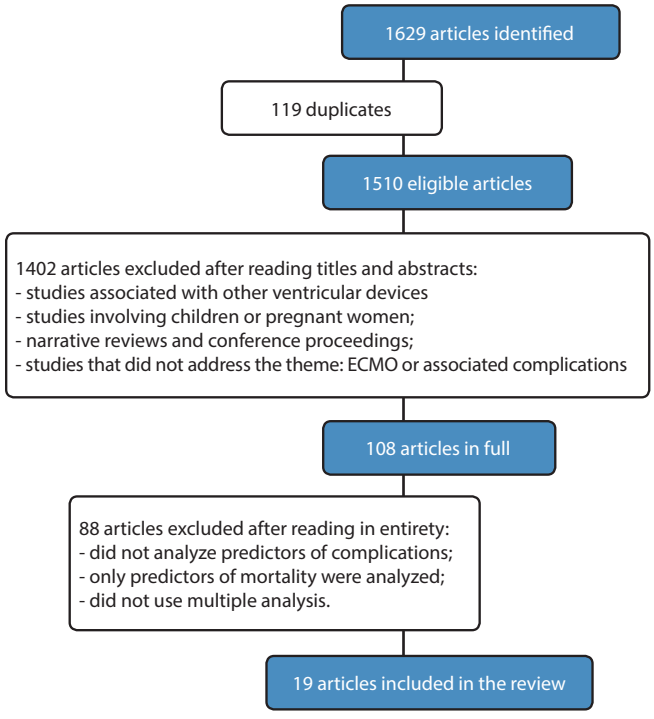


**Figure 1** - Flowchart of article selection

**Chart 2** - Distribution of the characteristics of the studies included in the review, based on article identification, type of study, sample/modality, objective, multivariate analysis results, and predictors of extracorporeal membrane oxygenation complications

| Article identification | Type of study/ quality | Sample/ECMO modality | Objective | Findings/Multivariate analysis | Predictors |
|---|---|---|---|---|---|
| Evans et al.[16] (2017), USA Perfusion Qualis: B2 FI: 0.65 | Cross-Sectional / High | 41 oxygenators were analyzed after treatment of 27 patients with cardiogenic shock and acute myocardial infarction / VV, VA ECMO | To quantify thrombus volume in the oxygenator and correlate it with demographic data, flow characteristics, and anticoagulation parameters | The mean volume of thrombi in oxygenators was 11.4 $cm^3$. Increase of 1L/min in the flow (p=0.038); VA / VV ECMO modality (p=0.026); each 1 $cm^3$ of visible thrombus (p<0.001), $R^2$ Coefficient adjusted from linear regression=0.39. | The combination of median flow (L/ min), VA modality of ECMO, and visible increase of thrombi in the oxygenator are predictors of internal volume in the thrombus. |
| Lorusso et al.[17] (2016), Holland / Crit Care Med Qualis: A1 FI: 3.88 | Retrospective Cohort / High | 4522 adults with cardiac, respiratory and CPR indications. Data collected from 230 ECMO centers from ELSO / VA ECMO records | To identify predictors of neurological complications | Neurologic complications occurred in 15.1% of patients. *Predictors in respiratory indication:* pre-ECMO CPR [OR: 2.44; 95% CI (1.48-4.02);p<0.0001]; hemolysis (plasma free Hb>50mg/dL) [OR:2.1; 95%IC(1.12-4.02);p=0.0001]; inotropes in ECMO [OR:1.74; 95%IC(1.06-2.84;p=0,027]. *Predictors in cardiac indication:* age [OR:0.99;95%IC(0.98-0.99); p=0.001]; pre-ECMO CPR (OR:2.34;95% CI(1.84-2.97); p<0.0001; inotropes in ECMO (OR:1.49; 95% IC (1.13-1.96);p=0.005; tamponade (OR: 1.73; 95%CI (1.14-2.64) p=0.01; DIC (OR: 1.70;9 5%IC (1.06-2.72); p=0.026); hypoglycemia (OR:2.50; 95% CI (1.42-4.40); p=0.001; Cr>3mg/dL (OR:1.77; 95% CI(1.32-2.37); p<0.0001; 1.5mg/dL<Cr<3mg/dL (OR:1.49; 95% CI(1.14-1.96); p=0.004. Predictors in E-CPR: age (OR:0.99; 95%CI(0.98-0.99); p=0.039; hypoglycemia (OR:4.81; 95%CI(1.46-15.87);p=0.010; need for hemodialysis (OR:2.01; 95%CI(1.29-3.13), p=0.002; Cr>3mg/dL (OR:1.66; 95%CI(1.13-2.42);p=0.009); 1.5mg/dL<Cr<3mg/dL (OR:2.19; 95%CI(1.49-3.00), p<0.0001. | *Predictors in respiratory indication*: pre-ECMO CPR, plasma free Hb> 50mg / dL, use of inotropes during ECMO. Predictors in cardiac indication: age (39-53 years), pre-ECMO CPR, use of inotropes ECMO,, tamponade, DIC, glucose <40mg/ dL, Cr>3mg/dL and 1.5mg/dL<Cr<3mg/ dL. *Predictors in the E-CPR:* age (39-53 years), glucose <40mg/dL, need of hemodialysis, 1.5mg/dL<Cr<3mg/ dL. |
| Lorusso et al.[18] (2017), USA/ Crit Care Med Qualis: A1 FI: 3.88 | Retrospective Cohort / High | 4988 adults on IR. Data collected from 350 ECMO centers from ELSO / ECMO VV registries | Investigate factors associated with neurological complications | Neurological injuries occurred in 7.1% of cases, such as intracranial hemorrhage, brain death, ischemic stroke, and seizure pre-ECMO CPR [OR:3.12; 95%CI(1.78-5.46); p<0.001]; Hyperbilirubinemia [OR:2.37; 95%CI(1.44-3.88); p=0.001]; Hemodialysis [OR:2.33; 95%CI(1.28-4.42); p=0.006]. | Pre-ECMO CPR, dialysis, and hyperbilirubinemia during ECMO are predictors of neurological complications. |
| Abrams et al.[19] (2016) USA/ Intensive Care Med Qualis: A1 FI: 4.92 | Retrospective Cohort / High | A hundred adults in severe AKI/ VV, VA ECMO | To verify the relationship between ECMO duration and other clinical characteristics during cannulation with the development of thrombocytopenia | APACHE II score (increase of 5 points) [OR: 1.35; 95% CI (0.94-1.94)], platelet count at cannulation <188,000 / µL (decrease of 25,000 / µL) [OR: 1.35; 95% CI (1.10-1.64)]. | Lower platelet count in cannulation and higher APACHE II score are predictors of severe thrombocytopenia. |
| Kim et al.[20] (2017), Korea/ J Korean Med Sci Qualis: S/A FI: 1.18 | Retrospective Cohort / High | 61 adults in cardiogenic shock / VA ECMO | To investigate the risk factors for nosocomial infection | 18 infections occurred (23.0%) in 14 individuals, with bloodstream infection prevalence Preoperative Cr [OR: 2.17, 95% CI (1.06-4.44), p = 0.033]; Time in ECMO [OR: 1.40; 95% CI (1.08-1.81); p = 0.011]. | Higher serum levels of preoperative Cr (mg / dL) and longer ECMO (days) were predictors of infection. |
| Omar et al.[21] (2016), USA/ J Crit Care Qualis: B1 FI: 2.48 | Retrospective Cohort / High | 171 adults in cardiogenic shock, post-cardiotomy, CPR, post-tx, massive pulmonary embolism, AKI/ VV, VA ECMO | To investigate the predictors of ischemic stroke | Ten patients developed ischemic stroke (5.8%) while on ECMO. Pre-ECMO lactic acid> 10 mmol / L [OR: 7.58; 95% CI (1.39-41.22); p = 0.019). | High serum level of pre-ECMO lactic acid was a predictor of ischemic stroke. |

To be continued

Chart 2

| Article identification | Type of study/ quality | Sample/ECMO modality | Objective | Findings/Multivariate analysis | Predictors |
|---|---|---|---|---|---|
| Ryu et al.[22] (2015), South Korea/ BMC Anesthesiol Qualis: B2 FI: 1.78 | Retrospective Cohort / High | 115 adults survived to E-CPR / VA ECMO | To investigate the predictors of neurological outcomes | 41% had poor neurological outcomes and 24 evolved to brain death. Dependent variable on multivariate analysis = good neurological outcomes: Pre-ECMO lactic acid [OR: 0.76; 95% CI (0.66-0.88), p <0.001]; pre-ECMO Hb [OR: 1.50; 95% CI (1.07-2.10), p = 0.019]; interval from CA to ECMO setup [OR: 0.96; 95% CI (0.92-0.99) p = 0.042]. | The highest pre-ECMO serum lactic acid level, the lowest pre-ECMO serum Hb level, and a longer CA interval before ECMO was established were predictors of poor neurological outcomes. |
| Arachchillage et al. [23] (2018), UK/ Semin Thromb Hemost Qualis: A2 FI: 3.12 | Retrospective Cohort / High | 149 adults in severe AKI / VV ECMO | To identify clinical and laboratory variables that predict intracranial hemorrhage | The prevalence and incidence of intracranial bleeding were 10.7% and 5.2%, respectively. Thrombocytopenia [OR: 22.6; 95% CI (2.6-99.5), p = 0.001]; creatinine clearance [OR: 10.8; 95% CI (5.6-16.2), p <0.0001]. | Thrombocytopenia and reduced creatinine clearance were predictors of intracranial hemorrhage. |
| Aubron et al.[24] (2016), France/ Ann Intensive Care Qualis: A1 FI: 4.82 | Retrospective Cohort / High | 147 adults with cardiovascular problems, post or pre-tx, with pneumonia, in CA, post cardiac surgery / VA , VV ECMO | To identify the risk factors for bleeding | The most common bleeds were: cannulation site (37%); hemothorax or cardiac tamponade (17%)<br>aPTT ≥ 70sec on the previous day (OR: 3.0, 95% CI (1.64-5.47), p = <0.01), APACHE III score (OR: 1.01, 95% CI (1: 1, 95% CI: 1.64-5.47), p = <0.01) (P = 0.01), ECMO post-surgery [OR: 3.04, 95% CI (1.62-5.69), p <0.01). | Elevated aPTT, high APACHE III score, and ECMO postoperatively were predictors of hemorrhagic complications. |
| Austin et al.[25] (2017), Australia/ Crit Care Resusc Qualis: A2 FI: 2.01 | Retrospective Cohort / High | 98 adults with primary graft dysfunction, HF, AMI, respiratory tract infection, severe asthma / VV, VA ECMO | To evaluate the risk factors for infections | Twenty-one (21.4%) patients presented infection: 8 developed bloodstream infection, 14 infections at the cannulation site, and two infections at the sternum.<br>Immunosuppression [OR: 2.9; p = 0.04]; VA ECMO [OR: 14.7; p = 0.01]. | Immunosuppression and treatment with VA ECMO were predictors of infection. |
| Chang et al.[26] (2017), China/ Int J Clin Exp Med Qualis: B1 FI: 0.83 | Retrospective Cohort / High | 71 adults with ARDS, post-cardiotomy or other cardiovascular or pulmonary problems / VV, VA ECMO | Determine the risk factors for AKI | Approximately 73% developed acute kidney injury. Length of ICU stay (<20 days vs. 20 days) [RR: 0.32; 95% CI (0.14-0.73); p <0.007]; infection [RR: 2.28; 95% CI (1.06-4.87); p <0.034]. | Length of ICU stay and infection were predictors of AKI. |
| Sandersjöo et al.[27] (2017), Switzerland/ J Intensive Care Qualis: S/A FI: S/A | Retrospective Cohort / High | 253 adults with cardiac or pulmonary indication or CA/ VV, VA ECMO | To identify predictors of intracranial hemorrhage | About 20% developed intracranial hemorrhage, with a mortality rate of 81% within one month.<br>Antithrombotic therapy [p = 0.011; $R^2$ = 0.037]; platelet count [p = 0.035; $R^2$ = 0.074]. | Pre-admission antithrombotic therapy and low platelet count are predictors of intracranial hemorrhage. |
| Hoshino H et al.[28] (2018), Japan/ J Artif Organs Qualis: S/A FI: 0.61 | Retrospective Cohort / High | 10 adults with acute RF / VV ECMO | To identify the coagulation / fibrinolysis markers as predictors for ECMO circuit replacement | Six circuit replacements were necessary. Soluble fibrin (10µg / mL) [OR: 1.20; 95% CI (10.6-1.36); p <0.01] | Soluble fibrin is a predictor for ECMO circuit exchange. |
| Lotz et al.[29] (2017), Germany/ ASAIO J Qualis: S/A FI: 0.55 | Retrospective Cohort / High | 59 adults with RF or HF / VV, VA ECMO | To identify risk factors for bleeding during ECMO | Bleeding occurred in 60% of the patients in VA ECMO and in 80% in VV ECMO. Fungal pneumonia [RR: 4.38; 95% CI (1.15-16.71); p = 0.031]. | Only fungal pneumonia remained a predictor of bleeding requiring therapeutic intervention. |
| Luyt et al.[30] (2016) France/ Intensive Care Med Qualis: A1 FI: 4.92 | Retrospective Cohort / High | 135 adults with indication for VV ECMO, but with a primary diagnosis of ARDS / VV ECMO | To investigate the risk factors for neurological complications | 18 (13.3%) patients developed neurological complications; the most common was intracranial bleeding (10 individuals). Kidney insufficiency [RR: 6.13; 95% CI (1.29-28.57)]; $PaCO_2$ <-27mmHg [RR: 6.02; 95% CI (1.28-28.57)]. | Kidney insufficiency at ICU admission and low pre-ECMO $PaCO_2$ were predictors of intracranial bleeding. |
| Lyu et al.[31] (2015), China/ J Cardiothorac Vasc Anesth Qualis: B2 FI: 1.57 | Retrospective Cohort / High | 84 adults post-cardiac, post-cardiotomy and in HF / VA ECMO | To investigate whether the increased serum of plasma free hemoglobin level is associated with AKI | The incidence of AKI was 48.8%, and 41.7% evolved to hemodialysis. Free hemoglobin [OR: 1.05; 95% CI (1.01-1.08); p = 0.005]. | Free plasma hemoglobin increased during ECMO was a predictor for AKI. |

To be continued

Chart 2 (concluded)

| Article identification | Type of study/ quality | Sample/ECMO modality | Objective | Findings/Multivariate analysis | Predictors |
|---|---|---|---|---|---|
| Otani et al.[32] (2017), Japan/ Am J Emerg Med Qualis: B2 FI:1.31 | Retrospective Cohort / High | 102 adults admitted after extra-hospital cardiac arrest and treated with E-CPR / VA ECMO | To verify the frequency of bleeding complications and determine their related factors | 70% had some type of bleeding, and the VA ECMO puncture site and the gastrointestinal tract were the most frequent bleeding events. Age (increase of one year) [OR: 1.053; 95% CI (1.00-1.10); p = 0.018]; platelet count (103 / µL increase) [OR: 0.984; 95% CI (0.97-0.99), p = 0.014]; D-dimer (1 µg / mL increase) [OR: 1.066; 95% CI (1.01-1.11); p = 0.006]. | Older age, lower platelet count, and higher serum D-dimer level at admission were predictors of bleeding complications. |
| Salna et al.[33] (2017), USA/ J Vasc Surg Qualis: A2 FI:1.40 | Retrospective Cohort / High | 192 adults in refractory cardiogenic shock / femoral VA ECMO | To evaluate the incidence and risk factors associated with lymphocele formation | Lymphocele formation was identified in 16% of individuals. Primary dysfunction of cardiac graft [OR: 8.66; 95% CI (3.38-22.16); p <0.001]. | Primary dysfunction of cardiac graft was a predictor of lymphocele formation. |
| Trudzinski et al.[34] (2016), Germany/ Ann Intensive Care Qualis: A1 FI: 4.82 | Retrospective Cohort / High | 102 adults in acute RF / VV ECMO | To analyze the incidence and predictive factors of thromboembolism | The highest incidence of thrombosis was related to cannulation and the incidence of pulmonary embolism was 11.1%. Time on ECMO [OR: 1.04; 95% CI (1.00-1.09); p = 0.026]; aPTT> 50s [OR: 0.97; 95% CI (0.95-0.99); p = 0.024]. | Longer time on ECMO and higher aPTT were predictors of thrombosis and pulmonary thromboembolism. |

*Note: AKI: acute kidney injury; APACHE: evaluation of acute physiological score and chronic disease; ARDS: acute respiratory distress syndrome; aPTT: activated partial thromboplastin time; CA: cardiac arrest; CPR: cardiopulmonary resuscitation; Cr: creatinine; DIC:Disseminated intravascular coagulation; ECPR: Extracorporeal cardiopulmonary resuscitation; ELSO: extracorporeal life support organization; HF: heart failure; ICU: intensive care unit; IF: impact factor; N/A: not evaluated; OR: odds ratio; 95% CI: 95% confidence interval; RR: Risk ratio; RF: respiratory failure; Tx: transplantation; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation; VV-ECMO: veno-venous extracorporeal membrane oxygenation.*

There was a balance in the context of cardiac and pulmonary indications, as the proportion between ECMO VV (n=13; 68.42%) and ECMO VA (n=14; 73.68%) was approximated. The main clinical situations that required ECMO were cardiogenic shock, respiratory failure, and cardiorespiratory arrest (Chart 2).

Neurological complications were the most frequently investigated (seven studies)[17-18,21-23,27,30], followed by hemorrhagic (three studies) [24,29,32], kidney (two studies)[26,31], infectious (two studies)[20,25], and mechanical (one study)[16] complications. Other complications were identified in the studies and were categorized as "other": formation of a lymphocele (one study)[33], thrombocytopenia (one study)[19], and thrombosis or pulmonary thromboembolism (one study)[34].

The frequent complications included: neurological (5.2%-15.1%) [17-18,21-22,23,27,30], bleeding (17%-80%)[24,29,32], infection (21.4%-23.0%) [20,25], kidney complications (48.8%-73%)[26,31], lymphocele formation (16% in the total sample, in which 93.5% received heart transplants)[33], thrombocytopenia (22%)[19], and thrombosis or pulmonary thromboembolism [34].

The frequency of mechanical complications was presented, because this was a study that used oxygenators to measure the volume of thrombi[16].

Nineteen predictors were identified for neurological complications: age[17], CA pre-ECMO[17-18], use of inotropes during ECMO[17], post-ECMO hypoglycemia[17], dialysis during ECMO[17-18], plasma free hemoglobin >50mg/dL, cardiac tamponade, disseminated intravascular coagulopathy, creatinine> 3mg/dL or creatinine between 1.5-3.0mg/dL[17], hyperbilirubinemia during ECMO [18], high level of pre-ECMO lactic acid[21-22], lower pre-ECMO serum hemoglobin level[22], interval between CA and ECMO[22], thrombocytopenia[23,27], reduced creatinine clearance[23], pre-admission antithrombotic therapy[27], kidney insufficiency at ICU admission, and low pre-ECMO $PaCO_2$[30].

For bleeding complications, high previous aPTT (≥70 sec), elevated APACHE III score, and post-surgery ECMO[24] were some of the predictors identified. In addition, a one-year increase in age incurs a 5.3% greater chance of major bleeding, while an increase of 1000 platelets/µL decreases the chance of bleeding by 1.6%. At each increase of 1 µg/mL serum D-dimer level, the chance of bleeding increases by 6.6% [32]. In the cases where therapeutic intervention for bleeding was necessary, fungal pneumonia was the only predictor[29], and the central catheter insertion and cannulation sites were the most common bleeding sites.

Three predictors for kidney complications were identified: the length of ICU stay> 20 days, infection - which increases the chance of AKI by 2.28 times[26], and the elevated serum free hemoglobin level[31].

The predictors identified for infectious complications were: VA modality[25], compromised immune system[25], preoperative creatinine level (increase the chance of infection in 2.17 times each mg/dL of increase in creatinine), and time in ECMO (increase in the chance of infection of 40% each day in ECMO)[20].

For mechanical complications, one study demonstrated a combination of variables (combination of median flow, VA modality, and increase in visible thrombus) predict the internal volume in the thrombus in the ECMO oxygenator in 39%[16].

Among other complications, severe thrombocytopenia, lymphocele, and thromboembolic phenomena were identified. The chance of severe thrombocytopenia increases by 35% with each 5 points increase in the APACHE II score, and each decrease in the platelet count of 25,000/µL from 188,000/µL after cannulation[19]. Primary cardiac graft dysfunction among transplanted individuals was associated with an 8.66 time increase in the chance of lymphocele[33]. For venous thromboembolism and venous thrombosis, one extra day in ECMO increases the chance by 4%, while a PTT > 50 sec decreases the chance by 3% [34].

## DISCUSSION

Even with the advances in ECMO treatment to promote proper recovery and prevent the progression of preexisting disease, this

same therapy can cause harm, with an unsatisfactory prognosis. In this review, we identified predictors of ECMO-related complications in adult patients.

The predominance of cohort studies reflects the appropriateness of this type of study to identify predictor variables. The publications in journals with relevant impact factors, as well as Qualis seniors for the nursing area, are a reflection of the high quality of the studies, verified by the Downs & Black criteria. Next, the findings will be discussed considering each category of complications.

Predictors of neurological complications: Neurological complications were more common in patients receiving extracorporeal cardiopulmonary resuscitation.

ECMO can very quickly normalize blood flow and oxygenation in patients in CA. However, it still presents limitations because of the need for anticoagulation and the time to prepare, install and perform the system cannulation. The whole device must be prepared and coordinated by a trained and specialized multidisciplinary team, in order to minimize the interval between the CA and the initiation of ECMO, as the sooner the patient is returned to spontaneous circulation, the lower the risk of neurological complications due to hypoxia[22].

Among the care to be provided, monitoring and analyzing other clinical and laboratory data is fundamental, as they subsidize the treatment of patients in CA. A high level of pre-ECMO lactic acid (>10 mmol/L) and low hemoglobin levels were found to be important predictors of neurological complications. Intensive and optimized adjustment of these factors can contribute to reducing the incidence of ischemic stroke and mortality[21-22].

Intracranial hemorrhage was one of the most prominent complications among the neurological lesions. Recent studies have shown that thrombocytopenia and impaired kidney function increase the risk of intracranial bleeding, especially subarachnoid hemorrhages. Therefore, evaluating each condition and considering preventive strategies, such as previous treatment of kidney function, can reduce the risk of bleeding during ECMO[23,27,30].

Predictors of bleeding complications: Bleeding complications in patients undergoing ECMO result in significant mortality (40% -60%)[24,29,32]. In order to reduce this rate of hemorrhagic complications, tranexamic acid and Factor VIIa demonstrated good results in interrupting bleeding in 34% of the cases[29].

This high rate of bleeding complications is associated with anticoagulation intensity, as aPTT and platelet level were found as predictors[24,32].

During ECMO, the consumption of platelets and coagulation factors occurs due to the contact of the blood with a non-endothelial surface, and anticoagulant administration is necessary to prevent thrombosis in the circuit. Maintaining adequate APT control (<70s) minimizes the risk of bleeding, and contributes to preventive bleeding measures, optimizing patient care[29,32].

In addition, post-CA patients may progress with hyperfibrinolysis or disseminated intravascular coagulopathy due to tissue hypoperfusion and hypoxia. As D-dimer is a product of fibrin degradation, and is a marker of CIVD, it should be monitored in patients treated with E-CPR to drive treatment[32].

Finally, preventive actions against bleeding in ECMO patients with fungal pneumonia and a high APACHE III score can be beneficial, as they were also predictors of bleeding[24].

Predictors of kidney complications: The definition of AKI was analyzed differently among the studies that investigated predictors of kidney complications: one used the Acute Kidney Injury Network (AKIN) criteria[31], and the second defined it as an increase equal to or greater than 300% of the baseline creatinine concentration[26]. However, these criteria did not influence the prevalence of this complication.

There are many potential causes of AKI in an individual undergoing ECMO therapy, but the pathophysiology of AKI during ECMO is still not well defined[26]. Among these reasons are the pre-ECMO patient's clinical conditions or the device's own mechanism. Thus, ICU stay and infection as predictors of AKI were expected findings.

Hemolysis - caused by the speed of the centrifugal pump, increased oxygenator/pump resistance, or the entire system, due to the presence of thrombi and fibrin - can result in AKI by decreasing tissue perfusion. Therefore, monitoring the system pressure gradient, maintaining adequate flow and avoiding very negative venous pressure can contribute as preventive measures for AKI[31].

Predictors of infectious complications: In the two studies investigating predictors of infectious complications, the eligibility criteria for the samples included staying on ECMO longer than 48 hours, as a shorter time was insufficient to identify ECMO-related infection[20,25]. Among the infections, the most common were bloodstream infections, among which the gram-negative pathogens were the most prevalent[20,25].

The length of stay in ECMO, and elevated serum creatinine levels, were significantly associated with the risk of infection due to an impaired immune system [18]. This was also observed in a study involving patients treated using the VV and VA modalities, in which one of the predictive factors for developing infection during ECMO was immunosuppression, and there was no significant difference regarding the use of antibiotics during hospitalization[25].

Among the modifiable factors, the increase in preoperative creatinine reflects kidney injury, by increasing the leukocytes in the renal system and, consequently, compromising the immune response. Although the origin of this pathophysiology is still unknown, it is essential to maintain adequate control of serum creatinine levels to optimize treatment[20].

Mechanical complications: Despite the use of continuous anticoagulant and a heparinized ECMO circuit, there is still a chance of thrombus development in the system. Thus, it is challenging for the multiprofessional team to establish an ideal level of anticoagulation, avoiding complications secondary to coagulopathy, bleeding, and the presence of thrombi and fibrin[16].

The fact that visualization of the thrombus external to the oxygenator is one of the predictors of thrombus volume in the internal part of the system could be an indication for clinical decision-making to replace the oxygenator[16]. In addition, monitoring for formation of visible thrombi in the oxygenator should be intensified during flow reduction at ECMO weaning.

A study that analyzed several markers of coagulopathy and fibrinolysis identified soluble fibrin - the product of fibrinogen with thrombin, whose high levels indicate hypercoagulopathy - as an independent predictor of ECMO circuit change, i.e., high

levels of soluble fibrin suggest the ideal time to replace the circuit, which improve the device performance and can avoid higher expenses[28].

Other complications: These "other" complications included severe thrombocytopenia, lymphocele, and thromboembolic phenomena.

The predictors for occurrence of severe thrombocytopenia were low platelet count after cannulation, as well as a higher score in the APACHE II severity score among individuals with respiratory support. The authors consider that the initial severity of critical illness, and the development of multiple organ failure during ECMO therapy, may explain thrombocytopenia associated with the device. Platelet counts after cannulation can be considered an indirect measure of the patient's platelet reserve, which is also affected by the severity of the critical illness, and exposes the individual to medications that induce thrombocytopenia over time[19].

These findings can help professionals, in clinical practice, to anticipate which patients with respiratory indication for ECMO are more likely to require blood product transfusions and to have increased risk for bleeding[19].

Lymphocele formation is a severe, specific complication due to femoral cannulation, and in some cases, requires surgical intervention. Cardiac transplant patients on Tacrolimus - an immunosuppressant associated with the incidence of post-transplant diabetes – have an strong association to this complication; its incidence was significantly influenced by primary graft dysfunction. The authors note that lymphocele formation in these patients is probably due to the combination of manipulation of the femoral arteries in patients with diabetes, and high doses of immunosuppressants[33]. Therefore, when caring for transplanted patients during ECMO, the surveillance for this occurrence, persistence, volume, and infectious characteristics of possible inguinal drainage should and must be intensified.

Although it is possible to obtain percutaneous access, studies have demonstrated an incidence of vascular complications of 17-35% in patients receiving ECMO through femoral cannulation, defined as: acute limb ischemia, bleeding during cannulation or decannulation, compartmental syndrome, pseudoaneurysm, lymphocele, distal thrombosis, and amputation[34-35]. However, no articles were identified that determined the predictive factors for vascular complications, and lymphocele formation was the only complication cited that had specific predictors.

The frequency of venous thromboembolism and venous thrombosis was influenced by the time on ECMO and anticoagulation level, although the institution where the study was conducted used usual anticoagulation recommendations. The main site where thrombi were identified was the inferior vena cava (51%)[36].

During extracorporeal care, changes can occur in blood composition and coagulopathy related to contact with a non-endothelial surface can occur, as well as those caused by the pump. In addition, vascular injury is common at the cannulation site, with vessel stiffening until the central areas are reached. This generates large areas of low blood flow and stasis along the cannula, favoring the formation of thrombi. Therefore, the authors recommend that the aPTT target should be higher, to prevent such complications in patients whose risk profile for thromboembolic phenomena is elevated[36].

### Study limitations

The results of this review are limited by the selection of studies published in only three languages, in the years 2014 to 2018, without inclusion of gray literature. However, the included articles showed important representativeness of studies on the related predictors of ECMO complications, as a significant number of databases were used for the search; the English language is widely used for dissemination of scientific research results; and ECMO publications basically doubled in the PUBMED database from 2014 to 2018, compared to the previous five-year period.

### Contributions to the Health Area

As the recommended care provided to the patient with ECMO is that which is performed by a multidisciplinary team, the knowledge of the predictors of the main ECMO complications enables the individualized targeting of preventive interventions for modifiable factors - such as, low levels of hemoglobin or platelets pre-ECMO and high previous aPTT – from the disciplinary knowledge of each profession, as well as intensification of monitoring for early recognition of non-modifiable factors, such as age, CA before ECMO, and dialysis during ECMO.

## CONCLUSIONS

Predictors for major ECMO-related complications were found in adult patients: 19 for neurological complications (age, pre-ECMO CA, use of inotropes during ECMO, post-ECMO hypoglycemia, dialysis during ECMO, plasma free hemoglobin >50mg/dL, cardiac tamponade, disseminated intravascular coagulopathy, creatinine >3mg/dL or creatinine between 1.5-3.0mg/dL, hyperbilirubinemia during ECMO, high level of pre-ECMO lactic acid, lower pre-ECMO hemoglobin serum, the interval between CA and initiation of ECMO, thrombocytopenia, reduced creatinine clearance, pre-admission antithrombotic therapy, kidney insufficiency at ICU admission, and pre-ECMO low PaCO2); seven for hemorrhagic complications (previous high (≥70 sec), high APACHE III score, post-surgery ECMO, older age, lower platelet count, higher serum D-dimer level, and fungal pneumonia); four for infectious complications (modality VA, immunological impairment, elevated preoperative creatinine level, and ECMO length of stay); three for renal complications (ICU length of stay >20 days, infection, and elevated serum free plasma hemoglobin level); and a combination of three factors for mechanical complications (combination of median flow, VA modality, and visible increase in thrombi).

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