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Clinical characteristics and predictive factors for mortality in adult patients treated with ECMO: a retrospective cohort study

Medical Science

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ABSTRACT

Objective: to characterize the profile of adult patients treated with ECMO according to survival and to identify predictors for mortality. **Method:** A retrospective cohort study performed at a high complexity hospital specialized in cardiology and pneumology, member of the Extracorporeal Life Support Organization (ELSO). All records of patients older than 18 years who used ECMO therapy in the last 6 years were evaluated. Patients younger than 18 years, treatment with other circulatory support modalities, and patients whose medical records were insufficient to perform the study were excluded from the analysis. For the data analysis the included patients were divided into survivors and non-survivors. **Results:** the mortality observed during the hospitalization period was 83%. There was no difference between the groups in relation to the male sex (70% vs. 50%, p=0,449), age (40 + 12 years old vs. 29 + 12 years old , p=0,156) and left ventricular ejection fraction (45,2 + 22% vs. 55 + 20%, p=0,504). Patients from the non-surviving group presented higher values of the SAPS 3 score when compared to the other group and this difference was significant (87 [77,75 – 92,5] vs. 70 [59,25 – 83,75], p=0,037). **Conclusion:** the mortality of critically ill patients with ECMO was 83,3%. The presence of HF (OR: 2,400, p=0,019) and the Need of dialysis during ECMO use (OR: 1,615, p=0,011) were associated with mortality.

KEYWORDS:

ECMO, Mortality; Heart Failure; Intensive Care Unit.

Introduction

The first record of Extracorporeal Membrane Oxygenation success (ECMO) installation was in the 70's by Hill and cols [1]. Since that time, the use of ECMO for treatment of critical patients has increased significantly throughout the world. Initially, the results of ECMO therapy for adult patients with acute respiratory distress syndrome (ARDS) were disappointing[2] and remained that way for a few years. However, the development of new membranes, associated with the results of other studies, has made it possible to increase the effectiveness in the use of ECMO therapy from 2009 in patients with H1N1[3-5].

ECMO therapy has been used as a bridge for adult patients awaiting transplant therapy (pulmonary and/or cardiac), in primary graft dysfunction after transplantation and as a bridge for recovery in patients with acute heart failure that use some type of ventricular assistance device [6-7]. However, some considerations must be observed with regard to the therapeutic indications for support with ECMO, due to the high cost of therapy and need of specialized team [3]. The support with ECMO has been shown to be effective in various scenarios, but the mortality rates and complications such as bleeding, ischemia of extremities, kidney injury, infection, hemolysis, stroke, intravascular disseminated coagulation and hepatic dysfunction related to therapy are still high. Due to the high risk and cost and the complexity of this type of support related to patient care, we aimed to describe the profile of adult patients treated with ECMO and to identify the predictive factors for mortality.

Methods

We conducted a retrospective review of all patients supported with ECMO for refractory cardiac and pulmonary failure who were 18 years and older between January 2010 and March 2015 at the Heart Institute (InCor) in Brazil. The Institutonal Review Board at the University of São Paulo approved the review of the medical records of patients, and the need for informed consent was waived.

The data collected in our study included patient demographic information; diagnosis information; indication for ECMO; ECMO support details; medical and surgical history; laboratory, microbiologic and radiographic data; information on organ dysfunction; complications and patient outcomes.

For the data collection, were evaluated the records of all patients over 18 years of age who used ECMO between January 2010 and March

2015. Patients treated with other types of circulatory care were excluded from the study, patients with ECMO when they were less than 18 years old, patients who remained in ECMO for less than 6 hours, and those patients with records that did not contain all the information necessary for the operationalization of the study (Figure 1).

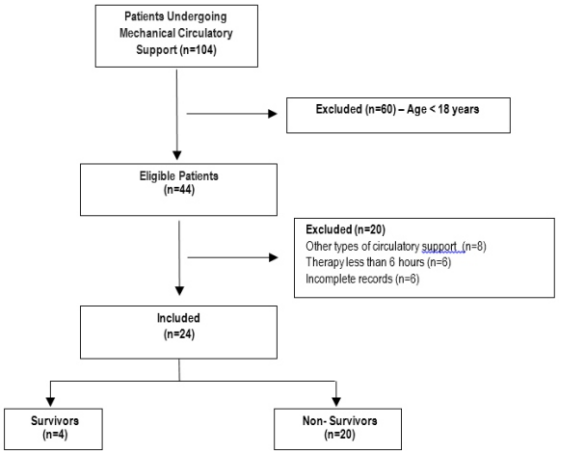

Figure 1. Study flowchart

The search of records of patients submitted to mechanical circulatory assistance was performed at InCor's Medical and Hospital Information Unit (MHIU). From this search, all records of patients treated, exclusively with ECMO, were used to acquire physical records and to collect information in the electronic medical record.

Data collection was performed between February and October 2015. A specific instrument with demographic data, clinical characteristics, procedure data, clinical evaluation, outcomes and the application of scores for the calculation of the probability of (SAPS 3) [8], for the evaluation of the degree of organic dysfunction Sequential Organ Failure Assessment (SOFA) [9] and the Charlson Comorbidity Index (ICC) [10] for the evaluation of comorbidities and prediction of mortality in 10 years. The sample was stratified into two groups: survivors and non-survivors, and for the statistical analysis the Shapiro-Wilk test was used to verify if the data presented normal distribution among the continuous variables. The difference between the groups was assessed using Student's t, Mann-Whitney U, Chi-square and Fisher's exact tests. A value of $p < 0.05$ was considered significant. To evaluate the predictive factors of death, we used multivariate analysis with logistic regression. Survival curves were constructed by the Kaplan-Meier method and compared by the Log-Rank method. The statistical software SPSS (version 20.0; IBM, Armonk, USA) was used for data analysis.

Results

Among 24 patients included in this study, 20 (83%) died and 4 (17%) survived during the hospitalization period. Table 1 presents the clinical-demographic and laboratory characterization of surviving and non-surviving adult patients treated with ECMO.

Table 1 – Clinical-demographic and laboratory characteristics of surviving and non-surviving adult patients treated with ECMO. Brazil, 2017.

Variable	Non-survivors (n=20)	survivors (n=4)	p (value)
Male	14 (70)	2 (50)	0,449
White	18 (90)	4 (100)	0,382
Age	40 + 12	29 + 12	0,156
BMI, kg/m^2	24,2 + 4,7	21,7+ 2,2	0,133
LVEF, %	45,2 + 22	55 + 20	0,504
Comorbidities			
RV dysfunction	13 (68,4)	4 (100)	0,100
Arterial Hypertension	8 (42,1)	0	0,050
Creatinine > 1,5 mg/dL	8 (40)	0	0,057
Cardiac Insufficiency	12 (70,6)	2 (50)	0,442
Atrial fibrillation	7 (35)	1 (25)	0,693
Hepatic dysfunction	4 (20)	1 (25)	0,825
Hypothyroidism	8 (42,1)	0	0,050
Previous	2 (10,5)	0	0,370
Charlson Score	3 [1,0 – 4,75]	1 [0,25 – 1,0]	0,045
Laboratory data (Pre-ECMO)			
SvO_2, %	64,5 + 13,4	56,3 + 21	0,500
Arterial blood pH	7,34 + 0,07	7,4 + 0,04	0,168
Hemoglobin, mg/dL	11,7 + 3,1	11,9 + 3,6	0,919
Lactate, mg/dL	41,3 + 46,6	12,8 + 3,3	0,019
CO_2-GAP, mmHg	10,5 + 7,7	5,5 + 0,8	0,040
PaO_2/FiO_2, ratio, mmHg	333,8 + 234,2	468,5 + 91,2	0,228
Reason for assistance			
Cardiogenic shock	9 (60)	2 (50)	0,140
Bridge to cardiac transplantation	4 (20)	0	
ARDS	2 (10)	1 (25)	
Post-cardiotomy syndrome	1 (5)	1 (25)	
Bridge to lung transplantation	1 (5)	0	
Arteriovenous cannulation	16 (80)	3 (75)	0,825
Use of blood products	CVA 11 (55)	3 (75)	0,447
Procedure time, hours	80,6 + 43	50 + 20	0,059
Mean arterial pressure mmHg	76,2 + 11,5	77,5 + 11,0	0,845
Central venous pressure, mmHg	12,2 + 6,8	9 + 4,2	0,470
Diuresis, ml/kg/h	1,4 + 1,0	2,0 + 0,5	0,264
Inotropic dose, mcg/kg/min	13,2 + 7	9,6 + 0,2	0,075
SOFA Score	8 [6 – 12]	5 [2,25 – 12,25]	0,324
SAPS III	87 [77,75 – 92,5]	70 [59,25 – 83,75]	0,037

Data were expressed in absolute (n) and relative frequency (%); mean ± standard deviation and median [interquartile range]. BMI: body mass index; LVEF: left ventricular ejection fraction; RV: right ventricle; CVA: cerebrovascular accident; SvO2: venous oxygen saturation; CO_2: carbon dioxide; PaO_2: partial pressure of oxygen; FiO_2: inspired fraction of oxygen; ARDS: acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment; SAPS: Simplified Acute Physiology Score.

There were no differences between the groups (70% vs. 50%, p = 0,449), age (40 + 12 years vs. 29 + 12 years, p = 0.156) and left ventricular ejection fraction (LVEF) (45.2 ± 22% vs. 55 ± 20%, p = 0.504). With regard to comorbidities the groups were similar, however, when comparing the ICC values, we observed a significant difference (3 [1.0 - 4.75] vs. 1 [0.25 - 1.0], p = 0.045), in the non-surviving and surviving groups, respectively. In the comparison of laboratory data, we found higher lactate values (41.3 ± 46.6 mg / dL vs. 12.8 ± 3.3 mg / dL, p = 0.019) and Gap-CO2 (10.5 ± 7, 7 mmHg vs. 5.5 ± 0.8 mmHg, p = 0.040) prior to the installation of ECMO in the non-survivors group, with no further differences for the other laboratory data. Patients from the non-surviving group had higher SAPS 3 scores when compared to the other group, and this difference was significant (87 [77.75 - 92.5] vs. 70 [59.25 - 83.75], p = 0.037).

Table 2 shows the clinical course and outcomes of the study patients. We found a significant difference among patients in the non - survivors group when compared to the group of survivors regarding length of ICU stay (14 [9 - 28] days vs. 48 [30.5 - 96.25] days, p = 0.012), and Hospital stay (17.5 [12.25 - 28.75] days vs. 79.5 [62 - 201.25] days, p = 0.005), respectively.

Table 2 – Clinical course and outcomes of surviving and non-

surviving adult patients treated with. Brazil, 2017.

Variable	non-survivors (n=20)	Survivors (n=4)	p (value)
AKI	20 (100)	3 (75)	0,051
Dialysis	7 (35)	1 (25)	0,693
Infection	16 (80)	3 (75)	0,825
Neurological complications	11 (55)	1 (25)	0,264
Time to use ECMO, hours	131 [48,75 – 243,75]	119,5 [101,75 – 157,5]	0,794
Length of stay in ICU, days	14 [9 – 28]	48 [30,5 – 96,25]	0,012
Length of hospital stay, days	17,5 [12,25 – 28,75]	79,5 [62 – 201,25]	0,005

Data were expressed in absolute (n) and relative frequency (%); mean + standard deviation and median [interquartile range]. AKI: acute kidney injury; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.

Table 3 shows the association of seven variables with mortality. For the logistic regression analysis, the lactate and Gap-CO2 variables were considered before ECMO and the SAPS 3 score because they presented different distributions in the non-surviving and surviving groups. Age, heart failure (HF), use of blood products and need for renal replacement therapy were part of the analysis because of the potential to influence outcomes. We observed that only the presence of HF (OR: 2,400, p = 0.019), the need for dialysis during ECMO use (OR: 1.615, p = 0.011) and the SAPS 3 score (OR: 0.882, p = 0.045) Associated with mortality. The presence of HF and the need for dialysis increased the risk of death. These influences were independently exerted.

Table 3 – Multivariate analysis of predictive factors for mortality in adult patients treated with ECMO. Brazil, 2017.

Variable	OR	CI (95%)	p (value)
Age	0,922	0,829 – 1,025	0,131
Heart Failure	2,400	1,133 – 22,105	0,019
CO2-GAP(pre-ECMO)	0,802	0,500 – 1,285	0,359
Lactate (pre-ECMO)	0,769	0,505 – 1,171	0,221
Dialysis	1,615	1,246 – 18,581	0,011
Use of blood products	1,573	0,532 – 4,650	0,413
SAPS III (>80 pre-ECMO)	0,717	0,493 – 1,044	0,083

CI: Confidence interval; SAPS: Simplified Acute Physiology Score.

The survival curves (Figure 2) during hospital stay showed no difference in the short-term between groups when dialysis was used as a factor (Fig 2.A) and the presence of HF (Fig 2.B).

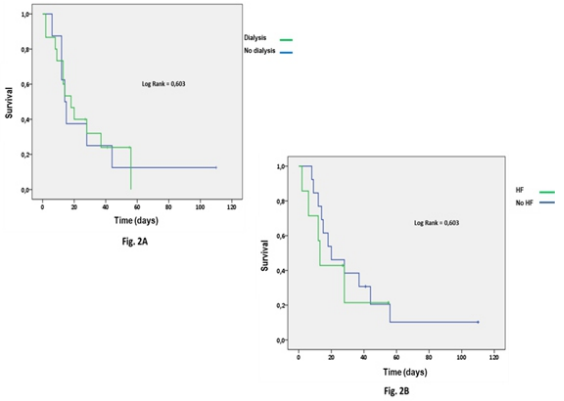

Figure 2. Patient survival curves according to the need for dialysis (Fig. 2A) and with HF (Fig.2B).

Discussion

According to the best of our knowledge, this is the first study in the country to evaluate the outcomes and clinical characteristics of adult patients undergoing ECMO therapy in a highly complex institution specialized in cardiopneumology. The observed mortality was high. Several studies have already demonstrated high mortality, with rates varying from 48% to 75%, for groups of patients treated with ECMO [11-15]. The analysis of our results confirmed this severe prognosis for the patients of this study, the in-hospital mortality was 83,3%.

Several studies have suggested that volume overload in severe patients is an independent risk factor for mortality, with worsening oxygen supply to cells, longer mechanical ventilation and hospital stay [16]. Hyperlactatemia is a marker of circulatory failure, with consequent cellular dysoxia, and it has been associated with higher mortality in various clinical conditions [17,18]. In the univariate analysis, the patients in the non-survivors group had significantly higher lactate values when compared to the survivors, suggesting that the degree of their cellular suffering was increased, even before the start of ECMO therapy. Aubron at al. [19], in a prospective study that identified the factors associated with outcomes, also found an association between elevated levels of lactate, before the installation of ECMO with worse outcomes.

In addition to hyperlactatemia, the severity scores in both groups of patients (non-survivors and survivors) were elevated, which also indicates the severity of this population. Although increased, we did not observe any difference between the groups for SOFA. However, when we evaluated SAPS we found a significant difference between the groups being higher in the non-survivors group (87 [77,75 - 92,5]) before the start of the therapy. Kim et al. [20] investigated the predictive factors for outcomes in 65 patients who used ECMO support. In the multivariate analysis, the authors identified that high SAPS values (greater than 80) were associated with increased risk of death in that population (OR: 1.189; CI: 1.032 - 1.370; p = 0.016).

Numerous conditions can induce AKI in patients treated with ECMO even before therapy is started. The development of AKI in patients supported with ECMO is usually related to hemodynamic changes associated with the patient's underlying disease [21]. In patients with low cardiac output, the biological defense mechanisms to maintain the perfusion of the central organs, such as the heart and brain, decrease the perfusion of peripheral organs such as the kidney. In such situations self-regulation leads to a decrease in renal cortical blood flow and may be responsible for AKI [22].

Acute renal injury is a very common complication in critically ill patients supported with ECMO, and it has been considered by several authors as a risk factor for mortality [13,23,24]. During the first 48 hours of therapy, oliguria and acute tubular necrosis (ATN) associated with capillary permeability and intravascular volume depletion are common because ECMO triggers an acute inflammatory reaction [25]. Lin et al. [26] evaluated 46 patients in ECMO, of whom 78.3% developed AKI, defined by the RIFLE criteria. These data corroborate our findings. Almost all patients (95.8%) evaluated in our study developed AKI after ECMO. When we evaluated the predictive factors for death among patients with an ECMO support, we did not observe a direct association between AKI and mortality, different from what is reported in the literature [13,24]. We believe that this association may not have been observed by the fact that, even among survivors, the incidence of AKI was high (75%).

However, the use of renal replacement therapy was a predictive factor for mortality in this group. Despite the diagnostic and therapeutic advances that have occurred, the mortality of patients with AKI has remained high in the last decades. Even with the use of new dialysis techniques and resources in intensive care units, prolonging the life of patients with AKI did not present a reduction in mortality [13,14,19]. When we performed a multivariate analysis to evaluate the independent association of factors with mortality, we realized that

patients requiring renal replacement therapy associated with ECMO support showed almost double the chance of death (CI: 1.246 - 18.581; p = 0.011).

We found that the survivors had longer ICU and hospital stay. Increased ICU length of stay is likely to explain the high infection rates, as observed by Guttendorf et al. [27] in a retrospective study evaluating 212 ECMO patients in Pennsylvania. Regarding the ECMO indication in the Pennsylvania study, heart failure after cardiogenic shock (CS) was the main one, this corroborates our findings, where more than half of the patients who used ECMO did so because of decompensation after cardiogenic shock.

One of the main causes of cardiogenic shock is the decompensation of HF. Cardiogenic shock is associated with high mortality and is increased according to the severity and degree of cardiac dysfunction [28,29]. Our results showed that all patients on vasoactive drugs (inotropes and vasopressors) were in an attempt to restore tissue perfusion and to compensate for the cardiovascular system, and patients who did not survive took higher doses of these drugs when compared to survivors. In addition, we observed that the presence of HF was an independent predictor of death, that is, HF patients had more than double the risk of death (OR: 2.4; CI: 1.133 - 22.105; p = 0.019).

This study has some limitations. First, we use a sample from a single center, which limits the generalization of our results. Second, the data were collected from patients' physical and electronic records, which may not provide high reliability information. Finally, the small number of patients studied in both groups (survivors and non-survivors) may have affected some comparisons between them. However, our findings are capable of providing valuable questions about the management of patients under it.

Conclusion

In conclusion, 83.3% of the adult patients supported with ECMO died during hospitalization. The presence of heart failure, the development of AKI and the need for renal replacement therapy concomitant with ECMO therapy increased the risk of death. Over the follow-up time, the survival curves of the patients in the survival and non-survival groups were not different in relation to the predictors of death (HF and dialysis).

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