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ORIGINAL PAPER

Comparison of Clinical and Functional Outcomes Patients with Use of Extracorporeal Membrane Oxygenation During the Perioperative of Lung Transplantation

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ABSTRACT

Objectives: To compare clinical and functional outcomes between lung transplant patients who used intra and/or postoperative extracorporeal membrane oxygenation (ECMO) and those who did not. **Methods:** Retrospective cohort study. Pre- and post-lung transplant data from 2009 to September 2023 were collected. Clinical outcomes considered were duration of invasive mechanical ventilation (IMV), length of stay in the intensive care unit (ICU) and hospital, and in-hospital mortality. Functional outcomes included time to achieve sitting at the bedside and initiate walking, patient's mobility at ICU discharge measured by the ICU Mobility Scale (IMS), and differences in functional performance measured by the 6-minute walk test (6MWT). **Results:** A total of 73 transplants were performed, with 43.8% utilizing ECMO. There was no difference in time on IMV, ICU, and hospital length of stay. In-hospital mortality was 43.8% (ECMO group) and 17.1% (non-ECMO group) ($p = 0.019$). The ECMO group took longer to achieve bedside sitting and initiate walking (median of 5 and 7 days, respectively) compared to the non-ECMO group (median of 2 and 3 days, respectively) ($p < 0.001$ and $p = 0.004$). However, there was no difference in patients' mobility at ICU discharge and the predicted 6MWT performance post-hospital discharge. **Conclusion:** Despite the association of ECMO use with clinical and structural barriers to mobilizing critical patients, functional rehabilitation was feasible and comparable to patients who did not use ECMO.

Descriptors: Lung Transplantation; Extracorporeal Membrane Oxygenation; Physical Therapy Modalities; Rehabilitation; Early Mobilization; Intensive Care Unit.

Comparação dos Desfechos Clínicos e Funcionais de Pacientes Transplantados Pulmonares em Relação ao Uso de Membrana de Oxigenação Extracorpórea

RESUMO

Objetivos: Comparar os desfechos clínicos e funcionais entre pacientes transplantados pulmonares que utilizaram membrana de oxigenação extracorpórea [*extracorporeal membrane oxygenation* (ECMO)] intra e/ou pós-operatório e aqueles que não utilizaram. **Métodos:** Estudo de coorte retrospectivo. Foram coletados dados pré- e pós-transplante pulmonar do período de 2009 a setembro de 2023. Foram considerados os desfechos clínicos: tempo em ventilação mecânica invasiva (VMI), tempo de internação no centro de terapia intensiva (CTI) e hospitalar e a ocorrência de óbito na internação. Foram considerados os desfechos funcionais: tempo para realização de sedestação à beira do leito e para treino de marcha, mobilidade corporal na alta do CTI medido pela ICU Mobility Scale (IMS) e diferença no desempenho funcional medido pelo teste da caminhada de 6 minutos (TC6M). **Resultados:** Foram realizados 73 transplantes, dos quais 43,8% utilizaram ECMO. Não houve diferença no tempo em VMI, tempo de internação no CTI e hospitalar. A ocorrência de óbito foi de 43,8% (grupo ECMO) e 17,1% (grupo sem ECMO) ($p = 0{,}019$). O grupo ECMO demorou mais para realizar a sedestação à beira do leito e iniciar o treino de marcha (mediana de 5 e 7 dias, respectivamente) e o grupo sem ECMO (mediana de 2 e 3 dias, respectivamente) ($p < 0{,}001$ e

p = 0,004). No entanto, não houve diferença na mobilidade corporal na alta do CTI e no desempenho no TC6M predito no pós-alta hospitalar. **Conclusão:** Apesar da associação de utilização de ECMO com barreiras clínicas e estruturais para mobilização do paciente crítico, a reabilitação funcional foi possível e semelhante aos pacientes que não utilizaram ECMO.

Descritores: Transplante Pulmonar; Membrana de Oxigenação Extracorpórea; Fisioterapia; Reabilitação; Mobilização Precoce; Terapia intensiva.

INTRODUCTION

In Brazil, there are currently only five specialized centers for lung transplantation, with the Hospital de Clínicas de Porto Alegre (HCPA) being one of these reference centers.[1] This reality is accompanied by an increase in the number of patients on the waiting list for lung transplantation, which is disproportionate to the available organ supply. Lung transplantation provides increased life expectancy and quality of life for patients with a low life expectancy due to lung disease. To ensure greater success in the procedure, well-established indication criteria exist for various diseases.[2,3]

Extracorporeal membrane oxygenation (ECMO) is a therapy that provides temporary support in cases of pulmonary and/or cardiac failure.[4] During lung transplantation, ECMO is primarily indicated for patients with pulmonary arterial hypertension, right ventricular dysfunction, and those who exhibit intolerance to single-lung ventilation.[5] ECMO can be used as a bridge to lung transplantation or as a bridge to recovery post-operation, particularly in instances of primary graft dysfunction. In this scenario, gas exchange primarily occurs through the extracorporeal circuit, allowing for lighter adjustments in mechanical ventilation parameters and reducing the risk of ventilator-induced lung injury.[4]

Early mobilization of patients in the intensive care unit (ICU) is a safe and effective rehabilitation process, and its initiation involves monitoring cardiovascular, ventilatory, and neurological parameters as safety criteria.[6] Prolonged immobility, duration of mechanical ventilation, and length of stay in the ICU are associated with neuromuscular and ventilatory dysfunctions, leading to ICU-acquired weakness and functional decline. Therefore, several studies have highlighted the benefits of early mobilization, including reduced mechanical ventilation weaning time, decreased delirium, improved functional independence, enhanced muscle strength, and shorter hospital stays.[7,8]

Patients on ECMO present a higher level of complexity, and early mobilization for these individuals can pose a challenge, especially for those with femoral cannulation.[9] Most studies on the functional rehabilitation of ECMO patients focus on mobilization within the ICU and the functional status of groups with different indications for ECMO use. However, few specifically address the rehabilitation of lung transplant patients in the ICU.[9-14] Therefore, this study aims to assess the clinical and functional differences among lung transplant patients concerning ECMO use in a referral hospital in southern Brazil.

METHODS

This is a retrospective cohort study that analyzed the medical records of all patients who underwent lung transplants at the HCPA, from the first procedure in 2009 until September 2023. The study included patients over 14 years old of both sexes who underwent unilateral or bilateral transplants. Patients were divided into two groups: those who received ECMO support during and/or after the procedure (ECMO group) and those who did not (non-ECMO group). The study obtained approval from the Research Ethics Committee of the HCPA under protocol number 66849523.1.0000.5327.

Preoperative data were collected from medical records, including sex, age, and diagnosis leading to lung transplant and comorbidities. Intraoperative data included the type of transplant (unilateral or bilateral), a score for predicting mortality upon ICU admission using the Simplified Acute Physiology Score (SAPS III), surgical duration, and the need for ECMO. Postoperative data collected included clinical outcomes such as ECMO duration, duration of invasive mechanical ventilation (IMV), length of stay in the ICU and hospital, complications, and in-hospital mortality. Additionally, functional outcomes were collected, including time taken to achieve sitting position and gait activity, ICU Mobility Scale (IMS) at ICU discharge, and performance in the 6-minute walk test (6MWT) before and after hospital discharge. The absolute values of the 6MWT were adjusted as percentiles considering predicted values based on sex, age, and body mass index (BMI).[15-17]

The data analysis was performed using the Statistical Package for the Social Sciences, version 21 (SPSS Inc., Chicago, IL, USA). After conducting the Kolmogorov-Smirnov normality test, continuous variables with a normal distribution were compared using Student's t-test, and the values were expressed as mean (M) and standard deviation (SD). Continuous variables without a normal distribution were compared using the Mann-Whitney U test, and the values were presented as median (Med) and interquartile range (IQR). Comparison of categorical variables was carried out using Pearson's chi-square test, and the results were presented in absolute values and frequencies. The adopted significance level was 5% ($p \leq 0.05$).

RESULTS

Until September 2023, the HCPA performed 73 lung transplants, of which 31 patients (43.8%) underwent ECMO support intraoperatively and/or postoperatively (ECMO group), and 42 patients (56.2%) did not use the support (non-ECMO group). Regarding age, the ECMO group had a median of 39 years (IQR = 31), and the non-ECMO group had a median of 60 years (IQR = 15) ($p < 0.001$). There was no statistical difference in sex distribution between the groups. However, a significant difference was observed in the distribution of transplant types: 84.4% of patients in the ECMO group underwent bilateral transplantation, while 63.4% underwent unilateral transplantation in the non-ECMO group ($p < 0.001$) (Table 1).

Table 1. Patient characteristics, predicted mortality score upon ICU admission, and surgery duration.

Variable	Groups n (%)		*p*-value
	ECMO (n = 32)	non-ECMO (n = 41)	
Sex Men	17 (53.1)	19 (46.3)	0.640*
Age (years), Med (IQR)	39 (31)	60 (15)	< 0.001†
Transplant type			
Unilateral	5 (15.6)	26 (63.4)	< 0.001*
Bilateral	27 (84.4)	15 (36.6)	
Comorbidities			
Gastrointestinal dysfunction	7 (21.9)	7 (17.1)	0.766*
Hypertension	5 (15.6)	12 (29.3)	0.264*
Heart disease	5 (15.6)	5 (12.2)	0.740*
Pulmonary hypertension	5 (15.6)	2 (4.9)	0.228*
Osteoporosis/osteopenia	3 (9.4)	7 (17.1)	0.497*
Depression/anxiety	2 (6.3)	7 (17.1)	0.283*
SAPS III (score), Med (IQR)	41 (25)	32 (19)	0.027†
Surgery duration (hours), Med (IQR)	11 (2.5)	6 (3.8)	< 0.001†

Source: Elaborated by authors. * Pearson's chi-square test; † Mann-Whitney *U* non-parametric test.

The pre-surgical comorbidities recorded in the medical records were analyzed, and the most prevalent ones included gastrointestinal dysfunction, hypertension, heart disease, pulmonary hypertension, osteoporosis and/or osteopenia, depression, and/or anxiety. There were no statistically significant differences between groups concerning these comorbidities (Table 1). Regarding the primary disease leading to lung transplantation, cystic fibrosis was the most frequent in the ECMO group, with 10 patients (32.3%), while chronic obstructive pulmonary disease (COPD) was more common in the non-ECMO group, with 21 patients (51.2%). There was a statistically significant difference in the distribution of underlying diseases between the groups ($p = 0.008$) (Table 2).

Table 2. Distribution of patients according to underlying disease.

	Groups n (%)		*p*-value
	Variable	non-ECMO (n = 41)	
Cystic fibrosis	10 (31.3)	2 (4.9)	0.008*
COPD	9 (28.1)	21 (51.2)	
Pulmonary fibrosis	3 (9.4)	7 (17.1)	
Bronchiectasis	3 (9.4)	1 (2.4)	
Pulmonary arterial hypertension	2 (6.3)	0 (0.0)	
Interstitial lung disease	1 (3.1)	5 (12.2)	
Bronchiolitis obliterans	1 (3.1)	2 (4.9)	
Hypersensitivity pneumonitis	1 (3.1)	2 (4.9)	
Systemic lupus erythematosus	1 (3.1)	0 (0.0)	
Primary ciliary dyskinesia	1 (3.1)	0 (0.0)	
Scleroderma	0 (0.0)	1 (2.4)	

Source: Elaborated by authors. * Pearson's chi-square test.

The SAPS III assessment showed a higher prediction of mortality upon admission to the ICU in the ECMO group, with a median of 41 points (IQR = 25) compared to the non-ECMO group, with a median of 32 points (IQR = 19) ($p = 0.027$). Additionally, there was a longer surgical time in the ECMO group, with a median of 11 hours (IQR = 2.5), compared to a median of 6 hours (IQR = 3.8) in the non-ECMO group ($p < 0.001$) (Table 1).

The patients who underwent ECMO intraoperatively and/or as a bridge to recovery in the postoperative period had a median duration of 4 days (IQR = 4.25). No statistically significant differences were observed between the groups regarding the duration of IMV, length of stay in the ICU and hospital stay (Table 3).

Table 3. Clinical variables.

Variável	Groups n (%)		*p*-value
	Variable	non-ECMO (n = 41)	
IMV duration (days), Med (IQR)	1 (2.00)	1 (2.00)	0.100*
ECMO duration (days), Med (IQR)	4 (4.25)		
Length of stay in ICU (days), Med (IQR)	8 (11.00)	6 (7.00)	0.126*
Length of hospital stay (days), Med (IQR)	46 (48.00)	27 (10.00)	0.194*
Complications			
Respiratory infections	17 (54.8)	15 (36.6)	0.154†
Hemodialysis	14 (45.2)	3 (7.5)	< 0.000†
Hemodynamic instability/shock	12 (37.5)	6 (14.6)	0.031†
Acute renal failure	9 (28.1)	7 (17.1)	0.393†
Gastrointestinal tract dysfunction	8 (25.0)	4 (9.8)	0.114†
Thromboembolism	5 (15.6)	3 (7.3)	0.453†
Tracheostomy	5 (15.6)	3 (7.3)	0.453†
Acute rejection	4 (12.9)	5 (12.2)	1.000†
Primary graft dysfunction	2 (6.3)	4 (9.8)	0.689†
In-hospital mortality			
Yes	14 (43.8)	7 (17.1)	0.019†

Source: Elaborated by authors. * Mann-Whitney *U* non-parametric test; † Pearson's chi-square test.

The most prevalent postoperative complications were respiratory infections, found in 54.8% of the ECMO group and 36.6% of the non-ECMO group ($p = 0.154$). There was a higher incidence of hemodynamic instability, with or without shock, occurring in 37.5% of patients in the ECMO group and 14.6% in the non-ECMO group ($p = 0.031$). Although there was no difference between groups in the occurrence of acute renal failure, the ECMO group required more hemodialysis (45.2%) compared to the non-ECMO group (7.5%) ($p = 0.000$). Other complications were also observed but with lower frequency in both groups, without statistically significant differences. Regarding in-hospital mortality, 14 patients (43.8%) in the ECMO group and seven (17.1%) in the non-ECMO group died during hospitalization ($p = 0.019$) (Table 3).

With regard to functional outcomes, patients who underwent ECMO took a median of 5 days (IQR = 3) to transfer a sitting position compared to those who did not undergo ECMO, who had a median of 2 days (IQR = 1.5) ($p < 0.001$). The ECMO group also took longer to start ambulation, with a median of 7 days (IQR = 12), while the non-ECMO group had a median of 3 days (IQR = 5) ($p = 0.044$). There were no differences in functional capacity at the time of ICU discharge, assessed by the IMS score, with the ECMO group presenting a median of 8 points (IQR = 1) and the non-ECMO group a median of 8 points (IQR = 2) ($p = 0.356$). Regarding the distance covered in the 6MWT after hospital discharge, patients in the ECMO group showed a greater absolute distance ($p = 0.043$). However, when considering the percentage of the predicted value for 6MWT performance post-hospital discharge, the ECMO group achieved an average of 60.7% ± 12.5 of the predicted value, while the non-ECMO group achieved 64.6% ± 16.4 ($p = 0.396$). Regarding the percentage difference between predicted values before and after transplantation, the ECMO group had a mean of 4.7% ± 15.5, and the non-ECMO group had 11.6% ± 22.2; however, without statistically significant differences ($p = 0.220$) (Table 4).

Table 4. Functional variables.

Variable	Groups		Valor de *p*
	ECMO	non-ECMO	
Time to bedside sitting (days), Med (IQR)	5 (3.0)	2 (1.5)	< 0.001*
Time to start ambulation (days), Med (IQR)	7 (12.0)	3 (5.0)	0.044*
IMS score at ICU discharge, Med (IQR)	8 (1.0)	8 (2.0)	0.356*
6MWT Pre (meters), M ± SD	343.0 ± 124.0	315.0 ± 113.0	0.354†
6MWT Pre (% predicted), M ± SD	52.0 ± 20.4	52.4 ± 17.5	0.930†
6MWTPost (meters), Med (IQR)	443 (134.5)	375 (75.0)	0.043*
6MWT Post (% predicted), M ± SD	60.7 ± 12.5	64.6 ± 16.4	0.396†
Pre-Post 6MWT difference (% predicted), M ± SD	4.7 ± 15.5	11.6 ± 22.2	0.220†

Source: Elaborated by authors. * Mann-Whitney *U* test; † Student's *t*-test.

DISCUSSION

In the ECMO group, the median age was 39 years, contrasting with the median of 60 years in the non-ECMO group. We believe this finding is related to the higher frequency of diagnosis of cystic fibrosis in the ECMO group (31.3%) and COPD in the non-ECMO group (51.2%). Except for genetic diseases like cystic fibrosis and certain forms of pulmonary arterial hypertension, the prevalence of end-stage lung diseases increases with age.[18] A study that assessed risk factors for prolonged pulmonary ventilation in post-lung transplant patients showed similar results to those found in the non-ECMO group in our study, with a median age of 56 years and a high frequency of patients diagnosed with pulmonary fibrosis (36%) and COPD (27%).[19]

In our study, we observed a significantly higher prevalence of bilateral transplants among patients who used ECMO (84.4%) compared to the non-ECMO group (36.6%), consequently leading to a longer surgical duration in this group. Another study evaluating 75 post-lung transplant patients demonstrated that 71.4% of ECMO-utilizing patients had bilateral transplants, while 72.2% of those who did not use ECMO underwent unilateral transplants.[20] Despite the groups not showing differences in pre-surgical comorbidities, we know that ECMO patients presented greater complexity and a higher risk of mortality, evidenced by a significantly higher SAPS III score. It is important to note that the probability of mortality considerably increases with higher SAPS III scores.[17]

We found an in-hospital mortality rate of 43.8% compared to 17.1% in the non-ECMO group, and we observed a higher prevalence of hemodynamic instability/shock and the need for hemodialysis among ECMO patients. A study assessing 61 patients using ECMO due to acute respiratory distress syndrome demonstrated an in-hospital mortality rate of 30%.[10] Other studies examining 107 patients who required ECMO as a bridge to lung transplantation or as a bridge to recovery showed a mortality rate of 24% in the bridge to recovery group.[9] Conversely, research investigating post-lung transplant patients found no significant differences in mortality at 30 and 90 days of hospitalization and revealed a difference in the 1- and 2-year survival curve, favoring ECMO use, although without statistical significance.[20]

In our analysis, we did not observe significant differences in mechanical ventilation time, ICU and hospital length of stay, with a median ECMO duration of 4 days. In a study investigating post-lung transplant patients, mechanical ventilation and ICU stay had medians of 3 and 17 days, respectively. Although they did not compare groups regarding ECMO use, these authors indicated that patients using the support had it discontinued within the first 24 hours, with a median of 0 days (IQR = 0-1).[19] Another study comparing two groups regarding ECMO use found no significant differences in mechanical ventilation duration, ICU stay, and hospitalization duration with medians of 3, 18, and 44 days, respectively. The median intra and/or postoperative ECMO duration in the study was 82 hours.[20] In another study evaluating post-lung transplant patients using ECMO, mechanical ventilation, ICU stay, and hospitalization duration had medians of 15.5, 31.5, and 60 days, respectively, with a median ECMO duration of 3 days.[11] The maintenance of perioperative ECMO use is associated with decreased need for anticoagulation and blood transfusions, along with lower risks of neurological and vascular complications. The preference for ECMO use remains in patients with pulmonary hypertension and those developing primary graft dysfunction.[21,26]

We found significant differences in the time required for patients using ECMO to achieve bedside sitting and start ambulation training in this study. This is an important finding regarding the rehabilitation process for lung transplant patients. However, we cannot assert whether this difference is due to the severity and clinical instability of these patients, which could contraindicate mobilization. Presently, literature increasingly demonstrates the feasibility and safety of early mobilization in ECMO patients, provided neurological, ventilatory, and hemodynamic parameters are considered as criteria for such interventions. It is crucial to highlight that physical training should be conducted in specialized centers under the supervision and collaboration of a highly qualified multidisciplinary team.[12,22,23]

Despite the differences observed in our study regarding the time for bedside sitting and initiation of gait training, we noticed that patients were discharged from the ICU with similar functional conditions, as evidenced by the IMS score. A study that also assessed functional capacity using the IMS score in post-lung transplant patients described a median of 6 points in the ECMO group at ICU discharge, compared to the non-ECMO group, which showed a median of 7 points ($p = 0.02$). Some factors are associated with a higher frequency of patient mobilization on ECMO outside the bed, such as the presence of venovenous cannulation and ECMO used as a bridge to transplant. Conversely, the use of mechanical ventilation and femoral cannulation is related to a lower frequency of mobilization outside the bed.[9] In a study that followed 61 patients on ECMO diagnosed with acute respiratory distress syndrome, it was found that only 17% of these patients were transferred to a sitting position.[10] Furthermore, in another study that followed post-lung transplant patients, out of 220 patients using ECMO as a bridge to recovery, 41% achieved orthostasis, and 16% ambulated while on ECMO.[9]

In this study, we observed that patients who underwent ECMO and were discharged from the hospital showed significantly better absolute values in the 6MWT compared to those in the non-ECMO group. However, it is important to highlight that patients in the ECMO group were younger compared to those in the non-ECMO group. Variations in 6MWT performance can be expressed through absolute differences in meters, percentage variations, or percentage variations in relation to the predicted value.[24] The 6MWT performance varies based on the individual's sex, age, weight, and height.[25] For this reason, we chose to describe the 6MWT comparisons as a percentage of the predicted value. In the post-hospital discharge 6MWT, the ECMO group achieved an average of 60.7% of the predicted value, while the non-ECMO group reached 64.6% of the predicted value, but this difference was not significant. Comparing the predicted value between pre- and post-transplant, both groups showed improvement in performance: the ECMO group had a mean increase of 4.7%, while the non-ECMO group had an increase of 11.6%. Although this difference did not reach statistical significance, it suggests a tendency toward better functional performance in patients who did not use ECMO. One study showed poorer performance in the 6MWT at hospital discharge for patients who used ECMO (285 ± 112 meters) compared to the non-ECMO group (384 ± 93 meters) ($p = 0.004$). Unlike this study, they described only absolute results and did not find a difference in age between the groups.[13]

Implications for clinical practice

ECMO is an increasingly utilized life support in intensive care centers, which requires studies to understand its impact on patient recovery. This study provides comprehensive information on the epidemiology, surgical characteristics, and clinical and functional outcomes of patients undergoing lung transplantation, allowing comparisons of these data regarding the use of ECMO. Therefore, understanding the rehabilitation process of these patients from a functional perspective offers support for care practice.

Limitations

This study included a sample of 73 participants, but when we discount the deceased, the number of patients in each group decreased, highlighting a limitation in our analysis due to the reduced sample size. Additionally, being a retrospective study, we lack information on the frequency and intensity of mobilizations performed by these patients. We do not have data on how many patients were not mobilized in the early years of lung transplantation at the hospital, possibly due to the team's inexperience or a lack of scientific evidence confirming the safety of physical training in these patients. A study with a larger and more recent sample could provide a broader and more detailed perspective.

CONCLUSION

As described in the literature, the use of ECMO has been associated with clinical and structural barriers to mobilizing critically ill patients. This was evidenced by the time needed to achieve sitting at the bedside and start gait training. However, functional rehabilitation was possible, resulting in discharge from the ICU and hospital with functional conditions similar to those of patients who did not receive ECMO support.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Vecchia ID, Deponti GN, Di Naso FC; **Conception and design:** Vecchia ID, Di Naso FC; **Data analysis and interpretation:** Vecchia ID, Andriotti MZ, Di Naso FC; **Article writing:** Vecchia ID; **Critical revision:** Deponti GN, Di Naso FC; **Final approval:** Di Naso FC.

DATA AVAILABILITY STATEMENT

The data will be available upon request.

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