Economic Outcomes of Extracorporeal Membrane Oxygenation With and Without Ambulation as a Bridge to Lung Transplantation

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BACKGROUND: An increasing number of centers are using active rehabilitation and ambulation for critically ill patients on extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation. This investigation assessed the economic impact at a single center of ambulatory versus non-ambulatory ECMO strategies as a bridge to lung transplantation. METHODS: We conducted a single-center retrospective cohort analysis of all subjects supported with ECMO as a bridge to lung transplantation ($N = 9$) from 2007 to 2012. Subjects who were rehabilitated while supported with ECMO before lung transplantation were compared with those who were not rehabilitated during ECMO. Hospital cost data for the month before transplantation through 12 months after the initial post-transplant hospital discharge were compared. RESULTS: The median cost (interquartile range [IQR]) in the 30 d before transplant for the ambulatory cohort was $88,137 (IQR $38,589-$122,111) compared with $52,124 (IQR $23,824-$69,929) for the non-ambulatory cohort ($P = .08$). The median post-transplant ICU cost for the ambulatory cohort was $38,468 (IQR $23,611-$64,126) compared with $143,407 (IQR $112,199-$168,993) for the non-ambulatory cohort ($P = .01$). The median total hospital cost for subjects supported with ambulatory ECMO was $213,086 (IQR $166,767-$264,536) compared with $273,291 (IQR $237,299–$374,175) for non-ambulatory ECMO subjects ($P = .05$). The median total cost for the ambulatory cohort was $268,194 (IQR $219,972–$517,320) compared with $300,307 (IQR $274,262–$394,913) for the non-ambulatory cohort ($P = .14$). CONCLUSIONS: Subjects supported with ambulatory ECMO had a 22% ($60,204) reduction in total hospital cost, 73% ($104,939) reduction in post-transplant ICU cost, and 11% ($32,133) reduction in total cost compared with non-ambulatory ECMO subjects. This analysis demonstrates the potential economic benefit of rehabilitation and ambulation during ECMO compared with a traditional strategy.
Key words: extracorporeal membrane oxygenation; lung transplantation; rehabilitation; economics; respiratory failure. [Respir Care 2016;61(1):1–7.

Introduction

Transplantation provides an opportunity for increased survival and improved quality of life in patients with irreversible pulmonary disease.[1] For some patients awaiting lung transplantation, disease progression leads to deterioration and respiratory failure necessitating life support, which is associated with worse post-transplant outcomes.[2-4] For individuals who require mechanical ventilation before lung transplantation, the 1-y survival rate is 57-62% in comparison with 75-80% for those who are not supported with invasive ventilation at the time of transplant.[2-4] Initial

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studies of subjects who required extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation demonstrated even lower survival rates.[4-6] These survival trends are likely representative of historically late initiation of ECMO for those patients in need of lung transplantation. Ambulation while supported with ECMO, which we hypothesize to be a survival benefit, has not been performed in prior survival analyses.

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A key contributor to the increased mortality of ECMO patients being bridged to lung transplantation is neuromuscular weakness and deconditioning related to immobility and pharmacologic sedation.[7-9] In addition, these patients are subject to the inherent risks of ECMO, including renal dysfunction, infection, and bleeding.[10] Several centers use ambulatory ECMO to rehabilitate patients to mitigate deconditioning in an attempt to improve outcomes in these critically ill patients.[11-15] Early studies demonstrated feasibility and potentially improved outcomes with this ECMO rehabilitation strategy as a bridge to transplantation.[14,16,17] In a single-center study, subjects who were spontaneously breathing while supported with ECMO had better 1-y survival rates post-transplant than did their mechanically ventilated counterparts who were supported with ECMO and proceeded to lung transplantation.[18]

While deconditioning, critical illness myopathy, and length of stay for these critically ill patients supported with ECMO as a bridge to lung transplantation may be improved by an ambulatory approach,[14] the economics of this strategy have not been investigated previously. ECMO is a therapy that is associated with significant cost and resource utilization,[19] and even without ECMO, data comparing cost and quality-adjusted life-years continue to demonstrate that lung transplantation is expensive.[20,21] Cost effectiveness is limited by significant morbidity and mortality,[22,23] with a significant portion of the cost associated with lung transplantation being related to post-transplant morbidity.[20,22,23] This morbidity may be exacerbated by the deconditioning and myopathy often associated with critical illness and longer ICU stays.[9,24] Hospital stay has been directly correlated with hospital cost.[25,26] The primary objective of this cohort analysis was to describe the difference in hospital costs between a group of ambulatory ECMO subjects and a group of non-ambulatory ECMO subjects, all of whom were supported with ECMO as a bridge to lung transplantation.

QUICK LOOK

Current knowledge

Transplantation provides an opportunity for increased survival and improved quality of life in patients with irreversible pulmonary disease. Disease progression while awaiting organ donation leads to respiratory failure, necessitating life support, which is associated with worse post-transplant outcomes. For individuals who require mechanical ventilation before lung transplantation, 1-y survival rates are 57-62% compared with 75-80% without ventilation. Late use of extracorporeal membrane oxygenation (ECMO) has not been associated with better outcomes. Ambulation while supported with ECMO has been hypothesized to portend a survival benefit.

What this paper contributes to our knowledge

Subjects supported with ambulatory ECMO had a 22% reduction in total hospital cost, 73% reduction in post-transplant ICU cost, and 11% reduction in total cost compared with non-ambulatory ECMO subjects. This analysis demonstrated the potential economic benefit of rehabilitation and ambulation with ECMO support compared with a traditional strategy.

Methods

After approval by the Duke University Medical Center institutional review board, we conducted a retrospective review of all patients who were supported with ECMO as a bridge to lung transplantation at the Duke University Medical Center. All ECMO patients who underwent lung transplantation were included in the analysis. There were no subject deaths during the waiting period between listing for lung transplantation and the actual transplantation. Subjects were categorized into 2 cohorts. The first cohort consisted of historical controls including all subjects supported with ECMO as a bridge to lung transplantation who did not participate in rehabilitation or ambulation. The second cohort, our study group, consisted of all subjects who were supported with ECMO as a bridge to lung transplantation who underwent active physical rehabilitation including ambulation. All subjects were mechanically ventilated in the ICU before initiation of ECMO. This was a longitudinal study, and subjects were analyzed consecutively. Thus, subjects in the non-ambulatory group were enrolled before initiation of the institutional ECMO rehabilitation program. Subjects in the rehabilitation group were not listed for lung transplantation until after demonstrating successful rehabilitation. The rehabilitation protocol utilized at our institution has been described previously.[15]

Subjects who underwent a novel strategy of ambulation were compared with subjects managed without rehabilitation; both groups were supported with ECMO. The 2 cohorts were compared with respect to demographics, stay, duration of ECMO support, and direct costs. Direct costs were defined as the hospital cost associated with labor (excluding physicians),

Table 1. Subject Demographics

Demographic	Non-Rehabilitated ECMO Group					Rehabilitated/Ambulatory ECMO Group						*P*
	Subject 1	Subject 2	Subject 3	Subject 4	Median	Subject 5	Subject 6	Subject 7	Subject 8	Subject 9	Median	
Primary diagnosis	IPF	UIP	NSIP	CF		CF	CF	IPF	CF	CF		
Sex	M	F	M	F		F	F	M	F	F		
Age, y	55	51	57	17	53	16	24	58	20	22	22	.50
APACHE III	68	65	51	47	58	116	97	64	111	44	97	.30

ECMO = extracorporeal membrane oxygenation
IPF = idiopathic pulmonary fibrosis
UIP = usual interstitial pneumonia
NSIP = fibrosing nonspecific interstitial pneumonia
CF = cystic fibrosis
M = male
F = female
APACHE III = Acute Physiology and Chronic Health Evaluation III

equipment, and supplies for direct patient care. Cost data were not discounted for each subject as costs were equalized and covered a standardized 13-month period.

Cost data included surgical, equipment, pharmacy, and lab costs, along with personnel, radiation, transfusion, and in-patient room services at Duke University Hospital. We compared cost groups organized into 5 categories: pre-transplant, post-transplant ICU, post-ICU to initial discharge, total hospital cost, and total cost. Pre-transplant costs were defined as all Duke-related costs from 30 d before transplant until the transplant date. Post-transplant ICU costs were defined as all related costs from the day of transplant until discharge from the ICU. Post-ICU to initial discharge costs were defined as all related costs from the day after ICU discharge to hospital discharge for the transplant hospitalization. Total hospital cost was defined as the sum of all Duke-related costs from 30 d before transplant to initial discharge. Total cost was defined as all Duke-related costs from 30 d before transplant through 12 months after initial discharge. Data were actual cost data and not charges or reimbursement data. Physician professional fees were not included in the analysis. These data were obtained via Duke University Hospital Finance using the Transitions Systems and Enterprise Performance Systems cost-accounting systems.

Statistical Analysis

Nonparametric testing was performed using the Wilcoxon rank-sum analysis with statistical significance defined as $P < .05$. Statistical testing was performed using Stata 12 (StataCorp, College Station, Texas). A one-way sensitivity analysis was also performed to assess uncertainty in our model and the impact of any individual parameter on the model's conclusions.[27] We conducted the sensitivity analysis by isolating each subject one at a time, repeating the analysis, and then assessing the impact. We also analyzed subgroup data costs by service line for all subjects.

Results

We identified 9 consecutive subjects who underwent bilateral lung transplantation after being supported with ECMO between April 2007 and May 2012. The control cohort consisted of subjects 1-4, who underwent lung transplantation with traditional ECMO support without rehabilitation or ambulation before transplantation. Subjects 5-9 were identified as the study cohort, and they participated in the rehabilitation protocol and underwent transplantation between January 2010 and May 2012. Other protocols for these 2 cohorts, such as surgical protocols and immunosuppressant regimens, were unchanged. There were no differences in age or APACHE III (Acute Physiology and Chronic Health Evaluation III) score between the 2 groups (Table 1). No subject deaths occurred during the analysis timeline.

Primary Analysis

Table 2 summarizes the cost analysis of our subjects by cohort. The unadjusted cost analysis demonstrated significantly lower post-transplant ICU costs for the ambulatory ECMO cohort. Despite the trend toward higher pre-transplant costs for the ambulatory ECMO cohort, there was a trend toward lower total hospital costs for this cohort.

Sensitivity Analysis

A sensitivity analysis identified a single high-cost outlier: a subject in the rehabilitation cohort who underwent retransplantation 8 months after the original transplantation. Excluding this statistical outlier, the adjusted cost analysis demonstrated that the post-transplant ICU costs remained lower for the ambulatory ECMO cohort, and total costs were also significantly lower in this group (see Table 2).

Table 2. Cost Outcomes

Cost Category	Unadjusted Cost (N = 9)		P	Adjusted Cost (n = 8)		P
	Non-Rehabilitated Group	Rehabilitated Group		Non-Rehabilitated Group	Rehabilitated Group	
Pre-transplant	$52,124 ($23,824-69,929)	$88,137 ($38,589-122,111)	.08	$52,124 ($23,824-69,929)	$98,460 ($38,589-122,111)	.14
Post-transplant ICU	$143,407 ($112,199-168,993)	$38,468 ($23,611-64,126)	.01	$143,407 ($112,199-168,993)	$43,929 ($23,611-64,126)	.02
Post-ICU through discharge	$27,541 ($16,817-94,639)	$18,896 ($11,499-57,612)	.46	$27,541 ($16,817-94,639)	$15,544 ($11,499-43,870)	.25
Total hospital	$273,291 ($237,299-374,175)	$213,086 ($166,767-264,536)	.05	$273,291 ($237,299-374,175)	$209,590 ($166,767-264,536)	.08
Total	$300,307 ($274,262-394,913)	$268,194 ($219,972-517,320)	.14	$300,307 ($274,262-394,913)	$244,508 ($219,972-268,914)	.02

Values are presented as the median (interquartile range).

Table 3. Total Subgroup Cost

Subgroup	Non-Rehabilitated ECMO Group	Rehabilitated/Ambulatory ECMO Group	P
Floor room/nursing	$28,032 ($10,966-46,747)	$17,187 ($3,750-37,083)	.33
ICU room/nursing	$67,024 ($54,001-80,235)	$35,659 ($18,164-66,240)	.03
Pharmacy	$54,603 ($36,392-104,316)	$51,621 ($30,754-183,618)	>.99
ECMO	$8,368 ($6091-31,993)	$18,262 ($12,479-26,852)	.22
Respiratory care	$26,558 ($12,398-37,317)	$34,824 ($17,000-45,014)	.22
Physical/occupational therapy	$8,688 ($5,591-18,939)	$5,636 ($3,935-7,809)	.08
Radiology	$11,612 ($6,299-13,885)	$6,098 ($4,078-14,146)	.22
Lab tests	$28,439 ($20,613-30,875)	$18,019 ($16,087-41,573)	.22
Organ procurement/transplantation	$57,491 ($50,787-59,743)	$55,865 ($55,865-108,023)	.80
Transfusion services	$11,266 ($3,000-35,440)	$11,683 ($3,978-15,378)	>.99

Values are presented as the median (interquartile range).
ECMO = extracorporeal membrane oxygenation

Subgroup Analysis

The results from the analysis of cost subgroups (floor room/nursing, ICU room/nursing, pharmacy, ECMO, respiratory care, physical/occupational therapy, radiology, lab tests, organ procurement/transplantation, and transfusion services) are listed in Table 3, with ICU room/nursing charges being significantly less in the ambulatory cohort.

Clinical Outcome Analysis

An analysis demonstrated shorter post-transplant ICU stays in the ambulatory group (Table 4). The stay from post-ICU to discharge and total hospital stay demonstrated a trend toward lower utilization. There was no difference in the pre-transplant stay. Subjects in the ambulatory ECMO cohort demonstrated a trend toward a longer duration of ECMO support. The duration of mechanical ventilation demonstrated a significant difference in both the pre-transplant and post-transplant periods.

Discussion

As described previously,[14,15] our institution has employed a strategy since January 2010 that incorporates physical rehabilitation and ambulation for patients supported with ECMO as a bridge to lung transplantation. In this program, patients undergo tracheostomy, rapid weaning of sedation, and progressive rehabilitation followed by ambulation while awaiting transplantation and being supported with ECMO.[15] As described previously,[14,15] for those subjects who were rehabilitated and ambulated while supported with ECMO, clinical outcomes were improved compared with non-ambulatory ECMO subjects, including less critical illness myopathy and shorter ICU stays. This study was undertaken to determine the economic impact of this approach compared with a cohort of subjects supported with ECMO as a bridge to lung transplantation who did not rehabilitate. This analysis demonstrated lower total and post-transplant ICU costs in the adjusted analysis for subjects who were rehabilitated and ambulated while supported with ECMO.

Table 4. Clinical Outcomes

Outcome	Non-Rehabilitated ECMO Group	Rehabilitated/Ambulatory ECMO Group	*P*
Pre-transplant ICU stay	12 (4-41)	20 (17-30)	.32
Pre-transplant mechanical ventilation duration	1 (1-5)	12 (5-15)	.02
Post-transplant mechanical ventilation duration	29.5 (22-54)	2 (1-5)	.01
Post-transplant ICU stay	45 (34-56)	8 (6-22)	.01
Post-ICU to discharge stay	34 (11-63)	11 (7-25)	.06
Total hospital stay	94 (51-151)	50 (31-63)	.05
ECMO support	1.5 (1-9)	9 (5-14)	.06

Values are presented as median days (interquartile range).
ECMO = extracorporeal membrane oxygenation

We analyzed cost and clinical data 30 d before transplantation to illustrate the baseline pre-transplant utilization of the health-care system for each subject. Our analysis utilized a date of 12 months from the initial lung transplantation, which is a commonly accepted end point.

Currently, only a limited number of programs follow the practice of active rehabilitation and ambulation while on ECMO[12-14,28]; however, this practice is growing. The employment of ambulatory ECMO as a bridge to lung transplantation is a complex process that has high-resource utilization. In this study, the pre-transplant ECMO duration was 1.5 d in the control group compared with 9 d in the ambulatory ECMO group. These longer ECMO courses were expected, as transplant listing was delayed until the subjects demonstrated successful rehabilitation, including the ability to ambulate. This delay likely contributed to the trend toward higher pre-transplant costs between the 2 groups and was a change in practice, as subjects in the control cohort did not have to ambulate before being listed for transplantation. Notably, however, the duration of mechanical ventilation support demonstrated a difference between the 2 groups. Although the duration of mechanical ventilation was longer for the study group before transplantation, it was shorter after transplantation. This highlights an important benefit of improved conditioning and physical status while awaiting lung transplantation.

An important finding in this study is that despite more intense resource utilization and a likely higher pre-transplant cost for the ambulatory subjects, recovery time was shortened, and overall cost was lower by the time these subjects were discharged from the hospital. These data suggest that there was an acceptable return on investment for the increased early cost, given the shorter post-transplant hospitalization stay and thus lower overall costs.

There are a number of factors that drive hospitalization costs. Hospital length of stay is an important consideration. Prior studies have demonstrated the association between hospital costs and length of stay.[29,30] Our study demonstrated a significant reduction in ICU stay after transplantation between the 2 groups, as well as a near-significant reduction in total hospital stay, with the study cohort having a total stay of almost half that of the control group (see Table 3). The reduction in stay and subsequent resource utilization in our study cohort is likely a significant contributor to the reduction in cost.

For children and adults with respiratory failure, the use of ECMO as a bridge to recovery has been shown to be a cost-effective strategy with good clinical outcomes.[31] The largest cost analysis of ECMO utilization for patients with respiratory failure to date was a randomized controlled trial in 180 adult subjects conducted across 68 centers in the United Kingdom that demonstrated improved disability-free survival at 6 months in subjects supported with ECMO compared with conventional ventilation.[32] The economic evaluation of that investigation revealed that the use of ECMO in this setting was a cost-effective strategy based on accepted thresholds.[32]

Although much of the data regarding the cost effectiveness of ECMO demonstrate increased cost, these increases are generally justified based on improvement in outcomes.[14] In our study, the addition of a rehabilitation and ambulation program to the routine care of patients being supported with ECMO as a bridge to lung transplantation demonstrated both lowered cost and improved outcomes in a population of critically ill subjects with almost certain mortality without lung transplantation. Although not statistically different, substantial heterogeneity did exist between these 2 cohorts, with variability in age (median in years of 53 vs 22), disease states before transplant, and disease severity (median APACHE III of 58 vs 97). This variability makes specific prediction of relative mortality between the 2 cohorts impossible, but these data suggest that both outcomes and cost may be improved by implementing an ambulatory approach before lung transplantation.[14]

Although important, this study was not without limitations. The largest limitation was our small cohort size from a single center. The impact of the small sample size was seen in several aspects. Comparing the cohort demographics, a non-significant difference was seen with age and severity of illness. The subjects in the control cohort appeared to have an older median age, but because of the small sample size, the difference was not recognized. Additionally, the subjects in the study cohort appeared to have a higher severity of illness. Again, the small sample size had an impact on the significance. Thus, although it may be reasonable to presume that the younger subjects in the study cohort would have a quicker recovery, this same group also had a higher severity of illness before transplantation. Additionally, costs are institution-specific; thus, attempting to incorporate additional centers into the analysis without standardization of the data would likely lead to inaccurate results. Discounting cost is a strategy used to correct for inflation over time so that more modern costs, which are typically increased, are standardized and compared with cost at initiation of the analysis. We did not incorporate cost discounting in our analysis given the relatively short time period of data collection.

Given the limited number of centers currently using this ambulatory approach and the growing interest in this technique, the reporting of the cost implications of such a program is an important consideration. In addition, a single subject in our ambulatory cohort underwent retransplantation after organ rejection, adding bias to our results. Rather than modifying the inclusion criteria, we performed a sensitivity analysis in an attempt to account for outliers in a small study. Both unadjusted and adjusted data are shown.

Another limitation is that this study was not performed as a cost-effectiveness evaluation with quality-adjusted life-year calculations, but was completed as a financial cost analysis. We did not collect subject quality-of-life data to calculate quality-adjusted life-years, nor was there adequate time to assess the long-term outcomes of this strategy. Although our study was not a quality-adjusted life-year investigation, prior studies regarding the cost effectiveness and cost of ECMO have been completed with mixed results. In children supported with ECMO after cardiac arrest or cardiac surgery, ECMO has been shown to be cost-effective; however, supporting children with ECMO as a bridge to heart transplantation has not, at least by typical thresholds, been shown to be cost-effective.[15,33,34]

Another potential limitation was that subjects were evaluated longitudinally, and improved proficiency in the more recent cohort may have led to the improvements seen rather than rehabilitation and ambulation. Additionally, before transplantation, subjects in the control cohort were cared for in an adult medical ICU, whereas 4 of the 5 subjects in the study cohort were cared for in a pediatric ICU. It is possible that differences in care that exist between these units may have led to a difference in outcome. Finally, our investigation was retrospective and subject to the limitations of any retrospective review.

Despite the limitations, this study suggests that an ambulatory ECMO program in patients as a bridge to lung transplantation not only potentially improves outcomes but also may decrease cost and overall resource utilization. Given the recently reported benefits demonstrated with rehabilitation and ambulation while on ECMO,[14] equipoise for a randomized trial may not exist. However, clinicians and investigators need to rigorously evaluate the implementation of this approach, including the financial implications and impact, realizing that these decisions may be center-specific and may change over time.

Conclusions

This study demonstrated that, in addition to improved clinical outcomes associated with rehabilitation and ambulation for subjects bridged to lung transplantation with ECMO, this approach may be financially beneficial. Subjects who underwent rehabilitation and ambulation while on ECMO had lower post-transplant costs through 12 months following transplantation compared with those supported with ECMO who did not receive rehabilitation. An important finding is that higher upfront costs were negated by significantly lower costs following lung transplantation. Additionally, a large contributor to this reduction in cost may have been an overall decrease in stay associated with an ambulatory strategy. Although further investigation is needed, this analysis suggests that rehabilitation and ambulation for patients supported with ECMO while awaiting lung transplantation not only improve clinical outcomes but also may be financially advantageous.

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