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MAIN TEXT

Cost effectiveness of commercial portable ex vivo lung perfusion at a low-volume US lung transplant center

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Abstract

Background: Portable ex vivo lung perfusion during lung transplantation is a resource-intensive technology. In light of its increasing use, we evaluated the cost-effectiveness of ex vivo lung perfusion at a low-volume lung transplant center in the USA.

Methods: Patients listed for lung transplantation (2015–2021) in the United Network for Organ Sharing database were included. Quality-of-life was approximated by Karnofsky Performance Status scores 1-year post-transplant. Total transplantation encounter and 1-year follow-up costs accrued by our academic center for patients listed from 2018 to 2021 were obtained. Cost-effectiveness was calculated by evaluating the number of patients attaining various Karnofsky scores relative to cost.

Results: Of the 13 930 adult patients who underwent lung transplant in the United Network for Organ Sharing database, 13 477 (96.7%) used static cold storage and 453 (3.3%) used ex vivo lung perfusion, compared to 30/58 (51.7%) and 28/58 (48.3%), respectively, at our center. Compared to static cold storage, median total costs at 1 year were higher for ex vivo lung perfusion (\$918 000 vs. \$516 000; $p = 0.007$) along with the cost of living 1 year with a Karnofsky functional status of 100 after transplant (\$1 290 000 vs. \$841 000). In simulated scenarios, each Karnofsky-adjusted life year gained by ex vivo lung perfusion was 1.00–1.72 times more expensive.

Conclusions: Portable ex vivo lung perfusion is not currently cost-effective at a low-volume transplant centers in the USA, being 1.53 times more expensive per Karnofsky-adjusted life year. Improving donor lung and/or recipient biology during ex vivo lung perfusion may improve its utility for routine transplantation.

KEYWORDS

cost effectiveness, ex-vivo lung perfusion, lung transplant

1 | INTRODUCTION

For patients with end-stage lung disease, lung transplantation can be lifesaving. In 2020, 2539 lung transplants were performed in the USA, a significant increase from 959 twenty years earlier.[1] Yet even with this increase, three people die weekly on the waiting list.[2] Ex vivo lung perfusion (EVLP) was developed to bridge the organ shortage by allowing for the assessment and potential "re-habilitation" of borderline allografts.[3–6] From 2015 to 2018, EVLP was used in 3% of lung transplants in the USA.[7,8] Donor lungs procured with EVLP have non-inferior 30-day and 1-year survival compared to lungs procured with static cold storage (SCS).[9–13]

However, evidence supporting an increase in donor organ availability using EVLP has been limited.[14] In addition, there are significant costs associated with the labor and materials needed for EVLP. At one academic center in the USA, hospital admissions with an EVLP transplant had a $64 984 median increase in direct hospital cost when compared to SCS transplants.[15] Two large centralized health systems – the National Health Service in the United Kingdom and Canadian Medicare in Canada – found that incorporating EVLP into regular practice was not cost-effective per quality-adjusted life-year (QALY).[16,17]

The USA is a fundamentally different healthcare system that does not assess cost during Federal Drug Administration approval of novel technology – indeed, 10/46 (21.7%) recently analyzed medical devices that received pre-market approval in the USA exceeded the commonly described $50 000/QALY threshold used by other countries.[18] Even so, the Institute of Medicine has declared that it is imperative "to curb [the] ever-escalating costs" that "[make] the status quo untenable."[19] Here, we determine if using EVLP is cost-effective compared to SCS at a low-volume US center.

2 | MATERIALS AND METHODS

2.1 | Patients

The United Network for Organ Sharing's (UNOS) Scientific Registry of Transplant Recipients (SRTR) database was queried for all patients age 18 or older who underwent lung transplantation from shortly prior to when EVLP use was integrated into the record (February 1, 2015) until January 31, 2021 ($N = 13\,930$).[8] Cost data were collected using patients from a high-volume EVLP but low volume overall lung transplant center at University of Chicago Medicine.[20] To collect cost data, we analyzed all patients age 18 or older listed for lung transplantation from the time University of Chicago Medicine (UCM), a high-volume EVLP transplant center first used portable EVLP (OCS™ Lung System, TransMedics, USA) in February 1, 2018 to September 30, 2021 ($N = 68$). The decision to place patients on EVLP was at the discretion of the attending surgeon. This study was approved by the University of Chicago Institutional Review Board (IRB20201124) with waived informed consent. This study was designed following the STROBE checklist and is in compliance with the ISHLT ethics statement.[21]

2.2 | Clinical outcome measures

The UNOS database was queried for the percentage of waiting list patients who received a lung transplant either with conventional SCS or with EVLP. Recipient characteristics including lung allocation score, survival (at 6, 12, 18, and 24 months), length of hospitalization, and time spent on the waiting list were collected. For patients that underwent lung transplants with EVLP, the mean length of time on EVLP was calculated.

2.3 | Cost outcome measures

Operating costs, defined as the sum of direct and indirect costs, accrued during the transplant encounter and up to 1-year post-transplant were collected. Costs were defined as operating costs provided by the UCM system (not charges that are presented to insurance companies). For patients who received transplants but the last follow-up date was before their 1-year post-transplant date ($n = 4/58$ [1 EVLP, 3 SCS] with median follow-up of 224 days), their 1-year follow-up cost (exclusive of transplant encounter) was estimated by dividing their costs by the percent of the year that had passed since their transplant date. One-year follow-up costs were determined both with and without patients who died prior to 1-year from transplantation ($n = 12/56$). Seven patients died prior to discharge from their transplant encounter (five EVLP, two SCS) and were excluded from the analyses of follow-up costs but included for analyses of the cost of transplant encounter (Figure S1). One patient's transplant encounter was excluded as an outlier among the SCS population for having a reported operating cost far below the mean of SCS transplantation ($72 000) due to an institutional accounting practice, but their 1-year follow-up costs were included in the analysis. Costs are listed in 2021 US Dollars (USD). For ease of interpretation, costs from prior publications were also converted to 2021 USD by adjusting for inflation.

2.4 | Karnofsky performance status (KPS)

KPS scores at time of transplant and at 1-year follow-up were collected to calculate the value of health outcomes after SCS and EVLP transplants. The KPS (ranging from 0% (dead) to 100% (no complaints and no evidence of disease)) is a validated marker of health-related quality-of-life and is widely used to assess functional status in patients undergoing transplantation.[22–26] For transplant recipients who died prior to their 1-year visit, KPS was recorded as 0%. For recipients who had a recorded 1-year visit in the UNOS database but had a missing KPS score, a standard imputation model was used. Patient KPS scores were categorized as: A (KPS 80–100%), normal activity levels and need no assistance; B (KPS 50–70%), unable to work but are able to live independently; and C (KPS 0–40%), cannot care for themselves independently and may require hospitalization.[22,23,25]

2.5 | Statistical analysis

Demographic and clinical data were stratified by receipt of lungs preserved via SCS or EVLP. Given non-parametric distributions of data, Chi-squared tests were used for categorical variables and Wilcoxon rank sum tests were used to evaluate continuous variables. Unadjusted post-transplant patient survival probability was evaluated with Kaplan–Meier curves and a log-rank test to compare survival of EVLP to SCS. Statistics were performed in R version 4.2.0 (R Foundations for Statistical Computing, Vienna, Austria).

2.6 | Cost-effectiveness analysis

To determine cost-effectiveness, we compared the quality-of-life of transplant recipients (KPS) to the cost of their transplant and follow-up. We accounted for patients who were already admitted to the hospital prior to being transplanted by calculating cost savings from being transplanted. The mean costs of patients hospitalized prior to transplantation was compared to those admitted solely for the purpose of transplantation. Using UNOS estimates that prior to transplantation 21% of patients are hospitalized and 14% are in the ICU, the savings from resolution of pre-existing hospitalization was determined and factored into the 1-year aggregate cost.[2] We multiplied the final mean 1-year aggregate cost (cost of transplant encounter + follow-up) by the total number of patients who received EVLP and SCS transplants in the UNOS database to determine the national cost burden of EVLP and SCS.

$$\text{Mean total cost} \times \text{Number of transplant recipients} = A$$

To determine the cost of living a year in KPS category A and B, we divided the national cost burden of EVLP and SCS by the number of patients falling into those categories. No calculation was done to determine the cost of producing an additional life year in KPS category C as it was considered not to be within care goals.

$$\frac{A}{\text{Number of Recipients with KPS} \geq 80\%} \times 100 = \text{Cost of 1 Year post transplant with KPS of} \geq 80\%$$

$$\frac{A}{\text{Number of Recipients with KPS} \geq 50\%} \times 100 = \text{Cost of 1 Year post transplant with KPS of} \geq 50\%$$

To determine the cost of adding a fully functional year (KPS 100%) to the population of transplant recipients after an SCS or EVLP transplant, we divided the national cost burden of EVLP and SCS by the sum of KPS scores of recipients of SCS and EVLP transplants and multiplied by 100.

$$\frac{A}{\Sigma(\text{All Recipients KPS at 1 Year Followup})} \times 100 = \text{Cost of 1 Year post transplant with KPS of } 100\%$$

In addition to our base cost-effectiveness analysis, we estimated costs of EVLP versus SCS in various scenarios as a sensitivity analysis to determine possible paths to cost-effectiveness.

3 | RESULTS

3.1 | UNOS patient characteristics

From February 1, 2015 to December 31, 2021, 13 930 patients received a lung transplant, of which 13 477 (96.7%) were SCS and 453 (3.3%) were EVLP. Overall, 39.8% were female, average age was 57.7 years, 77.8% were white, and median lung allocation score (LAS) was 41.4 (Table S1). Patients who underwent transplant utilizing EVLP were more likely to have bilateral transplants (83.7% vs. 74.1%, $p < 0.001$), grafts from a donor following cardiac death (30.9% vs. 4.3%, $p < 0.001$) and longer waitlist time (130 days vs. 111 days, $p = 0.02$). Following transplant, EVLP transplant patients had a longer length of stay (36.3 days vs. 28.4 days, $p < 0.001$). Patients who underwent transplant with EVLP had a lower survival compared to patients who underwent lung transplants with SCS ($p < 0.003$) (Figure S2).

3.2 | UCM patient characteristics

In the UCM cohort, 68 patients were listed between February 1, 2018 and September 30, 2021. As of December 31, 2021, 56 patients received a total of 58 transplants. Two patients underwent two transplants with greater than 1 year between transplant encounters and both transplant encounters were considered unique encounters in these analyses. In total, 30 of the 58 transplants were SCS (51.7%), and the remaining 28 were EVLP (48.3%). Overall, 25% of patients were female, average age was 57.7 years, 60.7% identified as white, and median LAS was 57.8 (Table S2). Compared to EVLP, there was no significant difference in transplant procedure type or median LAS (59.1 EVLP vs. 56.5 SCS, $p = 0.87$), but cold ischemia time was longer for donor using SCS (left lung 168.9 min EVLP vs. 320.6 min SCS, $p < 0.001$; right lung 165.9 min EVLP vs. 348.3 min SCS, $p < 0.001$). There was no significant difference in waitlist times between groups and no difference in unadjusted post-transplant survival stratified by EVLP and SCS transplant (Figure S3).

3.3 | KPS score

Of 13 930 patients who received a transplant in the UNOS database, 11 628 (83.5%) had KPS available at 1-year post-transplantation. Of 13 477 patients who received a transplant with SCS, 11 279 (83.7%) had KPS scores at 1 year with a mean KPS of 72.7% (Table 1). Of 453 patients who underwent a transplant utilizing EVLP, 349 (77%) had KPS scores at 1 year with a mean KPS of 66.5%. Patients who underwent a transplant with EVLP had a lower mean KPS at 1 year prior to multiple imputation ($p < 0.001$). Following multiple imputation, of 13 477 patients who received an transplant with SCS at the 1-year post-transplant visit, 9412 (69.8%) patients had a KPS ≥80%, and 11 720 (87.0%) had a KPS ≥50%. Of 453 patients who received an EVLP transplant, 280 (61.1%) had a KPS ≥80% and 358 (78.2%) had a KPS ≥50% at the 1-year visit.

3.4 | Operating cost of EVLP versus SCS

Transplant encounter cost data were available for 26 EVLP and 27 SCS patients, and 1-year follow-up care cost data were available for 21 EVLP patients and 25 SCS patients (Figure S1). During the initial transplant encounter, the median operating costs was higher for EVLP transplants ($708 000) than for SCS transplants ($289 000) ($p < 0.001$) (Table 2). At 1-year follow-up, there was no difference between median operating costs for EVLP and SCS regardless of whether patients who died prior to 1-year follow-up were included (EVLP: $16 500; SCS: $173 000; $p = 0.74$) or excluded (EVLP: $150 000; SCS: $173 000; $p = 0.50$). Aggregated median operating costs at 1 year for both initial transplant encounter and follow-up were higher for EVLP regardless of whether patients who died prior to 1-year follow-up were included (EVLP: $918 000; SCS: $516 000; $p = 0.007$) or excluded (EVLP: $744 000; SCS: $472 000; $p = 0.04$) (Figure 1). Following adjustment for cost savings from ultimately discharging patients who would have maintained inpatient status without transplantation, mean costs for 1-year transplantation were $1 010 000 for EVLP patients and $624 000 for SCS patients.

3.5 | Cost-effectiveness sensitivity analysis

The cost of living 1 year after an SCS transplant with a KPS ≥80% is $659 000 and with a KPS ≥50% is $529 000. The cost of living a year after an EVLP transplant with a KPS ≥80% is $1 510 000 and with a KPS ≥50% is $1 180 000. The cost of living a completely functional year (KPS 100) is $841 000 for an SCS transplant and $1 290 000 for an EVLP transplant. EVLP remained less cost-effective than SCS in simulated scenarios where: (A) all lungs procured with EVLP were transplanted; (B) 15% of all lungs transplanted used EVLP; (C) if cost savings accrued from discharging a patient who would remain inpatient without transplantation

TABLE 1 Distribution of patients with KPS scores >80 and >50 at 1-year visit following SCS and EVLP associated transplants prior to multiple imputation.

	Total # transplant recipients	Patients with KPS ≥80% at 1-year visit	Patients with KPS ≥50% at 1-year visit	Mean KPS at 1-year visit
SCS	11 279	7725 (68.5%)	9624 (85.3%)	72.7%
EVLP	349	226 (64.7%)	271 (77.7%)	66.5%
Overall	11 628	7951 (68.4%)	9895 (85.1%)	72.5%

TABLE 2 Total operating costs in 2021 USD for patients' transplant encounter, 1-year follow-up.

Total operating cost	EVLP ($N=26$)	SCS ($N=27$)	*p*-value (Wilcoxon)
Transplant encounter			
Mean (SD)	$908 000 ($555 000)	$454 000 ($335 000)	<0.001*
Median [min, max]	$708 000 [$365 000, $2 600 000]	$289 000 [$209 000, $1 540 000]	
Missing	0	1	
1-year follow-up (normalized)			
Mean (SD)	$197 000 ($127 000)	$297 000 ($351 000)	0.74
Median [min, max]	$165 000 [$31 100, $464 000]	$173 000 [$32 500, $1 610 000]	
Missing	5	2	
1-year aggregate including recipients who died prior to 1-year follow-up			
Mean (SD)	$1 070 000 ($594 000)	$738 000 ($526 000)	0.007*
Median [min, max]	$918 000 [$478 000, $3 060 000]	$516 000 [$241 000, $2 200 000]	
Missing	0	1	
1-year aggregate excluding recipients who died prior to 1-year follow-up			
Mean (SD)	$901 000 ($425 000)	$717 000 ($526 000)	0.04*
Median [min, max]	$744 000 [$478 000, $1840 000]	$472 000 [$241 000, $2 200 000]	
Missing	9	4	

P values less than 0.05 are identified with an *.

are tripled; (D) all patients survive 1-year following transplantation; (E) in which transplant encounters where patients were admitted for a reason other than transplantation are excluded (Table 3). The only scenario where EVLP was as cost-effective as SCS was (F) if the only cost difference in care was that of the EVLP technology.

4 | DISCUSSION

For a patient to live fully independently at 1 year after lung transplantation at a low-volume center, the cost associated with EVLP is 53% more than SCS ($1 290 000 vs. $841 000), indicating that each performance-adjusted life year gained from use of EVLP compared to SCS costs $449 000. EVLP showed higher median costs compared to SCS for both the transplant encounter and 1-year follow-up at our center, consistent with other studies examining total hospital costs for EVLP compared to SCS in the USA.[16] This higher cost was not associated with differences in LAS, age, or time on the waiting list, indicating that this was not a difference in disease severity. Further, the difference in mean cost for EVLP and SCS transplant encounters ($454 000) far exceeds previously reported costs of EVLP procedure itself ($7467–$28 731), indicating hidden costs beyond the perfusion technology.[17] Given these findings, portable EVLP is not currently cost-effective compared to SCS as a means of improving access to lung transplantation at low-volume centers in the USA.

While portable EVLP in the USA is less cost-effective in its current form, there are routes that could lead to this changing. If EVLP were able to triple the amount of savings from patients already hospitalized and on the wait list, the relative cost-effectiveness would improve to be only 18% more expensive than SCS per KPS adjusted life year. In another scenario, if the cost difference between EVLP and SCS patients could be reduced to the cost of the EVLP procedure itself, EVLP transplants would improve to being nearly as economical as SCS ($4000 difference) per performance-adjusted life year. This improvement in cost-effectiveness may be seen at high-volume transplant centers who are able to spread more indirect costs across multiple transplant encounters. Alternatively, a centralized EVLP center that can focus the national ex vivo perfusion expertise would have the potential to minimize procedural inefficiencies, optimize the use of EVLP equipment and improve outcomes.[27]

Alternatively, if scientific advancements could be applied to EVLP clinically to improve postoperative graft and patient survival, its utility may outweigh its increased cost. Promising interventions that could favorably alter intrinsic donor lung biology include thrombolysis, photodynamic therapy, steroids, gene therapy, or antibiotics.[6,28–31] Emerging technology that would allow the use of FpGalNAc deacetylase and FpGalactosaminidase to convert donor lungs of blood type ABO-A to ABO-O with EVLP, could increase the donor pool by overcoming ABO incompatibility.[32]

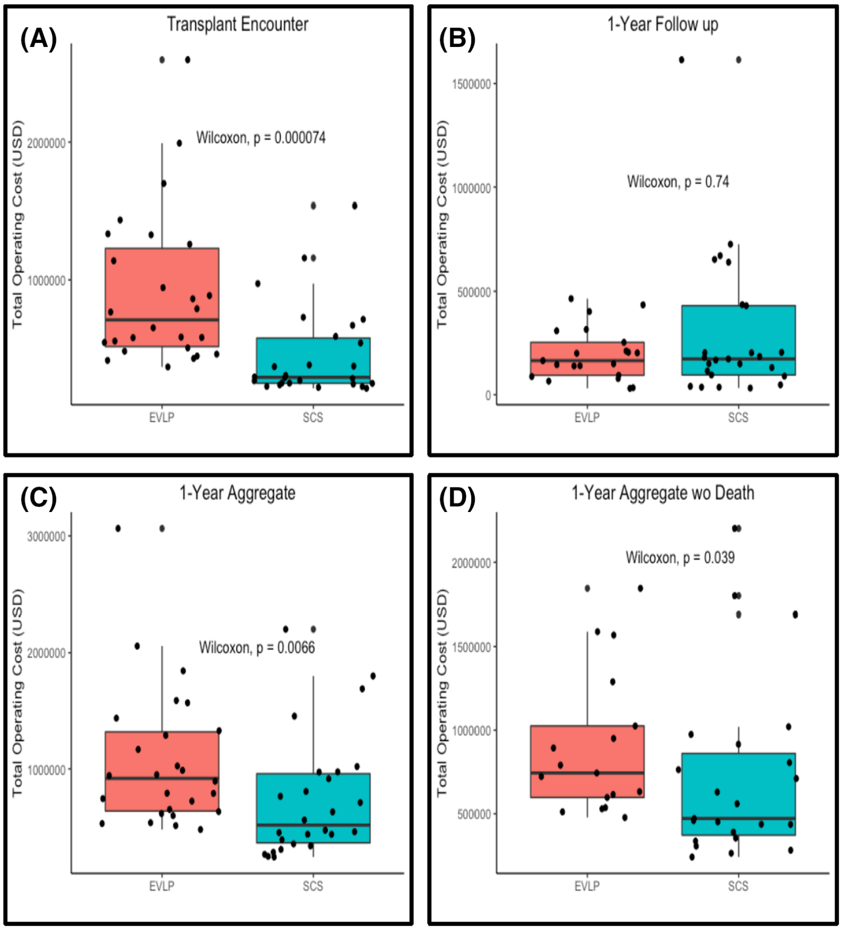

FIGURE 1 Box plots evaluating total operating costs of University of Chicago patients who had EVLP and SCS associated lung transplants including only the transplant encounter (A), normalized 1-year follow-up (B), 1-year aggregated costs including those patients who died (C) and exclusive of patients who died during their transplant encounter (D). Individual patient costs are indicated by dots. All costs presented in USD.

The results of this single-center study evaluating the cost-effectiveness of a commercially available, portable EVLP system contrast with the Toronto Lung Transplant Program experience where patients who underwent lung transplantation with EVLP had decreased total hospitalization costs compared to those with SCS ($76 686 EVLP vs. $102 904 SCS).[33] Though unable to identify the specific areas where cost-savings occurred during the transplant encounter, we believe that the Toronto group have several distinct advantages that make replicating their results difficult for a low-volume center. The Toronto group is one of the highest volume lung transplant centers in the world and this volume likely results in procedural efficiencies as well as increased bargaining power with Canada Medicare that may lower the total cost of hospitalization compared to a center in the USA. In addition, the Toronto group uses a home-grown EVLP circuit which only had a $25 difference in mean supply cost between EVLP and SCS groups, which is different from groups who must purchase the circuit commercially.[33]

4.1 | Limitations

Our study has several limitations. We did not have granular patient data from the UNOS database to assess differences in the health status of patients who underwent lung transplants with EVLP and SCS nationally. We were also unable to narrow our use of the UNOS database to only include similar low volume centers that used both commercially available, portable EVLP and SCS, which may affect the KPS outcomes observed in this study. Further, the KPS score that is recorded in the UNOS database, while validated and the only quality-of-life measure included in SRTR, is not the gold standard for determination of quality-of-life. There was a significant amount of missing data from the KPS (16.5%) that, while partially accounted for using a standard imputation model, may influence the nature of our findings. Within our single center cohort, our patients had higher LAS compared to the UNOS cohort and this greater illness severity could have translated to differences in the cost burden of our patients relative to those in other systems; the small sample size did not allow for controlling for differences in patient illness severity.[34] Our individual center data did not allow analysis of individual line items and it is not clear how the difference in cost-effectiveness could be allocated to labor, materials, and other fixed costs in both the hospital and post-discharge setting. As the data included in this manuscript reflects the centers first 3 years using EVLP, it is also possible

TABLE 3 Cost effectiveness sensitivity analysis incorporating mean aggregated costs of EVLP and SCS lung transplantation when adjusted for cost-savings of patients hospitalized prior to transplantation.

	Costs with SCS		Costs with EVLP		Cost-effectiveness ratio
Scenario	**Total cost at 1-year follow-up**	**Per aggregated 100 KPS**	**Total cost at 1-year follow-up**	**Per aggregated 100 KPS**	**EVLP/ KPS: SCS/KPS**
Base scenario	$624 000	$841 000	$1 010 000	$1 290 000	1.53
A. All EVLP organs are transplanted	$624 000	$841 000	$954 000	$1 290 000	1.53
B. 15% of all lungs transplanted use EVLP	$624 000	$841 000	$954 000	$1 230 000	1.47
C. If calculated wait list savings were tripled	$615 000	$829 000	$694 000	$976 000	1.18
D. All patients survive 1-year post transplant	$442 000	$596 000	$780 000	$976 000	1.64
E. Excluding patients already hospitalized	$434 000	$585 000	$817 000	$1 010 000	1.72
F. Only cost difference is EVLP	$624 000	$841 000	$631 000	$845 000	1.00

that with increased institutional experience further cost savings could be accrued. Our experience as a low-volume lung transplant center may not be generalizable to health systems that are able to provide EVLP and overall lung transplantation at higher volume and lower cost. However, as procedural efficiencies decrease the overall cost burden of lung transplantation, the fixed cost of the EVLP equipment will be magnified when comparing the costs of transplantation with EVLP and SCS. Finally, this study was performed from the perspective of a hospital system since we did not have access to the waiting list cost to society or insurers. Without this data, we were unable to create a Markov model, potentially missing societal cost savings that may accrue when a patient receives a lung transplant with a graft that would not have been transplanted without access to EVLP.

5 | CONCLUSION

We report that for a patient to live fully independently for a year after lung transplant, it would cost 53% more with commercial portable EVLP than SCS at a low-volume center. Commercial portable EVLP showed higher median total operating costs for the transplant encounter and at 1-year follow-up when compared to SCS. When hospitals consider moving to implement EVLP at their institutions, they must consider whether the current iteration of portable EVLP is worth the expense.

AUTHOR CONTRIBUTIONS

Johnathan Kent: Contributed to study design, data analysis, writing of manuscript, and revision of manuscript. Rachel Nordgen: Contributed to data analysis, writing of manuscript, and revision of manuscript. Daniel Ahn: Contributed to study design, data analysis, writing of manuscript, and revision of manuscript. Maria Lysandrou: Contributed to study design and revision of manuscript. Ashley Diaz: Contributed to study design and revision of manuscript. David Fenton, BS: Contributed to study design and revision of manuscript. Thirushan Wignakumar: Contributed to study design, data analysis, and revision of manuscript. Nicola McMeekin: Contributed to study design and revision of manuscript. Christopher Salerno: Contributed to study design and revision of manuscript. Jessica Donington: Contributed to study design and revision of manuscript. Maria Lucia L. Madariaga: Contributed to study design, data analysis, writing of manuscript, and revision of manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest with the contents of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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