ORIGINAL ARTICLE

Contemporary look at extracorporeal membrane oxygenation as a bridge to reoperative lung transplantation in the United States – a retrospective study

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SUMMARY

The purpose of this study was to examine the influence of extracorporeal membrane oxygenation (ECMO) as a bridge to reoperative lung transplantation (LT) on outcomes and survival. A total of 1960 LT recipients transplanted a second time between 2005 and 2017 were analyzed using the United Network for Organ Sharing (UNOS) Organ Procurement and Transplantation Network (OPTN). Of these recipients, 99 needed ECMO as a bridge to reoperative LT. Mean age was 50 ± 14 years, 47% were females, and the group with ECMO was younger [42 (30–59) vs. 55 (40–62) years]. In both univariate and multivariable analyses (adjusting for age and gender), the ECMO group had greater incidence of prolonged ventilation >48 h (83% vs. 40%, $P < 0.001$) and in-hospital dialysis (27% vs. 7%, $P < 0.001$). There were no differences in incidence of acute rejection (15% vs. 11%, $P = 0.205$), airway dehiscence (4% vs. 2%, $P = 0.083$), stroke (3% vs. 2%, $P = 0.731$), or reintubation (20% vs. 20%, $P = 0.998$). Kaplan–Meier survival analysis showed the ECMO group had reduced 1-year survival (66.6% vs. 83.0%, $P < 0.001$). After covariate adjustment, the ECMO group only had increased risk for 1-year mortality in the 2005–2011 era (HR = 2.57, 95% CI = 1.45–4.57, $P = 0.001$). For patients who require reoperative LT, bridging with ECMO was historically a significant predictor of poor outcome, but may be improving in recent years.

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Introduction

The use of extracorporeal support as a bridge to lung transplantation (LT) has become an accepted treatment for recipients with end-stage lung disease [1,2]. Over the past decade, a number of innovative and technological advances have served to improve the efficacy of the use of extracorporeal support in the management of the critically ill [3]. The outcomes in contemporary practice in recent years have shown such dramatic improvement that they have been referred to as the "ECMO-2 era" to distinguish them from the poorer outcomes and lower survival of the preceding era [4]. As such, there has been an exponential increase in the use of extracorporeal membrane oxygenation (ECMO) and, with it, improved outcomes across the spectrum of care and indication of mechanical support [3,5]. This increased use of ECMO has been of great utility in LT, which has benefitted from some of the best results in the treatment of severe primary graft failure and in the bridging to transplantation [3,6,7]. The demand has further been fueled by the lung allocation score (LAS) which, in 2005, shifted the prioritization of donor allocation to recipients based on acuity rather than time spent on the waiting list [8,9]. This recognition of the need to cater to the most acutely ill patients has driven the demand for mechanical support as a bridge to transplantation when conventional methods of support are proven insufficient [1,10,11]. In this vein, ECMO is used as a bridge to LT in an estimated 5–7% of total volume [1,3,12]. The outcomes have improved so dramatically that ECMO is increasingly considered to be a more optimal bridge than mechanical ventilation [3,13,14].

Re-transplantation accounts for 5% of all cases [15]. The use of ECMO as a bridge to reoperative LT remains controversial, and it is yet to be considered as standard practice. Until as recently as the past decade, mechanical support had in fact been deemed a relative contraindication to LT [3,11,16,17]. The reported outcomes in reoperative LT have been poor overall, and many centers remain reluctant to offer ECMO in this context [3,18,19]. However, the use of ECMO as a bridge to re-transplantation is undergoing a resurgence [14]. The aim of this study was to provide a contemporary update on the outcomes and risks associated with the use of ECMO as a bridge to lung re-transplantation.

Patients and methods

Data were analyzed retrospectively from the United Network for Organ Sharing (UNOS) Organ Procurement and Transplantation Network (OPTN) Database. Patient records were included for lung transplant recipients who were transplanted a second time between 2005 and 2017. Other solid organ recipients were excluded. A total of 1960 recipients met these inclusion criteria. The sample was categorized into two groups according to the use of ECMO as a bridge to repeat lung transplant: No (n = 1861) and Yes (n = 99). These two groups were compared on the incidence of perioperative complications and 1-year survival.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables are presented as frequency (percentage). Univariate comparisons between the ECMO and no ECMO groups were conducted with independent-samples t-tests or Mann–Whitney tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Perioperative complications were also examined by the ECMO group in multivariable logistic regression analyses adjusting for age and gender. Kaplan–Meier survival analysis was conducted to compare the "ECMO" and "No ECMO" groups on 1-year survival. A multivariable Cox regression was also conducted to compare the ECMO and no ECMO groups on survival, after adjusting for age and gender. Multivariable Cox regressions were also examined with respect to two eras [2005–2011 (n = 1200) vs. 2012–2017 (n = 760)], and 2012 was chosen as the breakpoint caused by substantial increase in ECMO as a bridge to LT shown at that time. Separate Cox regression analyses were conducted for each era to examine the impact of ECMO on survival within each era. All analyses were conducted with SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA), and a P value of <0.05 was considered statistically significant.

Results

A total of 1960 lung transplant recipients received a second lung transplant in this cohort, listed for allograft failure re-transplantation and 5% of those patients (n = 99) received ECMO as a bridge to the second lung transplant (Table S1). The likelihood for ECMO as a bridge to repeat lung transplant was significantly greater in the more recent era (2012–2017) than the older era (2005–2011; 9% vs. 3%, $P < 0.001$), and the average annual increase in ECMO usage as a bridge to reoperative transplantation was 17% (Fig. 1). The mean age of the sample was 50 ± 14 years, and 47% were female.

The recipient characteristics by ECMO group can be found in Table 1. Baseline characteristics were broadly not different between groups. However, the ECMO group was younger (45 vs. 50 years, $P = 0.001$) and the initial LAS was significantly higher for the ECMO group (64.8 vs. 37.2, $P < 0.001$).

Perioperative complications were relatively similar for patients with and without ECMO (Table 2). However, even after adjustment for age, gender, and initial LAS, the ECMO group remained at greater risk for prolonged ventilation (OR = 5.29, 95% CI: 2.99–9.34, $P < 0.001$) and in-hospital dialysis (OR = 4.91, 95% CI: 3.01–8.01, $P < 0.001$).

Kaplan–Meier survival analysis indicated that the ECMO group had reduced 1-year cumulative survival (66.6% vs. 83.0%, Log Rank = 20.7, $P < 0.001$). This result did not reach statistical significance in a multivariable analysis that adjusted for age, gender, and initial LAS (HR = 1.53, 95% CI: 0.99–2.37, $P = 0.058$). Separate multivariable Cox regression analyses split by era found that the excess hazard associated with ECMO for 1-year mortality was only significant in the older era (HR = 2.57, 95% CI: 1.45–4.57, $P = 0.001$; Fig. 2), and there was no difference in 1-year mortality risk by ECMO group in the more recent era (HR = 1.28, 95% CI: 0.63–2.61, $P = 0.501$; Fig. 2).

Discussion

The use of ECMO in the LT recipient in bridging patients or treating primary graft failure proved to be beneficial. The use of ECMO for re-transplantation, however, has previously been associated with poor results. Nevertheless, in the contemporary era of ECMO, this study identified that while ECMO as a bridge to second LT conferred a doubling of risk for 1-year mortality in the historical era, the ECMO groups did not differ on risk for 1-year mortality in the more recent era.

The vast improvements in technological design and circuitry have further fueled the increase in demand for extracorporeal support as a bridge to lung transplantation [3,5]. This rationale has undoubtedly been

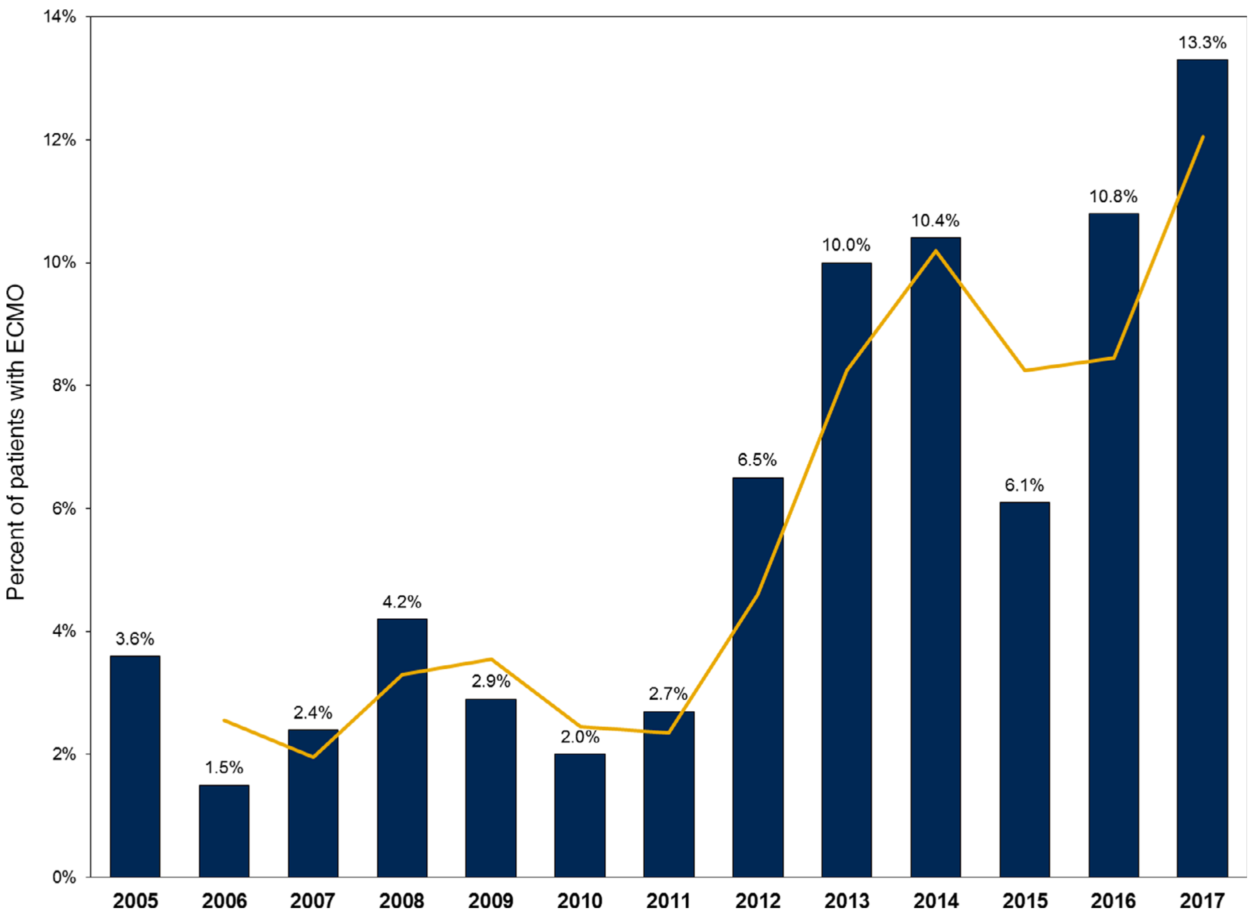

Figure 1 Percent of patients with ECMO as a bridge to reoperative lung transplant between 2005 and 2017 (yellow line represents moving average trendline).

Table 1. Reoperative lung transplant recipient characteristics.

	No ECMO (*n* = 1861)	ECMO (*n* = 99)	*P* value
Age (years)	55 (40–62)	42 (30–59)	0.002
Female	874 (47)	44 (44)	0.624
Caucasian	1577 (85)	86 (87)	0.565
Recent era (2012–2017)	694 (37)	66 (67)	<0.001
Body mass index	23.8 (20.3–27.8)	23.3 (18.9–27.7)	0.948
Preoperative creatinine	0.8 (0.7–1.1)	0.7 (0.5–1.1)	0.105
FEV_1	28 (19–47)	31 (18–40)	0.450
Diabetes	468 (25)	35 (36)	0.019
Initial LAS	37.2 (33.6–43.3)	64.8 (40.3–90.3)	<0.001

ECMO, extracorporeal mechanical oxygenation; FEV_1, forced expiratory volume; LAS, Lung Allocation Score.

Table 2. Complication rates in reoperative lung transplant recipients.

	No ECMO (*n* = 1861, %)	ECMO (*n* = 99, %)	*P* value
Acute rejection	11	15	0.205
Airway dehiscence	2	4	0.083
Stroke	2	3	0.731
Reintubation	20	20	0.998
Prolonged ventilation >48 h	40	83	<0.001
In-hospital dialysis	7	27	<0.001

ECMO, extracorporeal mechanical oxygenation.

influenced by ethical and economic considerations guiding responsible utilization of finite resources. It is increasingly clear however that the improvements in technological design and the growing ubiquity of polymethylpentene oxygenators, heparin-bonded circuits, and quadrox oxygenators have resulted in more efficient circuitry [3]. The expanding clinical expertise in clinical algorithms in intensive care has also contributed to this improvement benefitting patients across the spectrum of indications from postcardiotomy support to emergency cardiopulmonary resuscitation. This demand has thus been borne partially out of necessity as well as by the fact that donor allocation favors the sickest recipient, fostering an obligation for transplant centers to establish the infrastructure to cater to these recipients and to mitigate their attendant comorbidity. In this manner, ECMO has evolved as a competitive bridge to lung transplantation [1-3,13-14,20].

Previously, the outcomes associated with ECMO as a bridge to reoperative transplantation have been dismal [15,21,22]. Indeed, ECMO has been deemed a relative contraindication in this clinical context in view of the challenges proffered by the attendant coagulopathy, bleeding, profound adhesions, and comorbidity of chronic immunosuppression [23]. The gains in survival, however, that have been witnessed with bridging to first-time recipients have sparked an interest in revisiting outcomes in bridging to reoperative lung transplantation with the intuitive notion that those gains may be extrapolated to the reoperative setting. Our findings suggest that this may indeed be the case. National trends suggest that the evolution of ECMO as a bridge to reoperative lung transplantation may be following a similar evolution and trajectory as that witnessed over the past 5–7 years in the use of ECMO as a bridge to first-time transplantation. Indeed, bridging now boasts up to 80% success rate and up to 85% 1-year survival, near identical to that of recipients transplanted without bridging [1,24].

This contemporary analysis provides a portrait of the evolving experience with ECMO in reoperative lung transplantation. It challenges the previous reports that point to the use of mechanical support as an absolute contraindication in re-transplantation. Advocates may use this to suggest that centers should offer organs without prejudice and based on clinical merit, regardless

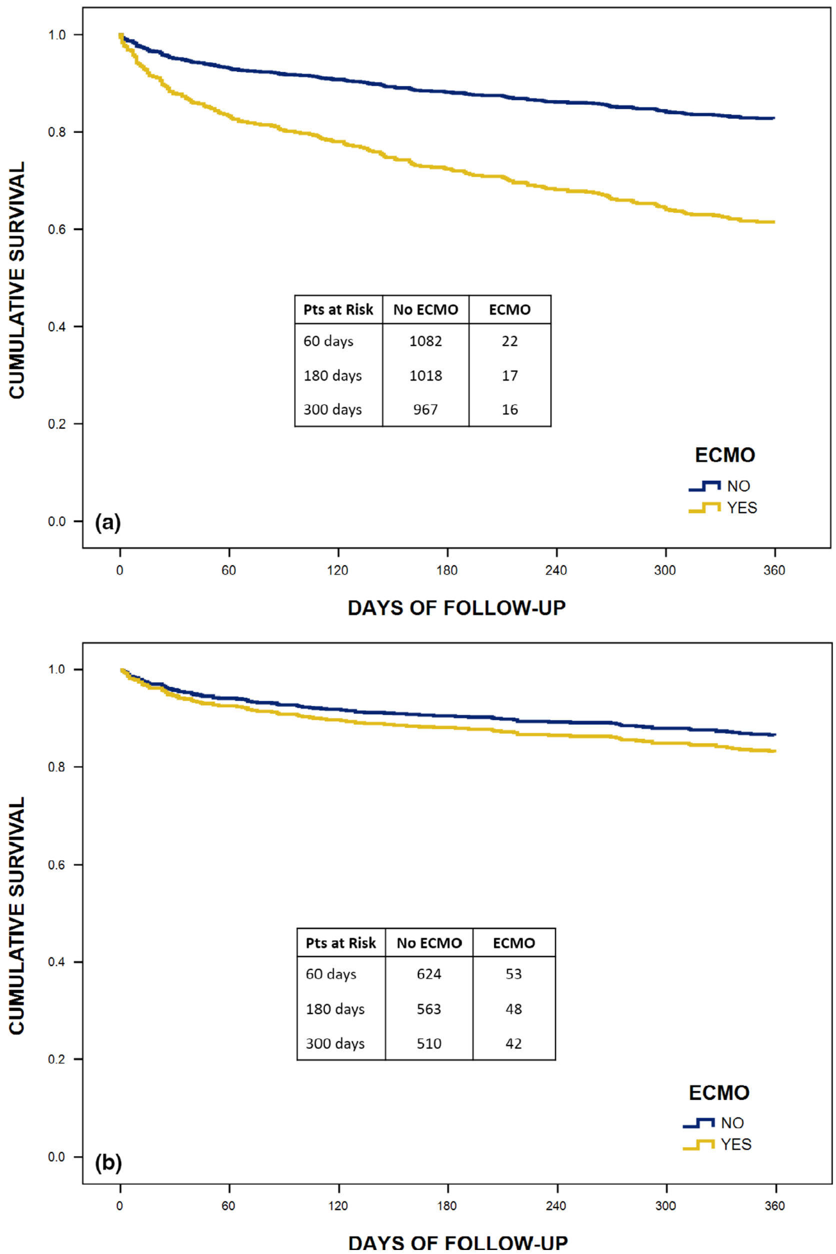

Figure 2 Freedom from 1-year mortality between ECMO groups in the (a) historic era (2005–2011; n = 1200) and (b) more recent era (2012–2017; n = 760).

of prior transplantation. The utilitarian argument, however, would maintain that without equivalent survival results, reoperative lung transplantation remains an ethical contraindication to re-transplantation, fueling the existential dilemma as to the value of life and the justification of distributing extraordinary and scarce resources repeatedly to the same recipient while another looks on. This is particularly poignant with the consideration that previously reported 1-year survival estimates were less than 45%, with a 5-year survival less than 25%, and effectively half the anticipated 90% 1-year survival compared to first-time candidates. This may be further compounded by the new "250 nautical mile rule" that may draw donors from a wider geographical radius.

The present study has a number of limitations to note. First, the absence of granular detail in the UNOS dataset does not permit distinction between veno-arterial (VA) or veno-venous (VV) ECMO or time to reoperation. Type of ECMO, however, has not been conclusively demonstrated to have a significant impact on outcomes following first-time transplantation though this may not necessarily hold true for re-transplantation [24]. Moreover, indication for reoperation and primary data about the index post-transplant course and donor details are poorly reported to the UNOS dataset. Second, our analysis was based only on short-term rather than long-term outcomes as a result of lack of sufficient group sample size at longer follow-up time points. Third, the cumulative experience with the use of ECMO as a bridge to reoperative lung transplantation is likely the testimony of a handful of highly experienced teams with a base sophisticated infrastructure driving the improvement in outcomes that may be more a manifestation of those particular resources in these individual centers rather than a reflection of care as a whole. Only 14 centers use extracorporeal support for more than one transplant [20]. This circumstance greatly limits the reproducibility in centers with little or no experience in extracorporeal support. Fourth, the use of administrative databases carries with it inherent risk of bias. The analysis focuses only on those recipients who successfully underwent transplantation, and the proportions are incomplete without quantification of the denominator. Indeed, because the data are without an estimation of wait list mortality, we are shielded from these data, which itself would lend a more useful and objective appraisal of survival. Nevertheless, with the proportion of reoperative lung transplant cases being relatively stable over the past decade, this bias is unlikely to greatly impact these findings. Finally, the data do not allow the estimation of the effect of contemporary improvements in anesthesia, infection control, critical care management, echocardiographic diagnostics, transfusion protocols, and intensive care delivery. While nearly all reoperative LT procedures are bilateral, the impact of single LT could not be assessed as a result of small sample size. Each of these plays a central role in outcomes and raises the possibility of confounding, with the inability to adjust for these as well as other generational confounders inherent in the constantly evolving clinical landscape.

In conclusion, this analysis provided evidence in support of the use of ECMO as a worthwhile tool in the armamentarium of transplantation, albeit with a complex matrix of ethical, financial, and resource utilization considerations. Indeed, the rift between utility and justice will likely deepen with further use of ECMO, particularly in the relatively ambiguous and subjective manner in which donor- and recipient-related decisions may be made economic costs incurred. It is plausible that the only means to bridge this gap will be by eradicating any excess risk borne by the explicit use of ECMO and achieve true parity in outcomes. The results suggest that this evolution may already be in progress and in the absence of a randomized, controlled, multi-institutional study, and national data analyses such as the present study may be the closest estimation we can proffer. Regardless, it is likely to remain a topic of controversy.

Authorship

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Conflict of interest

None of the authors have any relevant financial disclosures pertaining to this work.

SUPPORTING INFORMATION

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

Table S1. Number of patients per year with and without ECMO.

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