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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Extracorporeal membrane oxygenation following lung transplantation: indications and survival

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KEYWORDS:
lung transplantation;
ECMO;
primary graft dysfunction;
donor factors;
predictors of survival

BACKGROUND: Extracorporeal membrane oxygenation (ECMO) is employed to rescue patients with early graft dysfunction after lung transplantation (LTx). Rates of post-LTx ECMO and subsequent outcomes have been limited to single-center reports.

METHODS: UNOS registry was queried for LTx recipients from March 2015 to March 2016; 2,001 recipients were identified and stratified by need for post-LTx ECMO. Logistic regression was used to determine variables associated with post-LTx ECMO. Cox proportional hazards modeling identified factors associated with survival. Kaplan-Meier analysis with log-rank testing was employed for survival analysis.

RESULTS: Of 2,001 recipients identified, 107 required post-LTx ECMO (5.1%). Recipients requiring ECMO were younger (56 vs 60 years, $p = 0.007$) and had higher body mass index (27.2 vs 25.8, $p = 0.012$). Recipients requiring post-LTx ECMO were more likely to have required mechanical ventilation before transplant (9.3% vs 4.9%, $p = 0.049$) and were more likely to have required pre-transplant ECMO (15% vs 3.7%, $p < 0.001$). On multivariable analysis, pre-transplant ECMO and increasing ischemic time were associated with post-LTx ECMO. Six-month survival for recipients requiring ECMO was 62.2%. On multivariable analysis, need for post-transplant dialysis was associated with mortality. Six-month survival for recipients requiring ECMO with and without dialysis was 25.8% and 86.7% ($p < 0.001$).

CONCLUSIONS: In a nationally representative database, ischemic time and pre-transplant ECMO and/or ventilator requirement were associated with need for post-LTx ECMO. Need for post-transplant dialysis was associated with mortality in patients requiring post-LTx ECMO. These data may permit improved prediction of graft dysfunction. Strategies to minimize renal toxicity in the perioperative phase may lead to improved early survival post-LTx.

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Lung transplantation (LTx) is the gold standard therapy for many patients with end-stage lung disease. However, despite significant improvements in donor management, allograft preservation, and operative technique, early survival remains limited by the development of early severe graft dysfunction after transplantation.[1] The prevalence of primary graft dysfunction (PGD) after LTx has been estimated to be 15%–30%.[2,3] Appropriate management of PGD hinges on severity of illness, which in contemporary analyses is stratified by International Society for Heart and Lung Transplantation (ISHLT) criteria.[4,5] Under ISHLT

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2017.06.014

criteria, any recipient with a degree of PGD that requires ECMO support is considered by definition to have severe PGD (PGD grade 3). Multiple factors contribute to the pathophysiology of PGD after LTx, including periods of ischemia and reperfusion during the transplant procedure, increased permeability or damage to the pulmonary capillary bed, and pulmonary hypertension related to acutely increased pulmonary vascular resistance.

Extracorporeal membrane oxygenation (ECMO) provides a versatile and flexible support strategy for patients with respiratory failure, including outside of the realm of transplantation. In the setting of transplantation, ECMO can be deployed before transplantation as a means to bridge to transplantation[6–15]; intraoperatively as a means to facilitate improved gas exchange (in a venovenous [VV] configuration) with or without additional hemodynamic support (in a venoarterial [VA] configuration); or post-transplant to support recipients with severe graft dysfunction, whether primary in nature or secondary to other reversible causes of poor graft performance immediately post-transplant. ECMO supports recipients with severe PGD by supporting gas exchange and by permitting lung-protective ventilator strategies. Overall, the ability to tailor ECMO deployment strategies to the individual needs of the LTx candidate or recipient has made it an indispensable therapy in the care of these patients.

To our knowledge, to date, reports of rates of post-transplant ECMO and subsequent outcomes have been limited to single-center reports.[5,16–18] Although larger multicenter consortia have now established databases that permit larger scale studies of ECMO, none to our knowledge have focused on the use of ECMO in the LTx population. To facilitate better study of the use of ECMO in LTx, the United Network for Organ Sharing (UNOS) recently added a series of short-term variables that describe the condition of the recipient at 72 hours post-transplant. This analysis was performed to describe the use of ECMO in LTx in the United States, with the aim of assessing both pre-transplant and post-transplant factors in this clinical setting. Accordingly, the Organ Procurement and Transplantation Network (OPTN)/UNOS Standard Analysis and Research (STAR) database was queried for analysis to determine variables associated with the need for post-transplant ECMO at the registry level. In the second portion of the planned analysis, factors associated with survival in recipients requiring post-LTx ECMO support were elucidated.

Methods

The Institutional Review Board at Duke University approved this study before data collection.

Data source

A retrospective cohort analysis was performed using the OPTN/UNOS STAR database. UNOS administers the OPTN under contract with the US Department of Health and Human Services. This database contains data on all transplant candidates undergoing listing for solid-organ transplantation in the United States since October 1987. The data set used for this investigation included all recipients undergoing LTx between October 1987 and June 2016. As of 1999, all data in the OPTN/UNOS transplantation database are collected via UNet, an Internet-based database application. Data are entered by transplant professionals. Electronic data validation and on-site audits are performed for quality assurance.

Study design

The UNOS/OPTN STAR registry was queried for all adult (>17 years old) first-time, isolated LTx recipients from March 31, 2015 (the introduction of the variable), to March 31, 2016. There were 2,015 recipients identified. Recipients for which data regarding the use of ECMO post-transplant ($n = 14$) were not reported were excluded. In the UNOS transplant recipient registration form, these data are coded as a binary variable indicating if a recipient was supported by ECMO at 72 hours post-transplant. No granularity with respect to the deployment strategy (e.g., VA or VV) is provided. Recipients were stratified into recipients who did ($n = 107$) and did not ($n = 1,894$) require ECMO at 72 hours post-transplant.

Statistical analysis

Groups were stratified by the need for ECMO at 72 hours post-transplant. Demographic data were compiled and described. Baseline characteristics and outcomes were compared between groups using the Kruskal-Wallis analysis of variance test for continuous variables (reported by mean and SD) and Pearson's chi-square test for categorical variables (reported using frequency and percent).

To determine the extent to which the need for post-transplant ECMO is associated with survival, Cox proportional hazard regression modeling was employed. Variables included in the Cox model were based on clinical relevance and included recipient, donor, and transplant characteristics. Recipient characteristics included age, diagnosis, lung allocation score at match, need for ECMO pre-transplant, need for mechanical ventilation pre-transplant, medical condition at time of transplant, need for dialysis post-transplant, and need for ECMO post-transplant. Donor characteristics included donor age and diabetes status. Hazard ratio (HR) and 95% confidence interval were computed to estimate strength and precision of associations.

Logistic regression was performed to identify factors associated with the need for post-transplant ECMO and included the following clinically significant variables: ECMO status at the time of transplant, ventilator status at the time of transplant, age, sex, use of steroid, creatinine at time of transplant, medical condition at time of transplant, diagnosis, donor age, donor sex, and ischemic time. Diagnosis was categorized as idiopathic pulmonary fibrosis, restrictive lung disease, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary hypertension, alpha$_1$-antitrypsin deficiency, bronchiolitis obliterans, sarcoidosis, and other.

To further elucidate the role of ischemic time in the need for post-transplant ECMO, linear regression was performed treating ischemic time as a restricted cubic spline. A Cox proportional hazards model was subsequently used to identify factors associated with survival in patients requiring ECMO post-transplant. Factors assessed included recipient age, donor age, allograft ischemia time, need for ventilator at time of transplant, need for ECMO at time of transplant, and need for dialysis before discharge. Kaplan-Meier analysis with the log-rank test was then used for survival analysis of recipients requiring ECMO compared with recipients who did not require ECMO post-transplant. To better delineate the role of concomitant renal failure in patients requiring ECMO