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Neurological Sequelae and Clinical Outcomes After Lung Transplantation

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Background. Neurological complications are common after lung transplantation. However, no large cohort studies have examined the incidence, predictors, and clinical significance of neurological events sustained by lung transplant recipients. **Methods.** We conducted a retrospective cohort analysis of a consecutive series of lung transplant recipients, transplanted at Duke University Medical Center between May 2014 and February 2017 (n = 276). Early neurological complications (ie, occurring during the first week after transplant) were documented by transplant mental health specialists and included delirium, ischemic injury, and posterior reversible encephalopathy syndrome. Analyses accounted for age, native disease, sex, type of transplant, lung allocation score, and primary graft dysfunction. The objectives of the study were to characterize the prevalence and predictors of early neurological sequelae (NSE), occurring during the first week posttransplant, and the association between NSE and subsequent clinical outcomes, including length of stay and mortality. **Results.** Neurological sequelae were common, occurring in 123 (45%) patients. Fifty-seven patients died over a follow-up interval of 2.1 years. The most common NSE were postoperative delirium (n = 110 [40%]) and posterior reversible encephalopathy syndrome (n = 12 [4%]), followed by stroke/transient ischemic attack and neurotoxicity. Higher lung allocation score was the strongest predictor of delirium. The presence of a NSE was associated with longer length of hospital stay (32 days vs 17 days, $P < 0.001$) and greater mortality (hazard ratio, 1.90; 95% confidence interval, 1.09-3.32], $P = 0.024$), with the greatest mortality risk occurring approximately 2 years after transplantation. **Conclusions.** Neurological events are relatively common after lung transplantation and associated with adverse clinical outcomes.

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Lung transplantation remains an important treatment option for many individuals with advanced pulmonary disease, now a leading cause of death in the United States.^{1,2} Among solid organ transplant recipients, lung patients have experienced the most dramatic increase in recipient age over the past decade³ and are now tend to be older (ie, median age of approximately 60 years at transplant)

and are on higher amounts of oxygen support at the time of transplant due to the implementation of the lung allocation system (LAS).^{4,5} Despite the steady growth of lung transplantation and the increasing age of lung transplant recipients, relatively few studies have examined neurological sequelae after transplantation,^{6,7} and available studies have been limited by small sample sizes, select patient groups, and a small range of neurological events examined.⁸ In addition, neuroimaging correlates of neurological sequelae have yet to be characterized among lung transplant recipients.

Understanding the incidence and clinical consequences of postoperative neurological sequelae has important implications for lung transplant recipients. First, intact neurocognition is critical for long-term management of a complex medical regimen.⁹⁻¹¹ Second, neurocognitive functioning appears to worsen in the presence of delirium and other untoward neurological events^{12,13} and has been shown to be predictive of long-term survival.¹⁴ Third, it is possible that the risk of some neurological sequelae, and biobehavioral consequences after transplantation, can be mitigated by greater understanding of the occurrence and etiology of these events.^{15,16} We therefore sought to examine the incidence, predictors, and clinical implications of early postoperative neurological events in a recent cohort of lung transplant recipients.

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MATERIALS AND METHODS

The present study is a retrospective examination of a consecutive series of lung transplant recipients from Duke University Medical Center, transplanted between May 2014 and February 2017. The protocol was approved by the Duke Institutional Review Board (Pro00080875). Consistent with lung transplant guidelines at Duke, no patients were taking benzodiazepines or narcotics before transplantation. During their hospitalization, patients were managed postoperatively for pain with Propofol infusions until ready for extubation, at which point all sedatives were discontinued and thoracic epidural analgesia was provided.

Neurological Events

Comprehensive chart reviews were accomplished by 5 transplant psychologists (P.J.S., B.M.H., G.L.S., K.K.I., C.S.) and a transplant psychiatrist (B.W.) for neurological sequelae (NSE) occurring within the first postoperative week. Criteria for delirium were based on previously described approaches for retrospective chart review in which key neurobehavioral terms and/or the presence of mental status or behavioral changes are identified by a trained clinical abstractor.¹⁷ This chart-based review methodology has been shown to have good concordance with the Confusion Assessment Method.¹⁷ Delirium was not adjudicated until after sedation was weaned. Criteria for possible posterior reversible encephalopathy syndrome (PRES) were modeled after previously published data from the CYPRESS group.¹⁸ Posterior reversible encephalopathy syndrome was therefore defined as a combination of acute neurological changes (eg, consciousness impairment, seizures, visual abnormalities, focal neurological signs, etc) associated with neuroimaging findings consistent with PRES, such as vasogenic edema on magnetic resonance imaging. Acute hypertensive es were also documented, although not necessarily required for PRES diagnosis if neurobehavioral changes and magnetic resonance imaging evidence of PRES were observed. Neurotoxicity was also documented and included serotonin syndrome or tacrolimus toxicity for the purposes of our analyses.

Neuroimaging Data

A subset of patients underwent neuroimaging assessments posttransplant as part of their clinical evaluation to rule out stroke/transient ischemic attack (TIA), PRES, or other neurological etiologies of altered mental status. Although these patients were selected based on their clinical features (ie, patients with altered mental status were more likely to have had neuroimaging), these data can provide important information on the prevalence of occult neurological risk factors (eg, white matter burden, cortical atrophy, etc) that would otherwise not be examined in the context of routine, pretransplant assessments. Consistent with prior literature among patients undergoing cardiothoracic interventions, these data were used in secondary analyses to provide data on possible risk factors for NSE.

Demographic and Medical Predictors

Demographic and medical data were obtained from electronic medical records and verified with United Network for Organ Sharing data. Background characteristics included patient age at the time of transplant, sex, use of psychotropic medications (including antidepressants and anxiolytics), and native disease. To reduce the number of predictor variables in

our analyses, we grouped native diseases a priori into 4 groups: pulmonary fibrosis (IPF), cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD)/emphysema, and other (eg, sarcoidosis, primary pulmonary hypertension, etc). Medical predictors included LAS at the time of transplantation and primary graft dysfunction (PGD) at 72 hours. For PGD, we used a 3-level grading operationalization based on arterial blood gas levels (0/1, 2, or 3).¹⁹ We also examined the use of intraoperative mechanical support, including extracorporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (CPB).

Length of Hospital Stay and Survival

Mortality data were obtained from electronic medical records, with patients censored based on the timing of their last laboratory testing or contact with a health provider. To account for deaths occurring during transplant hospitalization, length of stay (LOS) for individuals who died in the hospital was imputed using the longest sample LOS, consistent with prior studies.²⁰

Data Analysis

All analyses were conducted using SAS 9.4 (Cary, NC) and R 3.4.1 (<https://cran.r-project.org/>). Examination of predictors of postoperative delirium was conducted using logistic regression, with postoperative delirium serving as the binary criterion variable. Within our delirium risk analyses, individuals who developed other forms of NSE were eliminated to reduce the potential for confounding of related neurological outcomes, leaving a total of 252 individuals. For all other analyses of NSE and clinical outcomes, the full sample of 276 participants was utilized. Following predictive modeling recommendations, we examined univariate predictors of delirium using a liberal threshold for inclusion ($P < 0.20$) with only predictors demonstrating at least a modest association with delirium retained in our final model ($P < 0.50$).^{21,22} To examine the association between NSE and LOS, we examined both generalized regression models using a negative binomial distribution to account for overdispersion, as well as a linear regression in which LOS days were log-transformed to reduce the impact of longer LOS and in-hospital mortality. Results from both methods were identical. Cox proportional hazards models were used to examine the association between NSE and mortality.

RESULTS

Background and medical characteristics are presented in Table 1. As shown, 276 participants were included in the present analyses. Participants tended to have IPF, were middle-aged, and male. Neurological sequelae were common, occurring in 119 recipients. The most common NSE was postoperative delirium ($n = 110$ [40%]), followed by PRES ($n = 12$ [4%]), stroke/TIA ($n = 11$ [4%]), and neurotoxicity ($n = 2$ [1%]). Several patients who experienced a mild stroke/TIA subsequently developed either delirium ($n = 7$) or PRES ($n = 4$) and were therefore included in both diagnostic groups. Neuroimaging data were collected for clinical evaluation after transplantation on a subset of 109 of patients, among whom 84 (77%) experienced an NSE, including 71 (65%) delirious patients, 13 (12%) ischemic injury, and 12 (11%) with PRES. Results revealed that more than half of patients demonstrated evidence of microvascular/ischemic

TABLE 1.
Background and demographic characteristics of sample (n = 276)

Variables		
Native disease		
IPF, n (%)	110 (40%)	
CF, n (%)	59 (21%)	
Chronic obstructive pulmonary disease, n (%)	47 (17%)	
Other, n (%)	60 (22%)	
Age, y	54.5 (15.7)	
Sex: male, n (%)	163 (59%)	
Race, white, n (%)	241 (87%)	
LAS	45.4 (14.9)	
PGD, grade		
0/1, n (%)	202 (73%)	
2, n (%)	63 (23%)	
3, n (%)	11 (4%)	
Mechanical Support (ECMO/CPB), n (%)	27 (10%)	
Psychotropic medication use, n (%)	124 (45%)	
Evidence of microvascular disease, n (%) ^a	70 (64%)	
Evidence of cortical atrophy, n (%) ^a	10 (9%)	

^aNeuroimaging data were available for 109 participants.

disease (n = 70 [64%]) with fewer patients (n = 10 [9%]) showing evidence of cortical atrophy.

Delirium Risk Factors

Due to the relatively small number of individuals with other NSE outcomes (eg, PRES, stroke/TIA, and neurotoxicity), as well as potential differences in potential etiologies of different NSEs, our analyses of NSE predictors were restricted to delirium. Greater pretransplant LAS score (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.15-1.89; $P = 0.002$), CF native disease (OR, 0.47; 95% CI, 0.19-1.14; $P = 0.009$ compared with COPD), "other" native disease (OR, 1.74; 95% CI, 0.78-3.84; $P = 0.015$ compared with COPD), mechanical support (ECMO/CPB; OR, 3.80; 95% CI, 1.49-9.68; $P = 0.005$), and use of psychotropic medications (OR, 1.61; 95% CI, 0.97-2.68; $P = 0.068$) were all predictive of postoperative delirium on univariate analysis. Examination of delirium rates across native diseases revealed that 22% of CF, 36% of IPF, 38% of COPD, and 52% of "other" native diseases developed delirium postoperatively. In a final model including all predictors, greater LAS score ($P = 0.028$) and native disease remained the strongest predictors of delirium (Table 2).

TABLE 2.
Full model predicting risk of delirium

Predictor (IQR)	OR (95% CI)	P
Native disease		
CF vs COPD	0.27 (0.10-0.72)	0.003
PF vs COPD	0.76 (0.36-1.64)	0.611
Other vs COPD	1.05 (0.45-2.47)	0.088
LAS (13)	1.39 (1.04-1.85)	0.028
PGD	1.36 (0.82-2.26)	0.231
Mechanical support (ECMO/CPB)	2.41 (0.82-7.07)	0.109
Psychotropic medication use	1.67 (0.97-2.88)	0.065

TABLE 3.
Full model predicting hospital LOS after transplantation

Predictor (IQR)	OR (95% CI)	P
PGD	0.14 (-0.01 to 0.29)	0.060
Mechanical support (ECMO/CPB)	0.55 (0.29-0.81)	<0.001
NSE	0.64 (0.48-0.80)	<0.001

Neurological Events and Clinical Outcomes

To examine the association between NSE and clinical outcomes, we examined the association between NSE and transplant LOS, as well as posttransplant mortality. Median LOS was 19 days (interquartile range [IQR], 21; range 6-304 days). Patients who experienced an NSE has substantially longer hospitalization compared to those patients without a posttransplant NSE (b = 0.70 [0.55, 0.86], $P < 0.001$). Other factors predicting longer LOS in univariate analyses included greater PGD severity at 72 hours (b = 0.18 [0.02, 0.34], $P = 0.031$), mechanical support (ECMO/CPB: b = 0.68 [0.39, 0.96], $P < 0.001$), and higher LAS score (b = 0.13 [0.05, 0.20], $P = 0.001$). In our multivariate model (Table 3), greater PGD severity at 72 hours ($P = 0.048$) and mechanical support during transplantation (ECMO/CPB) ($P < 0.001$) were also associated with longer LOS, in addition to NSE ($P < 0.001$). Estimated LOS among individuals with NSE was 32.3 days (28.8-36.3) compared with 17.2 days (15.5-19.1) among those without NSE, corresponding to more than a 2-week longer hospitalization after accounting for background and medical predictors. In sensitivity analyses, participants who died during their transplant hospitalization were eliminated, results were unchanged with greater NSE continuing to predict longer LOS ($P < 0.001$).

Over a median follow-up of 2.1 years (range, 1 day to 3.2 years), 57 patients (21%) died. The causes of death were respiratory failure (n = 18 [32%]), chronic rejection (n = 11 [19%]), infection (n = 8 [14%]), multiorgan failure (n = 8 [14%]), cardiovascular (n = 7 [12%]), and malignancy (n = 5 [9%]). Examination of univariate predictors of posttransplant mortality revealed that greater age (hazard ratio [HR], 1.96; 95% CI, 1.24-3.08; $P = 0.004$), IPF native disease (HR, 2.35; 95% CI, 0.91-6.05; $P = 0.078$), use of psychotropic medications (HR, 0.60; 95% CI, 0.35-1.04; $P = 0.067$), and NSE (HR, 1.79; 95% CI, 1.06-3.01; $P = 0.030$) all demonstrated associations with greater posttransplant mortality. In a multivariate model, greater age ($P = 0.002$) and the presence of NSE ($P = 0.024$) were

TABLE 4.
Full model predicting posttransplant mortality

Predictor (IQR)	HR (95% CI)	P
Native disease		
CF vs COPD	3.75 (1.08-12.98)	0.037
PF vs COPD	1.98 (0.75-5.21)	0.166
Other vs COPD	2.03 (0.69-6.00)	0.198
Age, 22 y	2.61 (1.41-4.82)	0.002
Mechanical support (ECMO/CPB)	1.91 (0.84-4.31)	0.121
PGD	0.70 (0.39-1.23)	0.211
Psychotropic medication use	0.57 (0.32-1.01)	0.054
NSE	1.90 (1.09-3.32)	0.024

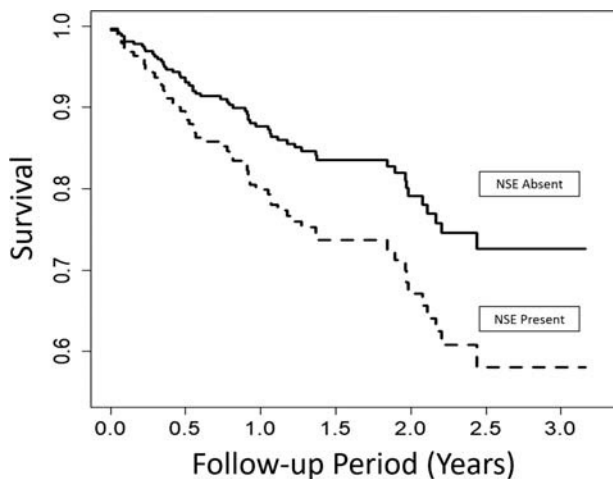


FIGURE 1. NSE and mortality during follow-up, adjusted for native disease and LAS score.

the strongest predictors of posttransplant mortality (Table 4, Figure 1). In sensitivity analyses in which in-hospital deaths were removed, mortality findings were unchanged, with NSE continuing to predict poorer survival (HR, 2.04; 95% CI, 1.17-3.55; $P = 0.012$). In addition, we found that the association between NSE and mortality varied significantly across time ($P = 0.001$ for proportional hazards test), with the strongest associations between NSE and mortality occurring approximately 2 years after transplantation (Figure 2).

DISCUSSION

These findings suggest that perioperative neurological events, particularly posttransplant delirium, are relatively common after lung transplantation affecting nearly half of patients undergoing lung transplantation, and are predictive of subsequent clinical outcomes.⁶⁻⁸ These findings extend previous

evidence suggesting that a substantial subset of patients experience significant neurological complications after transplant,⁶ although the predictors of neurological events and clinical implications have not been thoroughly examined.^{7,8}

Previous studies have reported that the overall presence of neurological events among lung transplant recipients is high, occurring in as many as 80% of some cohort studies,⁷ and that significant neurological complications (eg, stroke) were associated with greater mortality.^{6,7,14} Although most previous studies had examined severe neurological changes, recent studies from our group¹² and others⁸ have suggested that between 36% and 44% of patients exhibit postoperative delirium, which is associated with worse short-term clinical outcomes. Although delirium has frequently been associated with mortality in geriatric and other critical care samples,²³ our is the first to demonstrate an association between delirium and subsequent mortality. Of note, although previous studies have generally suggested that delirium is associated with worse 6-month²⁴ and 12-month mortality,²⁵ our findings suggest that the association between NSE (which was primarily delirium) and posttransplant mortality increased over time, rising to its greatest magnitude approximately 2 years postoperatively. Although the reasons behind the timing of this association are unclear, it is possible that impaired cognition, which is one of the primary long-term effects of severe delirium, leading to nonadherence with medical regimen or to more debilitated state, could explain this association.²⁶

Neurological sequelae and impaired cognition are increasingly recognized as an important consideration among lung transplant recipients,²⁷ in large part because of the increasing age of all solid organ transplant recipients.²⁸⁻³⁰ Although originally envisioned as a treatment for younger patients, the average age of transplant recipients has steadily increased as the number of patients with IPF has risen, increasing from an average age of approximately 45 years in the 1980s to nearly 60 years at present.³¹ Indeed, patients 65 years or older

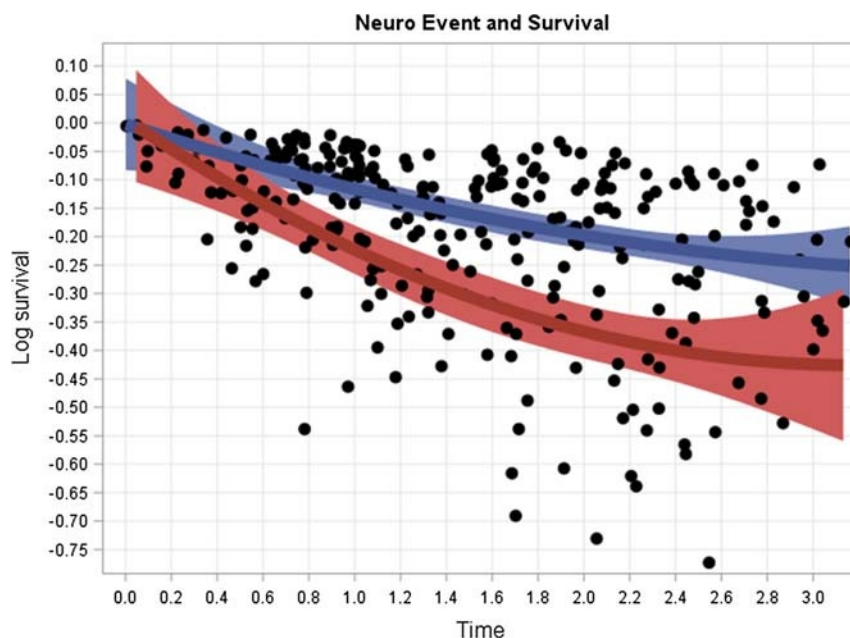


FIGURE 2. Time-dependent association between mortality and NSE among participants with (red) and without (blue) NSE after transplant. As shown, the association between NSE and mortality varied over time ($P < 0.01$ for interaction), with mortality risk demonstrating the strongest association approximately 2.5 years after transplant.

constitute approximately one third of all recipients,³²⁻³⁴ who experience comparatively lower quality of life improvement relative to younger recipients.³²

Although the mechanisms by which lung transplant affects NSE are unknown, it is likely that a combination of individual patient risk factors and perioperative events together contribute to risk. In the present study, we found a tendency for PGD to be associated with greater delirium risk, similar to our prior study.¹⁹ In addition, individual risk factors are the strongest predictor of postoperative NSE,³⁵ with greater age, poorer cognition, and medical acuity all increasing risk.¹² This is consistent with the finding that greater LAS predicted risk of delirium in the present study. In addition to diagnosed NSE, many more patients will likely experience undiagnosed, subclinical neurological changes after surgery,³⁶ suggesting that neuroimaging assessments could provide critical insights into how the brain is affected after lung transplantation.³⁶ Indeed, available evidence suggests that greater microvascular disease and systemic dysregulation of multiple brain networks are the key contributors to postoperative neurobehavioral impairments among pulmonary patients, but may only be detected using sensitive neuroimaging approaches.³⁷

The present study must be viewed with several limitations in mind. First, we documented NSE largely based on retrospective chart review. Future studies should therefore systematically collect data on NSE to determine the association between early postoperative NSE and clinical outcomes. However, the rates of adverse NSE reported here are nearly identical to those previously reported in similar cohorts, suggesting our assessments were reasonably sensitive to capturing NSE occurrences.^{8,12} Second, we only had a limited number of outcome assessments, primarily LOS and mortality. Future studies should examine the impact of NSE on relevant behavioral risk factors, such as adherence, as well as chronic lung allograft dysfunction. Finally, we do not have any mechanistic data to understand the etiology of NSE, or the causal association between NSE, LOS, and mortality. Future studies would therefore benefit from more comprehensive assessment of mechanistic data to further elucidate the association between NSE and clinical outcomes.¹⁹ For example, we have previously demonstrated that poorer cerebral perfusion pressure is predictive of delirium in lung transplant recipients¹⁹ and that alterations in default mode network brain circuitry are closely associated with postoperative cognitive decline after cardiac surgery.³⁸ In addition, cognitive impairment has been shown to predict noncompliance with medication adherence across multiple medical populations,^{10,39} and both cognitive impairment¹⁴ and medication nonadherence⁴⁰ have been shown to predict mortality in lung transplant recipients.

In conclusion, we found that NSEs are common and associated with adverse clinical outcomes. If replicated, these findings suggest that future interventions to either prevent or mitigate the impact of NSEs may be a strategy to improve patient outcomes. In addition, future studies should examine the impact of NSEs on patient quality of life, which would likely be adversely impacted and is one of the primary goals of treatment.

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REFERENCES

- Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report—2010. *J Heart Lung Transplant*. 2010;29:1104–1118.
- Ford ES. Trends in mortality from COPD among adults in the United States. *Chest*. 2015;148:962–970.
- Kozower BD, Meyers BF, Smith MA, et al. The impact of the lung allocation score on short-term transplantation outcomes: a multicenter study. *J Thorac Cardiovasc Surg*. 2008;135:166–171.
- Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. *Am J Transplant*. 2006;6(5 Pt 2):1212–1227.
- Gries CJ, Rue TC, Heagerty PJ, et al. Development of a predictive model for long-term survival after lung transplantation and implications for the lung allocation score. *J Heart Lung Transplant*. 2010;29:731–738.
- Shigemura N, Scabassi RJ, Bhama JK, et al. Early major neurologic complications after lung transplantation: incidence, risk factors, and outcome. *Transplantation*. 2013;95:866–871.
- Mateen FJ, Dierkhising RA, Rabinstein AA, et al. Neurological complications following adult lung transplantation. *Am J Transplant*. 2010;10:908–914.
- Sher Y, Mooney J, Dhillon G, et al. Delirium after lung transplantation: association with recipient characteristics, hospital resource utilization, and mortality. *Clin Transplant*. 2017;31.
- Sharma A, Yabes J, Al Mawed S, et al. Impact of cognitive function change on mortality in renal transplant and end-stage renal disease patients. *Am J Nephrol*. 2016;44:462–472.
- Stillel CS, Bender CM, Dunbar-Jacob J, et al. The impact of cognitive function on medication management: three studies. *Health Psychol*. 2010;29:50–55.
- Stillel CS, Sereika S, Muldoon MF, et al. Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. *Ann Behav Med*. 2004;27:117–124.
- Smith PJ, Rivelli SK, Waters AM, et al. Delirium affects length of hospital stay after lung transplantation. *J Crit Care*. 2015;30:126–129.
- Smith PJ, Rivelli S, Waters A, et al. Neurocognitive changes after lung transplantation. *Ann Am Thorac Soc*. 2014;11:1520–1527.
- Smith PJ, Blumenthal JA, Carney RM, et al. Neurobehavioral functioning and survival following lung transplantation. *Chest*. 2014;145:604–611.
- McPherson JA, Wagner CE, Boehm LM, et al. Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med*. 2013;41:405–13.
- Khan BA, Zawahiri M, Campbell NL, et al. Delirium in hospitalized patients: implications of current evidence on clinical practice and future avenues for research—a systematic evidence review. *J Hosp Med*. 2012;7:580–589.
- Inouye SK, Leo-Summers L, Zhang Y, et al. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc*. 2005;53:312–318.
- Legriel S, Schraub O, Azoulay E, et al. Determinants of recovery from severe posterior reversible encephalopathy syndrome. *PLoS One*. 2012;7:e44534.
- Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced cerebral perfusion pressure during lung transplant surgery is associated with risk, duration, and severity of postoperative delirium. *Ann Am Thorac Soc*. 2016;13:180–187.
- Kurland BF, Johnson LL, Egleston BL, et al. Longitudinal data with follow-up truncated by death: match the analysis method to research aims. *Stat Sci*. 2009;24:211.
- Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York: Springer; 2009.
- Harrell FE. *Regression Modeling Strategies: With applications to linear modeling, logistic regression, and survival analysis*. New York: Springer; 2001.
- Zhang Z, Pan L, Ni H. Impact of delirium on clinical outcome in critically ill patients: a meta-analysis. *Gen Hosp Psychiatry*. 2013;35:105–111.

24. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291:1753–1762.
25. Aliberti S, Bellelli G, Belotti M, et al. Delirium symptoms during hospitalization predict long-term mortality in patients with severe pneumonia. *Aging Clin Exp Res*. 2015;27:523–531.
26. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369:1306–1316.
27. Diamond JM, Mikkelsen ME. From research to clinical practice. Cognitive trajectory after lung transplantation. *Ann Am Thorac Soc*. 2014;11:1604–1605.
28. Mapelli D, Bardi L, Mojoli M, et al. Neuropsychological profile in a large group of heart transplant candidates. *PLoS One*. 2011;6:e28313.
29. Hajduk AM, Kiefe CI, Person SD, et al. Cognitive change in heart failure: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2013;6:451–460.
30. Schulz K, Kroencke S. Psychosocial challenges before and after organ transplantation. *Transplant Research and Risk Management*. 2015;7:45–58.
31. Yusef RD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report-2014; focus theme: retransplantation. *J Heart Lung Transplant*. 2014;33:1009–1024.
32. Singer JP, Katz PP, Soong A, et al. Effect of lung transplantation on health-related quality of life in the era of the Lung Allocation Score: A U.S. prospective cohort study. *Am J Transplant*. 2017;17:1334–1345.
33. Singer LG, Chowdhury NA, Faughnan ME, et al. Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. *Am J Respir Crit Care Med*. 2015;192:965–973.
34. Valapour M, Paulson K, Smith JM, et al. OPTN/SRTR 2011 annual data report: lung. *Am J Transplant*. 2013;13 Suppl 1:149–177.
35. Raats JW, van Eijnsden WA, Crolla RM, et al. Risk factors and outcomes for postoperative delirium after major surgery in elderly patients. *PLoS One*. 2015;10:e0136071.
36. Bendszus M, Stoll G. Silent cerebral ischaemia: hidden fingerprints of invasive medical procedures. *Lancet Neurol*. 2006;5:364–372.
37. Dodd JW, Chung AW, van den Broek MD, et al. Brain structure and function in chronic obstructive pulmonary disease: a multimodal cranial magnetic resonance imaging study. *Am J Respir Crit Care Med*. 2012;186:240–245.
38. Browndyke JN, Berger M, Harshbarger TB, et al. Resting-state functional connectivity and cognition after major cardiac surgery in older adults without preoperative cognitive impairment: preliminary findings. *J Am Geriatr Soc*. 2017;65:e6–e12.
39. Alosco ML, Spitznagel MB, van Dulmen M, et al. Cognitive function and treatment adherence in older adults with heart failure. *Psychosom Med*. 2012;74:965–973.
40. Castleberry AW, Bishawi M, Worni M, et al. Medication nonadherence after lung transplantation in adult recipients. *Ann Thorac Surg*. 2017;102:274–280.