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Delirium Affects Length of Hospital Stay Following Lung Transplantation

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Abstract

Background—Delirium is relatively common following lung transplantation, although its prevalence and prognostic significance have not been systematically studied. The purpose of the present study was to examine pre-transplant predictors of delirium and the short-term impact of delirium on clinical outcomes among lung transplant recipients.

Methods—Participants underwent pre-transplant cognitive testing using the Repeatable Battery for the Assessment of Neuropsychological Status and the Trail Making Test. Following transplant, delirium was assessed using the Confusion Assessment Method until discharge.

Results—Sixty-three patients were transplanted between March and November, 2013, of which 23 (37%) developed delirium. Among transplanted patients, 48 patients completed pre-transplant cognitive testing. Better pre-transplant cognitive function was associated with lower risk of delirium (OR = 0.69 [95%CI 0.48, 0.99], $P = .043$); demographic and clinical features including native disease ($P = .236$), the Charlson comorbidity index ($P = .581$), and the lung allocation score ($P = .871$) were unrelated to risk of delirium, although there was a trend for women to experience delirium less frequently ($P = .071$). The presence ($P = .006$) and duration ($P = .027$) of delirium were both associated with longer hospital stays.

Conclusion—Delirium occurs in more than one third of patients following lung transplantation. Delirium was associated with poorer pretransplant cognitive functioning and longer hospital stays, after accounting for other medical and demographic factors.

Keywords

Lung transplantation; delirium; length of hospital stay

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Introduction

Delirium is relatively common among hospitalized older adults and is associated with significant public health expenditures,[1] as well as 3- to 11-fold increased 6-month mortality risk after controlling for disease severity.[2] Delirium occurs in at least 20% of hospitalized older adults and may be even higher among post-transplant patients.[3, 4] Available evidence suggests that the presence of delirium may also result in adverse cerebrovascular outcomes, similar to other surgeries.[5, 6] For example, in the VISIONS prospective cohort magnetic resonance imaging study,[7] greater duration of delirium in the intensive care unit was associated with greater white matter damage at discharge, which persisted over a three-month follow-up period. Recent evidence also has demonstrated that the presence of delirium is independently associated with long-term cognitive impairment.[8]

Previous studies have demonstrated that advancing age and medical comorbidities are independently predictive of delirium following major surgery.[9, 10] In a systematic review of 25 studies, Dasgupta and colleagues [11] found that older age and greater comorbidities were associated with a greater incidence of delirium following noncardiac surgery. Recent evidence suggests that poorer cognitive function prior to surgery may also be associated with a greater incidence of delirium in both orthopedic [12] and cardiac patients samples.[13, 14] We have previously shown that poorer executive function was associated with increased risk of delirium among patients undergoing orthopedic surgeries,[12] independent of background and medical factors. Poorer cognitive function as measured by the mini mental status examination (MMSE) was recently shown to be associated with greater incidence of delirium among older adults.[15] In addition to being associated with greater likelihood of postoperative delirium, we recently demonstrated in a separate sample of lung transplant recipients followed for 11 years after transplant that poorer cognitive function prior to transplant was associated with greater mortality during follow-up.[16] Taken together, these data suggest that poorer cognitive function prior to transplant may represent a risk factor for both perioperative and long-term clinical outcomes.

Despite the clinical importance of delirium, to our knowledge, no studies have determined the prevalence and clinical impact of delirium in lung recipients. We conducted a prospective study in which we examined the prevalence of delirium following transplant in 63 consecutive lung transplant recipients and determined if impaired pre-transplant cognitive functioning would be associated with greater risk of delirium following transplant. We also sought to determine if the delirium following transplant would be associated with longer duration of hospitalization.

Methods

The sample consisted of 63 consecutive patients undergoing lung transplantation at Duke University Medical Center between March and November, 2013. All patients listed for transplantation or who had relocated to Durham in order to participate in pulmonary rehabilitation as a prerequisite to listing were approached for participation. The protocol was

approved by the Duke Institutional Review Board and written informed consent was obtained from all volunteers. All patients who were approached consented to participate.

All patients received similar management both during transplantation and during the immediate postoperative time period. Anesthesia was induced with propofol or etomidate and maintained with isoflurane, propofol, midazolam, and fentanyl as needed. The target oxygen saturation was > 90% in all patients and systolic blood pressure was maintained > 90 mm Hg using phenylephrine, vasopressin, and epinephrine as needed. Patients were sedated postoperatively with propofol infusions until they were ready to be extubated, at which point all sedatives were discontinued and thoracic epidural analgesia was provided. Consistent with lung transplant guidelines at Duke, no patients were taking benzodiazepines prior to transplant.

Assessment of Neurocognitive Functioning

Assessments of neurocognition were performed within four weeks prior to transplantation by a trained research assistant. Forty-eight participants were available and provided cognitive data for the present analyses.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[17]—The RBANS consists of multiple subtests, including List Learning, Story Memory, Figure Copy, Line Orientation, Picture Naming, Semantic Fluency, Digit Span, and Digit Coding, as well as recall sections for the List Learning, Story Memory, and Figure tests. The total index score, which is composite of all subtests, was used as one of the predictors of interest in the present analyses.

Trail Making Test.[18]—This test is used to measure visuomotor attention and executive function. For Part A of the test, participants draw lines to connect consecutively number circles; for Part B, participants connect consecutively numbered and lettered circles by alternating between numbers and letters (1-A-2-B-3-C, etc.). Time to test completion was used as one of the predictors of interest in the present analyses.

Medical Variables

Charlson Comorbidity Index.[19]—The Charlson Comorbidity Index incorporates multiple chronic conditions, including history of heart disease, diabetes, liver disease, and others, to calculate a predicted 10-year mortality score. Medical background information was collected during patients' pre-transplant clinic assessments.

Postoperative Morbidity—Postoperative morbidity was assessed using the Postoperative Morbidity Survey (POMS) [20], a validated system to document the presence of postoperative morbidity in multiple organ systems. The POMS was administered on all days in which a delirium assessment was obtained. POMS criteria were evaluated through direct patient questioning and examination, review of clinical notes and charts, retrieval of data from the hospital clinical information system, and/or consulting with the patient's caregivers. The POMS incorporates postoperative morbidity data that includes information on pulmonary, renal, gastrointestinal, hematological, cardiovascular, infectious disease, wound

complications, and pain. Neurological morbidity, including delirium, is typically obtained as part of this assessment but was not included in calculating the POMS score for the present analyses because delirium was the outcome of interest.

Lung Allocation Score (LAS).[21]—The LAS is a numerical value used to determine a patient's priority for transplantation. The value represents the statistical probability of a patient's survival in the next year without a transplant, with higher scores indicating a lower likelihood of survival. The LAS is determined by a number of medical factors, including native disease, age, medical comorbidities, six minute walk distance, serum creatinine, and level of oxygen required at rest. We used the LAS obtained most closely to the time of transplant in the present analyses (Mean = 46.6 [SD = 16.7], range 31.5 – 92.6).

Interim Assessments During Perioperative Period

In the days immediately following transplantation, patients were assessed daily for the presence and severity of postoperative delirium using two clinical instruments:

Confusion Assessment Method (CAM):[22]—The CAM is a bedside test of delirium based on a checklist of symptoms that requires less than five minutes to administer. The CAM was administered daily for the first week post-transplant. Beginning one week following transplantation (postoperative day eight), the CAM was discontinued if the patient exhibited three consecutive negative screens for delirium. Otherwise, the CAM was administered on a daily basis. The CAM has good reliability in the intensive care setting, with excellent sensitivity and specificity.[23]

Delirium Rating Scale (DRS-98):[24]—The DRS-98 also was administered following transplant to assess for delirium severity.[25] The DRS-98 is a 16-item scale assesses the severity of delirium based on all available information from patient interview, family, and nurses' reports, as well as cognitive and medical tests measures over a 24-hour period. The DRS-98 was administered at days 3, 5, 7, and immediately following any positive CAM.

Statistical Analyses

Analyses were carried out using SAS 9.2 (Cary, NC). In order to examine the relationship between pre-transplant factors and post-transplant delirium, we utilized a logistic model with pre-transplant characteristics serving as predictors and post-transplant delirium as a binary outcome (present or absent). Within this model we controlled for age, native disease (cystic fibrosis [CF] or non-CF), gender, LAS, Charlson comorbidity index, the pre-transplant cognitive function. Cognitive function was modeled using a unit-weighted composite of our pre-transplant cognitive measures, including the RBANS total index score, Trail Making A, and Trail Making B. We also examined the impact of delirium on length of hospital stay using a regression model in which a negative binomial distribution was specified and age, native disease, the POMS, LAS, and the Charlson comorbidity index were used as control variables. Within these models, we examined delirium as both a binary predictor and duration of delirium as a continuous predictor in separate models.

Results

Demographic and clinical characteristics of the study sample are presented in Table 1. Sixty-three individuals were transplanted during the study, all of whom were evaluated for delirium. One patient died during their hospitalization. Although 63 patients were consented, due to either an unexpectedly brief wait-list time (e.g., 1 day) or medical contraindications (e.g., intubation prior to surgery), 15 patients could not be assessed prior to transplant, leaving 48 individuals (76%) with pre-transplant cognitive assessments (Table 2). The primary native disease of the participants was idiopathic pulmonary fibrosis (IPF) (37%), followed by chronic obstructive pulmonary disease (COPD) (22%) and CF (17%).

Delirium

Twenty-three of 63 patients (37%) developed delirium at some point during their hospitalization, although COPD and IPF patients appeared more likely to experience delirium. Delirium was most commonly observed during patients' first assessment (57%), which typically occurred in the ICU (83%) during postoperative days 2 or 3. A subset of patients were not initially delirious but developed delirium during their second assessment (30%), which was typically assessed on postoperative day 4. On average, the duration of delirium was 1 day (mean duration 1.1 days [SD = 2.1], range 0 – 10 days) (Table 3), although the duration of delirium tended to be lower among CF patients. Better pre-transplant performance on our composite measure of cognitive function was associated with a lower incidence of delirium (OR = 0.69 [95%CI 0.48, 0.99], $P = .043$). Female gender also tended to be associated with lower incidence of delirium (OR = 0.21 [95%CI 0.04, 1.14], $P = .071$), whereas native disease ($P = .236$), medical comorbidities ($P = .581$), the LAS ($P = .871$), and age ($P = .791$) were not.

Delirium and Length of Hospitalization

Length of hospitalization ranged from six to 138 days (median = 17, IQR = 14). The presence of delirium ($P = .006$), greater POMS ($P = .012$), non-CF native disease ($P = .005$), and younger age ($P = .009$) were associated with longer duration of hospitalization. In contrast, Charlson comorbidity index ($P = .708$) and LAS ($P = .184$) were not predictive of hospital duration. Similarly, pre-transplant cognitive function was unrelated to the duration of hospitalization ($P = .337$). In a separate model, longer duration of delirium was also associated with longer hospital stays ($P = .027$).

Discussion

In this series of lung transplant recipients, poorer cognitive function prior to transplant was associated with greater risk of delirium, whereas demographic and medical predictors were not. For every standard deviation increase in performance (e.g., 12 points on the RBANS) there was a 31% decrease in the odds of developing delirium following transplantation. In addition, we found that the presence and duration of delirium were predictive of longer hospital stays following transplantation. The finding that poorer pre-transplant cognitive function was associated with greater incidence of delirium is consistent with previous studies among individuals undergoing elective[12] and cardiac surgeries,[14] demonstrating

that delirium is associated with longer hospital stays among older adults,[26] significant public health expenditures,[1] and a 3- to 11-fold increased 6-month mortality risk after controlling for disease severity.[2, 27] In addition, we have previously shown that poorer executive function is associated with greater incidence of delirium among individuals undergoing elective surgery independent of medical risk factors.[12] Similar findings have been reported in cardiac patients, with preoperative cognitive impairment independently predicting postoperative delirium.[28] However, no studies have previously examined this issue in lung transplant recipients or shown that neurocognitive predictors of delirium are independent of medical risk factors.

We found that poorer neurocognitive performance prior to transplantation was associated with a greater incidence of postoperative delirium. Delirium was associated with longer hospital stays. We found that patients who suffered from delirium remained in the hospital for an average of 10 additional days compared to patients who did not suffer delirium post-transplant. Previous studies have found that delirium may be associated with increased postoperative morbidity in lung transplant recipients.[29] In a meta-analysis of 16 studies examining ICU patients, Zhang and colleagues [30] found that the presence of delirium was associated with longer length of stay in both the intensive care unit and the hospital duration (6.5 days longer, on average). Interestingly, although we found that poorer cognitive function was associated with greater incidence of delirium, we did not observe a relationship between cognitive function and length of hospital stay. We believe that, although poorer cognitive performance was a risk factor for delirium, it was not independently associated with length of hospitalization as multiple factors may contribute to poorer cognitive function, only some of which increased the risk of postoperative delirium. For example, underlying cerebrovascular disease and neuronal dysfunction may have been associated with worse pre-transplant cognitive function and post-transplant delirium,[10, 31–33] whereas modifiable factors, including fatigue and shortness of breath, may have been associated with poorer cognitive performance but would not have conferred greater risk of delirium following surgery[34]. In addition to being associated with greater incidence of delirium, we have previously demonstrated that poorer pre-transplant cognitive function and persistent depressive symptoms were associated with greater mortality following transplant during an 11-year follow-up.[16] We found that poorer executive function and memory were associated with greater mortality, after controlling for age, time on wait list, FEV1, six-minute walk distance, stroke risk, and native disease.

Although few studies have examined the impact of delirium on clinical outcomes in transplant recipients, Lescot and colleagues[35] found that delirium following liver transplant was associated with significantly elevated length of hospital duration and mortality, independent of markers of disease severity. However, to our knowledge, no studies have previously demonstrated that delirium is associated with longer hospital duration among lung patients. Decreasing the length of stay for lung recipients is important not only in its impact on reducing medical costs but also in reducing risk of infection, which is elevated immediately following transplant. Although few studies examined the impact of delirium on clinical outcomes in solid organ transplant recipients, these findings are similar to previous studies among hospitalized older adults, in which delirium occurs frequently and is independently associated with cognitive impairment.[8]

Limitations

Our sample size was relatively small and one quarter of participants were unable to complete pre-transplant cognitive assessments. However, participants without pre-transplant data did not differ in age, gender, native disease, or other demographic and clinical characteristics from those who completed all assessments. The study also is limited in that we do not have data on the impact of delirium on the longer-term clinical outcomes. Finally, we were unable to collect data on intraoperative predictors of delirium, including hemodynamic changes and intraoperative hypoxia. Future studies would benefit from examining these as predictors of postoperative delirium.

Conclusions

Our study demonstrates that delirium occurs in more than one third of patients following lung transplantation and is associated with longer hospitalization stays. In addition, poorer pre-transplant cognitive function is associated with greater incidence of delirium. Future studies should investigate mechanisms responsible for delirium and develop interventions to reduce the occurrence of delirium in order to reduce hospital stays and potentially improve clinical outcomes.

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Table 1

Background and clinical characteristics of the sample (N=63).

Variable	Delirious (n = 23)	Non-Delirious (n = 40)	Total Cohort (n = 63)
Age, yrs	54.2 (16.7)	52.3 (16.9)	52.7 (16.8)
Male, n (%)	17 (74%)	6 (26%)	23 (35%)
Education, yrs	13.9 (2.9)	14.3 (3.0)	14.0 (2.8)
Charlson Index	1.30 (0.6)	1.35 (0.5)	1.27 (0.5)
Lung Allocation Score	44.4 (13.6)	47.9 (18.3)	46.8 (17.4)
Native Disease			
CF	3 (27%)	8 (73%)	11 (17%)
COPD	6 (43%)	8 (57%)	14 (22%)
IPF	9 (39%)	14 (61%)	23 (37%)
Other	5 (33%)	10 (67%)	15 (24%)

Table 2

Cognitive test scores among delirious and non-delirious patients (N = 48).

Variable	Delirious (n = 17)	Non-Delirious (n = 31)	Cohort (n = 48)
RBANS Total Score	87.6 (14.5)	92.3 (10.7)	90.6 (12.0)
RBANS Attention	86.1 (17.6)	90.5 (12.9)	89.0 (14.7)
RBANS Immediate Memory	92.8 (15.3)	97.5 (11.7)	95.8 (13.1)
RBANS Delayed Memory	94.1 (14.8)	96.7 (11.0)	95.8 (12.4)
RBANS Visuospatial	92.3 (16.2)	85.9 (18.3)	90.0 (17.0)
RBANS Language	94.2 (10.8)	95.6 (10.4)	95.1 (10.4)
Trail Making A, secs	41.5 (16.7)	33.9 (13.0)	36.6 (14.7)
Trail Making B, secs	105.4 (48.9)	88.9 (43.3)	94.7 (45.6)

Table 3

Delirium outcomes in the study sample.

Variable	CF (n = 11)	COPD (n = 14)	IPF (n = 23)	Other (n = 15)
Delirium, n (%)	3 (28%)	6 (43%)	10 (39%)	5 (22%)
Delirium Duration, days, median (SD)	1 (0)	2.3 (2.0)	2.9 (1.9)	5.8 (2.9)
Delirium Rating Scale, mean (SD)	6.7 (2.3)	9.1 (3.5)	7.7 (2.1)	8.5 (1.9)