Neurocognitive Changes after Lung Transplantation

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Abstract

Rationale: Neurocognitive impairments are associated with reduced quality of life and may adversely affect medical compliance, but their prevalence after lung transplantation has not been extensively studied.

Objectives: To examine the frequency of neurocognitive impairment after lung transplantation and to examine perioperative factors affecting post-transplant neurocognitive function.

Measurements and Main Results: We performed serial assessments of neurocognitive function in a consecutive series of 47 subjects who received transplants between March 2013 and November 2013 (45% women; mean age, 53.5 ± 17.2 yr). Neurocognitive function was assessed using a composite measure including the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score and Trail Making Test parts A and B obtained before transplant, at hospital discharge, and 3 months after discharge. The presence of neurocognitive impairment was assessed using the Montreal Cognitive Assessment Battery (MoCA),

and in-hospital delirium was assessed using the Confusion Assessment Method. Results demonstrated that neurocognitive performance initially worsened among non-cystic fibrosis patients and improved over follow-up ($P = 0.002$). Time effects were strongest on Trail Making Test part B ($P < 0.001$) and the RBANS ($P = 0.054$). Participants who exhibited delirium during their hospitalization showed poorer performance during follow-up assessments ($P = 0.006$). Examination of cognitive impairment rates demonstrated that 21 participants (45%) exhibited neurocognitive impairment (MoCA < 26) before lung transplant, whereas 27 (57%) participants exhibited impairment after transplantation, and 19 (57%) participants continued to neurocognitive impairment during a 3-month follow-up.

Conclusions: Neurocognitive impairments are prevalent among lung transplant candidates and appear to worsen in some patients after transplant. Delirium during hospitalization is associated with worse neurocognitive function after transplant among patients without cystic fibrosis.

Keywords: lung transplantation; neurocognitive performance; delirium

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Lung transplantation is an increasingly frequent treatment option for many individuals with end-stage lung disease (1). Although lung transplantation offers an opportunity to prolong life, postoperative mortality remains higher than with other solid organ transplants, with only 50% of patients surviving to 5 years (2). A

number of studies have examined the quality-of-life benefits of lung transplantation, with mixed results (3). Although physical quality of life appears to improve after transplantation, psychological quality of life may not improve to a comparable degree and remains lower than normative samples

(4). Neurocognitive functioning represents an important aspect of quality of life and has previously been associated with variations in medication compliance (5), which is crucial for post-transplant survival. Understanding changes in neurocognition are therefore important among lung transplant recipients because neurocognitive

deficits are prevalent among lung transplant candidates (6) and may worsen after transplant in some patients (7). To better understand neurocognitive changes after lung transplantation, we conducted a prospective study in a consecutive series of lung transplant patients to determine the prevalence of neurocognitive impairment after lung transplant and to identify factors associated with impaired neurocognitive functioning.

Methods

Participants

The sample consisted of 47 consecutive patients presenting for evaluation for lung transplantation at Duke University Medical Center between March 2013 and November 2013. All patients listed for transplantation or who had relocated to Durham, North Carolina before listing, with the assumption that they would be transplanted, were approached for participation (Figure 1). The protocol was approved by the Duke Institutional Review Board and written informed consent was obtained from all subjects.

Procedures

Medical background information was collected during patients' pretransplant evaluation. The Charlson Comorbidity Index (8) was used to quantify medical

comorbidities and incorporates multiple chronic conditions, including history of heart disease, diabetes, liver disease, and other conditions, to calculate a predicted 10-year mortality score.

Assessments of cognition were performed within 1 month before transplantation, 1 to 2 days before hospital discharge after transplant, and approximately 3 months after transplantation, depending on patient availability. Alternating forms of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Montreal Cognitive Assessment Battery (MoCA) test were used in a counterbalanced order at the different time points.

Psychological functioning was assessed before transplantation, concordant with the assessments of cognition. Pretransplant neurocognitive assessments were conducted as close to the time of transplant as possible, typically during the week before transplantation. Among the 77 patients initially approached for participation, 63 patients were transplanted, 47 of whom were available for assessment before to transplant. The final sample in the present analysis is therefore composed of 47 patients with pre- and post-transplant assessments. Patients completing all assessments did not differ in age, sex, native disease, or other demographic and clinical characteristics from those who did not complete all assessments. After transplantation, patients were followed during their hospitalization to assess for the presence and severity of delirium and neurocognitive functioning was reassessed before hospital discharge and again during one of their early outpatient follow-up clinic visits. Long-term assessments were collected during outpatient clinic visits, with a target time of approximately 3 months after transplantation for assessment (mean, 2.93 mo; SD, 1.2 mo). Assessments were timed so that patients could be assessed as outpatients but before they left the Durham area to return home. The average time between transplant and post-transplant assessment after hospital discharge was 94 days (median, 83 d; SD, 39 d) and extended up to 6 months in some cases (range, 1.3–6.7 mo). The average time from discharge to follow-up testing was 69 days (median, 55 d; SD, 41 d). The timing of assessments varied due to some patients having prolonged hospitalizations or being unavailable because of other medical procedures (e.g., bronchoscopies) during

their initial follow-up clinic visits. Every attempt was made to accommodate patients' schedules to obtain neurocognitive test data.

Neurocognitive assessment measures. The RBANS (9) 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 calculated based on a weighted average of the individual subtests, was used as the outcome variable from this test. Scores range from 40 to 160, with higher scores indicating better performance. The population age-adjusted mean and standard deviation for the RBANS global cognition score and for individual domain scores is 100 ± 15 . Alternate forms of the RBANS (A and B) were used in a counterbalanced order at the three time points.

The Trail Making Test parts A and B (10) are used to measure visuomotor attention and executive function. For part A of the test, participants draw lines to connect consecutively numbered circles; for part B, participants connect consecutively numbered and lettered circles by alternating between the two sequences (1-A-2-B-3-C, etc.). Total time to completion was used as the outcome variable for both sections A and B. Scores on the Trail Making Test range from 0 to 300 seconds, with higher scores indicating worse performance. In addition, we present the age-, sex-, education-, and ethnicity-adjusted mean T-scores (11). These range from 0 to 100, with a mean score of 50 and with higher scores indicating better performance. The same version of the Trail Making Test was used at each time point.

The MoCA (12) was used to identify the presence of mild cognitive impairment. The MoCA consists of multiple items measuring executive function, memory, and working memory and has been shown to have good validity and reliability (13). A score of <26 is considered to indicate neurocognitive impairment. Scores on the MoCA range from 0 to 30, with higher scores indicating better performance. Alternate forms of the MoCA were used at each time point.

Performance on the RBANS and Trail Making Tests were the primary outcomes in the present analyses. As a secondary outcome, we examined the

Figure 1. Flowchart of participant assessment schedule.

prevalence of cognitive impairment from the MoCA.

Psychological functioning. Depression and anxiety were assessed before transplantation using the Patient Health Questionnaire (PHQ-9) (14) and the Hospital Anxiety and Depression Scale (HADS) (15). The PHQ-9 is a nine-item, self-report measure developed to diagnose the presence and severity of depression based on Diagnostic and Statistical Manual of Mental Disorders IV criteria. Scores range from 0 to 27, with higher scores indicating greater depressive symptoms. The HADS consists of two seven-item, self-report subscales assessing depression and anxiety symptomatology in a nonpsychiatric hospital setting. For the purposes of the present analyses, the two subscales were combined, for a total score ranging from 0 to 42, with higher scores suggesting greater anxiety and depression.

Interim assessments during the perioperative period. In the days immediately after transplantation, patients were assessed daily for the presence and severity of postoperative delirium using two validated clinical instruments (16): the Confusion Assessment Method (CAM) and Delirium Rating Scale (DRS-98).

The CAM is a bedside screening test of delirium based on a checklist of symptoms that requires less than 5 minutes to administer (17). The CAM was administered daily for the first week after transplant. The CAM-ICU was administered for patients in the intensive care unit. Beginning 1 week after transplantation (Postoperative Day 8), the CAM was discontinued if the patient exhibited three consecutive negative screens for delirium. Otherwise, the CAM continued to be administered on a daily basis. The CAM and CAM-ICU have good reliability, with excellent sensitivity and specificity (18).

The DRS-98 (19) was administered after transplant to assess for delirium severity (20). The DRS-98 is a 16-item scale administered by a clinician to assess the severity of delirium based on all available information from patient interview, family, and nurses' reports and from neurocognitive and medical tests measures over a 24-hour period. It was administered at postoperative Days 3, 5, and 7 and immediately after any positive CAM.

Statistical analyses. Analyses were performed using SAS 9.2 (SAS, Cary, NC).

To examine changes in neurocognitive function after transplantation, we conducted a repeated measures analysis of covariance in which neurocognitive performance at all three time points (i.e., baseline, 2 wk after transplant, and 3 mo after transplant) served as our outcome variables, with native disease, education, and the Charlson comorbidity index as our predictors of interest. To examine the impact of delirium on neurocognitive function, we conducted a second repeated measures model in which post-transplant and follow-up neurocognitive performance served as our outcome variables, with pretransplant neurocognitive function, native disease, the Charlson comorbidity index, and delirium as covariates. Within both models, we also examined whether changes in neurocognitive performance over time were moderated by background or medical characteristics, including native disease, age, education, and comorbidities.

Neurocognitive function was modeled using a unit-weighted composite of our pretransplant neurocognitive measures, including the RBANS total index score, Trail Making A, and Trail Making B. The composite score was created by calculating individual z-scores for each test and then summing the scores, an approach we have used previously (21, 22) and that is recommended over modeling each predictor individually because it increases statistical power and reduces type-I error (23, 24). Because age was confounded with native disease (patients with cystic fibrosis [CF] are younger than

patients without CF), we did not control for age in our primary analyses of neurocognitive function. However, we did control for age in follow-up analyses of patients without CF because of the known impact of age on neurocognitive performance. Due to the small number of patients with CF, we examined the time effect only in our follow-up analyses, without adjustment for other covariates.

Results

Among the 63 patients transplanted, 47 individuals had pre- and post-transplant neurocognitive assessments and were included in the present analyses (Figure 1), including 21 women (45%) (Table 1). As expected, participant age differed by native disease classification (mean age of patients with CF, 24.0 yr [SD, 6.1 yr]; mean age patients without CF, 59.2 yr [SD, 11.5 yr]) (Table 1). The most common native disease was idiopathic pulmonary fibrosis (36%), followed by chronic obstructive pulmonary disease (17%) and CF (17%). Other diagnoses included interstitial lung disease, sarcoidosis, α_1 -antitrypsin deficiency, and graft versus host disease, among others. Regarding psychotropic medication use, seven individuals were taking antidepressant medications at the time of transplant, four were taking anxiety medications, and two were taking both depression and anxiety medications. Anxiety and depression levels on psychometric testing tended to be low when assessed before transplantation.

Table 1. Background and clinical characteristics of participants with pretransplant neurocognitive data (n = 47)

Variable	CF (n = 8)	COPD (n = 8)	IPF (n = 17)	Other (n = 14)
Age, yr*	24.0 (6.1)	61.6 (5.3)	63.0 (8.4)	54.1 (15.3)
Male, n (%)†	1 (13)	5 (63)	11 (65)	9 (64)
Education, yr	14.3 (2.5)	12.6 (1.6)	14.6 (3.7)	15.4 (3.3)
Minority, n (%)†	1 (13)	0 (0)	2 (12)	6 (20)
Charlson index	1.38 (0.5)	1.25 (0.5)	1.53 (0.7)	1.21 (0.6)
RBANS total score	93.4 (10.4)	93.4 (15.8)	90.6 (12.0)	85.2 (6.8)
Trail Making A, s	29.9 (25.5)	37.3 (12.7)	40.1 (11.0)	35.9 (12.2)
Trail Making B, s	69.9 (35.7)	116.6 (64.6)	101.4 (46.8)	92.0 (30.6)
MoCA*	27.6 (1.1)	25.0 (2.3)	24.4 (2.1)	24.9 (3.1)

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; MoCA = Montreal Cognitive Assessment Battery; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

* $P \leq 0.01$ for difference across native disease groups.

† $P \leq 0.05$ for difference across native disease groups.

Table 2. Changes in neurocognitive function among patients with cystic fibrosis and non-cystic fibrosis patients

Variable	Pretransplant (n = 47)		PredischARGE (n = 47)		Postdischarge Follow-up (n = 33)	
	CF (n = 8)	Non-CF (n = 39)	CF (n = 8)	Non-CF (n = 39)	CF (n = 6)	Non-CF (n = 27)
Total score index	93.4 (10.4)	89.2 (11.5)	94.1 (8.9)*	86.4 (12.0)	100.7 (13.8)	96.7 (12.3)
Attention index	89.0 (13.3)	88.1 (14.3)	84.3 (14.6)	82.1 (14.8)	96.7 (14.6)	90.6 (14.5)
Immediate memory index	103.5 (11.3)	93.9 (12.9)	101.6 (12.0)	93.3 (13.5)	108.0 (10.9)	103.6 (15.7)
Delayed memory index	98.1 (8.4)	94.6 (12.4)	98.1 (3.9)	89.2 (16.0)	101.7 (8.8)	99.9 (14.1)
Visuospatial index	89.9 (15.2)	89.2 (16.7)	95.8 (13.7)	89.2 (18.4)	100.7 (16.8)	99.0 (15.6)
Language index	96.8 (13.3)	94.6 (10.0)	101.1 (15.6)	95.9 (8.4)	100.3 (9.2)	96.5 (9.7)
Trail Making Test A, s	29.9 (25.5)*	38.0 (11.6)	21.6 (6.8) [†]	40.6 (12.6)	19.0 (8.5) [†]	37.2 (10.3)
Trail Making Test B, s	69.9 (35.7) [‡]	101.2 (45.7)	60.8 (23.2) [†]	122.3 (57.5)	40.3 (13.9) [†]	94.4 (38.7)
Montreal Cognitive Assessment Battery	27.6 (1.1) [‡]	24.7 (2.5)	26.3 (1.6)*	24.1 (3.1)	27.3 (1.8) [†]	24.2 (2.6)
Cognitive impairment, n (%)	0 (0) [‡]	21 (54)	2 (25) [‡]	25 (64)	1 (17) [‡]	18 (67)

Definition of abbreviation: CF = cystic fibrosis.

* $P \leq 0.10$ for difference between patients with and without CF. Comparisons are performed within each time period.

[†] $P \leq 0.01$ for difference between patients with and without CF. Comparisons are performed within each time period.

[‡] $P \leq 0.05$ for difference between patients with and without CF. Comparisons are performed within each time period.

Mean scores on the HADS and PHQ-9 were 6.4 (SD, 4.3) and 2.4 (SD, 3.4), respectively.

The majority of participants (n = 37 [79%]) underwent bilateral transplantation, with relatively fewer participants undergoing unilateral transplantation (n = 10 [21%]). The majority of participants were male (55%) and Caucasian (81%). Thirty-three individuals had data available during follow-up assessments. Fourteen participants were missing data at follow-up because they refused (n = 4), were unavailable (n = 6), or were hospitalized (n = 4). Participants with missing data at follow-up did not differ from the remainder of the sample in age ($P = 0.888$), sex ($P = 0.870$), LAS ($P = 0.595$), medical comorbidities ($P = 0.107$), baseline cognitive performance ($P > 0.137$), native disease ($P = 0.133$), or presence of post-transplant delirium ($P = 0.133$). Transplant outcomes did not appear to vary by type of transplant (i.e., bilateral versus unilateral; $P = 0.530$), use of cardiopulmonary bypass ($P = 0.553$), or extracorporeal membrane oxygenation ($P = 0.596$).

Pretransplant Neurocognitive Functioning

Examination of neurocognitive performance using available normative data demonstrated that participants performed in the 30th percentile on the RBANS (mean, 89.9; SD, 11.4), in the 30th percentile on the Trail Making Test part B (mean, 95.8 s [SD, 45.4]; T-value, 44.2 [SD, 8.7]), and in the 31st percentile on

Trail Making Test part A (mean, 36.6 s [SD, 14.9]; T-value, 45.1 [SD = 10.3]). Twenty-one patients (45%) were determined to have neurocognitive impairment before transplant based on MoCA scores < 26 , which occurred exclusively in patients without CF.

Changes in Neurocognitive Functioning after Transplant

Cognitive testing occurred several days before hospital discharge, which was approximately 2 weeks after transplant (median, 14 d; interquartile range, 15 d) and again approximately 3 months after transplant. Analysis of mean changes in the composite measure of neurocognitive function after transplant revealed a main effect for native disease ($P = 0.002$) and education ($P = 0.004$), such that CF participants and more educated participants exhibited better neurocognitive performance across all time points. Examination of changes in individual measures showed that performance worsened during predischARGE assessments and improved at the 3-month postdischarge follow-up (Table 2). Specifically, performance on the RBANS fell slightly to the 26th percentile (mean, 87.7; SD, 11.9) and subsequently improved to the 45th percentile (mean, 97.4; SD, 12.4). A similar pattern was observed for Trail Making part B, with performance falling to the 21st percentile (T-value, 41.8 [SD, 10.3]; mean, 111.6 seconds [SD, 58.0]) and subsequently improving to the 46th percentile (T-value, 48.9 [SD, 10.4]; mean, 84.3 s [SD, 41.2 s]). For Trail Making

Test part A, performance declined to the 29th percentile (T-value, 44.6 [SD, 8.8]; mean, 37.4 s [SD, 13.8 s]) and subsequently improved to the 42nd percentile (T-value, 48.2 [SD, 10.8]; mean, 33.8 s [SD, 12.2 s]). In addition, we observed a significant native disease-by-time interaction ($P = 0.028$) (Figure 2). Because the effects of time were moderated by native disease, we analyzed patients with CF and patients without CF separately.

For patients without CF, we observed a significant time effect ($P = 0.001$) such that neurocognitive function worsened during predischARGE assessments and improved during the postdischarge follow-up. We observed main effects of age ($P = 0.009$) and education ($P = 0.012$), such that older age and lower education were associated with poorer neurocognitive performance across time points. We also observed a time-by-age interaction ($P = 0.002$), such that younger non-CF participants experienced a greater decline in neurocognitive function during predischARGE assessments that improved during postdischarge follow-up.

Among patients without CF, examination of individual cognitive tests showed a significant time effect for Trail Making Test part B ($P < 0.001$) and a trend for a time effect for the RBANS ($P = 0.054$) and Trail Making Test part A ($P = 0.107$). Mean Trail Making Test part B performance was in the 29th percentile (T-value, 44.4 [SD, 7.7]; mean, 101.2 s [SD, 45.7]) at baseline, the 17th percentile during predischARGE assessments (T-value,

Figure 2. Changes in neurocognitive function after transplantation among patients with cystic fibrosis (CF) (blue) and patients without CF (red). Neurocognitive performance is displayed as percentile performance based on demographically corrected normative data. FU = follow-up; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; TMT-B = Trail Making Test part B.

40.5 [SD, 9.1]; 122.3 s [SD, 57.5 s]), and the 35th percentile during postdischarge follow-up (T-value, 46.2 [SD, 8.0]; 94.4 s [SD, 38.7 s]). Mean RBANS performance at baseline, at 2 weeks, and at 3 months for patients without CF were at the 28th percentile (mean, 89.2; SD, 11.5), the 24th percentile (mean, 86.4; SD, 12.0), and the 44th percentile (mean, 96.7; SD, 12.3). Mean performance on Trail Making Test part A was in the 29th percentile (T-value, 44.6 [SD, 8.6]; mean, 38.0 s [SD, 11.6 s]), the 25th percentile (T-value, 43.1 [SD, 8.1]; mean, 40.6 s [SD, 12.6 s]), and the 33rd percentile (T-value, 45.5 [SD, 7.9]; mean, 37.2 s [SD, 10.3 s]).

Among patients with CF, neurocognitive function appeared to improve after transplantation, although the test for a time effect was not significant ($P=0.136$), likely due to the small number of participants with CF. Examination of individual cognitive tests showed a significant time effect for Trail Making Test part B ($P=0.001$). Mean

Trail Making Test part B performance was in the 21st percentile (T-value, 42.0, [SD, 12.1]; 71.5 s, [SD, 32.6 s]) at baseline, in the 26th percentile during predischage assessments (T-value, 43.6; [SD, 14.9]; 73.2 s, [SD, 40.7 s]), and in the 78th percentile during postdischarge follow-up (T-value, 57.8, SD, 12.3; 44.1 s [SD, 17.1 s]). We did not observe a significant time effect for the RBANS ($P=0.382$) or for Trail Making part A ($P=0.212$).

As a secondary analysis, we examined the frequency of neurocognitive

impairment, defined as MoCA scores < 26 . Before hospital discharge, 27 patients (57%) exhibited impaired neurocognitive functioning. Among participants without impaired cognition at baseline, 13 (50%) were classified as newly impaired during predischage assessments, and 7 (33%) who were impaired at baseline were no longer impaired before discharge. During postdischarge follow-up assessments, 19 patients (58%) exhibited neurocognitive impairment. Among participants without impaired cognition at baseline, seven patients (39%) exhibited impairment at postdischarge follow-up, whereas 11 (61%) remained unimpaired. In contrast, 12 (80%) of the 15 patients who were impaired at baseline continued to exhibit impairment at postdischarge follow-up, and three patients (20%) who were impaired at baseline were no longer impaired at postdischarge follow-up.

Perioperative Delirium and Post-Transplant Neurocognitive Function

Sixteen (34%) of patients developed delirium after transplantation, including 13 patients without CF (33%) and 3 patients with CF (38%). Among those who exhibited delirium, the delirium generally lasted for 2 days (median duration, 2.0 d; mean, 2.7; SD, 2.5; range, 1–10 d) (Table 3). Delirium tended to be relatively mild (mean DRS, 7.2; SD, 1.7).

However, although patients with and without delirium could not be distinguished as a function of predischage neurocognitive performance on the composite index of RBANS and Trail Making Test ($P=0.111$), we observed a native disease by delirium interaction ($P=0.009$). Exploration of this interaction demonstrated that, for patients without CF, delirium was not associated with worse neurocognitive performance during

Table 3. Delirium outcomes in the study sample

Variable	CF (n = 8)	COPD (n = 8)	IPF (n = 17)	Other (n = 14)
Delirium, n (%)	3 (38)	2 (25)	7 (41)	4 (29)
Delirium duration, d, median (IQR)	1 (0)	1 (0)	2 (2.0)	5 (5.5)
Delirium rating scale, mean (SD)	6.7 (2.3)	6.6 (1.0)	7.1 (1.6)	8.2 (2.0)

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range.

predischarge assessments ($P = 0.112$) but was associated with worse neurocognitive performance during postdischarge follow-up ($P = 0.002$) (Figure 3). In contrast, for patients with CF, the presence of delirium was not associated with neurocognitive performance during predischarge assessments ($P = 0.690$) or during postdischarge follow-up ($P = 0.304$).

Discussion

The present study examined changes in neurocognitive function and the presence of delirium after lung transplant. After transplant, we observed a worsening of neurocognitive function among patients without CF, particularly those who experienced postoperative delirium. Although cognitive performance improved during a 3-month follow-up assessment, performance remained lower among those who experienced delirium. More than half of patients exhibited neurocognitive impairments before transplant, and two thirds were impaired at the time of hospital discharge. In contrast, cognitive performance tended to improve among patients with CF over time.

Our finding that neurocognitive function initially worsened after transplant and remained impaired among individuals who experienced delirium is consistent with other, larger cohort studies in

which individuals experiencing delirium had lower neurocognitive performance up to 6 months after cardiac surgery (25). Similarly, our finding that a significant number of patients exhibited neurocognitive impairment before surgery is consistent with previous studies among individuals with end-stage lung disease (6, 7, 26). We found that nearly 60% of patients exhibited cognitive impairment as measured by the MoCA, which is very similar to a recent retrospective cohort study by Cohen and colleagues (27) in which the authors observed mild cognitive impairments in more than two thirds of lung transplant recipients. Our findings are also consistent with Hoffman and colleagues' (7) prospective study of 49 lung transplant recipients, which showed that nearly one third of patients exhibited significant cognitive decline from baseline to post-transplant.

Patients with end-stage lung disease often exhibit impaired neurocognitive function in multiple domains, particularly on tests of memory and complex attention, due to hypoxemia, inflammation, and cardiovascular risk factors (6, 7, 26). In a sample of 94 individuals listed for lung transplantation, Parekh and colleagues (6) found that 96% of patients exhibited at least mild impairment on one or more neurocognitive measures, with nearly one third of patients exhibiting mild deficits on tests of attention and executive function.

It is possible that the improvements in neurocognitive performance noted among patients with CF were due to improved hypoxia and to nonspecific factors such as fatigue.

After transplant, neurocognitive performance improved for patients with CF, whereas patients without CF showed deterioration in neurocognitive performance, especially in younger patients, although their performance generally returned to pretransplant levels in the months after hospital discharge. Despite the observed improvements in performance, the majority of patients without CF continued to exhibit impairment as determined by the MoCA during follow-up assessments (67%), consistent with other case-control studies (27). In addition, neurocognitive performance among individuals with delirium remained lower than performance for nondelirious patients, although this effect was only observed among patients without CF.

The presence of neurocognitive deficits before transplantation has been shown to be associated with poorer clinical outcomes, including mortality (21). Neurocognitive deficits after transplantation are important because intact neurocognitive functioning is critical for decision-making capacity and for the ability to manage a complex medical regimen, both of which are essential elements of post-transplant care (28). Moreover, studies of other medical patients have suggested that neurocognitive deficits in executive function, memory, and working memory are associated with poorer medication adherence (5, 29–31), including patients with HIV (31–33) and cardiovascular disease (5) and healthy older adults (29). Indeed, lower neurocognitive function has been associated with nearly four times greater risk of medication noncompliance in older adults (29). Our finding that executive functioning, as measured by Trail Making Test part B, worsened after transplant may have important implications for patient management because executive functioning is predictive of self-management and objectively measured adherence among older adults (34). Indeed, previous studies among primary care patients have demonstrated that better executive function is associated with more than a 3-fold greater likelihood of medication adherence after adjustment for background

Figure 3. Changes in neurocognitive function after transplantation among non-cystic fibrosis patients who were or were not delirious after transplant. Data are adjusted for age, education, and the Charlson comorbidity index. F/U = follow-up.

characteristics (35), and we have previously shown that poorer executive functioning before lung transplantation is associated with greater mortality after transplant (21).

In addition to neurocognitive decline, transplant patients are at risk for postoperative delirium, which has been associated with a number of adverse outcomes, including mortality (36, 37). Delirium is common among hospitalized older adults and is associated with significant public health expenditures (38) and with a 3- to 11-fold increased 6-month mortality risk after controlling for disease severity (36). Delirium is also independently predictive of long-term neurocognitive impairment (25, 39), and randomized trials are currently examining strategies to mitigate the negative impact of delirium (40). In the present sample, patients who experienced delirium showed lower neurocognitive performance compared with their nondelirious counterparts during follow-up assessments. We also previously noted that patients with delirium displayed poorer cognition at baseline and had longer hospitalization stays compared with patients without delirium (16).

Limitations

The present findings must be viewed with several limitations in mind. First, our

sample was relatively small, and only 70% of our original sample was available for postdischarge follow-up evaluations. However, we did not find any significant differences in demographic characteristics or neurocognitive testing performance between participants who did and did not have follow-up data, suggesting that our follow-up sample was likely to be representative of the overall cohort. In addition, we feel that our use of the RBANS and Trail Making Tests as objective measures of neurocognition, assessing multiple cognitive domains (e.g., executive function, memory, attention, etc.) is a strength of the present analysis. Second, our study does not provide insight into the mechanisms underlying neurocognitive changes, and future studies would benefit from collecting data on intraoperative gas exchange and other potential mechanisms, including perioperative risk factors such as primary graft dysfunction and length of ICU stay, that may explain the observed relationships. It is possible that some individuals may have experienced intraoperative events that affected their post-transplant neurocognitive performance (e.g., intraoperative hypoxia, hypotension, or microembolic events).

Finally, our study is limited in that we do not have data on the impact of neurocognitive function and delirium on long-term clinical outcomes, such as rejection and mortality. Future studies would benefit from prospectively collecting data over a longer time period to understand the impact of neurocognitive function on clinical outcomes.

Conclusions

Our study demonstrates that neurocognitive impairment is common among lung transplant candidates and may worsen after transplantation in some patients. In addition, neurocognitive function may worsen among patients who experience delirium during their hospitalization. Future studies may benefit from the collection of neuroimaging markers to better understand the impact of lung transplantation on brain function. In addition, future studies would benefit from collection of sensitive intraoperative and postoperative mechanisms that might explain the observed relationships. ■

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