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Perioperative Neurofilament Light Plasma Concentrations and Cognition before and after Cardiac Surgery: A Prospective Nested Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients with coronary artery disease are at risk for neuropsychological decline
- Postoperative increases in neurofilament light concentration in blood, a marker of neuronal injury, have been associated with delirium after noncardiac surgery

What This Manuscript Tells Us That Is New

- In an observational study of 167 cardiac surgery patients nested within a randomized controlled study of blood pressure management, higher baseline neurofilament light concentration in blood is associated with worse baseline cognition, but improvement in cognition at 1 yr
- An increase in neurofilament light on postoperative day 1 is associated with a greater decline in cognition at 1 yr

ABSTRACT

Background: Neurofilament light is a marker of neuronal injury and can be measured in blood. Postoperative increases in neurofilament light have been associated with delirium after noncardiac surgery. However, few studies have examined the association of neurofilament light changes with postdischarge cognition in cardiac surgery patients, who are at highest risk for neuronal injury and cognitive decline. The authors hypothesized that increased neurofilament light (both baseline and change) would be associated with worse neuropsychological status up to 1 yr after cardiac surgery.

Methods: This observational study was nested in a trial of cardiac surgery patients, in which blood pressure during bypass was targeted using cerebral autoregulation monitoring. Plasma concentrations of neurofilament light were measured at baseline and postoperative day 1. Neuropsychological testing was performed at baseline, 1 month after surgery, and 1 yr after surgery. Primary outcomes were baseline and change from baseline in a composite z-score of all cognitive tests.

Results: Among 167 patients, cognitive outcomes were available in 80% (134 of 167) and 61% (102 of 167) at 1 month and 1 yr after surgery, respectively. The median baseline concentration of neurofilament light was 18.2 pg/ml (interquartile range, 13.4 to 28.1), and on postoperative day 1 was 28.5 pg/ml (interquartile range, 19.3 to 45.0). Higher baseline log neurofilament light was associated with worse baseline cognitive z-score (adjusted slope, –0.60; 95% CI, –0.90 to –0.30; $P < 0.001$), no change in z-score from baseline to 1 month (0.11; 95% CI, –0.19 to 0.41; $P = 0.475$), and improvement in z-score from baseline to 1 yr (0.56; 95% CI, 0.31 to 0.81; $P < 0.001$). Whereas some patients had an improvement in cognition at 1 yr and others a decline, an increase in neurofilament light from baseline to postoperative day 1 was associated with a greater decline in cognition at 1 yr.

Conclusions: Higher baseline neurofilament light concentration was associated with worse baseline cognition but improvement in cognition at 1 yr. A postoperative increase in neurofilament light was associated with a greater cognitive decline at 1 yr.

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Neurocognitive dysfunction is a common complication of cardiac surgery, affecting between 10 and 40% of patients in the first 1 to 3 months and 5 to 25% of patients at 6 months to 1 yr after cardiac surgery.[1–3] However, the causal role of cardiac surgery in the development of

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neurocognitive dysfunction is not clear. A cohort study that used nonsurgical control groups reported that long-term neurocognitive decline after surgery is similar to that of the trajectory seen in nonsurgical controls, emphasizing the importance of the natural progression of underlying brain pathology.[4] In support of this, a recent study found that cognitive trajectories before and after coronary artery bypass graft with cardiopulmonary bypass were similar.[5] In other words, baseline vulnerability may be the most important consideration in predisposing patients to postoperative neurocognitive decline. Others have suggested that perioperative insults play an important role in the pathophysiology of neurocognitive dysfunction, with potential mechanisms including inflammation, cerebral hypoperfusion, embolic events, and changes in functional connectivity, among others.[6]

The advent of ultrasensitive testing allows plasma markers of neuronal injury to be tested to assess both baseline brain vulnerability and perioperative neuronal injury in patients undergoing surgery. Neurofilament light is an intermediate filament protein that supports myelinated axons.[7] Neurofilament light increases in both blood and cerebrospinal fluid in proportion to neuronal injury, and concentrations in the cerebrospinal fluid correlate well with plasma concentrations.[7–10] Recent studies have demonstrated that peripheral concentrations of neurofilament light increase from baseline in the days after surgery.[11,12] Further, both baseline neurofilament light concentration and changes in neurofilament light from baseline have been associated with postoperative delirium in noncardiac surgery patients.[12,13] One of these studies also reported that the general cognitive performance at 1 month after surgery was worse in patients at the highest quartile of neurofilament light concentration at that timepoint.[13] However, the association of baseline and postoperative neurofilament light concentrations and longer-term neurocognitive outcomes has not been described in cardiac surgery patients, who are thought to be at the highest risk for brain injury and cognitive decline after surgery.

To examine this question, we measured baseline and postoperative day 1 blood concentrations of neurofilament light in patients enrolled in a trial of mean arterial pressure management strategies during cardiopulmonary bypass.[14] As part of this trial, patients underwent neuropsychological testing before surgery, 1 month after surgery, and 1 yr after surgery. We hypothesized that neurofilament light concentration (both baseline and change from baseline to postoperative day 1) would be associated with cognition at baseline and 1 month and 1 yr after cardiac surgery.

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Materials and Methods

Institutional Review Board and Consent

The parent study (including collection of blood samples) was approved by the Johns Hopkins Institutional Review Board (Baltimore, Maryland). All participants provided written informed consent. This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Study Design and Patients

This observational study was nested in a trial that randomized patients to blood pressure targets during cardiopulmonary bypass based on cerebral autoregulation monitoring *versus* the usual practice in which these targets are empirically chosen.[15] Briefly, cerebral autoregulation is the process by which cerebral blood flow is maintained across range of blood pressures, and monitoring may identify optimal blood pressure for cerebral perfusion. The parent trial was registered at www.clinicaltrials.gov (NCT00981474). Data from these patients have been reported previously, but the primary hypothesis of the current study has not previously been evaluated or reported.[15] Patients were included in this study if they were undergoing primary or reoperative coronary artery bypass and/or valve surgery and/or aortic root surgery that required cardiopulmonary bypass and who were at high risk for neurologic complications (stroke or encephalopathy) as determined by a Johns Hopkins risk score[16] composed of history of stroke, presence of carotid bruit, hypertension, diabetes, and age that generally excluded patients in the lowest quartile of risk. Exclusion criteria were renal failure, hepatic dysfunction, non–English-speaking, contraindications to magnetic resonance imaging (*e.g.*, pacemaker), and emergency surgery. Patients were enrolled between October 2012 and May 2016.

Perioperative Care

Patients received standard institutional monitoring, including radial arterial blood pressure monitoring. General anesthesia was induced with fentanyl, midazolam, and/or propofol and was maintained with isoflurane and a nondepolarizing muscle relaxant. Cardiopulmonary bypass was performed with a nonocclusive roller pump and a membrane oxygenator, and the circuit included a 40-μm or smaller arterial line filter. Nonpulsatile flow was maintained between 2.1 and 2.4 l/min.[2] Patients were managed with

alpha-stat pH management. Rewarming was based on institutional standards with a goal of maintaining nasal pharyngeal temperature less than 37°C. After surgery, patients were sedated with a propofol infusion until they qualified for tracheal extubation or for 24 h after surgery. Patients requiring more than 24 h of mechanical ventilation received an infusion of fentanyl and/or midazolam.

Measurement of Neurofilament Light

Arterial blood was collected into glass tubes after anesthesia induction and in the intenstive care unit on postoperative day 1. Within 2 h of collection, the samples were centrifuged at 1,500*g* for 8 min, and the serum was separated and stored at −80°C, with subsequent batch processing. Plasma neurofilament light was examined by the Single Molecule Array–based immunoassay technology on the HD-X platform (Quanterix Corporation, USA), with assays performed in 2020. The Single Molecule Array NF-Light Assay (Quanterix Corporation) was used for neurofilament light quantification. This ultrasensitive assay uses a combination of monoclonal antibodies along with purified bovine neurofilament light as a calibrator and allows detection of biomarkers at very low concentrations. All samples were measured in duplicate with an analytical sensitivity of less than 1.0 pg/ml. Samples were thawed for 30 min, vortexed for 10 s, and centrifuged (10,000*g*, 10 min, 5°C) before dilution. Samples were diluted four times per protocol. The intra-assay coefficient of variation was 6.1% and the inter-assay coefficient of variation was 15% for the quality control plasma sample.

Neuropsychologic Testing and Other Patient and Perioperative Characteristics

Neuropsychologic testing was generally performed within 2 weeks before surgery and then 4 to 6 weeks and 1 yr after surgery. The tests assessed a number of cognitive domains known to be affected by cardiac surgery.[17,18] The test battery consisted of the Rey Auditory Verbal Learning Test,[19] Rey Complex Figure Test,[20] Controlled Oral Word Association Test,[21] Symbol Digits Modalities Test,[22] Trail Making Tests A and B,[23] and Grooved Pegboard Test.[24] Other patient and perioperative characteristics were abstracted from the electronic health record by trained research staff.

Statistical Analysis

The sample size for this nested cohort study was determined by the number of patients with available blood samples and cognitive assessments from the parent trial. The sample size is also consistent with other studies that have examined changes in cognition after surgery.[4]

The primary exposures were concentrations of neurofilament light at baseline and change from baseline to postoperative day 1. The postoperative day 1 timepoint was based on a previous study suggesting that neurofilament light rises substantially from baseline to postoperative day 1, with only a slight increase at postoperative day 2. The distributions of neurofilament light concentrations were highly skewed (Supplement fig. 1, http://links.lww.com/ALN/C879), so all neurofilament light values were log-transformed (log neurofilament light). Changes in concentration of log neurofilament light from baseline were calculated as absolute change (postoperative day 1 minus baseline) and relative change ([postoperative day 1 minus baseline]/baseline).

The primary cognitive outcome was change in a composite cognitive z-score from baseline to 1 month after surgery. To obtain this score, first, individual cognitive test z-scores at each timepoint were calculated based on the mean and SD of baseline tests of all patients in the parent study. Second, timed tests were multiplied by −1 so that higher scores represented better performance. Third, the composite cognitive z-score was calculated as the average of the individual test z-scores at each timepoint, and the change from baseline to 1 month and 1 yr were computed. Previous work has considered changes in composite z-scores of 0.3 to 0.5 to be clinically significant.[4,25]

Baseline patient characteristics were compared with Student's *t* tests, Wilcoxon rank sum tests, and chi-square tests, as appropriate. Baseline cognitive z-scores and changes in cognitive z-scores from baseline were correlated with concentrations of neurofilament light at baseline and change from baseline to postoperative day 1 using linear regression. As advocated by others,[26] we did not account for learning effect or surgery, since all patients underwent surgery and had an opportunity for learning effect. Adjustment variables were decided based on review of the literature and included age, sex, race, and a cardiac risk score (logistic European System for Cardiac Operative Risk Evaluation, which includes patient factors [*e.g.*, age, sex, organ morbidity, critical preoperative state], cardiac factors [*e.g.*, unstable angina, cardiac function, recent myocardial infarction, pulmonary hypertension], and operation-related factors [*e.g.*, urgency and procedure]). We also examined demographics, individual comorbidities, and surgery type and characteristics from table 1 for potential inclusion into the model, based on qualitative associations with both the exposure and outcome. A written, date-stamped analytic approach was drafted and stored in the investigators' files before the full data were accessed. This analytic plan was based on previous methodology used by our research group. Additional details were agreed upon before analyzing the data for this analysis. The missing data approaches were decided after accessing the data and so were made *post hoc*. In the adjusted model with change in cognition as the outcome, we chose not to adjust for baseline cognitive scores due to the potential for bias that could be introduced.[27] We conducted several *post hoc* sensitivity analyses suggested by reviewers including adjusting for additional variables (duration of cross-clamp time, baseline anemia, and randomization group) and modifying

Table 1. Patient Characteristics*

	Overall (n = 167)	Baseline Neurofilament Light < Median Value (18.2 pg/ml) (n = 83)	Baseline Neurofilament Light ≥ Median Value (18.2 pg/ml) (n = 84)	*P* Value
Age (yr), mean ± SD	70 ± 8	68 ± 7	72 ± 8	< 0.001
Male, n (%)	123 (73.7)	61 (73.5)	62 (73.8)	0.963
Race, n (%)				0.453
Caucasian	132 (79.0)	68 (81.9)	64 (76.2)	
African-American	22 (13.2)	8 (9.6)	14 (16.7)	
Other	13 (7.8)	7 (8.4)	6 (7.1)	
Education (yr), median (interquartile range)	16 (72–17)	16 (12–17)	14 (12–17)	0.232
Comorbidities, n (%)				
Previous stroke	24 (14.7)	9 (11.3)	15 (18.1)	0.219
Hypertension	156 (93.4)	80 (96.4)	76 (90.5)	0.124
Atrial fibrillation	46 (27.5)	24 (28.9)	22 (26.2)	0.694
Myocardial infarction	47 (28.1)	24 (28.9)	23 (27.4)	0.826
Chronic obstructive pulmonary disease	13 (7.8)	6 (7.3)	7 (8.3)	0.808
Obstructive sleep apnea	36 (21.7)	21 (25.6)	15 (17.9)	0.226
Tobacco (current)	14 (8.4)	6 (7.3)	8 (9.5)	0.609
Diabetes	80 (47.9)	35 (42.2)	45 (53.6)	0.140
Anemia	77 (46.4)	26 (31.3)	51 (61.5)	< 0.001
Logistic European System for Cardiac Operative Risk Evaluation, median (interquartile range)	5.1 (2.8–10.0)	4.0 (2.3–6.7)	7.2 (3.3–14.0)	< 0.001
Surgery, n (%)				0.215
Coronary artery bypass graft	77 (46.7)	37 (45.1)	40 (48.2)	
Coronary artery bypass graft + valve	32 (19.4)	12 (14.6)	20 (24.1)	
Valve	54 (32.7)	32 (39.0)	22 (26.5)	
Other	2 (1.2)	1 (1.2)	1 (1.2)	
Cardiopulmonary bypass duration (min), median (interquartile range)	119 (90–154)	118 (91–154)	120 (87.5–159.5)	0.938
Aortic cross-clamp duration (min), median (interquartile range)	75 (57–97)	74 (58–97)	75.5 (51.5–97.5)	0.775

*All variables were complete except the following: education (n = 43 missing), previous stroke (n = 4 missing), chronic obstructive pulmonary disease, obstructive sleep apnea, curren tobacco, and anemia (all n = 1 missing).

our approach to address concerns of regression to the mean by setting cognition at 1 month and 1 yr to be the outcome, with adjustment for baseline cognition.

We conducted several sensitivity analyses to account for missing cognitive data, assuming both missing at random and missing not at random.[28] Missing cognitive data were considered as missing follow-up cognitive assessments among the patients with baseline cognitive assessments and baseline blood samples.

First, using PROC MI in SAS (SAS Institute, Inc., USA), we conducted a sensitivity analysis to account for missing 1-month and 1-yr follow-up cognitive data with multiple imputation, using "missing at random" assumptions. Missing data (50 datasets) were imputed based on linear regression models for 1-month and 1-yr cognitive z-scores including age, sex, race, education, logistic European system for cardiac operative risk evaluation, duration of aortic cross-clamp, type of surgery, duration of hospitalization, baseline log neurofilament light, and available baseline and 1-month cognitive data. These analyses were fit to each imputed data set and pooled using PROC MIANALYZE (SAS Institute, Inc.).

Second, we allowed for the possibility of missingness not at random; that is, patients with missing 1-yr cognitive z-scores might have worse cognition than otherwise similar observed patients. To address "missingness not at random," we used an analytic approach in which we reduced the imputed 1-yr cognitive z-scores by an offset referred to as delta.[29] The delta represents the mean 1-yr cognitive z-score among the observed patients. The delta was used to reduce the imputed 1-yr cognitive z-scores by 25%, 50%, 75%, and 100% of the delta, after which adjusted linear models were fit for the association of baseline log neurofilament light concentrations with change in composite cognitive z-score from baseline to 1 yr. A *P* value of less than 0.05 was considered significant for all analyses.

RESULTS

Patients

A total of 167 patients were included in this analysis, and Supplemental figure 2 (http://links.lww.com/ALN/C879) shows a patient flow diagram. The mean ± SD age of patients was 70.4 ± 7.6 yr, and 74% (123 of 167) were male.

The median logistic European System for Cardiac Operative Risk Evaluation score was 5.1 (interquartile range, 2.8 to 10.0). At 1 month after surgery, 134 (80%) patients had available neuropsychological data, and at 1 yr after surgery, 102 (61%) patients had available neuropsychological data.

Baseline Log Neurofilament Light and Association with Cognition

The median concentration of neurofilament light at baseline was 18.2 pg/ml (interquartile range, 13.4 to 28.1; range, 4.8 to 277.0) and was log-transformed for all analyses because the distribution was highly skewed. Patients with neurofilament light concentrations higher than the median value were older, had a higher prevalence of anemia, and had a higher baseline cardiac risk score (logistic European System for Cardiac Operative Risk Evaluation score; table 1) The mean ± SD change in composite cognitive z-score from baseline to 1 yr was 0.11 ± 0.34.

At baseline, higher log neurofilament light concentration was strongly associated with worse baseline composite cognitive z-score, in both unadjusted models and multivariable models adjusted for age, sex, race, and a cardiac risk score (unadjusted linear slope, –0.82; 95% CI, –1.12 to –0.52; $P < 0.001$; adjusted linear slope, –0.60; 95% CI, –0.90 to –0.30; $P < 0.001$; fig. 1A; table 2).

At 1 month, a higher baseline concentration of log neurofilament light was not associated with a change

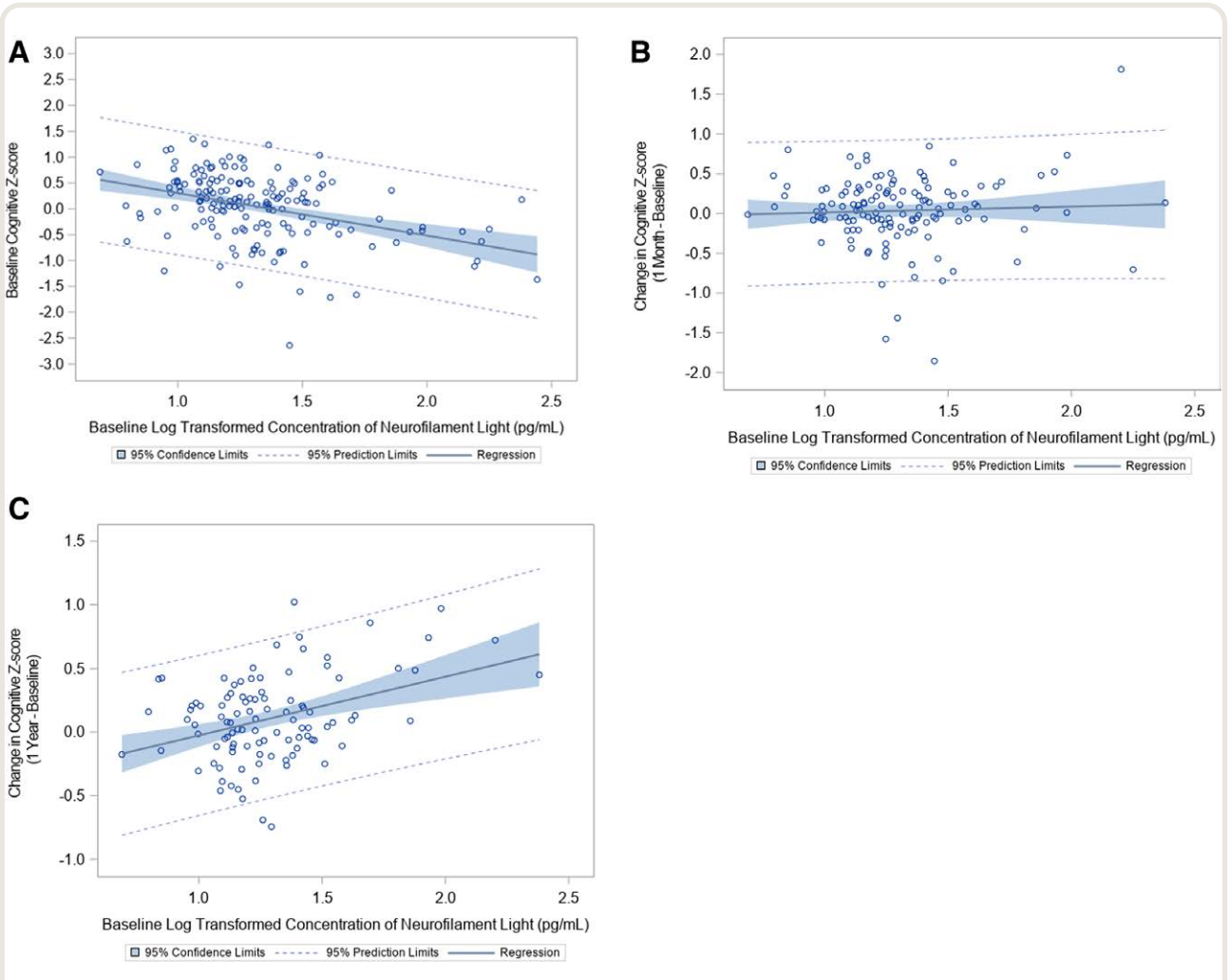

Fig. 1. Baseline log neurofilament light concentrations and composite cognitive z-scores (baseline and change). *A*, Baseline log neurofilament light concentrations and baseline composite cognitive z-score. *B*, Baseline log neurofilament light concentrations and change in composite cognitive z-score at 1 month. *C*, Baseline log neurofilament light concentrations and change in composite cognitive z-score at 1 yr. In all panels, concentrations of neurofilament light are expressed as picograms per milliliter and are log-transformed. The battery of neuropsychological tests to create the composite cognitive z-score was generally administered within 2 weeks before surgery (baseline) and then 4 to 6 weeks and 1 yr after surgery (1-month and 1-yr timepoints, respectively). The composite cognitive z-score was the average of the individual test z-scores at each timepoint, and the changes from baseline to 1 month and 1 yr were calculated using the composite cognitive z-scores at each timepoint.

Table 2. Association of Baseline log Neurofilament Light Concentrations with Composite Cognitive z-scores at Baseline, 1 Month, and 1 Year Postoperatively

	Unadjusted		Adjusted*		Adjusted with Multiple Imputation†	
	β-Coefficient (95% CI)	*P* Value	β-Coefficient (95% CI)	*P* Value	β-Coefficient (95% CI)	*P* Value
Outcome: baseline cognitive z-score						
Baseline log neurofilament light	–0.82 (–1.12 to –0.52)	< 0.001	–0.60 (–0.90 to –0.30)	< 0.001	Not applicable	Not applicable
Outcome: baseline to 1 month change in cognitive z-score						
Baseline log neurofilament light	0.07 (–0.20 to 0.34)	0.594	0.11 (–0.19 to 0.41)	0.475	0.10 (–0.20 to 0.39)	0.507
Outcome: baseline to 1-yr change in cognitive z-score						
Baseline log neurofilament light	0.46 (0.24 to 0.69)	< 0.001	0.56 (0.31 to 0.81)	< 0.001	0.41 (0.16 to 0.66)	0.001

*Adjusted by age, sex, race and logistic European System for Cardiac Operative Risk Evaluation score. The number of patients in each model is n = 167 (baseline), n = 134 (baseline to 1 month), and n = 102 (baseline to 1 yr). †Among 167 subjects, 134 had available neuropsychological data at 1 month, and 102 had available neuropsychological data at 1 yr. Variables used for the multiple imputation of 1-month and 1-yr cognitive outcomes (imputation number = 50) were age, sex, race, education, logistic European System for Cardiac Operative Risk Evaluation score, duration of aortic cross-clamp, type of surgery, duration of hospitalization, neurofilament light concentration at baseline, and any available neuropsychological data (*i.e.*, baseline and/or 1-month data, as appropriate).

in composite cognitive z-score from baseline in a model adjusted for age, sex, race, and a cardiac risk score (adjusted linear slope, 0.11; 95% CI, –0.19 to 0.41; $P = 0.475$; fig. 1B; table 2). At 1 yr, higher baseline concentration of log neurofilament light was associated with *improvement* in composite cognitive z-score in a model adjusted for age, sex, race, and a cardiac risk score (adjusted linear slope, 0.56; 95% CI, 0.31 to 0.81; $P < 0.001$; fig. 1C; table 2).

In sensitivity analyses to account for missing data under the "missing at random" assumption, the 1-yr results remained significant in a model adjusted for age, sex, race, and a cardiac risk score with multiple imputation of 1-yr data (adjusted linear slope, 0.41; 95% CI, 0.16 to 0.66; $P = 0.001$; table 2). In further sensitivity analyses assuming that patients with missing data at 1 yr would have lower cognitive scores by a fixed offset (*i.e.*, a "missing not at random" assumption in which the delta value is the fixed offset), the 1-yr results were similar (Supplemental table 1, http://links.lww.com/ALN/C879). In other words, as patients who were lost to follow-up were assumed to have progressively worse cognitive scores, the magnitude and significance of the association between baseline concentration of neurofilament light and change in cognitive z-scores were similar to the models which did not account for missingness not at random. Finally, we considered alternate methodologic approaches as *post hoc* sensitivity analyses suggested during the review process. First, we separately added three additional covariates (duration of cross-clamp, anemia, and blood pressure management group) to the adjusted models in table 2. Second, we changed the outcome of interest from change in cognition to follow-up composite cognitive z-score with adjustment for baseline cognition (Supplemental table 2, http://links.lww.com/ALN/C879). The measures of association were of similar magnitude but attenuated, and all inferences were unchanged.

Change in Log Neurofilament Light from Baseline to Postoperative Day 1 and Association with Cognition

The median concentration of neurofilament light on postoperative day 1 was 28.5 pg/ml (interquartile range, 19.3 to 45.0; range, 6.6 to 460.3), with 89% of patients having an increase from baseline to postoperative day 1. The mean ± SD increase in absolute concentration of neurofilament light from baseline to postoperative day 1 was 15.6 ± 39.3 pg/ml, and the relative increase was 74 ± 134%. The median absolute increase was 7.6 pg/ml (interquartile range, 2.9 to 15.1; range, –50.3 to 425.4), and the median relative increase was 42% (interquartile range, 16 to 74%; range, –32 to 1,217%). Patients with change in log neurofilament light values higher than the mean value in this study were more likely to have baseline atrial fibrillation and had a longer duration of cardiopulmonary bypass (Supplemental table 3, http://links.lww.com/ALN/C879). Lower neurofilament light concentration at baseline was associated with greater increase in neurofilament light concentration on postoperative day 1 (Supplemental fig. 3, http://links.lww.com/ALN/C879).

At 1 month, there was no association between absolute or relative change in log neurofilament light from baseline to postoperative day 1 and change in cognitive z-score from baseline to 1 month (fig. 2, A and B). Inferences were unchanged in adjusted models or when missing data at the 1-month assessment were imputed (table 3).

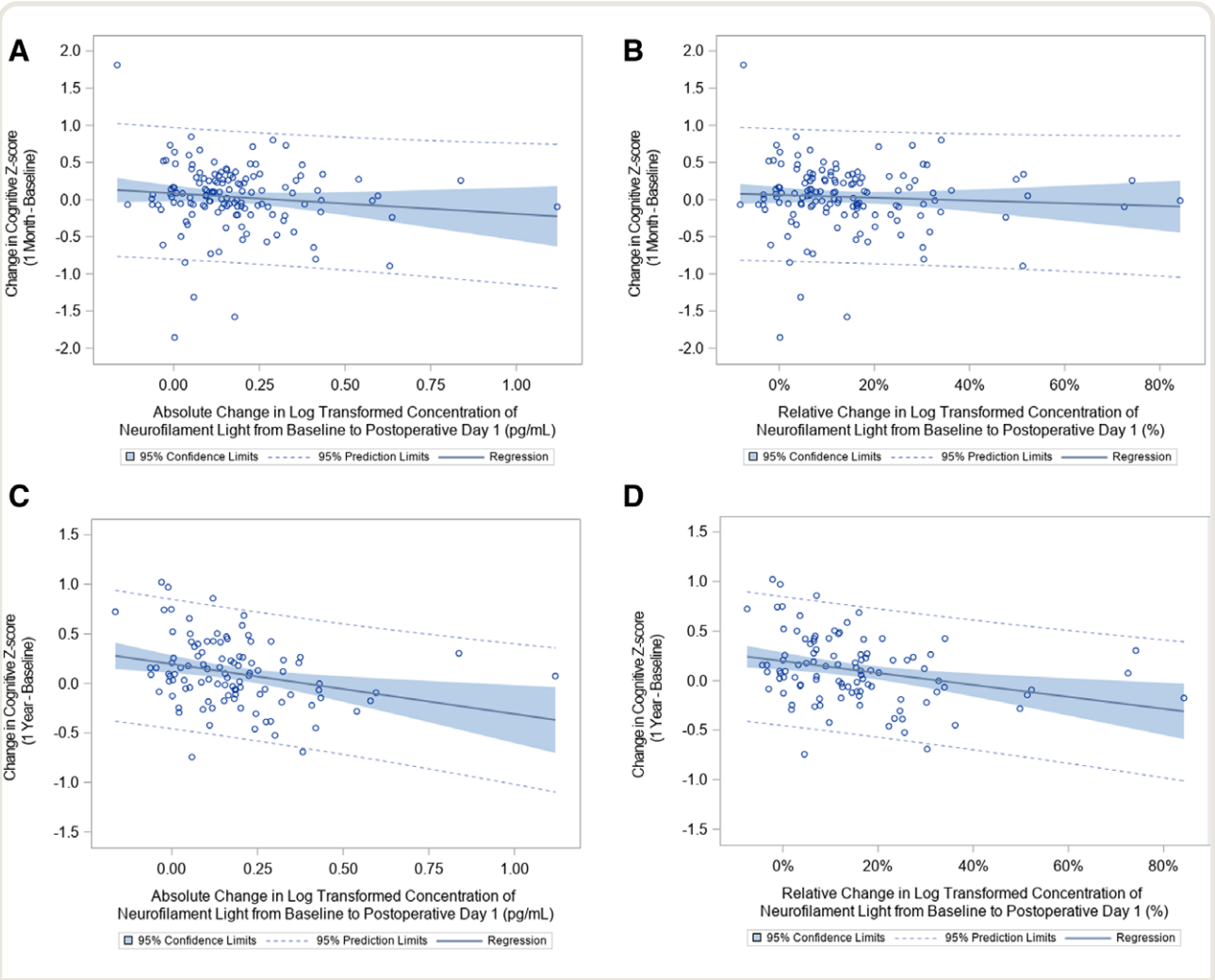

Fig. 2. Change in log neurofilament light concentrations and change in composite cognitive z-scores. Absolute and relative change in log neurofilament light concentrations from baseline to postoperative day 1 and associations with change in composite cognitive z-score at 1 month (*A* and *B*) and 1 yr (*C* and *D*). Relative change in the concentration of log neurofilament light is calculated as (postoperative day 1 log neurofilament light minus baseline log neurofilament light)/baseline log neurofilament light and is expressed as a percentage. The battery of neuropsychological tests to create the composite cognitive z-score was generally administered within 2 weeks before surgery (baseline) and then 4 to 6 weeks and 1 yr after surgery (1-month and 1-yr timepoints, respectively). The composite cognitive z-score was the average of the individual test z-scores at each timepoint, and the changes from baseline to 1 month and 1 yr were calculated using the composite cognitive z-scores at each timepoint.

Whereas some patients had an improvement in cognition at 1 yr and others a decline, there was a significant negative association between the absolute and relative change in log neurofilament light from baseline to postoperative day 1 and change in cognitive z-score from baseline at 1 yr, in both unadjusted models and multivariable models adjusted for age, sex, race, and a cardiac risk score (fig. 2, C and D; table 3). In other words, an increase in neurofilament light on the day after surgery was associated with a greater decline in cognition from baseline at 1 yr after surgery on average.

In sensitivity analyses to account for missing data under the "missing at random" assumption with multiple imputation of 1-yr cognitive data, the adjusted association of relative change (adjusted linear slope, 0.48, 95% CI, –0.87 to –0.09; $P = 0.016$) and absolute change (adjusted linear slope, –0.36; 95% CI, –0.70 to –0.03; $P = 0.034$) in log neurofilament light from baseline to postoperative day 1 remained significantly associated with change in cognition at 1 yr after surgery, in models adjusted for age, sex, race, and a cardiac risk score. In further sensitivity analyses under the "missing not at random" assumption, the estimates of the negative association between change in log neurofilament light from baseline to postoperative day 1 and change in composite cognitive z-score from baseline at 1 yr were larger (*i.e.*, more negative) and still significant, using a range of delta values (Supplemental table 4, http://links.lww.com/ALN/

Table 3. Association of Change in Log Neurofilament Light Concentrations with Composite Cognitive z-scores

	Unadjusted		Adjusted*		Adjusted with Multiple Imputation†	
	β-Coefficient (95% CI)	*P* Value	β-Coefficient (95% CI)	*P* Value	β-Coefficient (95% CI)	*P* Value
Outcome: baseline to 1-month change in cognitive z-score						
Absolute‡ change in log neurofilament light from baseline to postoperative day 1	–0.28 (–0.70 to 0.15)	0.198	–0.27 (–0.71 to 0.17)	0.232	–0.10 (–0.52 to 0.32)	0.627
Relative§ change in log neurofilament light from baseline to postoperative day 1	–0.18 (–0.67 to 0.30)	0.457	–0.19 (–0.70 to 0.32)	0.462	–0.06 (–0.54 to 0.43)	0.818
Outcome: baseline to 1-yr change in cognitive z-score						
Absolute‡ change in log neurofilament light from baseline to postoperative day 1	–0.50 (–0.85 to –0.16)	0.005	–0.52 (–0.88 to –0.15)	0.006	–0.36 (–0.70 to –0.03)	0.034
Relative§ change in log neurofilament light from baseline to postoperative day 1	–0.60 (–1.00 to –0.21)	0.003	–0.64 (–1.06 to –0.22)	0.003	–0.48 (–0.87 to –0.09)	0.016

*Adjusted by age, sex, race, and logistic European System for Cardiac Operative Risk Evaluation score. The number of patients in each model is n = 134 (baseline to 1 month) and n = 102 (baseline to 1 yr). †Among 167 subjects, 134 had available neuropsychological data at 1 month, and 102 had available neuropsychological data at 1 yr. Variables used for the multiple imputation (imputation number = 50) were age, sex, race, education, logistic European System for Cardiac Operative Risk Evaluation score, duration of aortic cross-clamp, type of surgery, duration of hospitalization, neurofilament light concentration at baseline, and any available neuropsychological data (*i.e.*, baseline and/or 1-month data, as appropriate). ‡Absolute change refers to the difference in log neurofilament light concentration from baseline to postoperative day 1. §Relative change refers to the difference in log neurofilament light concentration from baseline to postoperative day 1, divided by the baseline concentration.

C879). In other words, as patients who were lost to follow-up were assumed to have progressively worse cognitive scores, the magnitude of the estimated decline in composite cognitive z-score from baseline at 1 yr was larger and remained significant.

Finally, we considered alternate methodologic approaches as *post hoc* sensitivity analyses suggested during the review process. First, we separately added additional covariates (duration of cross-clamp and blood pressure management group) to the adjusted models in table 3. Second, we changed the outcome of interest from change in cognition to follow-up composite cognitive z-score with adjustment for baseline cognition (Supplemental table 5, http://links.lww.com/ALN/C879). The measures of association were of similar magnitude but attenuated. All statistical inferences were unchanged, with the exception that the association of absolute change in log neurofilament light with 1-yr cognition was no longer significant in the adjusted model with multiple imputation ($P = 0.03$ to $P = 0.06$).

Subgroup Analyses

The importance of two baseline characteristics (age older than 70 yr and baseline cognition) were examined using stratified analyses with *P*-interaction values to gauge the significance of a moderating effect of age and baseline cognition on the association of baseline or change in log neurofilament light and all cognitive outcomes. For age, there was not a consistent modifying effect (Supplemental tables 6 and 7, http://links.lww.com/ALN/C879). For cognition, patients with low baseline cognition had a stronger association between increasing change in neurofilament light from baseline to postoperative day 1 and more decline in a composite cognitive z-score from baseline to 1 yr (Supplemental tables 8 and 9, http://links.lww.com/ALN/C879). These exploratory results must be considered hypothesis-generating.

DISCUSSION

The important findings of this study are that higher neurofilament light concentration was associated with worse cognition at baseline, but improvement in cognition at 1 yr. A postoperative increase in neurofilament light was associated with greater decline in cognition at 1 yr. There were no associations of neurofilament light concentrations with change in cognition at 1 month. However, there was a substantial amount of missing data at 1 yr, and cerebrospinal fluid concentrations of neurofilament light were not obtained. Additionally, there was heterogeneity in cognitive outcomes among patients in the cohort, with both improvement and decline in cognition at 1 yr from baseline. Thus, although the results were consistent in multiple sensitivity analyses to account for missing data, they must be considered hypothesis-generating. Taken as a whole, these findings suggest that baseline and postoperative concentrations of neurofilament light may provide insight into cognitive outcomes after cardiac surgery.

In this study, higher baseline neurofilament light was associated with worse baseline cognition among patients undergoing cardiac surgery, a finding that is similar to results in other patient populations.[8,30] Baseline concentrations of neurofilament light likely reflect ongoing neurodegeneration before surgery and identify patients with baseline

vulnerability. These results support the internal consistency of the study methods. Similarly, baseline concentrations of neurofilament light were not associated with change in cognition at 1 month after surgery, implying that short-term cognitive changes may result from a myriad of additional factors, such as medications, alterations in sleep, and poor mobility, and so forth. However, an unexpected finding was that higher baseline concentrations of neurofilament light were associated with improvement in cognitive outcomes at 1 yr. These results were consistent in patients with complete data as well as using imputation of missing data using missing at random and not at random assumptions. One possible biologic explanation is that high neurofilament light concentrations at baseline might identify patients who derive cognitive benefit from cardiac surgery, perhaps due to improved cardiac function, enhanced mobility, or better medical management of cardiac risk factors.[31] Indeed, previous studies have suggested an association between increased cerebral blood flow and improved cognition.[32] Alternatively, this observation may be due to potential methodologic biases, including measurement error, regression to the mean, or selection biases based on follow-up compliance. In particular, multiple imputation methods may not account for systemic biases that might result if patients with cognitive impairment dropped out of this study due to unobservable reasons. We accounted for this possibility by imputing 1-yr outcome data using a range of realities (delta values) that systematically lower the imputed cognitive scores of patients who were lost to follow-up. As the delta values increased (reflecting that patients who were lost to follow-up had greater cognitive impairment), the magnitude of the association of baseline log neurofilament light values with cognitive change at 1 yr did not change. However, because of the missing data and because these results were not consistent with our hypotheses before the study, these results at 1 yr must be considered hypothesis-generating.

In terms of change in neurofilament light from baseline to postoperative day 1, our results demonstrate that increasing neurofilament light at postoperative day 1 is associated with greater cognitive decline at 1 yr after surgery, and these results were consistent in sensitivity analyses using imputation to account for missing cognitive data and under missing not at random assumptions. However, these associations were not present at 1 month after surgery, at a time when many factors may be contributing to cognitive status. There was heterogeneity in cognitive outcomes among patients, with both improvement and decline in cognition at 1 yr from baseline, and so the 1-yr associations reflect average values in the cohort. Nevertheless, these results imply that neuronal injury in the perioperative period may be a mechanism for long-term or accelerated cognitive change. Neurofilaments are highly sensitive to any form of neuronal injury and death, though not specific for any one disease. Additionally, neurofilament light measurements from peripheral blood have been shown to correlate with cerebrospinal fluid concentrations, which, together with advances in measurement,[33] have helped establish serum/plasma neurofilament light as a reliable peripheral biomarker of neuronal injury. The sources of neuronal injury during surgery are myriad and may include distant effects of tissue injury, inflammation, and hemodynamic changes, among others, so further studies will be needed to understand what factors are associated with greater release of neurofilament light. It will also be important to understand both the mechanisms and the specificity for neuronal injury that leads to increased peripheral concentrations of neurofilament light. The increases in neurofilament light in our study are similar to those that have been reported in orthopedic surgery, so they may not be unique to cardiac surgery patients.[11] A recent study in orthopedic surgery using intrathecal catheters reported that serum neurofilament light concentrations increased after surgery, but cerebrospinal fluid concentrations of neurofilament light did not increase, implying a potential peripheral source of neurofilament light or impaired renal clearance of neurofilament light due to renal dysfunction.[34] This study found no association of change in either cerebrospinal fluid or serum neurofilament light with cognitive outcomes 3 months after surgery. Alternatively, greater release of neurofilament light may simply reflect underlying neurodegeneration, which increases susceptibility to neuronal injury after perioperative insults. Additionally, neurofilament light appears to continue to increase after postoperative day 1,[11] so it will be important to conduct additional studies measuring concentrations of neurofilament light for several days after surgery.

The results of two exploratory subgroup analyses suggest that baseline cognition may modify the association of neurofilament light concentrations and cognitive outcomes at 1 yr. In patients with baseline cognition below the median cognitive z-score, the association of change in log neurofilament light from baseline to postoperative day 1 and a greater decline in cognitive status at 1 yr was stronger than in patients with cognition above the median cognitive z-score. These results may imply that neuronal injury in the perioperative period may have more cognitive sequelae in patients with lower cognition at baseline, perhaps because of decreased reserve or increased susceptibility to further injury. Since these analyses were secondary, only found in one subgroup, and may be affected by potential regression to the mean, these results must also be considered exploratory and hypothesis-generating.

Strengths of this study include a quantification of a novel peripheral marker of neuronal injury that provides mechanistic insight into post–cardiac surgery cognitive changes and a robust neuropsychological battery administered up to 1 yr after surgery. There are several limitations to consider. A major limitation of our study is that we only looked at a single biomarker, neurofilament light, and other markers of brain injury and function will be important to consider. Another limitation is that neurofilament light was

measured only at baseline and postoperative day 1, and further timepoints are needed to understand the dynamics of ongoing injury. Additionally, we only measured neurofilament light from the blood and not from cerebrospinal fluid, and therefore the rise in neurofilament light may simply reflect tissue injury and surgical stress, although neurofilament light does appear to be fairly specific for the central nervous system. There were missing outcome data, particularly at the 1-yr assessment. Multiple imputation of missing outcome data was used, as well as methods to account for missing data that may be due to unobservable data (*i.e.*, a missing not at random assumption). There are several ways to analyze cognitive data, and we used methods consistent with previous studies. The results were consistent in several post hoc sensitivity analyses that changed the definition of the outcome or included additional covariates. Several of our analyses could be affected by regression to the mean, including the primary analysis and subgroup analyses stratified by cognition. We did model the outcome using cognition at each follow-up timepoint as the outcome of interest and found that the model inferences were unchanged. We did not include a control group of nonsurgical patients because we were specifically interested in the associations of neurofilament light with cognitive outcomes in patients undergoing surgery, and a threshold for cognitive dysfunction was not used. We also highlight the heterogeneity in cognitive outcomes at 1 yr, with some patients showing an improvement and others a decline in scores from baseline. Finally, since this was an observational study, a major limitation is the potential for confounding variables (either measured or unmeasured) that were not accounted for in the models and might affect the results.

Important take-home findings from this study are that higher baseline neurofilament light concentrations before surgery are associated with worse baseline cognition, but improvement in cognition at 1 yr. Additionally, peripheral concentration of neurofilament light increases after cardiac surgery and is associated with a greater cognitive decline at 1 yr but not 1 month after cardiac surgery, although these results should be considered hypothesis-generating and need to be validated in future studies. Neurofilament light concentrations may provide insight into postoperative change in cognition at 1 yr after cardiac surgery.

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Competing Interests

Dr. Brown consulted for and has a data share agreement with Medtronic (Minneapolis, Minnesota) in unrelated areas. Dr. Hogue consulted for and received grant support from Medtronic in unrelated areas. Dr. Hogue also has financial relationships with Edwards Lifesciences, Inc. (Irvine, California), and Merck (Kenilworth, New Jersey). Dr. Moghekar reports contractual research support from Fujirebio Diagnostics Ltd. (Malvern, Pennsylvania) in unrelated areas. Dr. Kamath has a financial relationship with the Philadelphia Neuropsychological Society (Philadelphia, Pennsylvania). The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Results and Analyses, http://links.lww.com/ALN/C879

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