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# Relationships between Markers of Neurologic and Endothelial Injury during Critical Illness and Long-Term Cognitive Impairment and Disability

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## Abstract

**Purpose—**Neurologic and endothelial injury biomarkers are associated with prolonged delirium during critical illness and may reflect injury pathways that lead to poor long-term outcomes. We hypothesized that blood-brain barrier (BBB), neuronal, and endothelial injury biomarkers measured during critical illness are associated with cognitive impairment and disability after discharge.

**Methods—**We enrolled adults with respiratory failure and/or shock and measured plasma concentrations of BBB (S100B), neuronal (UCHL1, BDNF), and endothelial (E-selectin, PAI-1) injury markers within 72 hours of ICU admission. At 3 and 12 months post-discharge, we assessed participants' global cognition, executive function, and activities of daily living (ADL). We used multivariable regression to determine whether biomarkers were associated with outcomes after adjusting for relevant demographic and acute illness covariates.

**Results—**Our study included 419 survivors of critical illness with median age 59 years and APACHE II score 25. Higher S100B was associated with worse global cognition at 3 and 12 months (P=0.008; P=0.01). UCHL1 was nonlinearly associated with global cognition at 3 months (P=0.02). Higher E-selectin was associated with worse global cognition (P=0.006 at 3 months; P=0.06 at 12 months). BDNF and PAI-1 were not associated with global cognition. No biomarkers were associated with executive function. Higher S100B (P=0.05) and E-selectin (P=0.02) were associated with increased disability in ADLs at 3 months.

**Conclusions—**S100B, a marker of BBB and/or astrocyte injury, and E-selectin, an adhesion molecule and marker of endothelial injury, are associated with long-term cognitive impairment after critical illness, findings that may reflect mechanisms of critical illness brain injury.

### Keywords

Cognitive impairment; blood-brain barrier; endothelium; disability; critical illness

## INTRODUCTION

Cognitive impairment is common in survivors of medical and surgical critical illness, often with severity of impairment similar to that seen among patients with moderate traumatic brain injury or mild Alzheimer's disease.[1, 2] Delirium, a manifestation of acute brain dysfunction, is one of the strongest predictors of cognitive impairment after critical illness.[1] Furthermore, delirium has also been associated with long-term disability in activities of daily living (ADLs).[3, 4] A widely held interpretation of these relationships is that pathophysiologic changes in the brain during critical illness present acutely as delirium and lead to long-term impairments.

The mechanistic pathways underlying delirium and poor long-term outcomes are incompletely understood. We and others hypothesize that inflammatory signals through the blood-brain barrier (BBB) and endothelial dysfunction lead to neuroinflammation and microvascular blood flow perturbations, which result in neuronal injury.[5–9] We have demonstrated that increased markers of BBB injury and endothelial dysfunction (i.e., worse vasomotor function and increased release of biochemical mediators) are associated with longer delirium duration in critically ill patients.[10, 11] The relationship of these acute brain dysfunction injury pathways with long-term impairments after critical illness, however, has not been examined.

We therefore conducted a prospective cohort study to test the hypothesis that elevated plasma concentrations of BBB, neuronal, and endothelial injury biomarkers during critical illness are associated with worse cognitive impairment and worse disability in ADLs in survivors.

## PATIENTS AND METHODS

### Study Design and Population

We conducted this prospective cohort study, which we designed to investigate mechanisms of long-term cognitive impairment after critical illness rather than to test the diagnostic accuracy of biomarkers for clinical use, as part of the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study (NCT00392795) conducted at Vanderbilt University Medical Center and Saint Thomas Hospital (both in Nashville, TN, USA), analyzing participants who completed follow-up assessments after hospital discharge. Results from the BRAIN-ICU study have been previously reported [1, 2, 12], but the hypotheses and findings presented herein are original and have not been previously published. The study protocol was approved by each institution’s institutional review board.

Adults admitted to a medical or surgical ICU with respiratory failure and/or shock were eligible for enrollment in the BRAIN-ICU study as previously described [1] unless they met exclusion criteria: severe neurologic disease that prevented independent living; cardiac surgery within 3 months of ICU admission; suspected brain injury due to stroke or cardiopulmonary arrest; limited outpatient follow-up opportunity due to active substance abuse, psychotic disorder, or habitation > 200 miles from Nashville; inability to perform delirium assessments due to blindness, deafness, or inability to speak English; moribund state with life expectancy <24 hours; significant recent critical illness and/or more than 72 hours after onset of organ dysfunction; or lack of informed consent from the participant or an authorized surrogate.

### Exposures

We collected blood in EDTA anti-coagulated and citrate anti-coagulated collection tubes immediately upon study enrollment (i.e., within 72 hours of ICU admission). Tubes were placed on ice immediately after collection and were processed within 1 hour, including centrifugation at 1500 × g, removal of the supernatants, and then labeling and storage in 400

μL aliquots at −80°C until a later date, at which time we performed batched analyses in duplicate of plasma biomarker concentrations using commercially available enzyme-linked immunosorbent assays and electrochemiluminescent assays.

We studied five biomarkers based on our previous work finding associations with acute brain dysfunction and because they are considered indicators of mechanisms we hypothesized promote long-term cognitive impairment in survivors of critical illness (see Supplementary Material for additional information). As a marker of BBB and/or astrocyte injury, we measured plasma concentration of S100B, a protein secreted by astrocytes when injured (assay from Millipore; Billerica, Massachusetts).[13, 14] As plasma markers of acute neuronal damage, we measured plasma concentrations of ubiquitin C-terminal hydrolase L1 (UCHL1), a protein highly specific to neurons that is an important factor in the ubiquitin proteasome system (assay from Cloud-Clone Corp; Katy, Texas), and brain-derived neurotrophic factor (BDNF), the most abundant neurotrophin in the central nervous system, which plays a key role in brain plasticity (assay from Meso Scale Diagnostics; Rockville, Maryland).[15, 16] Finally, as markers of endothelial activation, we measured plasma concentrations of E-selectin, a cell adhesion molecule involved in leukocyte adhesion and activation (assay from Meso Scale Diagnostics; Rockville, Maryland), and plasminogen activator inhibitor-1 (PAI-1), a protein that inhibits tissue and urokinase plasminogen activator to prevent fibrinolysis (assay from Meso Scale Diagnostics; Rockville, Maryland).[17]

## Outcomes

Neuropsychology professionals blinded to each participant's hospital course and biomarker data assessed participants for cognitive impairment and disability in ADLs 3 and 12 months after hospital discharge. We assessed global cognitive function with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),[18] a validated neuropsychometric battery that measures domains of attention, language, immediate and delayed memory, and visuospatial construction. The RBANS has a mean (standard deviation) population age-adjusted score of 100±15 with lower scores indicating worse global cognitive function. The RBANS has also been used to assess patients with moderate traumatic brain injury [19] and mild Alzheimer's disease [18], with these populations having mean scores of 78 and 70, respectively. We assessed executive function with the Trail Making Test, Part B (Trails B),[20] a validated tool examining set shifting and cognitive flexibility. The Trails B has an age-, sex-, and education-adjusted mean score of 50±10 with lower scores indicating worse executive function. Finally, we assessed basic ADLs and instrumental ADLs with the Katz ADL[21] and the Functional Activities Questionnaire (FAQ),[22] respectively. A score greater than 0 on these assessments indicates disability in at least one domain of daily living.

## Covariates

We collected demographic data upon enrollment and hospital course data from admission until discharge, death, or a maximum of 30 days after enrollment. We chose the following covariates *a priori* based on clinical judgment and previous research suggesting they may confound the associations between our biomarkers of interest and cognitive impairment or

disability: years of education; comorbid disease burden per the Charlson comorbidity index; cerebrovascular disease per the Framingham stroke risk score; pre-existing cognitive deficit per the Short Form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF) score; functional disability at enrollment defined as a score >0 on either the Katz ADL and/or FAQ at baseline; severity of illness per the mean daily modified Sequential Organ Failure Assessment Score (which excluded Glasgow Coma Scale since we adjusted for coma separately); and durations of severe sepsis and coma.

## Statistical Analysis

We used separate multivariable regression models to determine whether individual biomarker plasma concentrations were independently associated with the outcome variables (RBANS, Trails B, Katz ADL, and FAQ scores at 3 and 12 months) after adjusting for the aforementioned covariates. After examining the distributions of each outcome, we used ordinary least squares (linear) regression to analyze associations with RBANS and Trails B scores and negative binomial regression to analyze associations with Katz ADL and FAQ scores.

All biomarkers were transformed by taking the logarithm with base 10 in order to improve model fit and reduce the influence of extreme values. With the exception of IQCODE-SF (which had too little variability), all continuous variables, including biomarker concentrations, were initially allowed to have a nonlinear relationship with the outcomes. Since systemic inflammation can lead to BBB and endothelial insults and may be associated with brain dysfunction,[5, 7, 23] and since advancing age is associated with increased BBB permeability, endothelial dysfunction, and brain dysfunction,[24, 25] we evaluated if the magnitude of the effect of biomarkers on long-term outcomes was modified by inflammation or age. We allowed for potential interactions between biomarkers and 1) IL-6 plasma concentration or 2) age using separate cross-product terms. If the global tests for nonlinearity were nonsignificant (P>0.20), those interaction terms were removed from the model for parsimony. Biomarkers of BBB and endothelial injury have been associated with delirium,[10, 11] itself a predictor of worse global cognition and executive function after critical illness.[1] We therefore hypothesized that delirium may be in the causal pathway between BBB and endothelial injury and poor long-term outcomes and did not include delirium in our primary models. We did, however, perform sensitivity analyses that included delirium duration in analyses assessing the association between biomarkers and global cognition and executive function to evaluate for potential full or partial mediation.

In order to reduce bias from missing data, we used multiple imputation to account for missing covariates and outcomes among patients with at least partial outcomes data available at a given time point. Among both covariates and functional outcomes (Katz ADL and FAQ, both of which could be assessed over the phone), we had very little missing data—a maximum of 3% per variable. Percent *partial* missing data for RBANS global and Trails B scores, which had to be assessed in person, ranged from 10%-14%, depending on the test and time point.

With our cohort of 419 patients, we could reliably fit a model with up to 28 degrees of freedom based on the general rule that at least 15 subjects are required per degree of

freedom for proper multivariable analysis and to be generalizable to future patients,[26] and thus we limited the number of covariates included to avoid overfitting. We used R version 3.4.1 for all statistical analyses. All p-values were calculated using the likelihood method, and we considered P≤0.05 as statistical significance for independent variables.

### Role of the funding source

The funding agencies of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## RESULTS

Patient characteristics from the cohort are presented in Table 1. The participant flowchart is displayed in Supplementary Figure 1, and data regarding screened and excluded patients were previously reported.[1] In general, patients had high severity of illness and frequent acute organ dysfunctions, including delirium. Relative to values reported in healthy subjects, plasma concentrations of S100B, UCHL1, BDNF, E-selectin, and PAI-1 were generally high in this critically ill cohort (Table 2). At 3 months post-discharge, we assessed 394 patients, and at 12 months, we assessed 343 patients. Overall, 419 unique patients contributed data to these analyses. The RBANS global cognition, Trails B, Katz ADL, and FAQ scores for the cohort at 3 and 12 months are reported in Table 1.

We found evidence that IL-6 modifies the association between S100B and long-term cognitive outcomes (P for the interaction = 0.03 at 3 months and 0.06 at 12 months), so Figure 1 displays the adjusted associations between all biomarkers and cognitive outcomes at different IL-6 plasma concentrations. Supplementary Figure 2 displays the associations at different ages (P for the interaction between S100B and age = 0.17 at 3 months and 0.17 at 12 months).

After accounting for interactions with IL-6 and age and adjusting for education level, comorbid disease burden, cerebrovascular disease, pre-existing cognitive deficit, severity of illness, and durations of severe sepsis and coma, higher S100B plasma concentrations were significantly associated with worse global cognition (RBANS) at both 3 and 12 months (P = 0.008 and 0.01, respectively). On average, a patient who had a S100B plasma concentration at the 75$^{th}$ percentile of our cohort—indicative of increased BBB injury—had a RBANS global cognition score about 2 points lower at 3 months (adjusted difference −2.02; 95% confidence interval −4.73 to 0.68) and 12 months (adjusted difference −1.86; 95% confidence interval −3.52 to −0.20) than a patient with a S100B plasma concentration at our cohort's 25$^{th}$ percentile level. The magnitude of the effect between S100B and global cognition, however, was greater among patients with higher IL-6 plasma concentrations, as shown in Figures 1 and 2. Supplementary Figure 3 displays the association of S100B and global cognition by age.

UCHL1 plasma concentration was also significantly associated with global cognition at 3 months in a nonlinear fashion (P=0.02, Supplementary Figure 4). This association was not modified by IL-6 plasma concentration or age. UCHL1 plasma concentration was not associated with global cognition at 12 months (P=0.70). As shown in Figures 1 and 3,

greater E-selectin plasma concentrations were associated with worse global cognition at 3 months (P=0.006) and were marginally associated at 12 months (P=0.06). These associations were not significantly modified by IL-6 plasma concentration or age. Supplementary Figure 5 displays the association of E-selectin and global cognition by age. On average, a patient who had an E-selectin plasma concentration at the 75$^{th}$ percentile of our cohort —indicative of increased endothelial activation—had a RBANS global cognition score about 2 points lower at 3 months (adjusted difference −1.80; 95% confidence interval −3.07 to −0.53) and 1 point lower at 12 months (adjusted difference −1.22; 95% confidence interval −2.52 to 0.08) than a patient with an E-selectin plasma concentration at our cohort's 25$^{th}$ percentile level.

Finally, neither BDNF nor PAI-1 plasma concentrations were associated with global cognition at either 3 or 12 months (Figure 1 and Supplementary Figure 2). The inclusion of delirium duration in sensitivity analyses did not significantly alter the associations between S100B, UCHL1, or E-selectin with global cognition, indicating that these associations were not mediated by delirium (Supplementary Table 1). The relationships between the additional covariates included in the statistical analyses and global cognition are demonstrated in Supplementary Table 2. No biomarkers were significantly associated with executive function as measured by Trails B scores at 3 or 12 months (Supplementary Figures 6 and 7).

Supplementary Figures 8–11 display the associations between biomarkers and disability outcomes. Higher S100B (P=0.05) and E-selectin (P=0.02) plasma concentrations were associated with small increases in Katz ADL scores at 3 months, indicating slightly greater disability in basic ADLs. These associations were not modified by IL-6 plasma concentration or age. No other biomarkers were associated with disability outcomes at either time point.

## DISCUSSION

In this study—the first to our knowledge to examine associations between BBB, neurologic, and endothelial injury markers measured during critical illness and cognitive impairment and disability up to one year after critical illness—greater plasma concentrations of S100B, a marker of BBB and/or astrocyte injury, were associated with worse global cognition 3 and 12 months after hospital discharge. Additionally, greater plasma concentrations of E-selectin, a marker of endothelial injury, were also associated with worse global cognition 3 and 12 months after critical illness. Though this observational study cannot prove these associations are causal, our results persisted after adjustment for multiple potential confounders and are consistent with our hypotheses that BBB disruption and endothelial dysfunction during acute critical illness are mechanisms that lead to subsequent poor outcomes among survivors.

Markers of neurologic injury, which are released into the plasma when the BBB or neurons are damaged, provide a clinically feasible measure of BBB and neuronal injury. Of the markers previously studied, S100B is the one most correlated with BBB injury.[13, 14] Levels of S100B have previously been associated with the development of cognitive changes after surgery, septic encephalopathy, and delirium during critical illness.[10, 27–29] Our

prior work found no evidence that BBB injury (measured using S100B plasma concentrations) mediated the association between endothelial dysfunction and delirium, but rather changes in the BBB and microcirculation (i.e., altered blood flow and signaling) likely contribute to delirium in an additive (possibly independent) manner.[10] In the current study of patients without structural brain injury during critical illness, we found that higher plasma concentrations of the BBB injury marker S100B were associated with worse global cognition up to 12 months after hospital discharge.

Our study is the first to examine UCHL1 as a neuronal injury pathway marker in the setting of critical illness. UCHL1 is highly abundant in the central nervous system, is specifically expressed in neurons, and plays an important role in the removal of damaged or excessive proteins. Low concentrations of UCHL1 have been associated with neurodegenerative diseases [30, 31], whereas elevated concentrations of UCHL1 have been associated with brain injury and ischemia.[32, 33] We found UCHL1 levels to be associated with global cognition 3 months after critical illness in a U-shaped nonlinear fashion. Our findings may suggest that increasing concentrations are indicative of increased neuronal damage but that increased bioavailability and ability to repair damaged proteins and neurons may offer protection against further injury.

BDNF is the most abundant neurotrophin in the central nervous system, where it plays a key role in brain plasticity.[16] BDNF plasma concentrations have been associated with acute neuronal damage, stroke, and worse cognition in dementia.[34–36] We did not find an association between BDNF plasma concentrations and long-term cognitive or functional impairment. This may indicate that plasma concentrations in critically ill patients, on average, cannot differentiate between the protective effects of increased BDNF availability in the brain versus the harm from increased neuronal structural damage. Thus, BDNF plasma concentration does not appear to be a clinically useful marker of cognitive outcomes after critical illness.

During sepsis and other conditions causing acute critical illness, inflammatory mediators bind to receptors on the endothelium and lead to changes in cell adhesion, microvascular thrombosis, vasomotor function, and permeability.[37, 38] Endothelial dysfunction has been associated with impaired cerebral microvascular blood flow, increased cerebral microvascular permeability, and BBB dysfunction.[39, 40] Endothelial cell changes have also been demonstrated in the setting of BBB and neurological injury, as well as critical illness polyneuropathy.[41, 42] In this heterogeneous critically ill cohort with multiple diagnoses, elevated E-selectin, a cell adhesion molecule involved in leukocyte activation that is released during endothelial injury, was associated with worse global cognition at 3 and 12 months. In contrast, PAI-1, a marker of microvascular thrombosis and fibrinolysis, was not associated with outcomes. These disparate findings may indicate that cellular adhesion and leukocyte transmigration during critical illness are more contributory to subsequent brain dysfunction than disturbed coagulation pathways. Interestingly, the long-term cognitive effects associated with endothelial dysfunction are influenced less by IL-6 than BBB injury pathways. This may indicate that an inflammatory threshold to cause endothelial injury pathways to occur is ubiquitous in critically ill patients (and that increase above that threshold does not change endothelial pathway performance) but that greater systemic

inflammatory insults are synergistic with BBB injury pathways. Overall, our results complement and extend those of previous studies showing that endothelial dysfunction is associated with brain dysfunction.[10, 11, 43, 44] Thus, this growing body of evidence supports that microcirculatory blood flow abnormalities from endothelial dysfunction contribute to both delirium in the hospital and cognitive impairment after discharge.

Our investigation was strengthened by a number of factors that warrant comment. We enrolled critically ill patients in medical and surgical ICUs with a broad range of diagnoses, which increases generalizability of our findings. We examined a complimentary array of plasma markers selected based on previous research findings associations with acute brain dysfunction during critical illness and because they reflect multiple components of BBB, neuronal, and endothelial injury that we hypothesized are mechanisms of cognitive impairment in this population. Neuropsychology professionals who were blinded to hospital course and biomarker data assessed patients for cognitive impairment and disability up to a full year after discharge using robust and widely validated testing measures. A large sample size allowed us to use multivariable regression to adjust for potential confounders while minimizing the possibility of overfitting.

Notable limitations of our investigation include the measurement of biomarkers only once at enrollment, which was early in the course of critical illness. This approach allowed us to determine whether early differences in biomarkers of these injury pathways are associated with subsequent long-term impairments, but we could not assess whether differences at later time points or if specific trajectories are better predictors of cognitive outcomes. Subsequent work should determine whether markers of BBB and endothelial injury change over time in response to disease progression and/or medical therapy and whether such changes affect associations with long-term outcomes. One possibility that should be examined is that BBB damage occurs early during critical illness whereas neuronal damage occurs later (and was therefore not detected in our study). We did not directly assess BBB, neuronal, or endothelial injury in the brain, but we did rely on well-validated circulating measures of these injury pathways, which previous studies have shown to reflect processes in the brain. By focusing on these specific mechanistic pathways, we chose not to investigate other potential biomarkers of interest (e.g., tau protein and beta-amyloid for neurodegeneration). Some markers of neurologic injury may be elevated in the plasma without overt BBB injury, as entry can occur via additional transport mechanisms (e.g., the glymphatic pathway), but unlikely to the levels witnessed in our cohort based on preliminary research.[45] To avoid overfitting our statistical models, we chose to include only one marker of systemic inflammation (IL-6) but acknowledge that an array of inflammatory and anti-inflammatory markers may be relevant. It should also be noted that due to our analysis cohort including only survivors of critical illness, survivor bias may exist, although we suspect this would bias our results towards the null.

In conclusion, this prospective cohort study of critically ill medical and surgical patients found that S100B, a marker BBB and/or astrocyte injury, was associated with long-term cognitive impairment after critical illness. E-selectin, a cell adhesion molecule and marker of endothelial injury, was also associated with cognitive impairment after critical illness. These findings support the hypothesis that injury to the BBB and endothelium during critical

illness contribute to worse outcomes after critical illness. Subsequent investigations—which should evaluate trajectories of these biomarkers, assess their utility in prediction rules, correlate their levels with neuroimaging findings, and examine whether long-term cognition after critical illness can be improved by interventions that modulate the BBB and endothelium (e.g., free radical scavengers, exercise protocols, antiepileptic medications, calcium channel and angiotensin receptor blockers, statins)—are needed before the observed relationships can be fully understood.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Take-home message**

In a large cohort of critically ill patients, S100B, a marker of BBB and/or astrocyte injury, and E-selectin, a cell adhesion molecule and marker of endothelial injury, were associated with cognitive impairment and disability. BBB and endothelial injury during critical illness likely contribute to worse outcomes after discharge, indicating that further studies of the contribution of BBB and endothelial injury to outcomes after critical illness are needed, including trials examining whether modulation of the BBB and endothelium can improve outcomes.

**Tweet**

Blood-brain barrier and endothelial injury biomarkers during critical illness are associated with long-term cognitive impairment

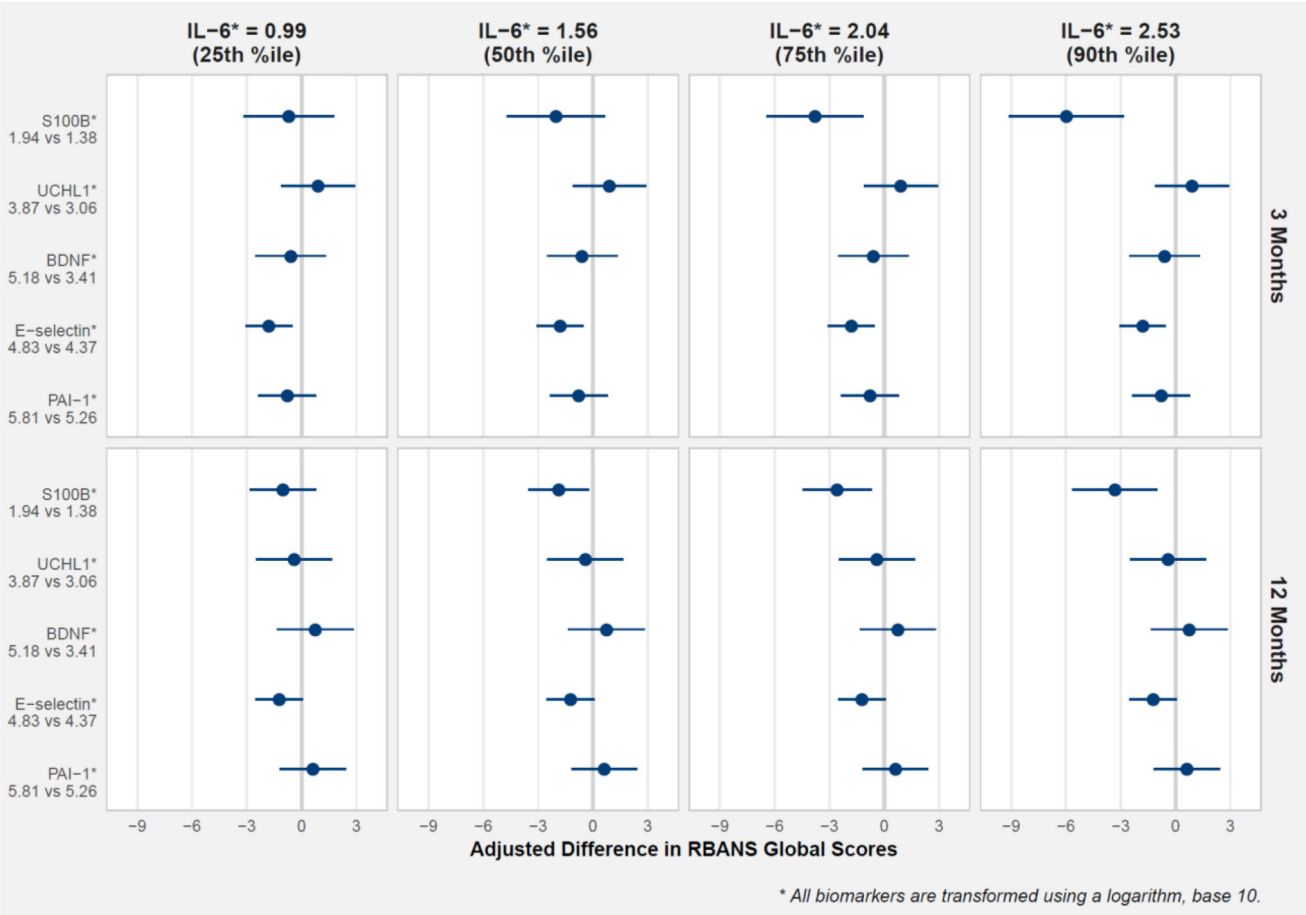


**Fig. 1. Associations of Biomarkers versus Global Cognition by Inflammation**

Displayed are the adjusted differences and 95% confidence intervals in RBANS global scores when the specified biomarker increased from the 25$^{th}$ percentile value to the 75$^{th}$ percentile value, representative of increased blood-brain barrier, neuronal, or endothelial injury. A negative adjusted difference indicates that higher biomarker concentration (i.e., worse injury) was associated with worse global cognition. Some of these associations were modified by IL-6 plasma concentration (e.g., that between S100B and RBANS global score). We, therefore, display the adjusted differences in global cognition at our cohort's 25$^{th}$, 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentiles of IL-6. A similar figure for those values of age can be found in the online supplement. Abbreviations: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

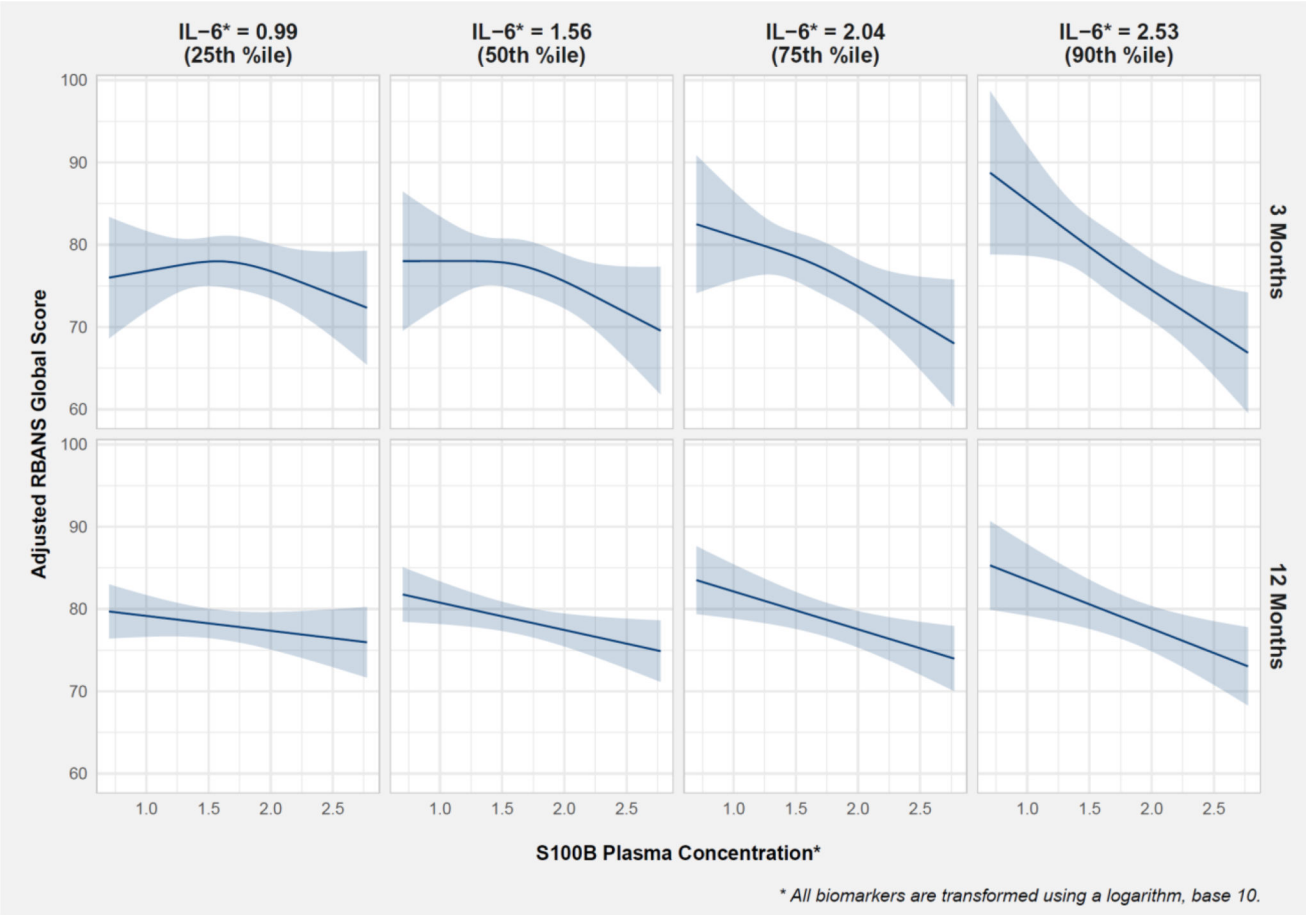


**Fig. 2. S100B versus Global Cognition by Inflammation**

Higher S100B plasma concentrations were significantly associated with RBANS global score at 3 months (P=0.008) and 12 months (P=0.01). This association was modified by IL-6 plasma concentration (and to a lesser extent age) at both time points. We, therefore, display the association between S100B and global cognition at our cohort's 25$^{th}$, 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentiles of IL-6. A similar figure for those values of age can be found in the online supplement. The solid lines demonstrate the point estimates of the association between S100B and RBANS global score, with the ribbons indicating the 95% confidence intervals. Abbreviations: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

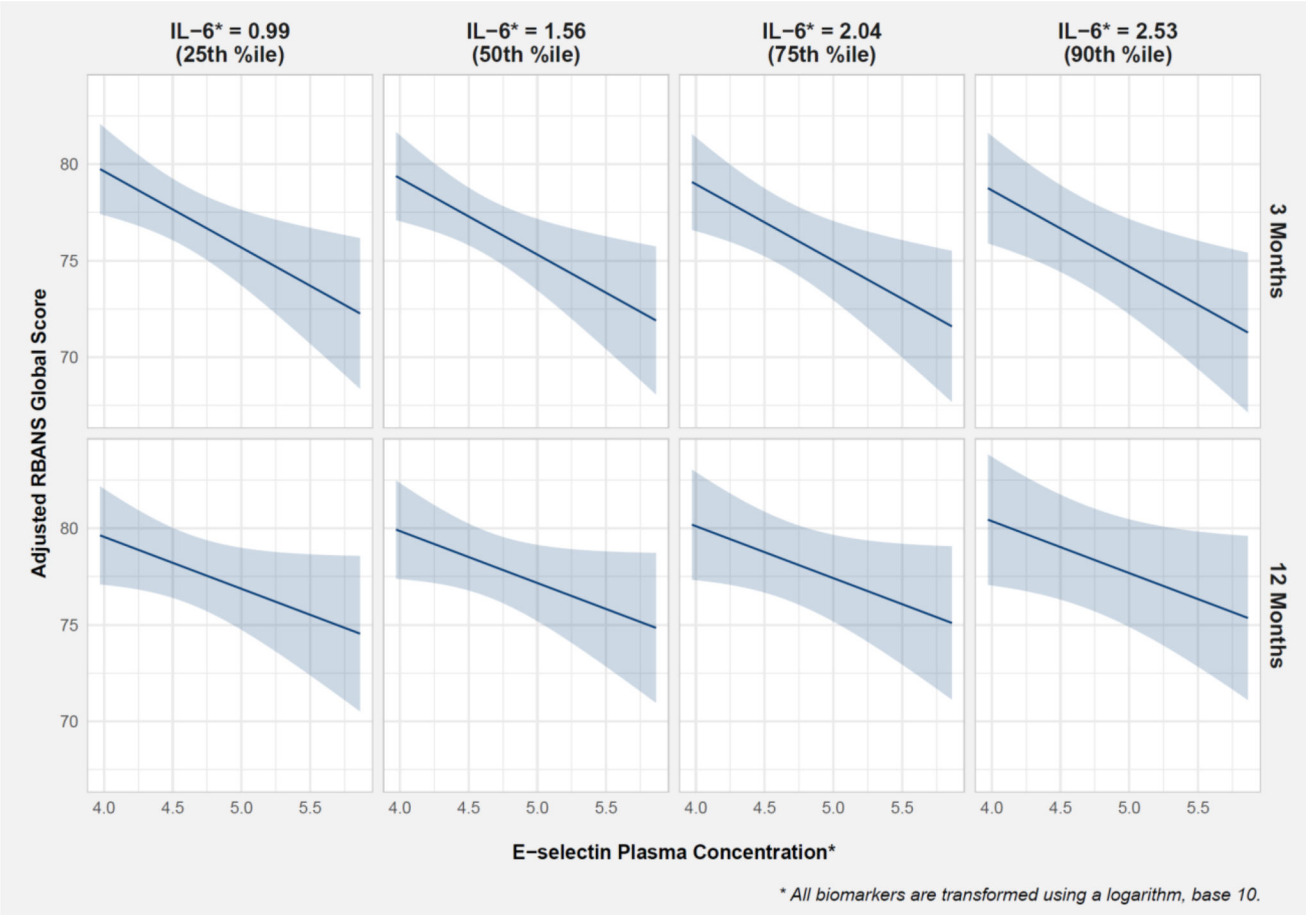


**Fig. 3. E-selectin versus Global Cognition by Inflammation**

Higher E-selectin plasma concentrations were significantly associated with worse RBANS global scores at 3 months (P=0.006) and marginal at 12 months (P=0.06). We display the association between E-selectin and global cognition at our cohort's 25$^{th}$, 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentiles of IL-6. A similar figure for those values of age can be found in the online supplement. The solid lines demonstrate the point estimates of the association between E-selectin and RBANS global score, with the ribbons indicating the 95% confidence intervals. Abbreviations: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

**Table 1**

Characteristics and Outcomes of Study Population

| Characteristic* | N=419 |
|---|---|
| Age at enrollment, years | 59 (48–69) |
| White race, N (%) | 368 (88%) |
| Male sex, N (%) | 215 (51%) |
| Education, years | 12 (12–14) |
| IQCODE-SF at enrollment | 3 (3.00–3.06) |
| Katz ADL at enrollment | 0 (0–1) |
| FAQ at enrollment | 0 (0–2) |
| Clinical Frailty Scale at enrollment, N (%) | |
| ▪ Very fit | 20 (5%) |
| ▪ Well | 77 (18%) |
| ▪ Well, treated comorbid disease | 138 (33%) |
| ▪ Apparently vulnerable | 82 (20%) |
| ▪ Mildly frail | 54 (13%) |
| ▪ Moderately frail | 42 (10%) |
| ▪ Severely frail | 6 (1%) |
| Charlson comorbidity index | 2 (1–4) |
| Framingham stroke risk | 9 (5–14) |
| SOFA score at ICU admission | 9 (7–12) |
| APACHE II at ICU admission | 25 (19–30) |
| ICU type | |
| ▪ Medical | 265 (63%) |
| ▪ Surgical | 154 (37%) |
| IL-6 at enrollment, ng/mL | 35.6 (9.6–108.3) |
| Severe sepsis in the ICU, N (%) | 271 (65%) |
| ▪ Duration among exposed, days | 4 (2–8.5) |
| Mechanical ventilation, N (%) | 382 (91%) |
| ▪ Duration among exposed, days | 2.3 (1.0–6.0) |
| Delirium, N (%) | 320 (76%) |
| ▪ Duration among exposed, days | 3 (2–6.5) |
| Coma, N (%) | 239 (57%) |
| ▪ Duration among exposed, days | 3 (1–5) |
| ICU length of stay, days | 4.9 (2.6–10.1) |
| Hospital length of stay, days | 10.8 (6.3–18.1) |
| RBANS global score | |
| ▪ 3-month follow-up (N=340) | 79 (70–86) |
| ▪ 12-month follow-up (N=295) | 80 (71–87) |
| Trails B T-score | |
| ▪ 3-month follow-up (N=353) | 41 (33–49) |
| ▪ 12-month follow-up (N=300) | 42 (35–50) |

| Characteristic* | N=419 |
|---|---|
| Katz ADL score | |
| ▪ 3-month follow-up (N=391) | 0 (0–1) |
| ▪ 12-month follow-up (N=341) | 0 (0–1) |
| FAQ score | |
| ▪ 3-month follow-up (N=385) | 3 (0–9) |
| ▪ 12-month follow-up (N=339) | 2 (0–8) |

*Median (interquartile range) or N (percentage).

Participant characteristics and cognitive and functional outcomes of the cohort at 3 and 12 months are displayed. The RBANS has a mean (standard deviation) population age-adjusted score of 100±15 with lower scores indicating worse global cognitive function. For comparison, reported mean scores among patients with moderate traumatic brain injury and mild Alzheimer's disease were 78 and 70, respectively. The Trails B has an age-, sex-, and education-adjusted mean score of 50±10 with lower scores indicating worse executive function. A Katz ADL or FAQ score greater than 0 indicates disability in at least one domain of daily living. The median RBANS global cognition scores were approximately 1.5 standard deviations below adjusted population mean, a level indicative of significant cognitive impairment. The median Trails B executive function scores were approximately 1 standard deviation below adjusted population mean. The median functional scores demonstrated some dependence in instrumental ADLs (FAQ score) but not on basic ADLs (Katz ADL score).

Abbreviations: ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; FAQ, Functional Activities Questionnaire; ICU, intensive care unit; IQCODE-SF, Short Form Informant Questionnaire on Cognitive Decline in the Elderly; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SOFA, Sequential Organ Failure Assessment.

## Table 2

Mean Plasma Concentrations of Neurologic and Endothelial Injury Biomarkers

| Biomarker | Cohort | Healthy Controls |
|---|---|---|
| S100B, pg/mL | 159 ± 1185 | 21 ± 36 |
| UCHL1, pg/mL | 5331 ± 6102 | 120 ± 20 |
| BDNF, ng/mL | 122 ±185 | 28.1 ± 8.9 |
| E-selectin, ng/mL | 117 ± 450 | 0.92 ± 0.66 |
| PAI-1, ng/mL | 626 ± 908 | 15.7 ± 11.7 |

* Concentrations are reported as mean ± standard deviation

Mean plasma concentrations of neurologic and endothelial injury biomarkers at enrollment in this critically ill cohort were elevated relative to previously published values for similarly aged healthy control subjects.[33, 46–49] Abbreviations: BDNF, brain-derived neurotrophic factor; PAI-1, plasminogen activator inhibitor-1; UCHL1, ubiquitin C-terminal hydrolase L1