Association of Central Nervous System-Related Biomarkers With Hospital Delirium in Patients With Respiratory Failure in the ICU

Andrew T. Pham, MD; Ryan A. Peterson, PhD; Suzanne Slaughter, MS; Morgan Martin, BS; Joseph A. Hippensteel, MD; and Ellen L. Burnham, MD

BACKGROUND: Delirium commonly occurs in critical illness and is associated with significant morbidity and mortality. Although risk reduction measures can mitigate the risk of delirium, identifying patients in whom delirium will develop remains clinically challenging.

RESEARCH QUESTION: In critically ill patients with respiratory failure, are central nervous system (CNS)-related biomarkers measured at admission associated with delirium diagnosis?

STUDY DESIGN AND METHODS: We performed a secondary analysis of a cohort of patients with respiratory failure in the medical ICU enrolled at a single medical center. Using serum collected at ICU admission, we measured CNS-related biomarkers including brain-derived neurotrophic factor (BDNF), chitinase-3-like protein 1, glial fibrillary acidic protein, neurofilament light chain (NF-L), neurogranin, S100 calcium-binding protein B, and triggering receptor expressed on myeloid cells 2 via a multiplex immunoassay. The primary outcome was diagnosis of in-hospital delirium, defined using validated methods. Associations between individual biomarkers and delirium diagnosis were examined using multivariable logistic regressions, adjusting for factors known to predispose and precipitate delirium. Secondary outcomes included in-hospital mortality, ventilator-free days, ICU-free days, and hospital-free days.

RESULTS: Serum biomarkers were measured in 100 patients. Delirium occurred in 73% of the cohort. Patients with vs without delirium did not differ significantly in terms of age, sex, comorbidities, severity of illness, or unhealthy alcohol use. After adjustment, NF-L was associated positively with delirium diagnosis (adjusted OR, 1.86; 95% CI, 1.09-3.43), whereas BDNF was associated negatively with delirium (adjusted OR, 0.43; 95% CI, 0.15-0.82). No associations were found between other measured biomarkers and delirium diagnosis. NF-L levels were associated negatively with ICU-free and hospital-free days.

INTERPRETATION: Our results indicate that CNS-related biomarkers measured at ICU admission are associated with delirium diagnosis in critically ill patients. Prospective investigations are necessary to validate the role of these biomarkers in predicting delirium.

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KEY WORDS: alcohol; brain-derived neurotrophic factor; critical illness; neurofilament light chain

Take-Home Points

Study Question: In critically ill patients with respiratory failure, are central nervous system (CNS)-related biomarkers measured at admission associated with delirium diagnosis?

Results: After adjustment for factors associated with development of delirium, neurofilament light chain was associated positively with delirium, whereas brain-derived neurotrophic factor was associated negatively with delirium in critically ill patients.

Interpretation: CNS-related biomarkers measured at ICU admission may be possible adjuncts in delirium prediction and also may support efforts to subcategorize patients with ICU delirium to investigate outcomes and pathophysiologic features.

Delirium is a clinical syndrome defined by acute onset of inattention, decreased awareness, and reduced cognition that fluctuates over time. It is a direct consequence of certain medical conditions, substance intoxication or withdrawal, or toxin exposure or can be multifactorial.[1] Major predisposing factors for delirium include older age, comorbidities, and alcohol misuse.[2,3] Precipitants include acute illnesses (eg, sepsis), along with benzodiazepine and opioid administration.[4,5] Although common in all hospital settings, delirium is particularly prevalent among patients admitted to the ICU. In mechanically ventilated patients in the ICU, up to 80% of patients may demonstrate delirium.[6,7] Importantly, delirium is associated with increased mortality, reduced odds of home discharge, and development of long-term cognitive impairment.[6,8-10]

Given the lack of effective pharmacologic treatments,[10,11] strategies to prevent delirium are paramount. Bundled therapeutic strategies for critically ill patients recommend avoiding deliriogenic medications and assessing and treating pain,[10] which reduce the odds of delirium and mortality.[12] Despite this efficacy, implementation barriers remain, including increased workload perception of medical staff.[13,14] Targeting risk reduction strategies toward higher-risk patients could address these barriers, although it remains challenging to predict which patients are at highest risk of delirium.

Although promising, clinical ICU delirium prediction models have not been adopted widely because of their burdensome performance characteristics and limited positive predictive value.[15,16] Prior studies have examined associations between circulating biomarkers and delirium, including nonspecific inflammatory markers, and central nervous system (CNS)-related biomarkers thought to reflect delirium pathophysiologic characteristics.[17-19] Notably, among studies of CNS-related biomarkers, most have examined neuron axonal injury markers,[20] despite the possibility that other cell types may contribute to delirium (eg, astrocytes, microglia[19]).

Accordingly, we examined a panel of biomarkers representing unique CNS components in association with hospital delirium diagnosis, including brain-derived neurotrophic factor (BDNF), chitinase-3-like protein 1 (CHI3L1), glial fibrillary acidic protein (GFAP), neurofilament light chain (NF-L), neurogranin, S100 calcium-binding protein B (S100B), and triggering receptor expressed on myeloid cells 2. We sought to determine if biomarkers at time of ICU admission among patients with respiratory failure would be associated with a subsequent delirium diagnosis, accounting for factors including age, severity of illness, and alcohol misuse.

Study Design and Methods

See e-Appendix 1 for full methods.

ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; AUC = area under the receiver operating characteristic curve; BDNF = brain-derived neurotrophic factor; CAM = Confusion Assessment Method; CCI = Charlson Comorbidity Index; CHI3L1 = chitinase-3-like protein 1; CNS = central nervous system; EHR = electronic health record; GFAP = glial fibrillary acidic protein; LASSO = least absolute shrinkage and selection operator; NF-L = neurofilament light chain; ROC = receiver operating characteristic; S100B = S100 calcium-binding protein B; TREM2 = triggering receptor expressed on myeloid cells 2

AFFILIATIONS: From the Division of General Internal Medicine (A. T. P.), Department of Medicine, the Department of Biostatistics and Informatics (R. A. P.), Colorado School of Public Health, and the Division of Pulmonary Sciences and Critical Care Medicine (S. S., M. M., J. A. H., and E. L. B.), Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO.

Drs Hippensteel and Burnham contributed equally to this manuscript.

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CORRESPONDENCE TO: Ellen L. Burnham, MD; email: ellen.burnham@cuanschutz.edu

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Patient Enrollment and Study Protocol

This investigation was performed in a subset of patients enrolled between January 2020 and January 2024 in a single-center prospective observational cohort study conducted at an academic medical center in Aurora, Colorado. The parent study was approved by the Colorado Multiple Institutional Review Board (COMIRB Identifier: 14-0630) with substudy approval for this investigation (COMIRB Identifier: 23-1631).

Patients admitted to the medical ICU for respiratory failure were enrolled. Eligibility criteria included acute respiratory failure requiring invasive mechanical ventilation, expectation of need for ICU-level care for $>$ 48 hours, and diagnosis of a primary pulmonary condition (eg, pneumonia, aspiration). Exclusion criteria included patients expected to survive for $<$ 48 hours, incarcerated people, those with an ongoing pregnancy, those with a diagnosis of a condition associated with immunosuppression (eg, lymphoma, prior transplantation), those with active use of immunosuppressive agents (eg, prednisone), or those with a preexisting prescription for home oxygen.

Trained research coordinators collected data from the electronic health record (EHR). Charlson Comorbidity Index (CCI)[21] was tabulated to quantify underlying comorbidities and Acute Physiology and Chronic Health Evaluation (APACHE) II[22] score on ICU admission was used to estimate baseline severity of illness. Blood samples were obtained within 24 hours of ICU admission. After centrifugation, CNS-related biomarkers were measured in serum, whereas RBC phosphatidylethanol was measured as an indicator of alcohol misuse (values $\geq$ 250 ng/mL).[23] Patients with admission hemoglobin of $<$ 8 g/dL or who required transfusions were excluded from blood collection.

Given the relationship between centrally acting medications and delirium,[3] days of medications administered for sedation and pain were abstracted. Sedative days were defined as the sum of days patients received infusions of benzodiazepines (midazolam and lorazepam), propofol, ketamine, dexmedetomidine, or a combination thereof. Opioid days were defined as the sum of days when patients received continuous infusions of medications that included morphine, hydromorphone, fentanyl, or a combination thereof. One administration day was considered to be present if the patient received an infusion for $\geq$ 1 hour of $\geq$ 1 of these medications within a 24-hour period.

Haloperidol administration and physical restraint days were abstracted for the duration of patients' hospital stays to corroborate delirium diagnosis.[24,25] Haloperidol days were defined by administration of at least 1 IV dose within a 24-hour period for any indication. Restraint days were assessed by the occurrence of restraint orders placed within a 24-hour period.

A retrospective delirium assessment was performed, using a strategy adapted from the Chart-Based Delirium Identification Instrument (CHART-DEL)[26] and its counterpart for ICU patients (CHART-DEL-ICU)[27], both of which have been validated.[28-30] In prior studies, CHART-DEL sensitivity and specificity were 74% and 83%, respectively; for CHART-DEL-ICU, they were 66% and 82%, respectively. Two trained research coordinators independently reviewed each EHR to assess for delirium. Patients were assigned definite delirium categorization if a delirium diagnosis was documented in the EHR by a provider experienced in identification of delirium, including physicians, advanced practice providers, nurses, or physical and occupational therapists. Probable delirium status was assigned to patients with $\geq$ 1 positive Confusion Assessment Method (CAM) or CAM for the ICU scores on $\geq$ 1 day, with supporting features of delirium, but no explicit diagnosis of delirium. Supporting features of delirium included the terms *encephalopathy*, *hallucinations*, or *delusions*; documentation of disordered or disorganized thinking; and evidence of symptom(s) reversibility.[31] Possible delirium included patients with a single positive CAM or CAM for the ICU score, supportive terms as mentioned above, or a single Richmond Agitation-Sedation Scale score of +2 to +4. Patients were assigned unable to determine delirium status when documentation was ambiguous regarding patient encephalopathy and CAM documentation was not present. Finally, patients with no evidence for delirium or who had multiple negative CAM or CAM for the ICU scores were categorized as no delirium. Discrepant categorizations between the 2 coordinators were adjudicated by 1 of the authors. For the primary and secondary analyses, individuals with definite delirium, probable delirium, or possible delirium were combined to represent a delirium diagnosis.[26]

In the subset of patients categorized with definite delirium, the first date of delirium was ascertained separately by 2 trained research team members. When dating discrepancies occurred, the first date of delirium was determined by consensus, led by a clinician author. Date of first delirium diagnosis was not ascertained for patients categorized with probable or possible delirium because of an absent clinical diagnosis of delirium in the EHR contributing to ambiguity. Numbers of days between hospital admission and

first delirium diagnosis were calculated. A threshold of 11 days was used to delineate patients into early vs late subgroups, because acute clinical features become less predictive of outcomes after 11 days.[32]

Patient serum aliquots were analyzed using an Ella Automated Immunoassay System (Bio-Techne) to assess potential aberrations in neural plasticity (BDNF), neurons (NF-L, neurogranin), glia (S100B, CHI3L1, and triggering receptor expressed on myeloid cells 2 [TREM2]), and astrocytes (GFAP), based on known pathophysiologic features of delirium.[19] Each sample was measured in triplicate.

Statistical Analysis

Individual biomarker values were assessed for association with delirium diagnosis, which was the primary outcome. Secondary outcomes included ventilator, ICU, and hospital-free days as well as in-hospital mortality and discharge disposition.

Biomarkers were log-transformed (base 2) before analysis because of right skew. In stratified analysis by delirium, Mann-Whitney Wilcoxon tests were used to assess for distributional differences in continuous variables, and Fisher exact tests were used for categorical variables. Pairwise associations between biomarkers were assessed using scatterplots and Pearson correlation coefficients.

Each biomarker was tested individually for its association with delirium via Mann-Whitney Wilcoxon tests. The relationships of biomarkers to outcomes were assessed with logistic or ordinal logistic regression as appropriate. Each biomarker also was assessed via a receiver operating characteristic (ROC) curve, which was summarized using the area under the ROC curve (AUC), and the decision rule (ie, the best biomarker threshold) that maximized the sum of the sensitivity and specificity.

Multivariable logistic regression models chosen a priori were constructed for each biomarker to assess its association with delirium (primary outcome) and in-hospital mortality (secondary outcome) adjusting for confounders including age, CCI, phosphatidylethanol of $\geq$ 250 ng/mL, and admission APACHE II score. Separate models were developed including sedative and opioid days as covariates to assess how medication exposure may have impacted these associations. Both unadjusted and multivariable logistic regression models used profile likelihood CIs and likelihood ratio tests for inference on model coefficients. The exponentiated model coefficients of interest are adjusted ORs. Each biomarker was included in a multivariable model separately to facilitate interpretation and to avoid overfitting. A sensitivity analysis examining the relationship between individual biomarkers and delirium also was conducted, limited to patients with early ($<$ 11 days) definite delirium and patients with no delirium.

Additionally, all biomarkers and covariates were assessed jointly as candidate independent risk factors for delirium using a least absolute shrinkage and selection operator (LASSO)-penalized logistic regression to select and estimate the effects of the most important features[33] using 10-fold cross-validated deviance. In-sample predicted probabilities from this LASSO model were used to construct an ROC curve.

For additional secondary length-of-stay outcomes (ventilator-free, ICU-free, and hospital-free days), proportional-odds ordinal regression models were used. These models assume that the associations of each confounder and log-transformed biomarker with higher vs lower outcome values were proportional across the outcome range.

R version 4.4.0 software (R Core Team) was used for all analyses. Hypothesis tests were determined to be statistically significant if P values were $<$ .05. Because the study was exploratory, P values are presented without adjustment for multiple comparisons to identify potential biomarkers for further research.

Results

Patient Characteristics and Outcomes

Between January 2020 and January 2024, 130 patients were enrolled consecutively and underwent a delirium assessment. Four patients had discrepant delirium classifications requiring adjudication. Because of practical constraints including no available blood sample (n = 7), cost, and available multiplex plate configurations, serum biomarker analyses were performed in a convenience sample of 100 patients. Delirium characterization was not significantly different between the patients with and without biomarker measures (P = .10,) (e-Appendix 1, e-Table 1), although patients without biomarker measures were younger and had fewer comorbidities. Among the 100 patients with

measured biomarkers, 8 patients were unable to have delirium classified and were excluded from primary outcome analyses. The remaining 92 patients had either definite (n = 49), probable (n = 15), or possible (n = 9) delirium. These 3 categories were combined, leading to a total of 73 patients with evidence of delirium in the cohort, whereas 19 patients were classified as having no delirium (Table 1).

In patients with or without evidence of delirium, baseline demographic characteristics, underlying comorbid conditions, admission APACHE II scores, and COVID-19 positivity rates did not differ. The proportion of patients with alcohol misuse was numerically greater among patients who demonstrated delirium. During hospitalization, patients with delirium received sedatives, opioids, and haloperidol for a significantly greater number of days and had more days with restraints ordered (Table 1). Although in-hospital mortality and ventilator-free, ICU-free, and hospital-free days were not significantly different between the no delirium and delirium groups, total ventilator-free, ICU-free, and hospital-free days were numerically higher in the delirium group (e-Appendix 1, e-Table 2).

TABLE 1] Patient Enrollment Characteristics and In-Hospital Interventions Grouped by Delirium Diagnosis

Variable	Overall (N = 100)	Delirium (n = 73)	No Delirium (n = 19)	*P* Value[a]	Unable to Determine Delirium (n = 8)
Baseline characteristics					
Age, y	55 (14)	56 (14)	54 (17)	.4	52 (12)
Sex at birth				.066	
Female	24 (24%)	14 (19%)	8 (42%)		2 (25%)
Male	76 (76%)	59 (81%)	11 (58%)		6 (75%)
Ethnicity				.4	
Hispanic or Latino	45 (45%)	35 (49%)	7 (37%)		3 (38%)
Not Hispanic or Latino	54 (54%)	37 (51%)	12 (63%)		5 (63%)
Unknown/declined to answer	1	1	0		0
Race (self-reported)				.8	
American Indian or Alaskan Native	1	1 (1.4%)	0		0
Black	10 (10%)	7 (9.9%)	1 (5.3%)		2 (25%)
Don't know	2 (2%)	2 (2.8%)	0		0
Asian/Pacific Islander	3 (3%)	1 (1.4%)	1 (5.3%)		1 (13%)
White	82 (82%)	60 (85%)	17 (89%)		5 (63%)
Unknown/declined to answer	2 (2%)	2 (2.7%)	0		0
Charlson Comorbidity Index	2.00 (1.82)	2.08 (1.80)	1.84 (1.98)	.5	1.63 (1.77)
APACHE II score at admission	19 (8)	19 (8)	18 (9)	.4	20 (6)
Unknown	0	1	0		0
Creatinine, mg/dL	1.64 (1.92)	1.69 (2.09)	1.10 (0.63)	.5	2.41 (2.24)
BMI, kg/m^2	32 (10)	32 (10)	33 (8)	.2	36 (12)
COVID-19 positivity	57 (57%)	40 (55%)	12 (63%)	.6	5 (63%)
Phosphatidylethanol ≥ 250 ng/mL	35 (35%)	28 (38%)	4 (21%)	.2	3 (38%)
In-hospital interventions					
Sedative days	20 (21)	23 (22)	10 (11)	< .001	17 (22)
Opioid days	11 (9)	12 (10)	5 (4)	< .001	7 (5)
Haloperidol days	0.76 (1.75)	0.99 (2.00)	0.05 (0.23)	.011	0.38 (0.52)
Total No. of days restraints were ordered	13 (12)	16 (13)	5 (3)	< .001	5 (5)

Data are presented as No. (%) or mean (SD). APACHE = Acute Physiology and Chronic Health Evaluation.
[a]Fisher exact test, Wilcoxon rank-sum test comparing delirium and no delirium groups. Unable to determine delirium group excluded from *P* value calculations.

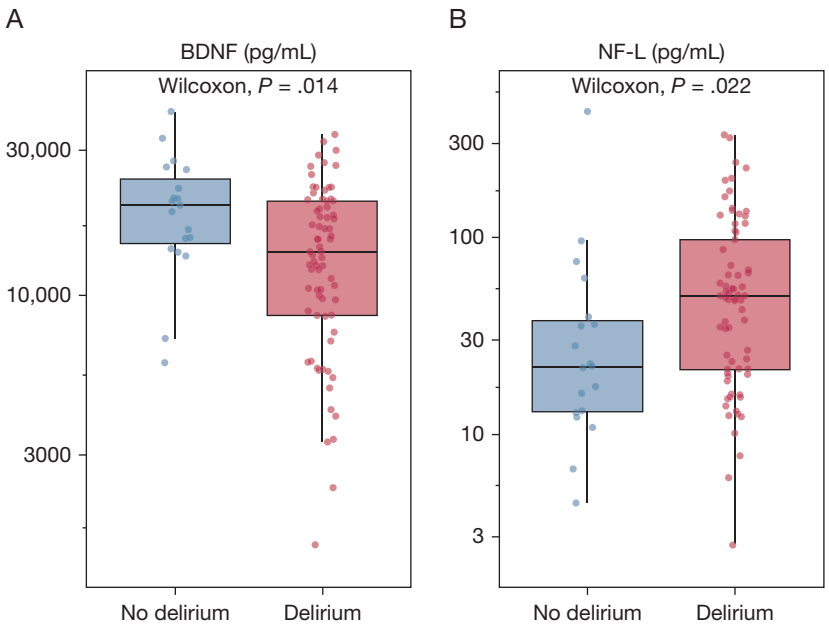

Figure 1 – *A, B, Distribution boxplots for notable CNS-related biomarkers in patients with and without delirium: BDNF (A) was lower in patients with delirium (median, 13,941pg/mL vs 19,764 pg/mL), and NF-L (B) was higher in patients with delirium (median, 50 pg/mL vs 22 pg/mL). BDNF = brain-derived neurotrophic factor; CNS = central nervous system; NF-L = neurofilament light chain.*

Biomarker Associations With Delirium Diagnosis

Measures of biomarkers at ICU admission (Fig 1) indicated that patients who demonstrated delirium showed significantly lower levels of BDNF ($P = .014$) and significantly higher levels of NF-L ($P = .022$). CHI3L1, GFAP, neurogranin, S100B, and TREM2 did not differ between groups.

In unadjusted multivariable logistic regression models, BDNF and NF-L were associated significantly with hospital delirium diagnosis (Table 2). In models adjusting for variables including age, alcohol misuse, admission severity of illness, and CCI, both BDNF (adjusted OR, 0.38; 95% CI, 0.15-0.82) and NF-L (adjusted OR, 1.86; 95% CI, 1.09-3.43) remained associated with delirium. Secondary models adjusting for these same variables and variables including opioid and sedation days revealed significant associations between BDNF, NF-L, and CHI3L1 with delirium diagnosis. Full results are presented in e-Table 3.

The optimal LASSO model identified BDNF and NF-L as the most important factors associated with delirium according to cross-validated error (e-Appendix 1, e-Fig 1). That is, only BDNF and NF-L independently improved classification of patients' delirium status,

TABLE 2] Unadjusted and Adjusted Multivariable Logistic Regression Models Evaluating Association Between Serum CNS-Related Biomarkers and Delirium

	Unadjusted			Adjusted for Delirium Risk Factors Before Hospitalization[a]			Adjusted for Delirium Risk Factors Before and During Hospitalization[b]		
Serum Biomarker	OR	95%CI	*P* Value	Adjusted OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
BDNF	0.40	0.17-0.81	.009	0.38	0.15-0.82	.011	0.43	0.17-0.91	.025
CHI3L1	1.24	0.93-1.71	.15	1.22	0.86-1.77	.3	2.03	1.24-3.64	.004
GFAP	1.16	0.84-1.66	.4	1.08	0.75-1.60	.7	1.15	0.78-1.75	.5
NF-L	1.50	1.04-2.23	.028	1.86	1.09-3.43	.021	1.72	1.02-3.13	.042
Neurogranin	1.16	0.78-1.81	.5	1.09	0.71-1.74	.7	1.13	0.72-1.88	.6
S100B	1.14	0.79-1.68	.5	1.09	0.73-1.66	.7	1.15	0.76-1.81	.5
TREM2	1.05	0.55-2.02	.9	0.90	0.43-1.84	.8	0.72	0.31-1.56	.4

BDNF = brain-derived neurotrophic factor; CHI3L1 = chitinase-3-like protein 1; CNS = central nervous system; GFAP = glial fibrillary acidic protein; NF-L = neurofilament light chain; S100B = S100 calcium-binding protein B; TREM2 = triggering receptor expressed on myeloid cells 2.
[a]Age, phosphatidylethanol ≥ 250 ng/mL, Charlson Comorbidity Index, and admission Acute Physiology and Chronic Health Evaluation II score.
[b]Age, phosphatidylethanol ≥ 250 ng/mL, Charlson Comorbidity Index, admission Acute Physiology and Chronic Health Evaluation II score, sedative days, and opioid days.

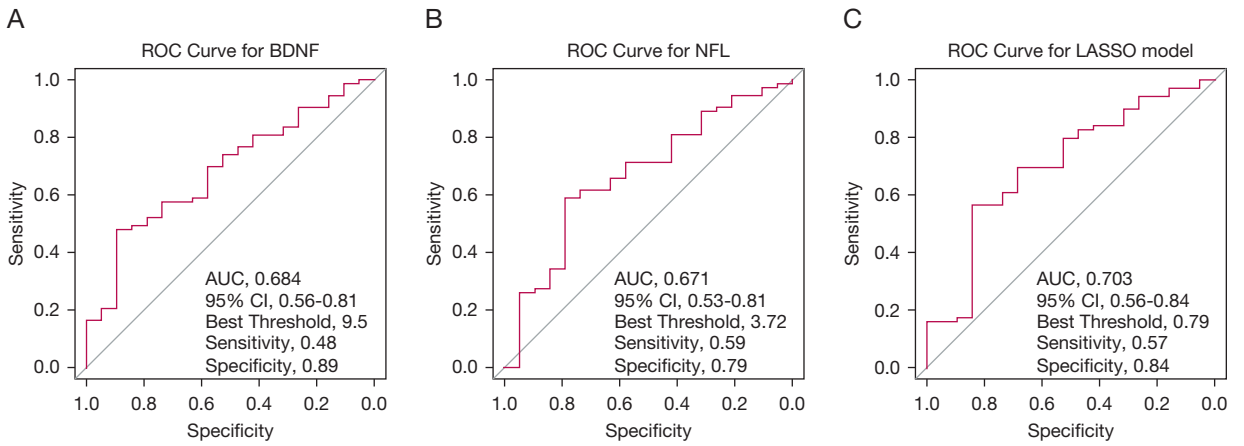

Figure 2 – *A-C, ROC curves showing association with delirium diagnosis using BDNF (A), which achieves an AUC of 0.684; NF-L (B), which achieves AUC 0.671; and BDNF and NF-L combined (C), which were selected exclusively to achieve optimal cross-validation error with the LASSO model, which achieves an AUC of 0.703. In this combined model, for every doubling of BDNF, the log odds of delirium decreased by 0.32 (or the odds of delirium decreased by a factor of 0.72, a 28% decrease) holding NF-L constant. Similarly, for every doubling of NF-L (holding BDNF constant), the log odds of delirium increased by 0.12 (or the odds of delirium increased by a factor of 1.12, a 12% increase). AUC = area under the receiver operating characteristic curve; BDNF = brain-derived neurotrophic factor; LASSO = least absolute shrinkage and selection operator; NF-L = neurofilament light chain; ROC = receiver operating characteristic.*

whereas APACHE II score, age, CCI, and all other biomarkers were not selected. Using BDNF alone achieved an AUC of 0.684, and an optimal decision rule yielded a sensitivity of 0.48 and a specificity of 0.89 (Fig 2A). Similarly, NF-L alone yielded an AUC of 0.671 with an optimal decision rule producing a sensitivity of 0.59 and a specificity of 0.79 (Fig 2B). The combined LASSO model ROC curve for these biomarkers yielded an AUC of 0.703 with sensitivity of 0.57 and specificity of 0.84 (Fig 2C).

In terms of timing the first day of delirium diagnosis, among the 49 patients with definite delirium, 6 (12%) showed discrepancies in first day of delirium that were resolved by consensus. Median time to delirium diagnosis was 8 days after ICU admission. Early delirium (before 11 days) occurred in 65% of the 49 total patients; no significant differences in biomarker values were present between early vs late groups (e-Appendix 1, e-Table 4). In a sensitivity analysis limited to patients with early delirium and patients with no delirium, the relationship between BDNF and NF-L with development of delirium was attenuated, although the magnitude and directionality of the association between these biomarkers and odds for delirium remained (e-Appendix 1, e-Table 5).

Biomarker Associations With Secondary Outcomes

In unadjusted comparisons, BDNF demonstrated a significant positive association with hospital-free days, whereas NF-L demonstrated a significant negative association with ventilator-free, ICU-free, and hospital-free days (Table 3). These relationships persisted

TABLE 3] Unadjusted and Adjusted Associations Between Serum Brain-Derived Neurotrophic Factor and Neurofilament Light Chain With Secondary Outcomes of Ventilator-Free, ICU-Free, and Hospital-Free Days

	Ventilator-Free Days			ICU-Free Days			Hospital-Free Days		
Serum Biomarker	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Unadjusted model									
BDNF	1.28	0.89-1.82	.2	1.35	0.95-1.93	.093	1.66	1.16-2.37	.005
NF-L	0.68	0.54-0.86	.002	0.62	0.48-0.79	< .001	0.56	0.44-0.72	< .001
Adjusted model[a]									
BDNF	1.25	0.85-1.84	.3	1.34	0.92-1.96	.13	1.83	1.23-2.72	.003
NF-L	0.74	0.54-1.00	.053	0.67	0.49-0.91	.012	0.58	0.42-0.80	.001

BDNF = brain-derived neurotrophic factor; NF-L = neurofilament light chain.
[a]Adjusted for age, phosphatidylethanol ≥ 250 ng/mL, Charlson Comorbidity Index, admission Acute Physiology and Chronic Health Evaluation II score, sedative days, and opioid days.

after adjustment for age, phosphatidylethanol level of ≥ 250 ng/mL, CCI, admission APACHE II score, sedative days, and opioid days, except for the association between NF-L and ventilator-free days. In adjusted comparisons, S100B was associated negatively with hospital-free days (e-Appendix 1, e-Table 6). In unadjusted models, NF-L and GFAP were associated with increased odds of in-hospital mortality (e-Appendix 1, e-Table 7). However, after adjustment for patient-related factors, severity of illness, sedative days, and opioid days, these relationships were no longer significant.

Discussion

In this exploratory investigation, we assessed the association of CNS-related biomarkers with a subsequent delirium diagnosis among high-risk critically ill patients. Using a multiplex platform to measure biomarkers thought to reflect several CNS processes, BDNF and NF-L—but not others—were associated with a diagnosis of delirium, which persisted after adjusting for risk factors. Our results suggest that circulating BDNF and NF-L are potential candidates for future CNS-related biomarker studies to identify patients at risk of ICU delirium. Measurement of BDNF, NFL, and other biomarkers also could provide an opportunity to improve precision delirium care, enabling subphenotyping of patients with delirium who may respond differentially to therapeutic strategies to improve the approach to delirium treatment.[34,35]

NF-L is an axonal-specific cytoskeletal protein of neurons. Correlations between cerebrospinal fluid and circulating levels of NF-L are reported.[36] Higher serum NF-L levels are seen in chronic neurocognitive disorders, indicating direct neuronal damage.[37] Serum NF-L measures also have been associated directly with delirium in surgical patients[38,39] and in a mixed cohort of patients treated in the medical and surgical ICU.[20] Our study adds further support to the potential usefulness of NF-L measures in a medically critically ill population, accounting for major delirium risk factors including age and alcohol use, the latter of which largely has been ignored in ICU delirium investigations.[3,36,40] BDNF is a ubiquitous neurotrophic factor in the CNS that crosses the blood-brain barrier[41] and plays a key neuroregulatory role through effects on synaptic plasticity and memory formation.[42,43] Higher circulating BDNF confers a more favorable clinical prognosis in chronic neurodegenerative diseases.[44,45] Low serum BDNF has been reported in postoperative patients who demonstrate delirium[46]; however, in nonsurgical hospitalized patients, results have been inconsistent.[47,48] Overall, our results corroborate prior evidence that both lower BDNF and higher NF-L levels are associated with delirium during acute illness, although we cannot draw conclusions about the link between these biomarkers and delirium pathophysiologic characteristics. Although BDNF and NF-L have been investigated individually in the context of delirium, we are—to our knowledge—the first to examine the 2 concurrently in a medically critically ill population. This approach both strengthens potential predictive ability and has possible biological plausibility.

Our findings are not without limitations. This was a relatively small single-center study. Patients with chronic lung conditions or who were immunosuppressed were excluded. Therefore, our findings may not generalize to these populations. In addition, although the CHART-DEL and CHART-DEL-ICU[26,27] methods have been validated previously in similar cohorts, they are retrospective tools for delirium diagnosis, and patients may have been misclassified. However, the incidence of delirium in this cohort was in line with investigations using prospective methodologies.[6,7] Additionally, patients classified with delirium showed increased antipsychotic and restraint use, supporting the validity of this approach.[25] Furthermore, although we did not collect information about coma duration, persistent associations between biomarkers and delirium when accounting for days receiving sedatives and opioids suggest that coma is unlikely to mediate these observations. Prospectively conducted investigations (including assessments of coma) would be preferable to understand the relationship between biomarkers with onset and duration of delirium. Although we did not observe differences in biomarker values between patients who demonstrated delirium earlier vs later, prospective studies likely would improve accuracy in determining when delirium first was present. The biomarkers we measured can originate from sites outside of the CNS. For example, circulating NF-L can be generated by the peripheral nervous system.[36,40] Measuring biomarkers with higher CNS specificity such as α-internexin could be explored in future studies to strengthen the validity of our observations.[36] Finally, we measured analytes at a single time point that may not fully reflect the dynamic nature of critical illness. Future prospective studies should consider serial measures to understand whether temporal trends can improve their usefulness.

The concurrent measurement of multiple CNS-related biomarkers in a critically ill population at the time of admission was a strength of our investigation, adding to previous studies that associate delirium with systemic factors including inflammation.[18] Lending translational relevance to our work, the platform used for our investigation can be used to analyze dozens of samples within hours, which would facilitate integration into clinical laboratory workflows.[49] Implementation of similar systems has been shown to be both feasible and cost-effective.[49] We acknowledge that the pathophysiologic characteristics of delirium are likely heterogeneous across clinical settings. Our results contribute to the understanding of this complex syndrome in critically ill patients with respiratory failure and alcohol misuse, a highly susceptible population; incorporating phosphatidylethanol and clinical characteristics present on admission in our model likely enhances its accuracy. However, it remains possible that unmeasured confounders influenced our results.

Given the limitations of our study design, our results primarily are hypothesis generating, and as such, may be at greater risk of being false discoveries. Further, because only 19 patients were categorized as having no delirium, our models are subject to imprecision and potentially are overfit. Accordingly, future studies should assess CNS-related biomarkers in larger multicenter, prospective cohorts to determine their associations with delirium onset, duration, and severity. Future translational studies also could evaluate whether BDNF and NF-L play mechanistic roles in delirium onset or could examine the role of enrichment strategies using BDNF levels, NF-L levels, or both in trials focused on delirium risk reduction and treatment.[50]

Interpretation

Our study found that BDNF and NFL measured early in critical illness were associated with a clinical diagnosis of delirium. Along with patient-related and hospital-related factors that increase vulnerability for delirium, CNS-related biomarker measures may have a complementary role in predicting which patients will require disproportionately more ICU resources to address delirium. Future prospective investigations will be necessary to validate this approach.

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Additional information: The e-Appendix, e-Figure, and e-Tables are available online under "Supplementary Data."

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR*. 5th ed. American Psychiatric Association Publishing; 2022.
2. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA*. 1994;271(2):134-139.
3. Ormseth CH, LaHue SC, Oldham MA, Josephson SA, Whitaker E, Douglas VC. Predisposing and precipitating factors associated with delirium: a systematic review. *JAMA Netw Open*. 2023;6(1):e2249950.
4. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272(19):1518-1522.
5. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing*. 2011;40(1):23-29.
6. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291(14):1753-1762.
7. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med*. 2004;32(11):2254-2259.
8. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443-451.
9. Davis DH, Muniz Terrera G, Keage H, et al. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain*. 2012;135(pt 9):2809-2816.
10. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873.
11. Girard TD, Exline MC, Carson SS, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*. 2018;379(26):2506-2516.
12. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6, 064 patients. *Crit Care Med*. 2017;45(2):171-178.
13. Costa DK, White MR, Ginier E, et al. Identifying barriers to delivering the awakening and breathing coordination, delirium, and early exercise/mobility bundle to minimize adverse outcomes for mechanically ventilated patients: a systematic review. *Chest*. 2017;152(2):304-311.
14. Collinsworth AW, Priest EL, Masica AL. Evaluating the cost-effectiveness of the ABCDE bundle: impact of bundle adherence on inpatient and 1-year mortality and costs of care. *Crit Care Med*. 2020;48(12):1752-1759.
15. Ruppert MM, Lipori J, Patel S, et al. ICU delirium-prediction models: a systematic review. *Crit Care Explor*. 2020;2(12):e0296.
16. Cowan SL, Preller J, Goudie RJB. Evaluation of the E-PRE-DELIRIC prediction model for ICU delirium: a retrospective validation in a UK general ICU. *Crit Care*. 2020;24(1):123.
17. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Crit Care*. 2011;15(6):R297.
18. Khan BA, Perkins AJ, Prasad NK, et al. Biomarkers of delirium duration and delirium severity in the ICU. *Crit Care Med*. 2020;48(3):353-361.
19. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers*. 2020;6(1):90.
20. Page VJ, Watne LO, Heslegrave A, et al. Plasma neurofilament light chain protein as a predictor of days in delirium and deep sedation, mortality and length of stay in critically ill patients. *EBioMedicine*. 2022;80:104043.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
22. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.
23. Afshar M, Burnham EL, Joyce C, et al. Cut-point levels of phosphatidylethanol to identify alcohol misuse in a mixed cohort including critically ill patients. *Alcohol Clin Exp Res*. 2017;41(10):1745-1753.
24. Marcantonio ER. Delirium in hospitalized older adults. *N Engl J Med*. 2017;377(15):1456-1466.
25. Joseph JW, Elhadad N, Mattison MLP, et al. Boarding duration in the emergency department and inpatient delirium and severe agitation. *JAMA Netw Open*. 2024;7(6):e2416343.
26. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST Jr, Leslie DL, Agostini JV. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc*. 2005;53(2):312-318.
27. Krewulak KD, Hiploylee C, Ely EW, Stelfox HT, Inouye SK, Fiest KM. Adaptation and validation of a chart-based delirium detection tool for the ICU (CHART-DEL-ICU). *J Am Geriatr Soc*. 2021;69(4):1027-1034.
28. Ferrante LE, Han L, Andrews B, et al. Effect of a three-component geriatrics bundle on incident delirium among critically ill older adults: a pilot clinical trial. *Ann Am Thorac Soc*. 2024;21(9):1333-1337.
29. Zarour S, Weiss Y, Kiselevich Y, et al. The association between midazolam premedication and postoperative delirium—a retrospective cohort study. *J Clin Anesth*. 2024;92:111113.
30. Chuen VL, Chan ACH, Ma J, Alibhai SMH, Chau V. The frequency and quality of delirium documentation in discharge summaries. *BMC Geriatr*. 2021;21(1):307.
31. Slooter AJC, Otte WM, Devlin JW, et al. Updated nomenclature of delirium and acute encephalopathy: statement of ten societies. *Intensive Care Med*. 2020;46(5):1020-1022.
32. Iwashyna TJ, Hodgson CL, Pilcher D, et al. Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. *Lancet Respir Med*. 2016;4(7):566-573.
33. Tibshirani R. Regression shrinkage and selection via the lasso. *J R Stat Soc Series B Stat Methodol*. 2018;58(1):267-288.
34. Bowman EML, Brummel NE, Caplan GA, et al. Advancing specificity in delirium: the delirium subtyping initiative. *Alzheimers Dement*. 2024;20(1):183-194.
35. Shah FA, Meyer NJ, Angus DC, et al. A research agenda for precision medicine in sepsis and acute respiratory distress syndrome: an official American Thoracic Society research statement. *Am J Respir Crit Care Med*. 2021;204(8):891-901.
36. Khalil M, Teunissen CE, Lehmann S, et al. Neurofilaments as biomarkers in neurological disorders—towards clinical application. *Nat Rev Neurol*. 2024;20(5):269-287.
37. Bridel C, van Wieringen WN, Zetterberg H, et al. Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(9):1035-1048.

38. Halaas NB, Blennow K, Idland AV, et al. Neurofilament light in serum and cerebrospinal fluid of hip fracture patients with delirium. *Dement Geriatr Cogn Disord*. 2018;46(5-6):346-357.

39. Fong TG, Vasunilashorn SM, Ngo L, et al. Association of plasma neurofilament light with postoperative delirium. *Ann Neurol*. 2020;88(5):984-994.

40. Zulehner G, Schörgenhofer C, Rommer P, et al. Serum neurofilament light chain as an early diagnostic biomarker for critical illness polyneuropathy. *Minerva Anestesiol*. 2023;89(12):1099-1104.

41. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology*. 1998;37(12):1553-1561.

42. Suen PC, Wu K, Levine ES, et al. Brain-derived neurotrophic factor rapidly enhances phosphorylation of the postsynaptic N-methyl-D-aspartate receptor subunit 1. *Proc Natl Acad Sci U S A*. 1997;94(15):8191-8195.

43. Caldeira MV, Melo CV, Pereira DB, Carvalho RF, Carvalho AL, Duarte CB. BDNF regulates the expression and traffic of NMDA receptors in cultured hippocampal neurons. *Mol Cell Neurosci*. 2007;35(2):208-219.

44. Mizoguchi Y, Yao H, Imamura Y, Hashimoto M, Monji A. Lower brain-derived neurotrophic factor levels are associated with age-related memory impairment in community-dwelling older adults: the Sefuri study. *Sci Rep*. 2020;10(1):16442.

45. Weinstein G, Beiser AS, Choi SH, et al. Serum brain-derived neurotrophic factor and the risk for dementia: the Framingham Heart Study. *JAMA Neurol*. 2014;71(1):55-61.

46. Wyrobek J, LaFlam A, Max L, et al. Association of intraoperative changes in brain-derived neurotrophic factor and postoperative delirium in older adults. *Br J Anaesth*. 2017;119(2):324-332.

47. Brum C, Stertz L, Borba E, Rumi D, Kapczinski F, Camozzato A. Association of serum brain-derived neurotrophic factor (BDNF) and tumor necrosis factor-alpha (TNF-α) with diagnosis of delirium in oncology inpatients. *Braz J Psychiatry*. 2015;37(3):197-202.

48. Grandi C, Tomasi CD, Fernandes K, et al. Brain-derived neurotrophic factor and neuron-specific enolase, but not S100β, levels are associated to the occurrence of delirium in intensive care unit patients. *J Crit Care*. 2011;26(2):133-137.

49. Herskovits AZ, Johnson WT, Oved JH, et al. A semiautomated microfluidic ELISA for the detection of hemophagocytic lymphohistiocytosis biomarkers. *Am J Clin Pathol*. 2025;163(1):80-86.

50. Woelfer M, Li M, Colic L, et al. Ketamine-induced changes in plasma brain-derived neurotrophic factor (BDNF) levels are associated with the resting-state functional connectivity of the prefrontal cortex. *World J Biol Psychiatry*. 2020;21(9):696-710.