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Associations of markers of inflammation and coagulation with delirium during critical illness

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Abstract *Purpose:* To assess the associations between a priori-selected markers of inflammation and coagulation and delirium during critical illness. *Methods:* In this prospective cohort study, we collected blood from mechanically ventilated medical intensive care unit (ICU) patients and measured nine plasma markers of inflammation and coagulation. We assessed patients daily for delirium using the Confusion Assessment Method for the ICU and used multivariable regression to analyze the associations between plasma markers and subsequent delirium, after adjusting for age, severity of illness, and sepsis. *Results:* Among the 138 patients studied, with median age of 66 years and median Acute Physiology and Chronic Health Evaluation (APACHE) II of 27, 107 (78 %) were delirious at some point during the study. Two markers of inflammation and one of coagulation were significantly associated with delirium. After adjusting for covariates, lower plasma concentrations of matrix metalloproteinase-9 (MMP-9) and protein C were associated with increased probability of delirium ($p = 0.04$ and 0.01, respectively), and higher concentrations of soluble tumor necrosis factor receptor-1 (sTNFR1) were associated with increased probability of delirium ($p < 0.01$). Concentrations of C-reactive protein ($p = 0.82$), myeloperoxidase ($p = 0.11$), neutrophil gelatinase-associated lipocalin ($p = 0.70$), D-dimer ($p = 0.83$), plasminogen activator inhibitor type 1 ($p = 0.98$), and Von Willebrand factor antigen ($p = 0.65$) were not associated with delirium. *Conclusions:* In this study, MMP-9, protein C, and sTNFR1 were independently associated with subsequent ICU delirium. These results suggest that specific aspects of inflammation and coagulation may play a role in the evolution of delirium during critical illness and that these markers should be examined in larger studies of ICU patients.

Keywords Delirium · Inflammation · Blood coagulation · Critical illness · Mechanical ventilation

Introduction

Delirium, an acute form of brain dysfunction or cerebral insufficiency [1] affecting 60–80 % of mechanically ventilated patients in the intensive care unit (ICU), is both pervasive and foreboding for the large and rapidly growing population of critically ill patients worldwide [2]. In addition to promoting adverse events, such as self-extubation [3], delirium delays extubation [4] and discharge from the ICU [4] and hospital [5] and is independently associated with increases in mortality [6–8] and cognitive impairment months to years after critical illness [9]. Despite the impact of delirium on outcomes and costs [10]—and despite the development of reliable and valid tools to identify delirium [11, 12]—little is known regarding the biological mechanisms that lead to this form of organ dysfunction during critical illness.

Studies among older non-ICU patients suggest that inflammation plays a role in the pathophysiology of delirium [13–15]. Though its acute effects on the brain are poorly understood, inflammation is known to cause dysfunction of other organs during critical illness [16], in part by stimulating a process of deranged coagulation, whose end product is microvascular damage and thrombosis in vital organs, such as the kidneys [17] and lungs [18]. The blood–brain barrier and brain are likely affected as well. Animal models show that inflammatory mediators circulating systemically during sepsis readily cross the blood–brain barrier [19]. It is suspected, therefore, that the systemic inflammation and attendant coagulation that commonly characterize critical illness are important contributors to the development and continuation of delirium [20–22].

To explore the hypothesis that inflammation and deranged coagulation are risk factors for delirium during critical illness, we assessed the associations between five markers of inflammation and four markers of coagulation and delirium during critical illness in a prospective cohort study, seeking to generate hypotheses about specific biomarkers for definitive testing in larger studies. In light of our overarching hypothesis, we expected that delirium would be predicted by elevations in each of the plasma markers studied, except for protein C, which we expected to be reduced in association with delirium [23].

Patients and methods

Study design and population

We conducted this nested prospective cohort study at a single center (Saint Thomas Hospital, Nashville, TN, USA) participating in the Awakening and Breathing Controlled trial (ClinicalTrials.gov number NCT00097630) [24], a randomized trial assessing the efficacy of a paired sedation and ventilator weaning protocol. All medical ICU patients mechanically ventilated >12 h were eligible for enrollment except patients admitted after cardiopulmonary arrest, moribund patients, those with profound neurological deficits (e.g., due to large stroke or severe dementia), patients enrolled in another clinical trial, and those whose current episode of mechanical ventilation had lasted ≥2 weeks. At the time of enrollment, we obtained informed consent from authorized surrogates because most participants did not have capacity to consent; when capable, patients could consent or withdraw. The institutional review boards at Saint Thomas Hospital and Vanderbilt University Medical Center (Nashville, TN, USA), site of the coordinating center, approved the study protocol.

Measurement of inflammation and coagulation

On the morning after enrollment (or, in the rare case that blood could not be collected at that time, within 2 days after enrollment), we collected initial venous blood samples from patients using ethylenediaminetetraacetic acid (EDTA) tubes for inflammatory markers and citrate tubes for markers of coagulation. Within 4 h of collection, the tubes were centrifuged; plasma was removed and stored at −80 °C until batched measurement of biomarkers. We collected a second follow-up blood sample on study day 5, except when unavailable due to discharge or death.

A priori, we selected five markers of inflammation and four markers of coagulation—all nine markers are described in the Electronic Supplementary Material (ESM)—based on previous studies examining inflammation and coagulation during critical illness. Markers of inflammation included (1) C-reactive protein (CRP), (2) matrix metalloproteinase-9 (MMP-9), (3) myeloperoxidase (MPO), (4) neutrophil gelatinase-associated lipocalin (NGAL), and (5) soluble tumor necrosis factor receptor-1 (sTNFR1). Markers of deranged coagulation included (1) D-dimer, (2) protein C, (3) plasminogen activator inhibitor type 1 (PAI-1), and (4) Von Willebrand factor antigen (VWF).

A detailed description of the methods used to measure biomarkers is provided in the ESM. All laboratory personnel were blinded to patients' clinical characteristics and outcomes, including delirium.

Measurement of covariates and outcome

To adjust for potential confounders, we selected covariates a priori based on biological plausibility and previous research [25]. These covariates, collected at enrollment, included age, severity of illness, and admission with severe sepsis, which was identified according to treating physicians' diagnosis and confirmed using consensus criteria [26]. Severity of illness was measured using the acute physiology score (APS) of the Acute Physiology and Chronic Health Evaluation (APACHE) II score [27].

Using the Confusion Assessment Method for the ICU (CAM-ICU) [28, 29], research personnel assessed patients for delirium daily in the morning from study day 1 until death or ICU discharge. Based on the CAM-ICU, delirium was categorized as present or absent on each study day that the patient was not comatose according to the Richmond Agitation–Sedation Scale (RASS) [30, 31]; RASS −4 or −5 were considered coma. When a neurologic assessment was missing—which was the case for only 1.9 % of all patient-days—mental status was assigned for that day using multiple imputation [32] that relied on mental status observed the day prior to the missing assessment and patient status the day after the missing assessment, e.g., observed mental status, ICU discharge, or death. None of the biomarker results were known at the time patients were assessed for delirium.

Statistical analysis

Our primary goal in this hypothesis-generating study was to narrow the field of inflammatory and coagulation markers that should be studied in large, multicenter investigations. To determine which candidate markers of inflammation and coagulation (the continuous exposure variables of interest) are independently associated with delirium (the dichotomous outcome), we used logistic regression with generalized estimating equations (GEE) to analyze the probability of being delirious the day following each biomarker measurement, adjusting for age, severity of illness, and severe sepsis. Since both exposures and outcomes were measured more than once per patient, GEE was used to account for correlation between multiple observations from the same patient. We specifically analyzed the temporal (i.e., before–after) associations between biomarkers and delirium assessed within 24 h after biomarker measurement; if a patient could not be assessed for delirium on a particular day (e.g., because of coma, discharge, or death), the biomarkers measured on the previous day were excluded from analysis.

To reduce the risk of type I error, we performed a global test based on Wald statistics, which assesses the combined association of the nine biomarkers with delirium after adjusting for covariates. We then included each plasma marker individually in a separate logistic regression model with GEE to avoid multicollinearity, assessing for associations between individual biomarkers and delirium.

In addition to the primary analyses, we performed several sensitivity analyses, which are described, along with other details regarding the statistical analyses, in the ESM. We used R (version 2.11.1) for all statistical analyses [33].

Results

From March 2004 to March 2006, blood was collected from 138 mechanically ventilated medical ICU patients whose baseline characteristics are presented in Table 1. The majority of patients were 65 years old or older, and one-quarter were ≥75 years old. Nearly half were admitted with severe sepsis and/or acute respiratory distress syndrome. Delirium was common, with 78 % of patients being delirious at some point during their ICU stay. On the days of biomarker measurement included in the analyses, most patients were alert or mildly sedated; the median [interquartile range] RASS on these days was 0 [−2 to 0].

Initial and follow-up plasma marker concentrations are displayed in Table 2. Nineteen (14 %) patients died within 5 days of enrollment such that only the initial biomarker concentration could be obtained for these patients.

After adjusting for age, severity of illness, and severe sepsis, the Wald global test found that the group of nine

Table 1 Baseline characteristics and outcomes of the study population

Variable	Cohort (n = 138)
Age (years)	66 [55–75]
Female	50 % (69/138)
APACHE II	27 [22–33]
Admission diagnoses	
Severe sepsis/ARDS	43 % (60/138)
Myocardial infarction/congestive heart failure	20 % (28/138)
Chronic obstructive pulmonary disease/asthma	9 % (12/138)
Altered mental status	7 % (9/138)
Stroke/intracranial hemorrhage	6 % (8/138)
Hepatic or renal failure	5 % (7/138)
Other	10 % (14/138)
Days from ICU admission to study enrollment	2 [1–3]
Delirium[b]	
Prevalence	78 % (107/138)
Duration (days)	2 [1–5]
28-Day mortality	33 % (45/138)

All results expressed as median [interquartile range] or % (n/total)

[a] During the ICU stay (truncated at 28 days)

Table 2 Plasma marker concentrations according to study day

Plasma marker	Initial[a]	Follow-up[b]
Inflammation markers		
CRP (μg/mL)	93.0 [46.5–165.8]	55.1 [23.9–130.9]
MMP-9 (ng/mL)	42.0 [13.5–137.4]	83.6 [21.1–154.9]
MPO (ng/mL)	147.2 [51.1–318.9]	124.8 [44.9–285.3]
NGAL (ng/mL)	150.3 [82.7–356.1]	108.0 [78.6–221.7]
sTNFR1 (pg/mL)	4,397 [2,860–8,274]	4,028 [2,887–6,179]
Coagulation markers		
D-dimer (ng/mL)	2,323 [1,058–5,415]	3,191 [1,504–5,735]
Protein C (% control)	109.7 [88.6–138.9]	119.0 [98.1–141.2]
PAI-1 (ng/mL)	67.5 [46.8–99.8]	73.8 [50.5–107.2]
VWF (% control)	370.0 [294.2–556.3]	399.5 [294.3–515.8]

All results expressed as median [interquartile range]

[a] Collected on the morning after study enrollment or (in the rare case that blood could not be collected at that time) within 2 days of enrollment

[b] Collected on study day 5, except in cases of ICU discharge or death prior to day 5

plasma markers studied was significantly associated with delirium ($p = 0.02$), indicating that one or more markers was associated with delirium and allowing us to proceed with examining the associations of individual biomarkers with delirium. In separate models including individual biomarkers, two inflammatory markers and one marker of coagulation were significantly associated with delirium (Table 3). Higher MMP-9 concentrations were associated with reduced probability of delirium ($p = 0.04$). Figure 1a shows the association, which was nonlinear; an increase in MMP-9 from 0.20 to 20 ng/mL (for this nonlinear association, values for comparison were selected based on the graph) was not significantly associated with a change in probability of delirium [odds ratio (OR) 1.3, 95 % confidence interval (CI) 0.2–9.3], whereas an increase from 20 to 300 ng/mL was associated with a significant decrease in probability of delirium [OR 0.3, 95 % CI 0.1–0.7]. As shown in Fig. 1b, higher concentrations of sTNFR1 were associated with increased probability of delirium ($p < 0.01$); an increase in sTNFR1 from 2,900 to 6,302 pg/mL (values for comparison are the 25th and 75th percentiles) was associated with a 2.1-fold increase in the odds of delirium (95 % CI 1.2–3.6). Finally, low protein C was associated with increased probability of delirium ($p = 0.01$). Figure 1c shows this nonlinear association; an increase in protein C from 60 to 140 % of the pooled control plasma standard was associated with a 90 % decrease in the odds of delirium (OR 0.1, 95 % CI 0–0.4), whereas an increase from 140 to 200 % control was not significantly associated with a change in the odds of delirium (OR 3.3, 95 % CI 0.9–12.2).

The sensitivity analyses found similar results to the primary analyses; detailed results are provided in the ESM.

Discussion

In this prospective cohort study, MMP-9, sTNFR1, and protein C were independently associated with delirium during critical illness. Though the specific biological significance of these associations is as yet unknown, these findings lend support to the hypothesis that inflammation and deranged coagulation are related to delirium and suggest that certain plasma markers might be useful in the

Table 3 Associations between plasma markers of inflammation/coagulation and subsequent delirium

Biomarker	Percentile[a]			Multivariable regression results		
	n[b]	25th	75th	Odds ratio[c]	95 % CI	p-Value
Inflammation markers						
CRP (μg/mL)	127	25.7	123.2	1.1	0.6–1.8	0.82
MMP-9 (ng/mL)	126	14.9	152.5	0.4[d]	0.2–0.8	0.04
MPO (ng/mL)	121	38.7	282.0	0.6[d]	0.3–1.3	0.11
NGAL (ng/mL)	121	65.9	248.4	1.1	0.6–1.9	0.70
sTNFR1 (pg/mL)	103	2,900	6,302	2.1	1.2–3.6	<0.01
Coagulation markers						
D-dimer (ng/mL)	126	1,134	4,529	1.1	0.6–2.0	0.83
Protein C (% control)	103	96.2	139.9	0.4[d]	0.2–0.9	0.01
PAI-1 (ng/mL)	103	47.1	94.7	1.0	0.6–1.6	0.98
VWF (% control)	103	293.1	512.2	1.1	0.7–1.9	0.65

[a] The 25th and 75th percentile concentrations for biomarkers measured the day prior to a delirium assessment

[b] The number of observations (n) included in each model was determined by the number of biomarkers measured within 24 h before an assessment for delirium

[c] The odds ratio represents the change in odds of being delirious (on the day following biomarker measurement) associated with an increase in biomarker concentration from the 25th percentile to the 75th percentile, after adjusting for age, severity of illness, and severe sepsis

[d] Nonlinear p values <0.20 indicated these associations are nonlinear; for additional details regarding significant associations that were nonlinear, please see the figures

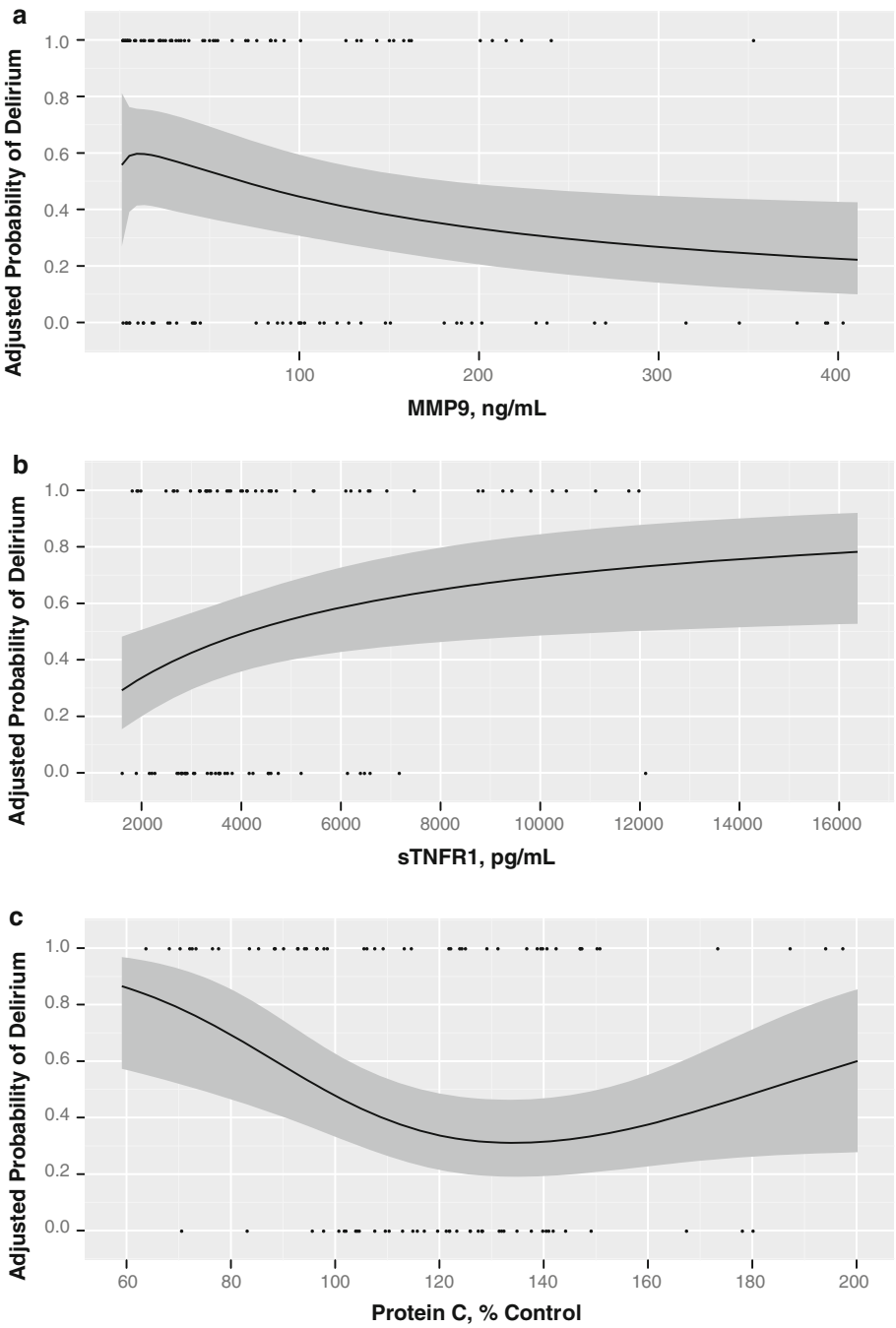

Fig. 1 Plasma markers associated with delirium. The probability of delirium that was independently associated with matrix metalloproteinase-9 (MMP-9), soluble tumor necrosis factor receptor-1 (sTNFR1), and protein C concentrations, after adjusting for age, severity of illness, and sepsis at admission is indicated by *solid black lines*. The *gray ribbons* indicate the 95 % confidence limits of these associations. Each *black circle* represents an observation with position along the x axis indicating the biomarker value and position along the y axis indicating presence ($y = 1$) or absence ($y = 0$) of delirium. Panel **a** shows that MMP-9 had a significant nonlinear association with delirium ($p = 0.04$). Panel **b** shows that sTNFR1, which was log transformed to improve model fit, had a significant linear association with delirium ($p < 0.01$). Panel **c** shows that protein C had a significant nonlinear association with delirium ($p = 0.01$).

study of the pathogenesis of delirium, as diagnostic or prognostic tools, or as potential targets for therapeutic interventions.

Delirium was predicted by elevated sTNFR1. Numerous experimental models show that TNF-alpha is an important mediator of organ dysfunction during critical illness, but this proinflammatory cytokine has not been consistently associated with outcomes in human studies [34, 35], perhaps due to its rapid decline to undetectable levels after an initial increase early during illness. We chose therefore to study sTNFR1, which is released into circulation from cells after activation by TNF-alpha, because it is measurable for days in most critically ill patients and serves as a marker of the proinflammatory state. Though sTNFR1 had not been previously studied as a marker of delirium, our results are consistent with studies that have found other plasma markers of inflammation to be associated with delirium in older

hospitalized non-ICU patients [13, 14], postoperative patients [15, 36], and critically ill patients [37–40]. Notably, only one other ICU study [40] adjusted for severity of illness, a potential confounder associated with both inflammation and delirium. Our analyses found sTNFR1 to be an important independent predictor of delirium even after accounting for age, sepsis, and severity of illness. Larger studies are needed to confirm our findings and determine which marker of inflammation is most useful for prediction and/or diagnosis of delirium, since the current results suggest that not all markers are consistent predictors.

Though some studies of non-ICU patients [14, 15] found that CRP was associated with delirium, ICU studies have yielded conflicting results. Our study found that CRP was not associated with delirium in the ICU after adjusting for potential confounders, including severity of illness, a result consistent with two recent ICU studies finding no association [40, 41]. Alternatively, two other studies found CRP was higher in delirious ICU patients than in those without delirium, but neither adjusted for severity of illness so the reported associations may be due to confounding [37, 38]. In sum, this evidence might indicate that nonspecific acute-phase reactants such as CRP are not consistently useful in the study of delirium in the ICU. It is also possible that systemic inflammation does not play a role in delirium, which would mean that complex mechanisms other than inflammation are responsible for the association between sTNFR1 and delirium. In addition to its role in immune signaling, TNF-alpha interacts with receptors and ion channels in the brain to regulate neuronal excitability and synaptic plasticity [42]. Thus, disease-induced changes in levels of TNF-alpha in the circulation and the central nervous system may contribute to delirium via disruption of the cytokine's normal adaptive roles in the brain.

Our finding that low protein C was associated with increased probability of delirium might reflect a role of deranged coagulation in the pathogenesis of delirium during critical illness, since activated protein C blocks microvascular coagulation and low protein C concentrations therefore are associated with increased coagulation [23]. Alternatively, our finding could result from one or more of protein C's pleiotropic effects. In addition to numerous anti-inflammatory properties—including suppression of proinflammatory cytokines and inhibition of leukocyte adhesion and chemotaxis [43]—activated protein C has been found to have neuroprotective effects, which are attributed to attenuation of glutamate-induced excitotoxicity [44] and prevention of neuronal apoptosis [45]. Thus, the association between low protein C and delirium shown in our study could reflect a role of increased coagulation, increased inflammation, and/or reduced neuroprotection in delirium during critical illness. Any of these effects may explain the results of a recent observational study that suggested treatment with recombinant human activated protein C [drotrecogin alfa (activated)—a drug not available for clinical use] may reduce sepsis-associated delirium or encephalopathy [46].

Unlike the findings regarding sTNFR1 and protein C, the association between lower concentrations of MMP-9 and delirium was unexpected; elevated MMP-9 is generally considered an indicator of inflammation, so we hypothesized that elevated MMP-9 would be associated with delirium. One possible explanation for our finding is that the relationship between MMP-9 and delirium during critical illness may be influenced more by MMP-9's direct role in brain function than by its role in inflammation. Like leukocytes, neurons can express this protease, which operates extracellularly in the brain after being released in response to enhanced neuronal activity [47]. Animal models suggest that MMP-9 plays an important physiologic role in neuroplasticity [48, 49], making it important in memory and learning, processes that are frequently impaired during delirium. It remains unclear, however, whether the normal physiologic effects of MMP-9 remain intact during critical illness or if the enzyme promotes damage in this setting. Though our results are more consistent with the former, studies of MMP-9 in the setting of other neurologic diseases or conditions have found the marker to be elevated, e.g., in Alzheimer's disease [50], stroke [51], and traumatic brain injury [52]. Our finding may also result from confounding due to unmeasured covariates. Statins, for example, have been reported to reduce MMP-9 activity [53] and may have effects on delirium during critical illness [54, 55]. Future studies are needed to clarify the role of MMP-9 in brain function during critical illness after accounting for potential confounders, including statin exposure.

Strengths of this investigation include measurement of plasma markers before assessment of outcomes; use of a well-validated tool to diagnose delirium; and a diverse population of medical ICU patients, with varying ages and diagnoses. One limitation was our measurement of biomarkers twice rather than daily, preventing detailed examinations of kinetic profiles and testing of additional hypotheses, such as the hypothesis recently proposed on the basis of a study involving healthy volunteers [56], i.e., that sustained elevation of proinflammatory cytokines is more important to the pathophysiology of brain dysfunction during critical illness than the absolute peak reached by these cytokines. Also, though we studied nine separate markers, limitations in funding prevented us from measuring other inflammatory markers of interest; interleukin (IL)-6 [39] and IL-8 [57], for example, warrant examination in future studies of delirium during critical illness. Other limitations include measurement of circulating levels of markers in plasma rather than levels in the cerebrospinal fluid, which would presumably be more reflective of changes in the brain but which would be difficult to obtain [58]; potential confounding by hemodialysis (which was not tracked in the study and which

may alter some biomarker concentrations [59]) or by death or coma, outcomes that may be increased by inflammation and which prevent assessment for delirium; a single-center study design, which may limit generalizability; and our separate analyses of multiple biomarkers. In a single model that is less subject to type I error than multiple separate models, the Wald global test was significant, indicating that one or more plasma markers was associated with delirium. However, we also examined nine markers in separate models, which could result in false positives. We chose not to adjust for these multiple comparisons, in keeping with authoritative recommendations [60] and to avoid type II errors, since we planned for our results to direct future research rather than directly inform clinical practice.

In conclusion, this investigation found that three plasma markers of inflammation and coagulation, MMP-9, sTNFR1, and protein C, are associated with delirium in the ICU. These results, which lend support to the hypothesis that inflammation and deranged coagulation are important mechanisms of delirium during critical illness, need confirmation and further study in larger, multicenter investigations of critically ill patients with and without severe sepsis. Additionally, related markers should be studied to enhance understanding of the mechanisms of delirium, and potential associations between inflammatory markers and other manifestations of brain dysfunction, including coma, should be examined, since delirium is one of several manifestations of acute brain dysfunction that occur during critical illness [61].

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Conflicts of interest Drs. Girard, Pandharipande, Shintani, and Ely have received honoraria from Hospira Inc. Dr. Pandharipande has received honoraria from Orion Corporation. Drs. Pandharipande and Ely have received grant support from Hospira Inc. Dr. Ely has also received grant support from Eli Lilly and Company and Masimo Corporation and is an advisor to Healthways Inc. All other authors have no disclosures.

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