Intensive Care Med (2024) 50:687–696
https://doi.org/10.1007/s00134-024-07388-6

ORIGINAL

Systemic inflammation and delirium during critical illness

Nathan E. Brummel[1,2,3], Christopher G. Hughes[3,4,8], J. Brennan McNeil[3,5], Pratik P. Pandharipande[3,4,8], Jennifer L. Thompson[3,6], Onur M. Orun[3,6], Rameela Raman[3,6], Lorraine B. Ware[3,5], Gordon R. Bernard[5], Fiona E. Harrison[3,7,8], E. Wesley Ely[3,9,10,11] and Timothy D. Girard[3,12*]

Abstract

Purpose: The purpose of this study was to determine associations between markers of inflammation and endogenous anticoagulant activity with delirium and coma during critical illness.

Methods: In this prospective cohort study, we enrolled adults with respiratory failure and/or shock treated in medical or surgical intensive care units (ICUs) at 5 centers. Twice per day in the ICU, and daily thereafter, we assessed mental status using the Richmond Agitation Sedation Scale (RASS) and the Confusion Assessment Method-Intensive Care Unit (CAM-ICU). We collected blood samples on study days 1, 3, and 5, measuring levels of C-reactive protein (CRP), interferon gamma (IFN-γ), interleukin (IL)-1 beta (IL-1β), IL-6, IL-8, IL-10, IL-12, matrix metalloproteinase-9 (MMP-9), tumor necrosis factor-alpha (TNF-α), tumor necrosis factor receptor 1 (TNFR1), and protein C using validated protocols. We used multinomial logistic regression to analyze associations between biomarkers and the odds of delirium or coma versus normal mental status the following day, adjusting for age, sepsis, Sequential Organ Failure Assessment (SOFA), study day, corticosteroids, and sedatives.

Results: Among 991 participants with a median age (interquartile range, IQR) of 62 [53–72] years and enrollment SOFA of 9 [7–11], higher concentrations of IL-6 (odds ratio [OR] [95% CI]: 1.8 [1.4–2.3]), IL-8 (1.3 [1.1–1.5]), IL-10 (1.5 [1.2–1.8]), TNF-α (1.2 [1.0–1.4]), and TNFR1 (1.3 [1.1–1.6]) and lower concentrations of protein C (0.7 [0.6–0.8])) were associated with delirium the following day. Higher concentrations of CRP (1.4 [1.1–1.7]), IFN-γ (1.3 [1.1–1.5]), IL-6 (2.3 [1.8–3.0]), IL-8 (1.8 [1.4–2.3]), and IL-10 (1.5 [1.2–2.0]) and lower concentrations of protein C (0.6 [0.5–0.8]) were associated with coma the following day. IL-1β, IL-12, and MMP-9 were not associated with mental status.

Conclusion: Markers of inflammation and possibly endogenous anticoagulant activity are associated with delirium and coma during critical illness.

Keywords: Delirium, Coma, Inflammation, Critical illness

Introduction

Delirium—an acute neuropsychiatric syndrome characterized by inattention, disorganized thinking, altered level of consciousness, and a fluctuating course—affects up to half of all patients with critical illness [1, 2], and duration of delirium in this population predicts greater mortality and, among survivors, cognitive impairment and disability in activities of daily living [3–6]. Despite the pervasiveness and poor long-term outcomes of delirium, its underlying biological mechanisms remain unclear.

Acute inflammation and decreased endogenous anticoagulant activity promote organ dysfunction during critical illness syndromes such as sepsis, acute respiratory

*Correspondence: timothy.girard@pitt.edu
[3] Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center, Nashville, TN, USA
Full author information is available at the end of the article

distress syndrome (ARDS), and surgery, and these interrelated mechanisms are hypothesized to contribute to delirium [7–9]. Indeed, elevated levels of inflammatory markers and low levels of markers of endogenous anticoagulant activity have been associated with delirium and coma (a risk factor for delirium) during critical illness [10–16]. These studies, however, were limited by small sample sizes, a limited number of markers, and inconsistent associations. Moreover, these studies did not account for other potential risk factors for delirium and coma, subjecting prior findings to bias. Thus, these potential mechanisms of delirium and coma during critical illness need further study.

We therefore examined associations between markers of inflammation and endogenous anticoagulant activity and delirium and coma in a multicenter, prospective cohort study of adults with critical illness. We hypothesized that higher concentrations of markers of inflammation and lower concentrations of markers of endogenous anticoagulant activity are associated with both delirium and coma during critical illness.

Take home message

In this prospective cohort study of nearly 1000 patients with medical and surgical critical illness, higher levels of markers of inflammation (i.e., IL-6, IL-8 and IL-10) and lower levels of endogenous anticoagulant activity (i.e., protein C) showed consistent associations with delirium and coma the day following marker measurement as well as the number of delirium/coma-free days over the next week.

These data support the hypothesis that systemic inflammation and disordered coagulation play a role in the pathophysiology of delirium and coma during critical illness.

Methods

Study design and population

We collected data and biological samples for this prospective cohort study during two multicenter studies with identical designs: the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in intensive care unit (ICU) Survivors Study (BRAIN-ICU) [5] and the MIND-ICU Study: Delirium and Dementia in Veterans Surviving ICU Care [17]. Detailed inclusion and exclusion criteria have been published elsewhere [5, 17] and may be found in the supplementary material. We included adults (≥ 18 years old) treated for respiratory failure and/or shock in a medical or surgical ICU from 5 United States (US) centers. We excluded participants if they had acute organ dysfunction for > 72 h, a recent ICU stay > 5 days, severe preexisting cognitive impairment, or an inability to communicate in English. The parent studies included long-term follow-up and therefore also excluded those with substance abuse disorders, homelessness, or residence > 200 miles from an enrolling center. From the present analyses, we further excluded participants who did not provide at least one blood sample. Thus, the sample size of our current analyses was determined by the size of the parent cohorts and the availability of blood samples. Participants or their authorized representatives provided informed consent at the time of enrollment and again (when appropriate) after regaining capacity. The institutional review board at each center approved the study and therefore the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Exposures: markers of inflammation and endogenous anticoagulant activity

We collected plasma samples at study enrollment (i.e., study day 1) and on study days 3 and 5. We collected blood using ethylenediaminetetraacetic (EDTA) tubes for inflammatory marker assays and citrate tubes for anticoagulant marker assays. We placed samples on ice, processed them within one hour of collection, and stored plasma at − 80 °C for batched analysis conducted at the Vanderbilt Coordinating Center (VCC, Nashville, TN). Samples from centers outside of Nashville were packed in dry ice and shipped via overnight courier to the VCC.

Based on prior studies in patients with critical illness [7–12], we a priori selected ten markers of inflammation and one marker of endogenous anticoagulant activity. Described in detail in the supplementary materials, the markers of inflammation included C-reactive protein (CRP), interferon gamma (IFN-γ), interleukin (IL)-1 beta (IL-1β), IL-6, IL-8, IL-10, IL-12, matrix metalloproteinase-9 (MMP-9), tumor necrosis factor-alpha (TNF-α), and soluble tumor necrosis factor receptor 1 (TNFR1). Protein C was the marker of endogenous anticoagulant activity.

Laboratory personnel, masked to participants' baseline clinical characteristics and details of the hospital course including mental status, used validated laboratory protocols to measure, in duplicate, plasma concentrations of each biomarker using commercially available immunoassays [18].

Outcome: following day's mental status and delirium/coma-free days

Twice daily from the time of enrollment until ICU discharge and once per day thereafter until hospital discharge (for up to 30 days), trained research personnel determined participant mental status using the Richmond

Agitation-Sedation Scale (RASS) [19] to assess level of consciousness and the Confusion Assessment Method for the ICU (CAM-ICU) [20] to assess for delirium. We considered coma to be present if the RASS was − 4 or − 5. We considered delirium to be present if the RASS was − 3 or greater and the CAM-ICU was positive. We considered normal mental status to be present if neither coma nor delirium were present. Though we measured mental status for up to 30 days, for the purposes of these analyses, we used mental status data for 11 days after study enrollment (i.e., for the 7 days including and after the study day 5 biomarker measurement). We chose this approach because 75% of participants with delirium or coma had these conditions for 5 days or fewer and because the plausible biological effects of the markers of interest on mental status fall within this timeframe. We used these data to calculate the number of days alive and free of delirium and coma (i.e., delirium/coma-free days). Figure S1 in the supplementary materials presents a schematic of these analyses.

Covariates: clinical characteristics

We a priori selected the following potential confounders of the associations between markers of interest and mental status: age, severe sepsis (defined as the presence of two or more systemic inflammatory response syndrome (SIRS) criteria plus a Sequential Organ Failure Assessment (SOFA) score of 2 or greater [indicating organ dysfunction] in the setting of known or suspected infection), mean modified SOFA score (with the neurologic component removed because our outcomes of interest were delirium and coma), study day, receipt of corticosteroids (yes/no), and mean 24-h doses of sedatives and opiates. Detailed descriptions of these covariates are included in the supplementary materials.

Statistical analysis

When a marker's concentration was above the upper limit of detection, we assigned the value for the upper limit. When a marker's concentration was below the lower limit of detection, we assigned a value between 0 and the lower limit using a uniform distribution.

To test the hypothesis that markers of inflammation and endogenous anticoagulant activity during critical illness are associated with delirium and coma after adjusting for potential confounders, we used multivariable regression and adjusted for all previously listed covariates, which we selected based on previous research, biological plausibility, and effective sample size. We analyzed mental status outcomes in two ways. First, we determined the association between markers (measured on days 1, 3, and 5) and mental status (categorized as normal, delirium, or coma) on the following day (i.e., assessed on days 2, 4, and 6) using multinomial logistic regression with bootstrapping to account for correlation amongst observations due to repeated measurements from a single subject. Second, to avoid confounding by death, which can truncate the duration of delirium and/or coma, we calculated the number of delirium/coma-free days as the number of days during the study period during which participants were alive with a normal mental status. We modeled the association between plasma markers and the number of delirium/coma-free days during the 7 days following marker measurement (i.e., days 1–7, 3–9, or days 5–11) using proportional odds logistic regression with Huber-White sandwich estimation to account for repeated measures. We present associations expressed as odds ratios (OR) and 95% confidence intervals (CI) comparing the biomarker concentration at the 75th percentile with that at the 25th percentile, with all covariates adjusted to their median or mode value. Odds ratios from multinomial regression models represent the odds of having delirium or coma on the following day, compared with normal mental status, associated with a change in the biomarker concentration from the 25th to the 75th percentile value. Odds ratios for proportional odds logistic regression models represent the odds of having more delirium/coma-free days, compared with fewer delirium/coma-free days, associated with a change in the biomarker concentration from the 25th to the 75th percentile value.

We used the plasma marker concentrations as the primary exposure for all analyses to reduce the influence of outliers and improve model fit. Missing data were handled using predictive mean matching, described in detail in the supplementary materials. We allowed associations with continuous covariates to be nonlinear using restricted cubic splines and excluded nonlinear terms when the P-value for the global test for nonlinearity was > 0.20. We used R (version 3.0.1) for all analyses.

Results

Between January 2007 and December 2010, we enrolled 1,047 participants. During the index hospitalization, 7 participants withdrew their permission to use their data. We were unable to collect blood from 49 participants (supplementary Figure S2). Thus, 991 participants with a median (interquartile range [IQR]) age of 62 (53 to 72) years old and a high severity of illness comprised the cohort (Table 1).

Delirium and coma

Mental status assessments were completed on over 97% of eligible participant-days. Supplementary Table S2 reports the frequency of missing mental status data by

Table 1 Baseline characteristics and clinical outcomes

Variable	n = 991
Age (years)	62 (53–72)
Male	61% (605)
Race	
Caucasian	90% (899)
African American	9% (86)
Other	1% (6)
Education (years)	12 (12–14)
Charlson comorbidity index	2 (1–4)
APACHE II at admission	24 (18–30)
SOFA at enrollment	9 (7–11)
Mean daily SOFA in the ICU	7 (6–10)
Admission diagnoses	
Sepsis	32% (314)
Acute respiratory failure	17% (164)
Cardiogenic shock, myocardial ischemia, or congestive heart failure	17% (168)
Airway protection or upper airway obstruction	10% (103)
Surgical procedure*	16% (163)
Neurologic disease or seizure	1% (12)
Other diagnoses	7% (67)
Mechanically ventilated	
Ever	88% (875)
Duration†	3 (2–8)
Sepsis	
Ever	70% (687)
Duration†	4 (2–7)
Delirium	
Ever	70% (691)
Duration†	3 (2–5)
Coma	
Ever	60% (587)
Duration†	3 (1–5)
Length of stay (days)	
ICU	5 (3–11)
Hospital	10 (6–18)
Mortality in hospital	19% (189)

APACHE Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment

*Includes gastric, colonic, vascular, urologic, orthopedic, obstetric/gynecologic, hepatobiliary/pancreatic, otorhinolaryngologic, or transplant

† Among participants who had the clinical condition during the 11-day study period

study day. During the 11-day study period, approximately 7 out of every 10 participants developed delirium lasting a median (IQR) of 3 (2–5) days (Table 1). Coma occurred in 6 out of every 10 participants and lasted a median of 3 (1–5) days. The distribution of mental status (i.e., delirium, coma, or normal) on study days 2, 4, and 6 is presented in supplementary Table S1 in the electronic supplement.

Marker concentrations

Marker concentrations were measured on over 90% of eligible participant-days. Supplementary Table S3 reports the frequency of missing biomarker data by study day. Concentrations of each marker stratified by mental status on study days 1, 3, and 5 are presented in Fig. 1. The median concentrations of each marker from study days 1, 3, and 5 are presented in Table S4 in the electronic supplement.

Associations between markers of inflammation with delirium and coma the following day

After adjusting for age, severe sepsis, modified SOFA score, study day, steroid use, and doses of sedatives and opiates, higher concentrations of IL-6 (OR 1.8, 95% CI [1.4–2.3]; Table 2, Fig. 2A), IL-8 (OR 1.3, 95% [1.1–1.5]; Table 2, Fig. 2B), IL-10 (OR 1.5, 95% [1.2–1.8]; Table 2, Fig. 2C), TNF-α (OR 1.2, 95% [1.0–1.4]; Table 2, supplementary Figure S3A), and TNFR1 (OR 1.3, 95% [1.1–1.6]; Table 2, supplementary Figure S3B) were associated with greater odds of delirium versus normal mental status the following day, whereas lower concentrations of protein C (OR 0.7, 95% [0.6 to 0.8]) were associated with greater odds of delirium the following day (Table 2, Fig. 2D). CRP, IFN-γ, IL-1β, IL-12, MMP-9, and protein C concentrations were not associated with delirium (Table 2).

After adjusting for covariates, greater concentrations of CRP (OR 1.4, 95% [1.1–1.7]; Table 2, supplementary Figure S3C), IFN-γ (OR 1.3, 95% [1.1–1.6]; Table 2, supplementary Figure S3D), IL-6 (OR 2.3, 95% [1.8–3.0]; Table 2, Fig. 2A), IL-8 (OR 1.8, 95% [1.4–2.3]; Table 2, Fig. 2B), and IL-10 (OR 1.5, 95% [1.2–2.0]; Table 2, Fig. 2C) were associated with greater odds of coma on the following day. Lower concentrations of protein C (OR 0.6, 95% [0.5–0.8]) were also associated with greater odds of coma on the following day (Table 2, Fig. 2D). IL-1β, IL-12, MMP-9, TNF-α, and TNFR1 concentrations were not associated with coma (Table 2).

Association between markers of inflammation and delirium/coma-free days

After adjusting for covariates, higher levels of IL-6 (OR 0.6, 95% CI [0.5–0.7]), IL-8 (OR 0.7, 95% [0.6–0.8]), and IL-10 (OR 0.7, 95% [0.6–0.8]) and lower levels of protein C (OR 1.3, 95% [1.1–1.5]) were associated with fewer delirium/coma-free days during the seven days following marker measurement (Table 3 and Fig. 3). CRP, IFN-γ, IL-1β, IL-12, MMP-9, TNF-α, and TNFR1 concentrations

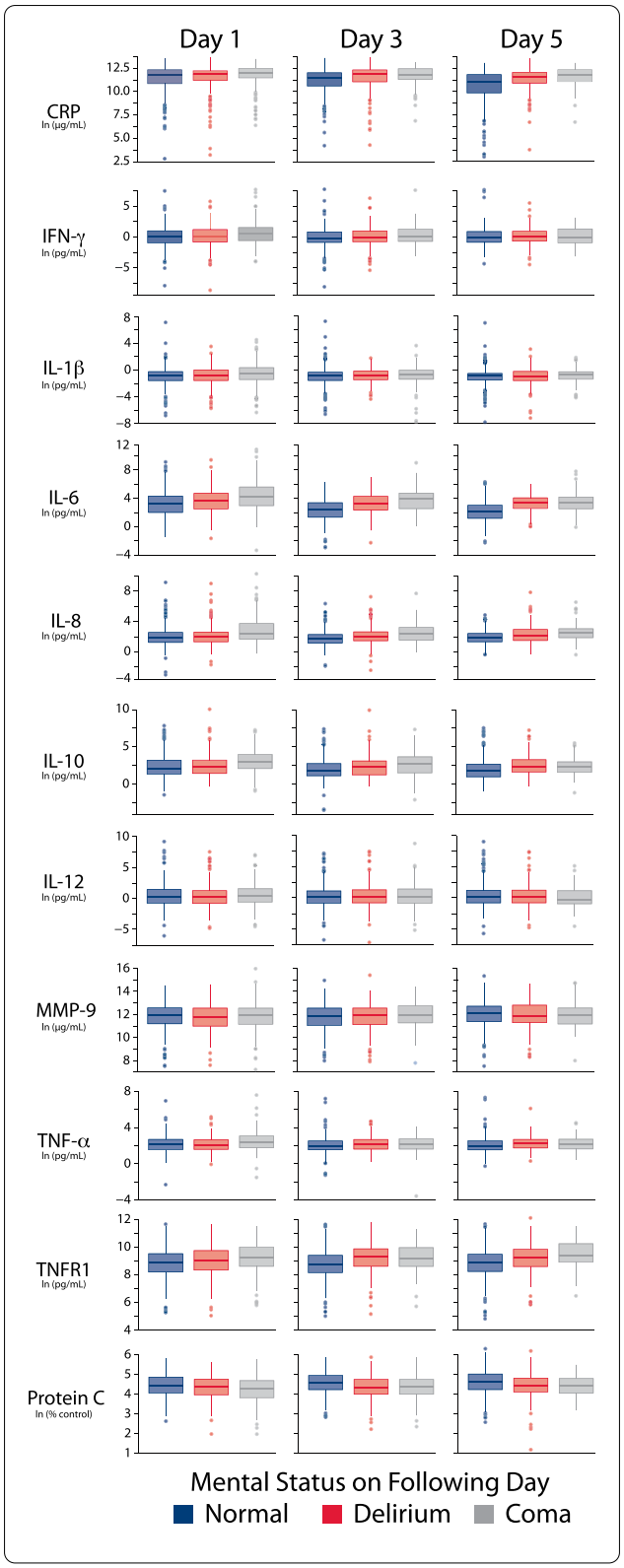

Fig. 1 Natural log concentration of each marker stratified by mental status on study days 1, 3, and 5. These box plots display the natural log concentration of each marker on study days 1, 3, and 5 according to mental status on the day following marker measurement (i.e., days 2, 4, and 6) with blue representing normal mental status, red representing delirium, and gray representing coma. The bold horizontal line represents the median. The top and bottom of the boxes represent the 75th and 25th percentiles, respectively

were not associated with the number of delirium/coma-free days (Table 3).

Discussion

This large, multicenter, prospective cohort study shows that markers of acute systemic inflammation and endogenous anticoagulant activity are independently associated with delirium and coma during critical illness. After adjusting for potential confounders, higher concentrations of IL-6, IL-8, IL-10, TNF-α, and TNFR1 and lower concentrations of protein C were associated with delirium the day after marker measurement. Likewise, higher concentrations of CRP, IFN-γ, IL-6, IL-8, and IL-10 and lower concentrations of protein C were associated with coma the following day. The four markers associated with both delirium and coma the next day (i.e., IL-6, IL-8, IL-10, and protein C) were also associated with the number of days alive and free of delirium or coma in the week following marker measurement.

Our findings build on prior studies to support the hypothesis that acute systemic inflammation is important in the pathogenesis of delirium in patients with critical illness. The potential pathways by which inflammation and delirium are linked are reviewed in detail elsewhere [7, 8, 21, 22]. Nevertheless, the understanding of these pathways is derived in large part from animal models or studies of healthy volunteers exposed to bacteremia or lipopolysaccharide who developed sickness behavior (i.e., lethargy, fever, and reduced appetite), which can resemble some features of delirium [23–26]. Therefore, future mechanistic work in both animal models and human studies evaluating the effect of systemic markers of inflammation and anticoagulation on pathways related to neuroinflammation, blood–brain barrier integrity, endothelial function, neuronal injury, and neurotransmission are needed to understand better potential causal pathways of delirium during critical illness. The present study—the largest study of inflammation and delirium to date and the first to show the associations in question are independent of many potential confounders—serves to focus the spectrum of specific markers to be studied.

Table 2 Associations between markers of inflammation with delirium and with coma the following day

Marker	75th percentile[a]	25th percentile[a]	Delirium			Coma		
			OR[b]	95% CI	p value[c]	OR[b]	95% CI	p value[c]
CRP (ng/mL)	12.2	10.9	1	0.8–1.2	0.11	1.4	1.1–1.7	0.02
IFN-γ (pg/mL)	1.1	− 0.9	1.1	1–1.3	0.21	1.3	1.1–1.6	0.02
IL-1β (pg/mL)	− 0.2	− 1.5	1	0.9–1.1	0.42	1.1	0.9–1.3	0.38
IL-6 (pg/mL)	4.2	2	1.8	1.5–2.3	< 0.0001	2.3	1.8–3	< 0.0001
IL-8 (pg/mL)	2.7	1.3	1.3	1.1–1.5	0.03	1.8	1.4–2.3	< 0.0001
IL-10 (pg/mL)	3.2	1.3	1.5	1.2–1.8	< 0.001	1.5	1.2–2	0.005
IL-12 (pg/mL)	1.4	− 0.7	1.1	1–1.3	0.42	1.1	0.9–1.3	0.57
MMP-9 (ng/mL)	12.6	11.2	0.9	0.8–1.1	0.66	1	0.8–1.2	0.93
TNF-α (pg/mL)	2.7	1.6	1.2	1–1.4	0.04	1.2	1–1.5	0.14
TNFR1 (pg/mL)	9.7	8.4	1.3	1.1–1.6	0.01	1.2	0.9–1.5	0.39
Protein C (% control)	4.8	4.1	0.7	0.6–0.8	< 0.001	0.6	0.5–0.8	< 0.001

CI confidence interval, *CRP* C-reactive protein, *IFN* interferon, *IL* interleukin, *MMP* matrix metalloproteinase, *OR* odds ratio, *TNF* tumor necrosis factor, *TNFR* tumor necrosis factor receptor

[a] Values represent the natural log biomarker concentration

[b] Odds ratios compare the odds of being delirious (or comatose) rather than normal (the reference category) on the following day for a patient with a biomarker concentration at the 75th percentile vs. a patient with a biomarker concentration at the 25th percentile, with all other covariates adjusted to the median or mode. Thus, for IL-6, a patient with a concentration at the 75th percentile has 80% greater odds of being delirious on the following day than a patient with an IL-6 concentration at the 25th percentile

[c] The P-value represents the significance of the overall model, whereas the odds ratio represents the magnitude of the association between biomarker and delirium or coma the following day

Prior studies have explored the association between inflammatory markers and delirium in patients with critical illness [10–16, 27]. Of these studies, six have explored this association with adjustment for potential confounders common among critically ill patients [10–12, 14–16]. A Dutch cohort found IL-8 was associated with delirium in those with inflammatory (i.e., septic) critical illness, and IL-10 was associated with delirium in those with non-inflammatory (i.e., non-septic) critical illness [10]. A Brazilian cohort reported an association between TNFR1 and TNFR2 and delirium in patients from a mixed ICU [14]. Likewise, we reported an association between TNFR1 and delirium in a cohort of mechanically ventilated patients [12]. In a second study, we found higher levels of CRP to be associated with a trend toward fewer delirium/coma-free days [11]. A Chinese study found CRP at ICU admission to be an associated with development of delirium [15]. Finally, Khan and colleagues measured IL-6, IL-8, IL-10, and TNF-α at study enrollment in patients with delirium and reported those with the highest quartile of biomarker levels had the fewest number of delirium/coma-free days, longest durations of delirium, and highest severity of delirium [16].

Differences between these studies and the present one may explain these divergent results. First, each of these prior studies enrolled fewer than 321 participants, whereas we studied nearly 1000. Thus, our study had greater statistical power, thereby reducing the chance of false negative findings (i.e., type II errors). Second, our larger sample size allowed for adjustment of a greater number of covariates in our statistical models, reducing confounding and improving the precision of our estimates. Third, we measured markers up to three times and analyzed mental status outcomes up to a week afterwards. Because inflammatory marker levels may change over time [28], our more comprehensive approach to biomarker measurement may explain the differences with prior studies where markers were measured at one time point. Fourth, in our models, we allowed mental status to transition between normal, delirium, and coma on a daily basis and considered these mental states in light of potential confounding related to death and discharge, representing an advance in statistical technique. Fifth, the markers in previous studies varied and were in some cases analyzed in the same regression model. We adjusted for baseline and clinical covariates but not for concentrations of other markers. Because the effects of specific inflammatory markers are complex, interrelated, and environment specific [22, 29], future studies are needed to determine the predictive validity of specific markers (or panels of markers) in the development of delirium while also considering clinical covariates.

Low concentrations of protein C were associated with greater odds of delirium, confirming our prior work in a smaller cohort [12]. Protein C, best known for its anticoagulant properties, exerts anti-inflammatory and

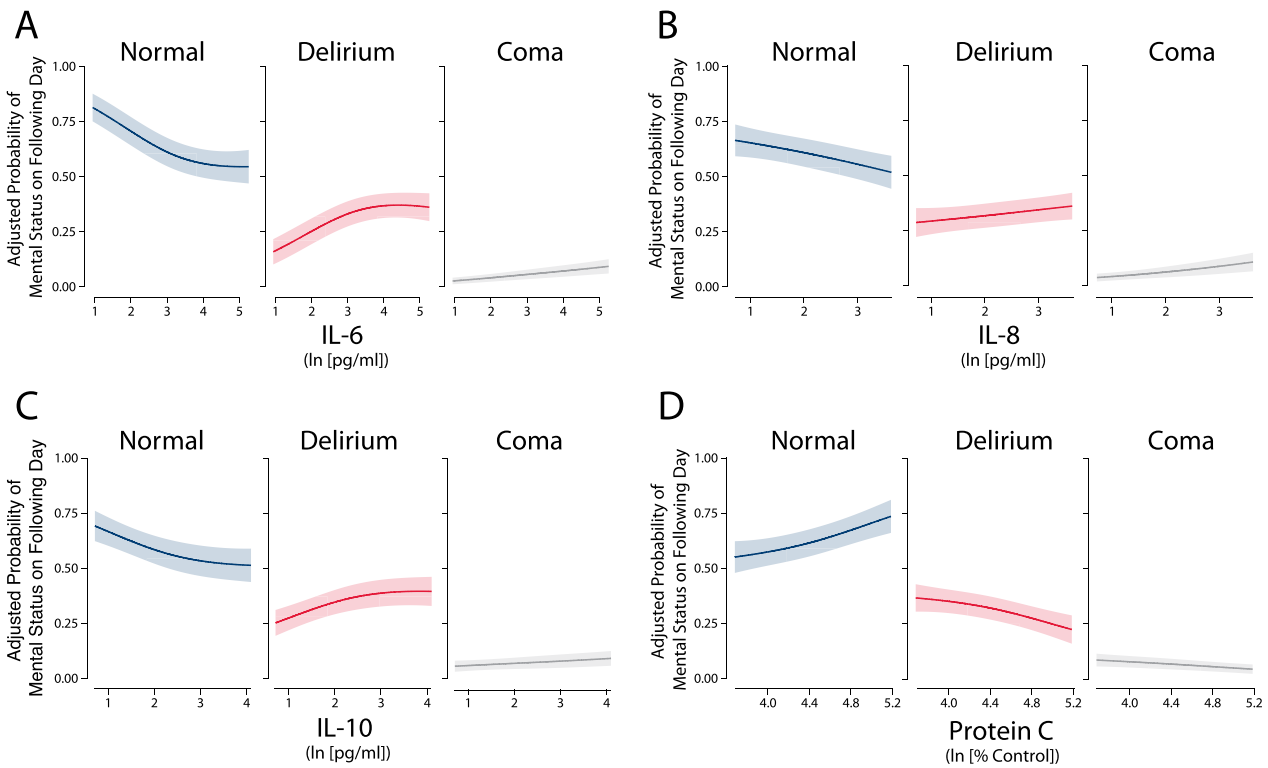

Fig. 2 Associations between markers of inflammation and mental status. These figures display the natural log concentration of each biomarker level (*x*-axis) versus the adjusted probabilities of mental status on the following day (*y*-axis). For each figure, the 3 panels from left to right, display the association between marker concentration and normal mental status (blue), delirium (red), or coma (gray), respectively. Solid lines indicate associations. Shading indicates 95% confidence intervals. Higher concentrations IL-6 (**A**), IL-8 (**B**), and IL-10 (**C**) were associated with a lower adjusted probability of normal mental status the following day and higher probabilities of delirium or coma (see Table 2). In contrast, higher concentrations of protein C (**D**) were associated with a higher adjusted probability of normal mental status on the following day and lower probabilities of delirium or coma (see Table 2)

cytoprotective effects on endothelial cells and neurons, potentially interacting with a number of pathways hypothesized to result in delirium [30]. Though studies of recombinant human activated protein C (rhAPC) demonstrated no mortality benefit in sepsis, the effect of rhAPC on delirium remains unknown [31–33]. Given the neuroprotective and neurogenic effects of activated protein C in mouse models of other forms of neurological injury (e.g., stroke and traumatic brain injury) [34], the role of activated protein C on delirium should be investigated in future pre-clinical and clinical studies.

Two prior studies have examined markers of inflammation and coma [13, 16]. Skrobik and colleagues reported IL-6 levels were lower in patients with coma than in those with delirium, but not different than those with normal mental status. Levels of IL-8 did not differ according to mental status [13]. These unadjusted findings suggest different mechanisms might underlie delirium and coma. Khan et al., alternatively, reported higher levels of IL-6, TNF-α, and CRP were associated with the number of days of coma, whereas IL-8 and IL-10 were not, in a 321-patient cohort, all of whom had delirium at study enrollment. In our cohort, we adjusted for potential confounders common among those with critical illness, included participants with and without delirium or coma, and found that the same markers (IL-6, IL-8, IL-10, and CRP) that were associated with delirium were also associated with coma, suggesting that inflammation and coagulation are pathways that underlies both syndromes. These data suggest that studies targeting these pathways during critical illness should also examine delirium and coma outcomes.

Despite the strengths of the current investigation, our findings should be considered in the context of several limitations. We collected markers only during the first 5 days of study enrollment and therefore cannot comment on the association between the persistence or resolution of inflammation and disordered endogenous anticoagulation or the kinetics of these biomarkers with delirium and/or coma. Indeed, the lack of marker data after day 5 may explain our previous analyses found no associations between markers of inflammation or coagulation and

Table 3 Associations between markers of inflammation and delirium/coma-free days during the following week

Marker	75th Percentile[a]	25th Percentile[a]	OR[b]	95% CI	p value[c]
CRP (ng/mL)	12.2	10.9	0.9	0.7–1	0.68
IFN-γ (pg/mL)	1.1	− 0.9	0.9	0.8–1	0.12
IL-1β (pg/mL)	− 0.2	− 1.5	1	0.9–1.1	0.60
IL-6 (pg/mL)	4.2	2	0.6	0.5–0.7	< 0.0001
IL-8 (pg/mL)	2.7	1.3	0.7	0.6–0.8	< 0.0001
IL-10 (pg/mL)	3.2	1.3	0.7	0.6–0.8	0.0002
IL-12 (pg/mL)	1.4	− 0.7	1	0.9–1.1	0.91
MMP-9 (pg/mL)	12.6	11.2	1	0.9–1.1	0.92
TNF-α (pg/mL)	2.7	1.6	1	0.8–1.1	0.47
TNFR1 (pg/mL)	9.7	8.4	0.8	0.7–1	0.21
Protein C (% control)	4.8	4.1	1.3	1.1–1.5	0.008

CI confidence interval, *CRP* C-reactive protein, *IFN* interferon, *IL* interleukin, *MMP* matrix metalloproteinase, *OR* odds ratio, *TNF* tumor necrosis factor, *TNFR* tumor necrosis factor receptor

[a] Values represent the natural log biomarker concentration

[b] Odds ratios compare the odds of having more days alive without coma or delirium (i.e., more delirium/coma-free days) during the seven days after marker measurement to the odds of having fewer days alive without coma or delirium for a patient with a marker concentration at the 75th percentile vs. a patient with a biomarker concentration at the 25th percentile, with all other covariates adjusted to the median or mode. Thus, for IL-6, a patient with a concentration at the 75th percentile has 40% lower odds of having more delirium/coma free days than a patient with an IL-6 concentration at the 25th percentile

[c] The P-value represents the significance of the overall model, whereas the odds ratio represents the magnitude of the association between biomarker and the number of delirium/coma-free days

long-term cognitive outcomes [35]. Second, we measured 11 markers but did not examine an exhaustive list of markers. The markers we studied may not represent all direct and indirect pathways by which systemic inflammation and endogenous anticoagulation affect the brain to result in delirium and coma. Third, we assessed the relationship between individual markers with delirium and coma. Because these markers function in larger biological pathways, future studies should explore the downstream signaling pathways of these markers and determine whether specific patterns (or profiles) involving multiple markers and transitions are associated with delirium and coma, to aid in further mechanistic understanding of delirium and coma. Fourth, many patients were delirious or comatose at the time of study enrollment, reflective of the high severity of illness in this cohort. Thus, we are not able to test the association between markers of inflammation and incident delirium and coma. Nevertheless, our findings show that marker concentrations were associated with subsequent days of acute brain dysfunction, an important finding given the prognostic implications of delirium duration [3, 5, 6]. Fifth, we did not collect data on use of medications that could affect endogenous anticoagulant activity (e.g., heparin, low-molecular weight heparins [LMWH]) and might confound the association between protein C concentrations and mental status. These medications block activation of protein C, resulting in lower activity. Nevertheless, two studies found that heparin and LMWH were associated with a lower risk of delirium, a relationship which, if present in our study,

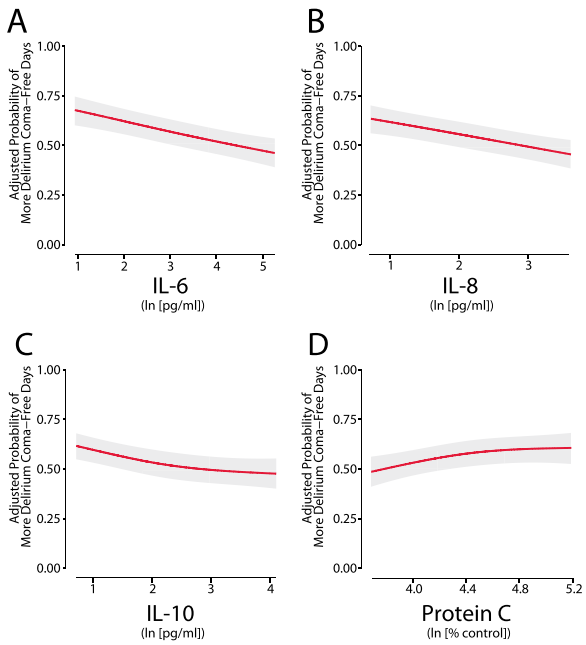

Fig. 3 Associations between markers of inflammation and delirium/coma-free days. These figures display the natural log concentration of each marker level (*x*-axis) versus the adjusted probabilities of more delirium/coma-free days during the next week (*y*-axis). The association with IL-6 is indicated in panel **A**, with IL-8 in panel **B**, with IL-10 in panel **C**, and with protein **C** in panel **D**. Solid lines indicate associations. Shading indicates 95% confidence intervals. The adjusted probability of more delirium/coma-free days decreased as the concentrations of IL-6 (Fig. 2A), IL-8 (Fig. 2B) and IL-10 (Fig. 2C) increased (see Table 3 for effect size). As the concentration of protein C increased (Fig. 2D), however, the probability of more delirium/coma-free days increased (see Table 3 for effect size)

would bias our findings toward the null [36, 37]. Thus, without adjusting for anticoagulant medications, our models may be conservative. Future studies of the effect of endogenous anticoagulant activity on mental status in critical illness should account for administration of these medications and measure plasma activity of these drugs to advance the understanding of the relationship between endogenous anticoagulation with mental status. Finally, as with all observational studies, we cannot rule out the possibility of unmeasured confounding.

In summary, we found consistent associations between IL-6, IL-8, IL-10, and protein C with delirium and coma the day following marker measurement as well as the number of delirium/coma-free days over the next week. These data support the hypothesis that systemic inflammation and possibly disordered coagulation play a role in the pathophysiology of delirium and coma during critical illness.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-024-07388-6.

Author details
[1] Division of Pulmonary, Critical Care, and Sleep Medicine, The Ohio State University College of Medicine, Columbus, OH, USA. [2] Davis Heart and Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, OH, USA. [3] Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center, Nashville, TN, USA. [4] Division of Anesthesia Critical Care Medicine, Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA. [5] Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [6] Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, USA. [7] Vanderbilt Brain Institute, Vanderbilt University School of Medicine, Nashville, TN, USA. [8] Vanderbilt Memory and Alzheimer's Center, Vanderbilt University School of Medicine, Nashville, TN, USA. [9] Center for Quality Aging, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [10] Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN, USA. [11] Geriatric Research, Education and Clinical Center (GRECC) Service, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN, USA. [12] Clinical Research Investigation and Systems Modeling of Acute Illness (CRISMA) Center, Department of Critical Care Medicine, University of Pittsburgh, 638 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA 15261, USA.

Author contributions
All authors contributed to study conception and design as well as acquisition, analysis, or interpretation of data. JLT, OMO, and RC conducted statistical analyses. All authors interpreted the results. NEB and TDG drafted the manuscript, and all authors critically revised the manuscript and approved the final version.

Funding
This study was supported by the National Institutes of Health K76AG054864, K23AG034257, R01AG027472, R01AG035117) and VA MERIT. In addition, WE received support from the Veterans Affairs Tennessee Valley GRECC.

Data availability
Data and supporting documents from this study are available for academic research purposes upon request from the Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center, Nashville, TN, USA (www.icudelirium.org).

Declarations

Conflicts of interest
CGH is a consultant for Sedana Medical and has received research grant from Kohler Chemie GMBH. PP has received a research grant from Hospira. WE has received research grants and/or honoraria from Hospira, Orion, Pfizer, Abbott, and Kohler Chemie GMBH. The remaining authors declare no competing interests.

Publisher's Note

Received: 10 October 2023 Accepted: 10 March 2024
Published: 22 April 2024

References

1. American Psychiatric Association, American Psychiatric Association, DSM-5 Task Force (2013) Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association, Washington, D.C.
2. Brummel NE, Girard TD (2019) Delirium in the critically ill patient. Handb Clin Neurol 167:357–375
3. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH (2009) Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 180:1092–1097
4. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, Dittus RS, Bernard GR, Ely EW (2010) Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med 38:1513–1520
5. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW, Investigators B-IS (2013) Long-term cognitive impairment after critical illness. N Engl J Med 369:1306–1316
6. Brummel NE, Jackson JC, Pandharipande PP, Thompson JL, Shintani AK, Dittus RS, Gill TM, Bernard GR, Ely EW, Girard TD (2014) Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. Crit Care Med 42:369–377
7. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB (2010) The neuroinflammatory hypothesis of delirium. Acta Neuropathol 119:737–754
8. Cunningham C (2011) Systemic inflammation and delirium: important co-factors in the progression of dementia. Biochem Soc Trans 39:945–953
9. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C (2008) Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res 65:229–238
10. van den Boogaard M, Kox M, Quinn KL, van Achterberg T, van der Hoeven JG, Schoonhoven L, Pickkers P (2011) 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 15:R297
11. McGrane S, Girard TD, Thompson JL, Shintani AK, Woodworth A, Ely EW, Pandharipande PP (2011) Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care 15:R78
12. Girard TD, Ware LB, Bernard GR, Pandharipande PP, Thompson JL, Shintani AK, Jackson JC, Dittus RS, Ely EW (2012) Associations of markers of inflammation and coagulation with delirium during critical illness. Intensive Care Med 38:1965–1973
13. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J (2013) Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors. Crit Care Med 41:999–1008

14. Ritter C, Tomasi CD, Dal-Pizzol F, Pinto BB, Dyson A, de Miranda AS, Comim CM, Soares M, Teixeira AL, Quevedo J, Singer M (2014) Inflammation biomarkers and delirium in critically ill patients. Crit Care 18:R106
15. Zhang Z, Pan L, Deng H, Ni H, Xu X (2014) Prediction of delirium in critically ill patients with elevated C-reactive protein. J Crit Care 29:88–92
16. Khan BA, Perkins AJ, Prasad NK, Shekhar A, Campbell NL, Gao S, Wang S, Khan SH, Marcantonio ER, Twigg HL 3rd, Boustani MA (2020) Biomarkers of delirium duration and delirium severity in the ICU. Crit Care Med 48:353–361
17. Hughes CG, Patel MB, Jackson JC, Girard TD, Geevarghese SK, Norman BC, Thompson JL, Chandrasekhar R, Brummel NE, May AK, Elstad MR, Wasserstein ML, Goodman RB, Moons KG, Dittus RS, Ely EW, Pandharipande PP, Mind-Icu B-ICUi (2017) Surgery and anesthesia exposure is not a risk factor for cognitive impairment after major noncardiac surgery and critical illness. Ann Surg 265:1126–1133
18. Bastarache JA, Koyama T, Wickersham NE, Ware LB (2014) Validation of a multiplex electrochemiluminescent immunoassay platform in human and mouse samples. J Immunol Methods 408:13–23
19. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessler CN, Dittus RS, Bernard GR (2003) Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 289:2983–2991
20. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R (2001) Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 286:2703–2710
21. van Gool WA, van de Beek D, Eikelenboom P (2010) Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 375:773–775
22. Wilson CJ, Finch CE, Cohen HJ (2002) Cytokines and cognition: the case for a head to toe inflammatory paradigm. JAGS 50:2041–2056
23. Cunningham C, Campion S, Lunnon K, Murray CL, Woods JF, Deacon RM, Rawlins JN, Perry VH (2009) Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. Biol Psychiatry 65:304–312
24. Murray C, Sanderson DJ, Barkus C, Deacon RM, Rawlins JN, Bannerman DM, Cunningham C (2012) Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. Neurobiol Aging 33:603–616
25. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, Pollmacher T (2001) Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 58:445–452
26. Krabbe KS, Reichenberg A, Yirmiya R, Smed A, Pedersen BK, Bruunsgaard H (2005) Low-dose endotoxemia and human neuropsychological functions. Brain Behav Immun 19:453–460
27. Plaschke K, Fichtenkamm P, Schramm C, Hauth S, Martin E, Verch M, Karck M, Kopitz J (2010) Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. Intensive Care Med 36:2081–2089
28. van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE (2008) Time-course of cytokines during delirium in elderly patients with hip fractures. J Am Geriatr Soc 56:1704–1709
29. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL, Angus DC, Gen IMSI (2007) Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med 167:1655–1663
30. Christiaans SC, Wagener BM, Esmon CT, Pittet JF (2013) Protein C and acute inflammation: a clinical and biological perspective. Am J Physiol Lung Cell Mol Physiol 305:L455-466
31. Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, Francois B, Guy JS, Bruckmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias WL, Administration of Drotrecogin Alfa in Early Stage Severe Sepsis Study G (2005) Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med 353:1332–1341
32. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr, Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis Study Group (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
33. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gardlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD (2012) Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 366:2055–2064
34. Petraglia AL, Marky AH, Walker C, Thiyagarajan M, Zlokovic BV (2010) Activated protein C is neuroprotective and mediates new blood vessel formation and neurogenesis after controlled cortical impact. Neurosurgery 66:165–171
35. Brummel NE, Hughes CG, Thompson JL, Jackson JC, Pandharipande P, McNeil JB, Raman R, Orun OM, Ware LB, Bernard GR, Ely EW, Girard TD (2021) Inflammation and coagulation during critical illness and long-term cognitive impairment and disability. Am J Respir Crit Care Med 203:699–706
36. Arbabi M, Ziaei E, Amini B, Ghadimi H, Rashidi F, Shohanizad N, Moradi S, Beikmarzehei A, Hasanzadeh A, Parsaei A (2022) Delirium risk factors in hospitalized patient: a comprehensive evaluation of underlying diseases and medications in different wards of a large Urban Hospital Center in Iran. BMC Anesthesiol 22:147
37. D'Ardes D, Carrarini C, Russo M, Dono F, Speranza R, Digiovanni A, Martinotti G, Di Iorio A, Onofrj M, Cipollone F, Bonanni L (2021) Low molecular weight heparin in COVID-19 patients prevents delirium and shortens hospitalization. Neurol Sci 42:1527–1530