ORIGINAL ARTICLE

Inflammation and Coagulation during Critical Illness and Long-Term Cognitive Impairment and Disability

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Abstract

Rationale: The biological mechanisms of long-term cognitive impairment and disability after critical illness are unclear.

Objectives: To test the hypothesis that markers of acute inflammation and coagulation are associated with subsequent long-term cognitive impairment and disability.

Methods: We obtained plasma samples from adults with respiratory failure or shock on Study Days 1, 3, and 5 and measured concentrations of CRP (C-reactive protein), IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, MMP-9 (matrix metalloproteinase-9), TNF-α (tumor necrosis factor-α), soluble TNF receptor 1, and protein C. At 3 and 12 months after discharge, we assessed global cognition, executive function, and activities of daily living. We analyzed associations between markers and outcomes using multivariable regression, adjusting for age, sex, education, comorbidities, baseline cognition, doses of sedatives and opioids, stroke risk (in cognitive models), and baseline disability scores (in disability models).

Measurements and Main Results: We included 548 participants who were a median (interquartile range) of 62 (53–72) years old, 88% of whom were mechanically ventilated, and who had an enrollment Sequential Organ Failure Assessment score of 9 (7–11). After adjusting for covariates, no markers were associated with long-term cognitive function. Two markers, CRP and MMP-9, were associated with greater disability in basic and instrumental activities of daily living at 3 and 12 months. No other markers were consistently associated with disability outcomes.

Conclusions: Markers of systemic inflammation and coagulation measured early during critical illness are not associated with long-term cognitive outcomes and demonstrate inconsistent associations with disability outcomes. Future studies that pair longitudinal measurement of inflammation and related pathways throughout the course of critical illness and during recovery with long-term outcomes are needed.

Keywords: inflammation; coagulation; dementia; disability; critical illness

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At a Glance Commentary

Scientific Knowledge on the Subject: Despite the pervasiveness of poor long-term outcomes after critical illness, the underlying biological mechanisms are unclear. Activation of inflammatory and coagulation pathways promotes organ dysfunction during critical illness, but the relationships between these pathways and longer-term outcomes are unclear.

What This Study Adds to the Field: This large, prospective, multicenter cohort study shows that, after adjusting for potential confounders, markers of acute systemic inflammation and coagulation collected early during critical illness are not consistently associated with long-term cognitive or disability outcomes 3 and 12 months after hospital discharge. Future studies that measure inflammation and related pathways throughout the course of critical illness and during recovery in conjunction with cognitive and disability assessments are needed.

Up to one-third of patients who survive critical illness suffer from long-term cognitive impairment and disabilities in activities of daily living (1–7). Although previous studies have begun to describe the clinical risk factors associated with these outcomes (1–5, 8–10), the biological mechanisms that may underlie long-term cognitive impairment and disability in survivors of critical illness remain unknown.

Activation of inflammatory and coagulation pathways promotes acute organ dysfunction during critical illness syndromes such as sepsis, acute respiratory distress syndrome, and surgery (11–13). In those without critical illness, these interrelated mechanisms are associated with greater odds of developing dementia and disability (14–17). Whether these mechanisms are associated with similar adverse long-term outcomes in survivors of critical illness is unknown.

To address these knowledge gaps, we measured circulating plasma markers of acute inflammation and coagulation and assessed long-term cognition and disability outcomes in a multicenter, prospective cohort study of adults with critical illness. We tested the hypothesis that higher concentrations of markers of inflammation and lower concentrations of a marker of coagulation during critical illness are associated with worse cognition and disability 3 and 12 months after critical illness.

Portions of these data were presented in abstract form (20).

Methods

Study Design and Population

During the identical (except for different enrolling sites) BRAIN-ICU (Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors; NCT00392795) and MIND-ICU (Delirium and Dementia in Veterans Surviving ICU Care; NCT00400062) multicenter, prospective cohort studies, we enrolled patients ⩾18 years old who were treated in medical and surgical ICUs for acute respiratory failure and/or shock. Detailed inclusion and exclusion criteria have been previously published (3, 9, 18, 19) and are provided in the online supplement. For this long-term outcomes study, we also excluded those who died, withdrew, or were lost to follow-up before 3 months and those who did not have at least 1 day of complete biomarker measurement. Each center's institutional review board approved the study protocol. Patients or their proxies provided informed consent.

Exposures

We enrolled participants within 72 hours of acute organ failure and collected blood samples on Study Days 1, 3, and 5. Using commercially available immunoassays and validated laboratory protocols (21), we measured, in duplicate, plasma concentrations of CRP (C-reactive protein), IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, MMP-9 (matrix metalloproteinase-9), TNF-α (tumor necrosis factor-α), sTNFR1 (soluble tumor necrosis factor receptor 1), and protein C. Descriptions of sample collection and processing and the rationale for inclusion of each marker are provided in the online supplement.

Outcomes

At 3 and 12 months after hospital discharge, study personnel blinded to events of the hospitalization measured participants' global cognition using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (22), executive function using the Trail Making Test Part B (Trails B) (23), disability in basic activities of daily living (BADLs) using the Katz ADL (24), and disability in instrumental ADLs (IADLs) using the Functional Activities Questionnaire (FAQ) (25).

Covariates

Based on prior research and biological plausibility, we chose covariates *a priori* that we hypothesized may confound the association of interest between marker levels and outcome. In all models, we adjusted for age, sex, years of education, Charlson comorbidity index score (26), Short Informant Questionnaire on Cognitive Decline in the Elderly score (27), and mean daily doses of sedatives and opioids. In addition, in cognitive outcome models, we adjusted for underlying stroke risk using the Framingham Stroke Risk Score (28), and in disability models, we adjusted for baseline disability using the Katz ADL (24) and FAQ scores (25). Details of each covariate are provided in the online supplement.

Statistical Analysis

We calculated the mean value of each marker and then performed $\log_{10}$-transformation, using the transformed value as the exposure variable for all models. In addition to these primary analyses, we conducted a sensitivity analysis using Study Day 1 biomarker levels as the exposure variable and another using the percent change in biomarker level as the exposure variable. To measure associations with long-term cognitive outcomes, we performed multiple linear regression, adjusted for covariates. To measure the associations with disability outcomes, we performed zero-inflated negative binomial regression, adjusted for covariates.

To reduce the effect of bias due to differences between patients who were included in these analyses and those who were not because of death, study dropout, or loss to follow-up (i.e., attrition-related selection bias), we used inverse probability of attrition weighting (29, 30). In brief, we estimated the probability that each patient would be alive, not withdrawn, and included in each of the four potential follow-up cohorts (e.g., cognitive or disability at 3 or 12 mo). We included the

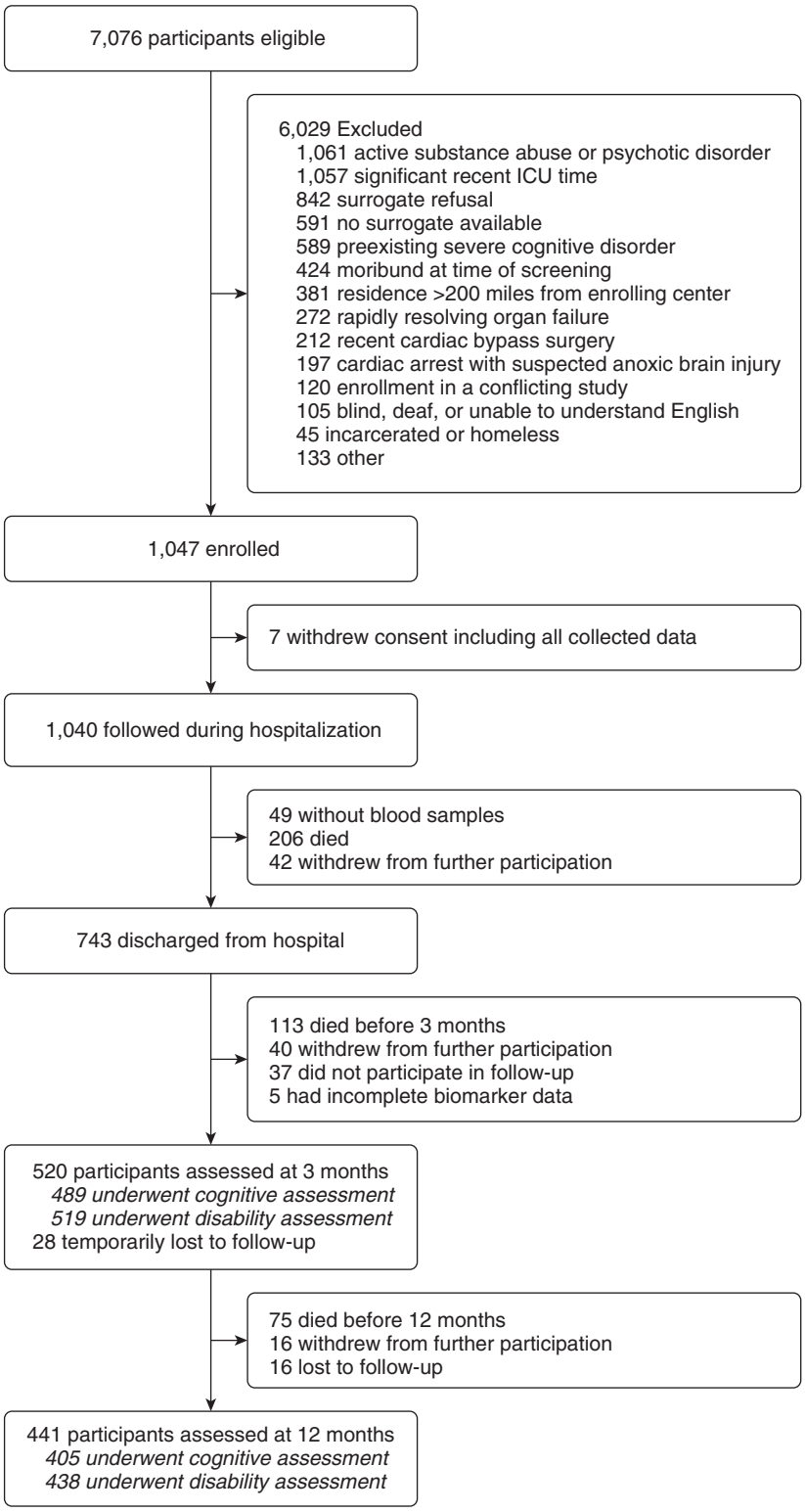

Figure 1. Flow of participant enrollment and follow-up.

inverse of these weighted variables in the respective models. A description of models used to calculate the weighted variables is included in the online supplement.

In cognitive outcome models, we allowed associations with continuous covariates to be nonlinear using restricted cubic splines. In disability outcome models, all covariates were forced linear except biomarkers, which were allowed to be nonlinear using restricted cubic splines. In all models, we excluded nonlinear terms if the global test for nonlinearity was $P > 0.20$. We used multiple imputation to account for missing follow-up outcomes data in those who participated in some follow-up testing using predictive mean matching, but we did not impute outcomes for those who died, withdrew, or were lost to follow-up. All analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna Austria). P values $<$ 0.05 were considered significant.

Results

Between March 2007 and December 2010, we recruited 1,047 participants, 7 of whom withdrew permission to use their data. We followed 1,040 participants during their hospitalization (Figure 1). Blood samples were not obtained from 49 of these participants. Thus, 991 participants were eligible for this cohort study (Table E1 in the online supplement). Before hospital discharge, 206 participants died and 42 withdrew consent. Before 3-month follow-up, an additional 113 participants died, 40 withdrew, and 37 did not participate in follow-up. Among those who participated in follow-up, there were five who did not have at least 1 day of complete biomarker data. Therefore, 548 unique participants were analyzed for the current study, the majority of whom were mechanically ventilated and who had a high severity of illness (Table 1). Among survivors (i.e., including participants who withdrew or were lost to follow-up), we assessed cognition in 489/672 (73%) and disability in 519/672 (77%) at 3 months and cognition in 405/597 (68%) and disability in 438/597 (73%) at 12 months.

Marker Concentrations

Marker concentrations were obtained on more than 98% of eligible participant-days. The median time between ICU admission and study enrollment was 1 (0.7–2.0) day. Median concentrations of each marker from Study Days 1, 3, and 5 are presented in Table E2.

Cognitive Function and Disability at Follow-up

Complete cognitive outcomes assessments were performed in 423/489 (87%)

Table 1. Demographic and Clinical Characteristics of Participants

Characteristic	Participants (*N* = *548*)*
Age, yr	61 (52–70)
Sex, M, *n* (%)	328 (60)
White race, *n* (%)	488 (89)
Years of education	12 (12–14)
IQCODE score at enrollment	3.0 (3.0–3.1)
Charlson comorbidity index score	2 (1–4)
APACHE II score at admission	23 (17–29)
Mean SOFA score at admission	8 (7–11)
Diagnosis at admission, *n* (%)	
Sepsis	166 (30)
Acute respiratory failure	90 (16)
Cardiogenic shock, myocardial infarction, or arrhythmia	96 (17)
Airway protection/upper airway obstruction	55 (10)
Surgical procedure†	99 (18)
Neurologic disease or seizure	7 (1)
Other diagnosis	35 (6)
Enrolling center, *n* (%)	
Academic	295 (54)
Community	135 (25)
Veterans Affairs	118 (22)
Mechanical ventilation	
Patients, *n* (%)	483 (88)
Days of mechanical ventilation‡	2 (1–6)
Delirium	
Patients, *n* (%)	389 (71)
Days of delirium‡	3 (2–7)
Coma	
Patients, *n* (%)	288 (53)
Days of coma‡	2 (1–5)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; IQCODE = Short Informant Questionnaire on Cognitive Decline in the Elderly; SOFA = Sequential Organ Failure Assessment.
Data are shown as median (interquartile range) unless noted otherwise.
**N* represents the number of participants who were assessed at either 3- or 12-month follow-up. Overall, we assessed 520 patients at 3 months and an additional 28 patients at 12 months who were temporarily lost to follow-up at 3 months.
†Includes gastric, colonic, vascular, urologic, orthopedic, obstetric/gynecologic, hepatobiliary/pancreatic, otolaryngologic, or transplant.
‡Among participants who had the clinical condition.

Table 2. Cognitive and Disability Outcomes at Follow-up

Outcome	3 mo	12 mo
RBANS global cognition composite score*†	80 (71–88)	82 (72–90)
Trail Making Test Part B score*‡	41 (33–49)	43 (35–51)
Katz ADL score§‖	0 (0–2)	0 (0–1)
Functional Activities Questionnaire score§¶	3 (0–9)	2 (0–8)

Definition of abbreviations: Katz ADL = Katz Index of Independence in Activities of Daily Living; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.
Data are shown as median (interquartile range).
*Among 489 participants at 3 months and 405 participants at 12 months.
†RBANS scores have an age-adjusted mean of 100 with an SD of 15. Lower scores indicate worse cognition.
‡Trail Making Test Part B scores have an age-, sex-, and education-adjusted mean of 50, with an SD of 10. Lower scores indicate worse cognition.
§Among 519 participants at 3 months and 438 participants at 12 months.
‖Katz ADL scores range from 0 to 12. Scores of ⩾1 indicate disability.
¶Functional Activities Questionnaire scores range from 0 to 30. Scores ⩾1 indicate disability.

participants at 3 months and in 365/405 (90%) participants at 12 months. Likewise, complete disability outcomes assessments were performed in 462/519 (89%) participants at 3 months and in 391/439 (89%) participants at 12 months. At both 3- and 12-month follow-up, RBANS and Trails B scores were approximately 1 SD below age-adjusted population means, where lower scores indicate worse cognitive function (Table 2). Katz ADL and FAQ scores at 3 and 12 months indicated that disabilities in BADLs and IADLs were present in one-quarter of survivors (Table 2).

Association of Markers of Inflammation and Coagulation with Long-Term Cognitive Outcomes

At 3 and 12 months, none of the markers studied were associated with RBANS global cognition scores (Figure 2A). Likewise, none of the markers were associated with Trails B scores at either 3- or 12-month follow-up (Figure 2B). Sensitivity analyses that used Study Day 1 biomarker level or percent change in biomarker level as the main exposure did not alter these findings (Tables E3 and E4).

Association of Markers of Inflammation and Coagulation with Long-Term Disability Outcomes

Higher levels of four markers—CRP, IL-1β, IL-6, and MMP-9—were associated with higher 3-month Katz ADL scores, indicating worse disability in BADLs (Figure 3A). In contrast, higher levels of the antiinflammatory marker IL-10 were associated with lower Katz ADL scores at 3 months. At 12 months, higher levels of two markers, CRP and MMP-9, were associated with higher Katz ADL scores (Figure 3A). Higher levels of TNF-α, however, were associated with lower Katz ADL scores at 12 months. No other markers were associated with Katz ADL scores at 3 or 12 months.

Higher levels of two markers—CRP and MMP-9—were associated with higher 3- and 12-month FAQ scores (Figure 3B) indicating worse disability in IADLs. Higher levels of IL-8 were associated with lower FAQ scores at 3 months. Higher levels of three markers—IFN-γ, IL-8, and TNF-α—were associated with lower 12-month FAQ scores (Figure 3B). No other markers were associated with FAQ scores at either 3 or 12 months. In models using Study Day 1 biomarker level or percent change in biomarker level as the main exposure, CRP and MMP-9 were no longer

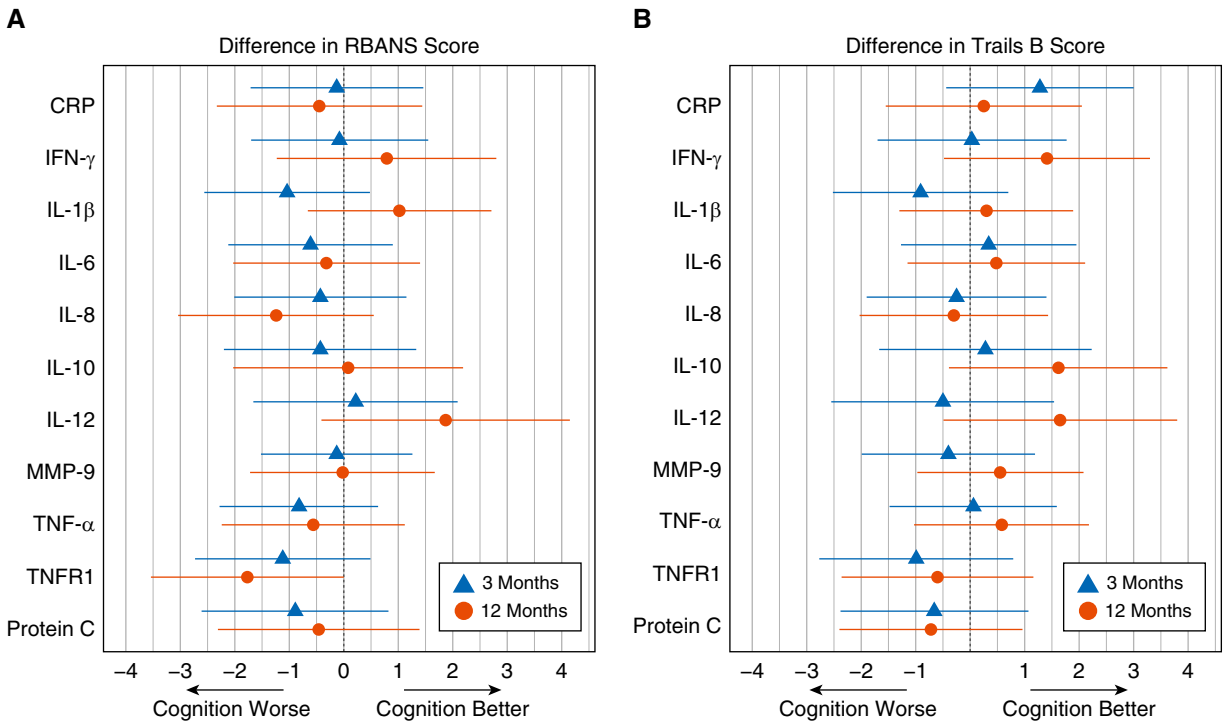

Figure 2. Associations of markers of inflammation and coagulation with long-term cognition. These figures display the difference in score on the (*A*) RBANS or (*B*) Trails B tests for each of the 11 biomarkers of interest. Blue triangles represent the point estimate at 3 months and red circles represent the point estimate at 12 months. Horizontal lines represent the 95% confidence interval. Each comparison is of participants with biomarker concentration at the 75th percentile to participants with a biomarker concentration at the 25th percentile, with all covariates adjusted to their mean or mode value. Negative changes in scores (i.e., point estimates to the left of 0) represent worse cognitive function. CRP = C-reactive protein; MMP = matrix metalloproteinase; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor; Trails B = Trail Making Test Part B.

associated with Katz ADL or FAQ scores (Tables E5 and E6).

Discussion

In this large, multicenter, prospective cohort study, we found that markers of acute systemic inflammation and coagulation measured early in the course of a critical illness are not associated with long-term cognitive function in survivors. Likewise, these markers demonstrated inconsistent associations with disabilities in basic and instrumental activities of daily living. These results do not support the hypothesis that the interrelated pathways of systemic inflammation and coagulation during the acute phase of critical illness are risk factors for the development of adverse long-term outcomes in survivors.

The present study, the largest to date to measure the association of markers of inflammation and coagulation with long-term cognitive function in survivors of critical illness, extends the findings from two prior Dutch studies. Van den Boogaard and colleagues found no association between markers of inflammation (e.g., CRP, IL-1β, IL-1ra [IL-1 receptor antagonist], IL-6, IL-8, IL-10, IL-17, IL-18, MIF [macrophage inhibitory factor], and TNF-α) collected once during critical illness and self-reported cognitive function in 52 survivors (31). A second study measured daily CRP levels during critical illness and self-reported cognitive function in 363 survivors at 1 year and found no association between serial CRP measurements and 1-year cognition (32). In contrast, we performed serial measurement of a number of *a priori* defined biomarkers and used objective, robust, and well-validated direct assessments of global cognition and executive function to measure cognitive function in more than 500 survivors at follow-up, with high follow-up rates. Moreover, we used advanced statistical techniques to reduce bias related to death and study dropout. In total, this emerging body of evidence suggests that markers of acute systemic inflammation and coagulation, measured early in the course of a critical illness, are not associated with long-term cognitive impairment in survivors.

The findings that markers of acute inflammation are not associated with long-term cognitive impairment seem to stand in contrast to those from preclinical studies that implicate such a relationship exists and is mediated through microglial activation and ongoing neuroinflammation (33–38). Several possible explanations for this divergence exist. It may be the case that animal models subject to inflammatory insults (e.g., via exposure to LPS, cecal ligation and puncture, or bacterial injection) do not adequately model the complexity and heterogeneity of critical illness, effects related to coexisting illnesses and frailty, or effects of multiple organ failures (39). Many of these preclinical studies, for example, include younger animals, whereas in human studies most patients are in their 50s or 60s or older (40). Thus, differences related to biological processes of aging (e.g., cellular senescence and epigenetic modifications) could account for differences between preclinical

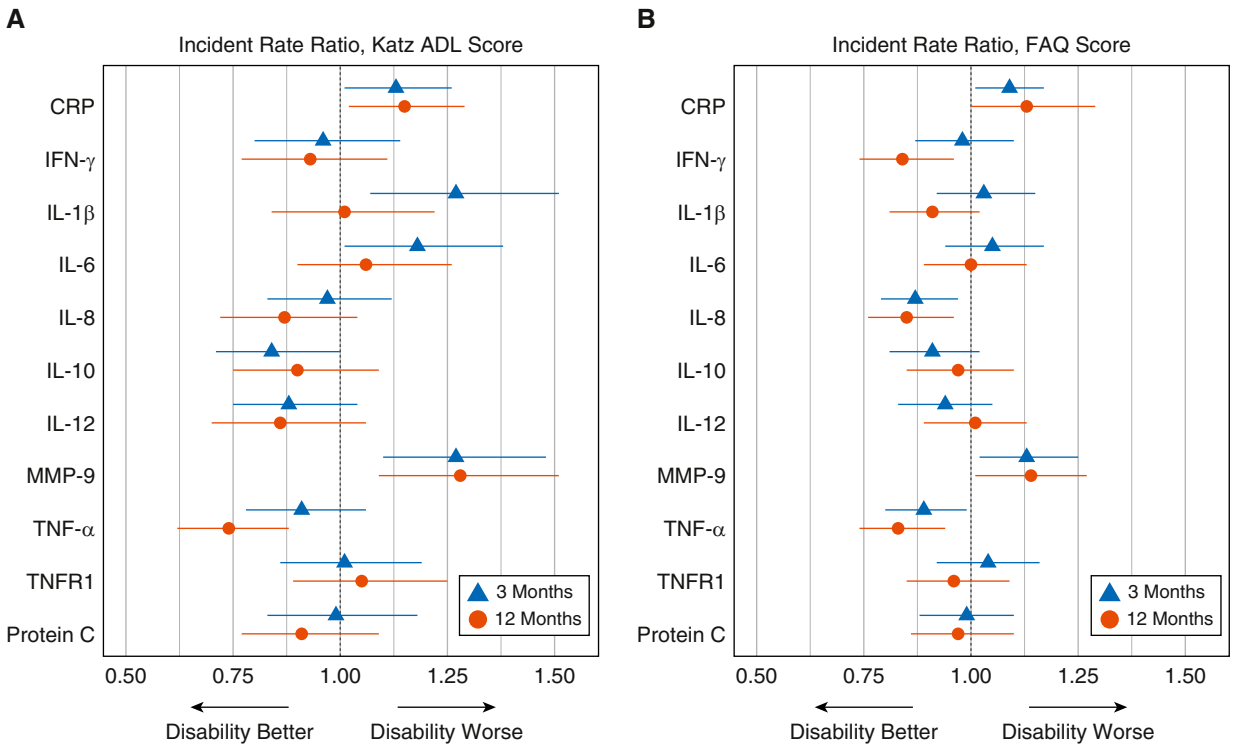

Figure 3. Associations of markers of inflammation and coagulation with disability in activities of daily living. These figures display the incident rate ratio for (*A*) Katz ADL or (*B*) FAQ scores for each of the 11 biomarkers of interest. Blue triangles represent the point estimate at 3 months and red circles represent the point estimate at 12 months. Horizontal lines represent the 95% confidence interval. Each comparison is of participants with biomarker concentration at the 75th percentile to participants with a biomarker concentration at the 25th percentile, with all covariates adjusted to their mean or mode value. Incident rate ratios (IRRs) of 1 represent no change in disability, IRRs greater than 1 (i.e., to the right of 1.0) represent greater disability, and IRRs less than 1 (i.e., to the left of 1.0) represent less disability. CRP = C-reactive protein; FAQ = Functional Activities Questionnaire; Katz ADL = Katz Index of Independence in Activities of Daily Living; MMP = matrix metalloproteinase; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor.

and human studies. On the other hand, most clinical studies, including the current investigation, have been limited by the use of markers of peripheral inflammation rather than direct measures of neuroinflammation. In addition, the neuroanatomical and neuropathologic changes seen in animal models of cognitive impairment after critical illness have only been studied in small case–control studies (34–36, 38, 41). Future studies should seek to address these limitations and to evaluate the effect of critical illness–related chronic inflammation and related pathways on blood–brain barrier integrity, endothelial function, neuronal injury, and neurotransmitter pathways hypothesized to underlie other forms of acquired cognitive impairment and dementia.

We found that two markers, CRP and MMP-9, were associated with worse long-term disability in activities of daily living in survivors of critical illness. Nevertheless, because these markers were evaluated in the context of nine other markers at two time points, and our analyses found only inconsistent associations with disability outcomes, the small number of significant associations should be interpreted as exploratory. A body of literature has reported an association between greater inflammation and worse disability among older adults without critical illness (42–46). To our knowledge, however, the present study is among the first to explore this association in patients who survive critical illness. Prior studies enrolled older adults without acute or critical illness and therefore reported associations between chronic inflammation and disability. In contrast, we studied the association between acute inflammation during critical illness with subsequent disability. Indeed, a limitation of our study is that we did not measure inflammatory markers through the full course of recovery from critical illness (e.g., at or after hospital discharge). Moreover, in prior studies, the association between inflammation and disability was shown over years of follow-up, in contrast to our 12 months of follow-up. Finally, the biological mechanisms of progressive disability in community-dwelling older adults may differ from those that cause the accelerated disability in survivors of critical illness. Future longitudinal studies are needed to explore the time course of inflammation after critical illness with longer follow-up of disability than was available in the present study.

In addition to the strengths of the current investigation described above, we included, of patients from a diverse group of academic, community, and Veterans Affairs hospitals with heterogeneous reasons for medical and surgical critical illness, an approach that enhances the generalizability to our findings. We assessed cognition and disability at two time points, allowing a determination of the association between acute inflammation and these outcomes at both the intermediate and long-term phase of recovery. Finally, all follow-up assessments and biomarker measurements

were performed by different personnel masked to each other's findings.

Nevertheless, our findings should be considered in the context of several limitations. We measured biomarkers during the first week of critical illness. Therefore, our data cannot comment on potential associations between persistent inflammation and coagulation and long-term outcomes after critical illness (47–49). Future longitudinal studies, which pair the measurement of biomarkers of inflammation throughout the course of critical illness and recovery with cognitive and disability assessments, are needed.

Second, the 11 markers we studied may not represent all of the direct and indirect pathways by which systemic inflammation can affect the central nervous system to result in long-term cognitive impairment. Thus, future studies using biomarkers obtained from both peripheral blood and cerebrospinal fluid should evaluate inflammation-associated pathways—such as endothelial dysfunction, microvascular thrombosis, blood–brain barrier disruption, neuroinflammation, and neuronal injury—implicated in other forms of cognitive impairment, dementia, and acquired brain injury. Finally, we did not capture data on events following the hospitalization (e.g., rehospitalizations, rehabilitation interventions, nutritional status, and perceived stress) that may affect the relationship between inflammation and cognitive status or disability. Nevertheless, in our statistical models, we accounted for a number of potential confounders related to a patient's baseline health status and function as well as those related to index critical illness.

Conclusions

In conclusion, we found no consistent associations between markers of acute systemic inflammation and coagulation during critical illness and long-term cognitive function or disability in survivors. Future longitudinal studies are needed to determine whether the subset of critical illness survivors who develop chronic inflammation are at increased risk for long-term cognitive impairment and disability. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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