Relationship Among Clinically Obtained Biomarkers of Inflammation, Hypercoagulability, and Macrophage Activation, and Delirium in Critically Ill Patients With COVID-19

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OBJECTIVES: Critically ill patients with COVID-19 experience high rates of delirium and coma. Whether delirium occurs through novel mechanisms in COVID-19 is not known. We analyzed the relationship among biomarkers of inflammation (C-reactive protein [CRP]), hypercoagulability (D-dimer), and lung macrophage activation (ferritin), and the primary composite outcome of delirium/coma next day. We also measured associations between biomarkers and next day delirium and coma independently, and delirium severity.

DESIGN: Retrospective, observational cohort study.

SETTING: ICUs at two large, urban, academic referral hospitals.

PATIENTS: All consecutive adult patients admitted to the ICU from March 1, 2020, to June 7, 2020, with COVID-19 with clinical biomarkers and delirium assessments performed.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Daily concentrations of CRP, D-dimer, and ferritin were obtained. Coma (assessed by Richmond Agitation-Sedation Scale) and delirium (assessed by Confusion Assessment Method for the ICU/Confusion Assessment Method for the ICU-7) were measured bid. A cohort of 197 ICU patients with COVID-19 were included. Higher D-dimer (odds ratio [OR], 1.57; 95% CI, 1.17–2.12; $p < 0.01$) and ferritin quartiles (OR, 1.36; 95% CI, 1.02–1.81; $p < 0.01$) were associated with greater odds of the composite outcome of delirium/coma next day. D-dimer was associated with greater odds of next day delirium (OR, 1.49; 95% CI, 1.14–1.94; $p < 0.01$) and coma independently (OR, 1.52; 95% CI, 1.08–2.14; $p = 0.017$). Higher ferritin quartiles were associated with greater odds of next day delirium (OR, 1.33; 95% CI, 1.04–1.70; $p = 0.026$) and coma independently (OR, 1.59; 95% CI, 1.14–2.23; $p < 0.01$). Higher CRP quartiles were associated with coma (OR, 1.36; 95% CI, 1.03–1.79; $p = 0.030$) and delirium severity the next day ($\beta = 0.30$; SE, 0.07; $p \leq 0.01$).

CONCLUSIONS: Our hypothesis-generating study found D-dimer and ferritin were associated with delirium/coma the following day, as well as delirium and coma independently. CRP was associated with next day coma and delirium severity. Larger studies to validate these results are needed.

KEY WORDS: biomarkers; coma; COVID-19; critical care; delirium; delirium severity

Severe infection with early variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with admission to the ICU, greater risk of invasive mechanical ventilation, high rates of delirium

KEY POINTS

Question: Are clinically measured biomarkers of inflammation, hypercoagulability, and macrophage activation associated with delirium/coma the next day?

Findings: Higher values of D-dimer and ferritin were associated with greater odds of the composite outcome of delirium/coma the following day. Higher values of C-reactive protein were associated with greater delirium severity next day.

Meaning: D-dimer and ferritin were associated with next day delirium/coma, suggesting pathways of hypercoagulability and macrophage activation in delirium. Larger studies to validate our results are needed.

and coma, and increased mortality (1–3). SARS-CoV-2's tropism for the angiotensin-converting enzyme 2 receptor leads to increased angiotensin and tissue factor-mediated prothrombotic sequelae precipitating vascular and endothelial injury (4, 5). Together, persistent inflammation, immune activation, endothelial injury, and microthrombi are considered major pathophysiological mechanisms in severe COVID-19 (5–9). In high-impact studies where 88% of COVID-19 ICU patients received invasive mechanical ventilation, delirium/coma (acute brain dysfunction) occurred in nearly 80% of patients and persisted for a median 12 days (10, 11). Pandemic-era restrictions on family visitation, prolonged invasive mechanical ventilation requiring deep sedation and neuromuscular blockade, increased use of deliriogenic medications (e.g., benzodiazepines), and high severity of illness are well-recognized delirium and coma risk factors that may at least partly explain these rates (11). Whether delirium/coma are also related to COVID-19 pathophysiologic mechanisms is not fully known but of great scientific and clinical interest (10–13).

To address these knowledge gaps, we conducted this study measuring the association among peripheral biomarkers of inflammation, hypercoagulability, and immune activity, and the composite endpoint of delirium/coma the following day. We conducted additional analyses to measure the association between biomarkers and next day delirium and coma

independently, and next day delirium severity. Our study used clinically obtained biomarkers and delirium assessments in a cohort of COVID-19 patients during the early phase of their critical illness (14–18). We hypothesized that higher levels of C-reactive protein (CRP) (associated with systemic and vascular inflammation), D-dimer (associated with hypercoagulability and microthrombi), and ferritin (associated with macrophage activation), would be associated with delirium/coma, and higher delirium severity (19, 20).

METHODS

This is a retrospective, observational cohort study utilizing electronic medical records (EMRs) from two large, urban, academic referral hospitals (Indiana University Health Methodist Hospital and Eskenazi Health Hospital) affiliated with Indiana University School of Medicine (Indianapolis, IN). The study received ethical approval from the Institutional Review Board at Indiana University (IUIRB). Given the low-risk nature of the study, informed consent was waived by the IUIRB (Protocol No. 2004321390, COVID-19 Case Series on Critically Ill Adults, Exempt Study, Initial Approval April 17, 2020). The study was conducted in accordance with ethical standards of the local Institutional Review Board and Helsinki Declaration of 1975. All consecutive patients admitted to the ICU with acute respiratory failure due to COVID-19 (during the first pandemic surge) and a documented positive result by nasopharyngeal swab polymerase chain reaction test for SARS-CoV-2 from March 1, 2020, to June 7, 2020, were included. We excluded patients under the age of 18, those admitted after June 7, 2020, patients with no delirium or coma assessments available, patients remaining admitted at the end of the study follow-up period (i.e., August 8, 2020), and those without any clinically measured biomarkers of interest (CRP, D-dimer, or ferritin).

Exposures and Outcomes

Exposure variables included demographics, comorbidities, daily severity of illness, and daily invasive mechanical ventilation status (on or off the ventilator). Concentrations of biomarkers of interest (CRP, D-dimer, ferritin) collected daily comprised the main independent variables.

The main outcome was the composite endpoint of delirium/coma observed the following day. Secondary outcomes were delirium and coma occurring independently (both observed the following day) and delirium severity (observed the following day).

Coma was included as an outcome of interest given its strong relationship with poor clinical outcomes, its prevalence in the COVID-19 ICU population, the inability to screen for delirium when the patient has coma, and because delirium and coma have been analyzed together in other high impact publications in ICU delirium and COVID-19 (11).

Coma was assessed using the Richmond Agitation-Sedation Scale (RASS) (21). Delirium was evaluated using the Confusion Assessment Method for the ICU (CAM-ICU) (22). Coma was defined as a RASS score of −4 or −5, making patients ineligible for a CAM-ICU screening, while patients with a RASS score of −3 or greater were eligible for a CAM-ICU assessment. ICU nurses administered the RASS and CAM-ICU bid (between 0700 and 0800, and then between 1900 and 2000) to measure level of sedation and delirium, respectively. Bedside nurses performed the RASS and CAM-ICU in accordance with CAM-ICU guidelines and the morning assessment was performed around protocolized, daily sedation vacations and ventilator liberation trials (spontaneous awakening and breathing trials). These protocolized sedation vacations were performed in accordance with the institution's guidelines if the patient met safety criteria (based on positive pressure settings, hemodynamics, oxygenation requirements, and need for continuous neuromuscular blockade). For the subset of patients admitted to Eskenazi Hospital, bid delirium severity measurements were also assessed by bedside nurses as part of routine clinical care. Delirium severity was assessed bid using the Confusion Assessment Method for the ICU-7 (CAM-ICU-7) (23). CAM-ICU-7 scores range from 0 to 7, with 0–2 indicating no delirium, 3–5 mild to moderate delirium, and 6–7 as severe delirium (23).

Critical care teams routinely ordered once daily CRP, D-dimer, and ferritin for patients admitted to the ICU with COVID-19, for up to 14 days at the discretion of the treating teams. Daily values of CRP, D-dimer, and ferritin were extracted from the medical records for the duration of the follow-up period, if available.

Other Data Measures

EMR data were queried using a combination of automated and manual data extraction. Data pulls from the Regenstrief Medical Record System were supplemented through manual data extraction when needed by highly trained research assistants (24). Patient-level data obtained from the EMR included demographics (age, sex, race), insurance status, comorbidities, daily vital signs, daily laboratory values including biomarkers, bid level of sedation (RASS), mechanical ventilation, date/time, and bid delirium assessments for up to the first 14 days of ICU stay (CAM-ICU positive or negative, including the four CAM-ICU features as applicable: altered mental status, disorganized thinking, altered level of consciousness, disorganized thinking, and CAM-ICU-7 scores), SARS-CoV-2 test results, daily sedative medication orders and medication status if available (administered, held, discontinued), and dates of admission and discharge from hospital and ICU. Comorbidities were obtained and used to compute Charlson Comorbidity Index (25). Acute Physiology and Chronic Health Evaluation (APACHE-II) score was calculated using daily laboratory values, vital signs, and neurologic assessments (26).

Statistical Analysis

Given the transient nature of delirium and to use daily biomarker measures, we used generalized mixed-effects logistic regression models to determine the association between each biomarker using daily biomarker measures and the composite endpoint of delirium/coma status observed the following day. To minimize influence from biomarker outliers, we used biomarker quartiles defined by patients' first biomarker measures. To allow nonlinear time trend in the relationship between biomarker quartiles and delirium/coma status, we used a generalized mixed-effects linear spline model with a change point at day 8. Thus, potential independent variables included biomarker quartiles, day of biomarker measure, an indicator variable for time period (second week vs first week) and two-way interactions among biomarker quartiles, day and time period while adjusting for demographic variables and medical conditions. For all models, we did not detect any interaction effects or nonlinear trends. The models contained a random effect for patient to account for correlations among repeated measures

within patients. We included variables identified as delirium risk factors in systematic reviews to ensure the biological plausibility of our mixed-effects models (27). The models included two time-varying covariates such as daily APACHE-II score and mechanical ventilation status during the day of assessment.

Analysis of Delirium and Coma Independently. To separate biomarkers' association with delirium from coma, we also performed a generalized mixed-effects multinomial model of a daily outcome with three levels (coma the following day, delirium the following day, or no delirium or coma the following day) with biomarker quartiles as the independent variables of interest while adjusting for other covariates.

Delirium Severity. Mixed-effects models were used to examine the association between daily biomarker measures and delirium severity (CAM-ICU-7 score) observed the following day with the same set of independent variables as the models for delirium/coma. All observations with nonmissing data from day 1 to day 14 (or until date of discharge/death for those with length of stay < 14 d) were included in the analysis. Patients who died in the ICU were not excluded from the analyses since their daily biomarker and outcome assessment data were included up to the time of death. The mixed-effects models used in our analyses use repeated measures of biomarkers and clinical outcomes observed the following day and allow varying numbers of observations from patients. Separate models were run for each individual biomarker.

Sensitivity Analyses. We ran several sets of sensitivity analyses. The first sensitivity analysis included running the models separately for those who were discharge alive and for those who died in hospital. The second sensitivity analysis included an analysis excluding patients who had delirium or coma at the time of ICU admission.

RESULTS

After application of eligibility criteria, 235 COVID-19 patients were identified. After excluding patients with incomplete delirium assessments or missing daily APACHE-II laboratory values, 197 patients were included in the final analysis (we show characteristics of the cohort in **Table 1**). The mean age of the cohort was 58.3 years (SD, 15.3 yr), 43.6% were female, 44.1% African American, 20.5% Hispanic, and

TABLE 1.

Characteristics of Critically Ill Patients Admitted With COVID-19

Demographic/Clinical Characteristic	Patients Included in Analysis (*n* = 197)
Age, mean (SD)	58.3 (15.3)
Age, stratified, *n* (%)	
18–49	57 (28.9)
50–64	61 (31.0)
65+	79 (40.1)
Sex, *n* (%)	
Female	86 (43.6)
Race, *n* (%)	
African American	86 (44.1)
Caucasian	61 (31.3)
Hispanic	40 (20.5)
Other	8 (4.1)
Insurance, *n* (%)	
Medicare	46 (23.5)
Medicaid	30 (15.3)
Medicare and Medicaid	25 (12.8)
Commercial	51 (26.0)
Self-pay	27 (13.8)
Other	17 (8.7)
Comorbidities, *n* (%)	
Hypertension	118 (59.9)
Diabetes	86 (43.6)
Obesity, body mass index > 30	110 (61.5)
Tobacco use	50 (25.4)
Chronic obstructive pulmonary disease or asthma	43 (21.8)
Chronic kidney disease	32 (16.2)
Chronic heart failure	27 (13.7)
Cardiac artery disease	23 (11.7)
Dementia	7 (3.6)
Charlson Comorbidity Index, median (IQR)	1.0 (0.0–2.0)
Acute Physiology and Chronic Health Evaluation-II, median (IQR)	18.5 (13.5–25.0)
Respiratory, clinical, and laboratory characteristics	
Invasive mechanical ventilation, *n* (%)	158 (80.2)
Pao_2, mm Hg, median (IQR)	73.0 (58.0–95.0)
Pao_2:Fio_2 ratio, median (IQR)	89.0 (66.0–129.9)
Richmond Agitation-Sedation Scale (14 d), median (IQR)	−1.5 (−2.5 to −0.25)
Glasgow Coma Scale (0–15), median (IQR)	10.0 (7.0–15.0)
WBC count, ×10⁹/L, median (IQR)	9.0 (6.7–12.9)
C-reactive protein, mg/L, median (IQR)	14.6 (8.6–19.0)
D-Dimer, ug/mL, median (IQR)	1.0 (0.6–2.3)
Ferritin, ug/L, median (IQR)	711.3 (379.4–1,295.0)

IQR = interquartile range.

Data are presented as *n* (%) or median (IQR) unless otherwise specified.

15.3% had Medicaid insurance. Hypertension was the most frequent comorbidity (59.9%), the median Charlson Comorbidity Index was 1.0 (interquartile range [IQR], 0–2), and the median APACHE-II score at admission was 18.5 (IQR, 13.5–25.0). In our cohort, 80% of patients underwent invasive mechanical ventilation, the median Pao_2:Fio_2 ratio was 89 (IQR, 66.0–129.9) consistent with severe acute respiratory distress syndrome by Berlin criteria. Additional laboratory and clinical characteristics are shown in Table 1. The median RASS over the first 14 days for the cohort was –1.5 (IQR, –2.5 to –0.25). Median values of CRP, D-dimer, and ferritin at admission are shown in Table 1.

Relationship Between Biomarkers and the Composite Outcome of Delirium/Coma Next Day

To assess the relationship among daily quartiles of biomarker of inflammation, hypercoagulability, and macrophage activation, and the composite outcome of delirium/coma the next day, we performed separate regression models for each of the three biomarkers (CRP, D-dimer, and ferritin). As shown in **Table 2**, we found no significant effect of age, race, sex, or comorbidities (assessed as Charlson Comorbidity Index) in models for CRP, D-dimer, or ferritin. Greater severity of illness, assessed by daily median APACHE-II scores ($p < 0.01$) and invasive mechanical ventilation ($p < 0.01$), were significantly associated with higher odds of delirium/coma the next day in all three biomarker models.

We found higher CRP quartiles were not significantly associated with delirium/coma the next day (odds ratio [OR], 1.11; 95% CI, 0.88–1.41; $p = 0.381$), as shown in Table 2. By contrast, higher D-dimer (OR, 1.57; 95% CI, 1.17–2.12; $p < 0.01$) and ferritin quartiles (OR, 1.36; 95% CI, 1.02–1.81; $p < 0.01$) were associated with greater odds of delirium/coma next day (**Supplementary Table 1**, http://links.lww.com/CCX/B132 for cutoff values for biomarker quartiles). We also found a significant effect

TABLE 2.
Association Between Daily Biomarker Quartiles and Delirium/Coma Status Observed the Following Day ($n = 197$)[a]

Variable	C-Reactive Protein		D-Dimer		Ferritin	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.00 (0.97–1.02)	0.831	1.00 (0.97–1.02)	0.726	1.00 (0.97–1.02)	0.794
Race						
White	0.51 (0.09–2.84)	0.440	0.86 (0.14–5.11)	0.867	0.62 (0.11–3.43)	0.584
Black	0.44 (0.08–2.48)	0.354	0.68 (0.11–4.07)	0.674	0.67 (0.12–3.67)	0.644
Hispanic	0.63 (0.11–3.54)	0.599	1.03 (0.17–6.20)	0.970	0.79 (0.14–4.40)	0.786
Other (reference)						
Male	1.20 (0.61–2.37)	0.597	1.09 (0.55–2.18)	0.806	0.94 (0.46–1.91)	0.858
Acute Physiology and Chronic Health Evaluation-II	1.21 (1.15–1.28)	< 0.001	1.21 (1.14–1.27)	< 0.001	1.21 (1.15–1.28)	< 0.001
Charlson Comorbidity Index	1.20 (0.94–1.54)	0.144	1.17 (0.91–1.50)	0.220	1.18 (0.92–1.50)	0.188
Hypertension	0.50 (0.22–1.13)	0.094	0.58 (0.25–1.31)	0.188	0.49 (0.22–1.09)	0.080
Invasive mechanical ventilation	8.60 (4.62–15.99)	< 0.001	9.83 (5.23–18.47)	< 0.001	10.29 (5.50–19.26)	< 0.001
Biomarker quartile	1.11 (0.88–1.41)	0.381	1.57 (1.17–2.12)	0.003	1.36 (1.02–1.81)	0.033
Time, d	1.10 (1.03–1.18)	0.008	1.03 (0.95–1.11)	0.482	1.10 (1.03–1.17)	0.007

OR = odds ratio.

[a]Generalized mixed-effects logistic models adjusting for daily Acute Physiology and Chronic Health Evaluation-II calculated on day of coma/delirium assessment.

of time in days, with odds of delirium/coma next day increasing over time in models for CRP (OR, 1.10; 95% CI, 1.03–1.18; $p < 0.01$) and ferritin (OR, 1.10; 95% CI, 1.03–1.17; $p < 0.01$). There were no significant biomarker quartile and time interactions in any of the models.

Sensitivity Analyses

We conducted a sensitivity analysis to measure associations among daily biomarker quartiles and odds of delirium/coma the following day in patients who had normal cognitive status at first ICU assessment. As shown in **Supplementary Table 2** (http://links.lww.com/CCX/B132), in patients without delirium/coma on first assessment, higher CRP quartiles were not significantly associated with delirium/coma next day (OR, 1.02; 95% CI, 0.66–1.57; $p = 0.941$). Greater D-dimer quartiles trended toward higher odds of delirium/coma the following day but did not reach significance (OR, 1.71; 95% CI, 0.97–3.04; $p = 0.065$). Ferritin quartiles were also not associated with greater odds of delirium/coma next day (OR, 1.39; 95% CI, 0.81–2.39; $p = 0.230$).

We added sedatives to our models to delineate effect of medications on our results. As shown in **Supplementary Table 3** (http://links.lww.com/CCX/B132), results for CRP remained not significant (CRP OR, 1.09; 95% CI, 0.80–1.48; $p = 0.583$). Higher D-dimer quartiles were significantly associated (OR, 1.90; 95% CI, 1.26–2.87; $p < 0.01$), whereas ferritin quartiles were not associated with greater odds of delirium/coma next day (OR, 1.20; 95% CI, 0.81–1.78; $p = 0.358$).

Sensitivity Analysis by Mortality Status

Patients who died in the ICU were not excluded from the analyses. Their daily biomarker and delirium assessment data were included in the models up to the date of death. To examine potentially different association between biomarker measures and delirium, we performed sensitivity analyses by conducting separate models in patients who were discharged alive and in those who died in the ICU. As shown in **Supplementary Table 4** (http://links.lww.com/CCX/B132), among patients who survived, only higher D-dimer quartiles were associated with greater odds of delirium/coma. OR estimates for associations of CRP and ferritin with delirium/coma were similar between patients discharged alive and those who died in the ICU.

Relationship Among Biomarkers and Outcome of Next Day Delirium and Coma Independently

Given the high prevalence of sedative-associated coma, we conducted additional analyses to measure associations among the selected biomarkers and next day delirium and coma independently. As shown in **Table 3**, higher CRP quartiles were not associated with delirium (OR, 1.05; 95% CI, 0.85–1.30; $p = 0.655$) but were associated with greater odds of coma next day (OR, 1.36; 95% CI, 1.03–1.79; $p = 0.030$). Higher D-dimer quartiles were associated with greater odds of delirium the next day (OR, 1.49; 95% CI, 1.14–1.94; $p < 0.01$) and greater odds of coma next day (OR, 1.52; 95% CI, 1.08–2.14; $p = 0.017$). As we show in Table 3, higher ferritin quartiles were also associated with

TABLE 3.

Associations Between Daily Biomarker Quartiles and Delirium Versus Normal and Coma Versus Normal Observed the Following Day ($n = 197$)[a]

Variable	Delirium vs Normal		Coma vs Normal	
	OR (95% CI)	p	OR (95% CI)	p
Model 1: C-reactive protein quartile	1.05 (0.85–1.30)	0.655	1.36 (1.03–1.79)	0.030
Model 2: D-dimer quartile	1.49 (1.14–1.94)	0.003	1.52 (1.08–2.14)	0.017
Model 3: Ferritin quartile	1.33 (1.04–1.70)	0.026	1.59 (1.14–2.23)	0.007

OR = odds ratio.

[a]Results were obtained from generalized mixed-effects multinomial models with daily outcomes with three levels (delirium, coma, or cognitively normal) adjusting for age, race, sex, daily Acute Physiology and Chronic Health Evaluation-II calculated on day of delirium or coma assessment, Charlson Comorbidity Index, hypertension, daily mechanical ventilation status, and time (d).

greater odds of delirium (OR, 1.33; 95% CI, 1.04–1.70; p = 0.026) and coma the next day (OR, 1.59; 95% CI, 1.14–2.23; p < 0.01).

Relationship Among Biomarkers and Delirium Severity Next Day

Table 4 shows the results of mixed-effects models for each of the three biomarkers (CRP, D-dimer, and ferritin) and their association with mean delirium severity (measured by CAM-ICU-7) the next day. Among patients that survived, only higher CRP quartiles were significantly associated with increased mean delirium severity the following day (β = 0.30; SE, 0.07; p < 0.001). Among patients that died, none of the biomarkers were significantly associated with delirium severity.

Sensitivity Analysis

We conducted a sensitivity analysis to measure associations among daily biomarker quartiles and delirium severity the following day in patients who had normal cognitive status on their first ICU assessment. As shown in **Table 5**, only higher quartiles of CRP were significantly associated with increased delirium severity on the following day (β = 0.24; SE, 0.10; p = 0.017). There was a significant interaction between time in days and time period (first vs second week of ICU stay).

DISCUSSION

Over 80% of critically ill patients with COVID-19 experience delirium/coma, which can last for as long as 14 days, in sharp contrast to the duration of delirium (4 d) and coma (1 d) reported in acute respiratory failure populations without COVID-19 (28, 29). Whether the increased prevalence and severity of delirium, and high rates of coma, are related to biological mechanisms unique to COVID-19 (such as systemic vascular inflammation, vascular endothelial injury, hypercoagulability, dysregulated immune activation), or are largely explained by the severity of illness, exposure to deliriogenic medications, and mechanical ventilation is not yet fully understood. We conducted this study to expand our understanding of delirium mechanisms in COVID-19. We found that D-dimer was associated with nearly 1.5× odds of the composite outcome of delirium/coma the next day, as well as delirium and coma

occurring independently the next day. These findings were consistent across our sensitivity analyses. We also found higher quartiles of ferritin were associated with greater odds of delirium/coma the next day, as well as delirium and coma occurring independently. In our study, higher values of CRP were associated with greater odds of coma next day, and increased delirium severity the next day among patients who survived. CRP's relationship with increased delirium severity persisted even in patients who had no delirium/coma on their first ICU assessment.

Our study also had some nuanced findings that need further clarification. In our models that included daily sedatives, only D-dimer remained associated with greater odds of delirium/coma next day. While this suggests hypercoagulability's role in delirium, D-dimer was not associated with delirium severity. In our delirium severity models, CRP was the only biomarker associated with increased delirium severity, while hypertension (a delirium risk factor) was associated with lower delirium severity. Finally, among the patients who died, none of the biomarkers we measured were significantly associated with delirium/coma next day. These seemingly discrepant results are likely due to the small sample size in our sensitivity analyses for mortality, delirium severity (subset of patients who were admitted to an ICU where delirium severity was routinely measured) and medication exposures (subset of patients admitted to the hospital where detailed medication administration data was available, but delirium severity was not measured). Therefore, our findings will need further study in larger mechanistic cohort studies.

While we found invasive mechanical ventilation and severity of illness are most strongly associated with greater odds of delirium/coma, our study suggests other pathways may also be implicated in COVID-19 acute brain dysfunction. Our findings for CRP and D-dimer contrast with studies in acute respiratory failure populations prior to the COVID-19 pandemic (30). Based on those studies, CRP has been consistently associated with delirium duration and severity, supporting the neuroinflammatory hypothesis of delirium. Elevated levels of CRP have been used in biomarker models to predict ICU delirium as CRP is an independent risk factor for delirium, and change in CRP is associated with a greater than four-fold increase in delirium risk (31, 32). In our study, however,

TABLE 4.
Association Between Daily Biomarker Measures and Delirium Severity (Confusion Assessment Method for the ICU-7) Observed the Following Day for Those Discharged Alive Versus Those Died[a]

Variable	Discharged Alive (n = 102)								
	C-Reactive Protein			D-Dimer			Ferritin		
	Estimate SE		p	Estimate SE		p	Estimate SE		p
Age	0.004 (0.01)		0.695	0.01 (0.01)		0.495	0.004 (0.01)		0.732
Race									
White	0.75 (0.65)		0.253	0.62 (0.72)		0.390	0.65 (0.68)		0.348
Black	−0.27 (0.64)		0.671	−0.20 (0.72)		0.779	−0.33 (0.68)		0.628
Hispanic	0.04 (0.63)		0.953	0.04 (0.70)		0.953	−0.08 (0.67)		0.900
Other (reference)	0.00			0.00			0.00		
Sex									
Male	0.23 (0.26)		0.380	0.30 (0.28)		0.288	0.29 (0.28)		0.315
Severity of illness and comorbidities									
APACHE-II	0.09 (0.01)		< 0.001	0.09 (0.01)		< 0.001	0.09 (0.01)		< 0.001
Charlson Comorbidity Index	0.18 (0.09)		0.055	0.17 (0.10)		0.097	0.16 (0.09)		0.097
Mechanical ventilation	2.19 (0.22)		< 0.001	2.42 (0.22)		< 0.001	2.32 (0.21)		< 0.001
Hypertension	−0.64 (0.31)		0.043	−0.53 (0.33)		0.114	−0.49 (0.32)		0.130
Time, d	0.10 (0.04)		0.004	0.08 (0.04)		0.028	0.08 (0.03)		0.019
Time period	1.57 (0.62)		0.012	1.37 (0.63)		0.030	1.68 (0.60)		0.006
Biomarker quartile	0.30 (0.07)		< 0.001	−0.02 (0.08)		0.797	0.13 (0.09)		0.158
Interaction (time [d][a] period of first 7 d vs second 7 d)	−0.24 (0.07)		0.001	−0.23 (0.07)		0.001	−0.26 (0.07)		< 0.001
Variable	Discharged Deceased (n = 43)								
	C-Reactive Protein			D-Dimer			Ferritin		
	Estimate SE		p	Estimate SE		p	Estimate SE		p
Age	−0.02 (0.02)		0.516	−0.02 (0.02)		0.337	−0.02 (0.02)		0.492
Race									
White	−0.44 (0.85)		0.605	−0.48 (0.90)		0.597	−0.55 (0.87)		0.533
Black	−0.49 (0.79)		0.542	−0.51 (0.86)		0.561	−0.55 (0.82)		0.508
Hispanic	−0.34 (0.99)		0.729	−0.57 (1.09)		0.602	−0.47 (1.03)		0.649
Other (reference)	0.00			0.00			0.00		
Sex									
Male	−0.06 (0.43)		0.888	−0.16 (0.45)		0.725	−0.16 (0.44)		0.725

(*Continued*)

TABLE 4. (*Continued*).

Association Between Daily Biomarker Measures and Delirium Severity (Confusion Assessment Method for the ICU-7) Observed the Following Day for Those Discharged Alive Versus Those Died[a]

	Discharged Alive (n = 102)							
	C-Reactive Protein			D-Dimer			Ferritin		
Variable	Estimate SE	p	Estimate SE	p	Estimate SE	p
Severity of illness and comorbidities						
APACHE-II	0.07 (0.01)	< 0.001	0.04 (0.01)	< 0.001	0.07 (0.01)	< 0.0001
Charlson Comorbidity Index	0.04 (0.13)	0.765	0.02 (0.13)	0.890	0.04 (0.13)	0.772
Mechanical ventilation	1.33 (0.35)	0.000	1.19 (0.24)	< 0.001	1.07 (0.32)	0.001
Hypertension	−0.56 (0.53)	0.299	−0.44 (0.55)	0.430	−0.63 (0.53)	0.242
Time, d	0.04 (0.04)	0.339	0.02 (0.03)	0.453	0.01 (0.04)	0.781
Time period	0.71 (0.57)	0.208	0.49 (0.38)	0.203	0.29 (0.54)	0.596
Biomarker quartile	−0.02 (0.07)	0.813	0.05 (0.08)	0.539	0.05 (0.09)	0.625
Interaction (time [d][a] period of first 7 d vs second 7 d)	−0.07 (0.06)	0.286	−0.06 (0.04)	0.178	−0.01 (0.06)	0.832

APACHE = Acute Physiology and Chronic Health Evaluation.

[a]Mixed-effects models adjusting for APACHE-II calculated on day of coma/delirium assessment.

increased levels of CRP were not associated with the composite outcome of delirium/coma the following day. CRP values were associated with coma occurring independently and delirium severity, likely reflecting severity of illness.

Recently published studies have identified elevated levels of ferritin and D-dimer at ICU admission in COVID-19 patients with delirium compared with those without delirium (33, 34). Rather than a cross-sectional analysis, we chose to study the temporal relationships among these biomarkers measured daily and next day delirium/coma, delirium and coma independently, and delirium severity. Our results for D-dimer differ from ICU delirium studies in patients without COVID-19, where D-dimer was not associated with delirium. Our findings for D-dimer further support the role of microthrombi and immune dysregulation in development and persistence of both delirium and coma in patients with COVID-19.

In the leading pathophysiologic models for delirium, systemic inflammation is thought to lead to blood-brain barrier disruption, peripheral cytokine-mediated astrocyte and glial cell activation culminating in neuronal injury, network failure, and delirium (35). Our results for CRP suggest other mechanisms may be involved in COVID-19 delirium. Neurovascular injury, astrocyte activation, and neurodegeneration have recently been identified as likely mechanisms for encephalopathy and cognitive impairment among patients admitted to the ICU with COVID-19 compared with non-COVID-19 controls. While the studies used research biomarkers (e.g., neurofilament light [NfL], ubiquitin c-terminal hydrolase L1 [UCH-L1], S100 calcium-binding protein B, etc.) in cohorts with low rates of invasive ventilation, delirium/coma, elevated levels of NfL, glial fibrillary acidic protein, and UCH-L1 were positively correlated with delirium (36). These findings implicate blood-brain barrier disruption, astrocyte and microglial cell activation in the CNS leading to axonal injury. These studies suggest important neuropathological differences between patients with COVID-19 compared with non-COVID-19 controls and identify elevated biomarker levels also associated with Alzheimer's disease pathology (37, 38). Our findings fit within the biological framework of neuronal injury as systemic inflammation, microthrombi, and macrophage activation may precede neurovascular injury and glial cell activation. Follow-up studies evaluating these multiple pathways and what role they may play in long COVID-19, and post-intensive care

TABLE 5.

Association Between Daily Biomarker Measures and Delirium Severity (Confusion Assessment Method for the ICU-7) Observed the Following Day for Those Without Coma or Delirium at First Assessment in ICU (n = 50)a

Variable	C-Reactive Protein			D-Dimer			Ferritin		
	Estimate SE		p	Estimate SE		p	Estimate SE		p
Age	0.002 (0.01)		0.903	0.004 (0.01)		0.767	0.005 (0.01)		0.732
Race									
White	0.44 (0.81)		0.586	0.49 (0.77)		0.525	0.37 (0.79)		0.636
Black	−0.51 (0.73)		0.489	−0.46 (0.68)		0.505	−0.62 (0.71)		0.387
Hispanic	−0.09 (0.77)		0.910	−0.16 (0.72)		0.825	−0.24 (0.75)		0.752
Other (reference)	0.00			0.00			0.00		
Sex									
Male	0.08 (0.37)		0.825	−0.16 (0.34)		0.629	0.04 (0.36)		0.919
Severity of illness and comorbidities									
Acute Physiology and Chronic Health Evaluation-II	0.10 (0.02)		< 0.001	0.09 (0.02)		< 0.001	0.12 (0.02)		< 0.001
Charlson Comorbidity Index	0.15 (0.10)		0.154	0.14 (0.10)		0.138	0.12 (0.10)		0.226
Mechanical ventilation	2.75 (0.41)		< 0.001	2.82 (0.36)		< 0.001	2.78 (0.41)		< 0.001
Hypertension	−1.19 (0.44)		0.010	−1.26 (0.42)		0.005	−1.10 (0.45)		0.018
Time, d	0.22 (0.05)		< 0.001	0.23 (0.05)		< 0.001	0.20 (0.05)		< 0.001
Time period	1.95 (0.82)		0.019	2.35 (0.76)		0.002	1.91 (0.85)		0.025
Biomarker quartile	0.24 (0.10)		0.017	0.13 (0.12)		0.278	0.22 (0.12)		0.066
Interaction (time [d]a period of first 7 d vs second 7 d)	−0.28 (0.09)		0.003	−0.37 (0.09)		< 0.001	−0.28 (0.10)		0.004

aMixed-effects models adjusting for Acute Physiology and Chronic Health Evaluation-II calculated on day of coma/delirium assessment.

syndrome, are needed to better understand delirium and other cognitive sequelae in COVID-19.

Our study's strengths include the use of a large cohort of critically ill patients with bid level of sedation, delirium, and delirium severity assessments, all collected during routine clinical care. Limitations of our study include a limited duration of follow-up, and a study period limited to the first wave of the COVID-19 pandemic, prior to availability of vaccines. The more recent availability of therapeutic agents, vaccines, and new variants of the SARS-CoV-2 virus may alter the results of our findings. Our findings are also limited by relatively smaller sample sizes due to exclusions for missing delirium or medication data and because delirium severity assessments were not performed at all the hospital sites. Our study aims to be hypothesis

generating and therefore a larger study for validation of our findings is needed.

CONCLUSIONS

Our hypothesis-generating study found higher values of D-dimer and ferritin associated with greater odds of next day delirium/coma, as well as delirium and coma occurring independently. CRP was associated with greater odds of coma next day and greater delirium severity. Larger studies to validate our results are needed.

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