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Chemokines in ICU Delirium: An Exploratory Study

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OBJECTIVES: The pathophysiology of delirium is complex and incompletely understood. Inflammation is hypothesized to be integral to its development due to effects on blood brain barrier integrity, facilitation of leukocyte extravasation into brain parenchyma, and propagation of neuroinflammation. Septic shock is the prototypical condition associated with ICU delirium; however, the relative contribution of resultant hypotension and systemic inflammation to the development of delirium is unknown.

DESIGN: This was a prospective exploratory study.

SETTING: A multidisciplinary ICU at an academic medical center in Phoenix, AZ.

PATIENTS: Critically ill patients older than or equal to 18 years old admitted to the ICU.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Screening for delirium was performed using the Confusion Assessment Method for the ICU tool. The levels of C-C motif ligand 2 (CCL2), C-C motif ligand 3, C-X-C motif chemokine ligand 1, C-X-C motif chemokine ligand 10, and interleukin-8 were measured in serum samples obtained within 12 hours of ICU admission. Univariate and multivariate analyses were performed to assess the association of delirium with patient data pertaining to hospital course, laboratory values, vital signs, medication administration, and levels of the aforementioned chemokines. Forty-one of 119 patients (34.5%) in the study cohort developed ICU delirium. Each chemokine studied was associated with delirium on univariate analyses; however, CCL2 was the only chemokine found to be independently associated with the development of delirium on multivariable analysis. The association of increased CCL2 levels with delirium remained robust in various models controlling for age, presence of shock, Sequential Organ Failure Assessment score, Acute Physiology and Chronic Health Evaluation IV score, mean arterial pressure at presentation, lowest mean arterial pressure, and total opioid, midazolam, propofol, and dexmedetomidine exposure.

CONCLUSIONS: The demonstrated relationship between CCL2 and delirium suggests this chemokine may play a role in the development of delirium and warrants further investigation.

KEY WORDS: chemokine; cytokine; delirium; inflammation; intensive care unit

Delirium is acute brain dysfunction characterized by impaired attention, fluctuating consciousness, altered cognition, delusions, and hallucinations (1, 2). It is commonly seen in critically ill patients treated in the ICU (3). Despite the prevalence of this syndrome and its known morbidity (4), mortality (5, 6), and cost (7), understanding of its pathophysiologic mechanisms remains incomplete (8). This lack of knowledge is an impediment to the discovery of effective strategies for both the prevention and treatment of delirium (9).

Known precipitants of delirium include critical illness, infection, pain, metabolic derangements recent surgery, and medications (1, 2). Typically, multiple

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triggers are present simultaneously with an acute event compounding an underlying predisposition (10). Although the etiology of delirium is complex and poorly understood, it has been proposed delirium could represent a common pathway of cerebral response to different insults (1).

It is established that systemic inflammation is associated with delirium (11). Previous studies have identified the peripherally produced proinflammatory cytokines tumor necrosis factor (TNF)–α (12), interleukin (IL)–1β (13), and IL-6 (14) as being elevated in those patients who develop delirium. Exposure of the blood brain barrier to inflammatory mediators, such as cytokines and chemokines, adversely affects its integrity (9). Blood brain barrier disruption permits extravasation of leukocytes and cytokines directly into the parenchyma, activation of resident glial cells, and further propagation of the inflammatory process (15). It is hypothesized that the resultant neuroinflammation contributes to the pathogenesis of delirium (16).

Our preeminent interest is in the role of chemokines, those cytokines that drive leukocyte migration, in the pathogenesis of delirium. This component of the inflammatory milieu is downstream to the aforementioned prototypical deliriogenic cytokines (17). In this exploratory study, our aim was to identify the relative association of several chemokines with the development of delirium. We sought to determine whether any such chemokine investigated was independently associated with delirium after controlling for variables known to increase the risk of delirium (1, 2).

METHODS

Study Population

This prospective study was conducted from May 1, 2019, to October 31, 2020, at a 30-bed multidisciplinary ICU in Mayo Clinic Hospital, Phoenix, AZ. This ICU is fully staffed by intensivists 24/7. Approval was provided by the Mayo Clinic Institutional Review Board (approval no. 18-005104 granted on May 24, 2021) prior to initiation of data collection; the need for patient consent was waived. This study was performed in accordance with the Helsinki Declaration pertaining to medical research involving human subjects.

Daily ICU admissions were screened by the investigators for assessment of inclusion and exclusion criteria. Inclusion criteria included consecutive critically ill patients older than or equal to 18 years old admitted to the ICU during the study period with available residual blood from clinically indicated blood extraction. Exclusion criteria included patients with do not resuscitate/do not intubate orders or being treated with comfort care measures only, presence of delirium at the time of ICU admission, admission diagnosis of stroke or traumatic brain injury, and patients who had not agreed to the use of their medical records for research. When patients required readmission to the ICU after discharge, only data from the first admission were analyzed. We used the Third International Consensus Definition (Sepsis-3) (18) and the Society for Cardiovascular Angiography and Interventions (19) shock stages C, D, and E to define both septic shock and cardiogenic shock, respectively. For the purposes of this study, we define shock to include both of the aforementioned definitions of septic shock and cardiogenic shock; no patients in our study suffered from hypovolemic or obstructive shock. The following variables were used to describe hemodynamic instability in our patient population: initial ICU MAP was defined as the first measurement of mean arterial pressure (MAP) at ICU admission, and lowest ICU MAP was the lowest MAP either over the course of the entire ICU stay in those patients who did not develop delirium or prior to the onset of delirium in those who did.

Data Collection

Comprehensive data on patient characteristics, hospital course, laboratory values, vital signs, surgical procedures, and medication administration were collected throughout their hospitalization, and all patients enrolled into the study. The validated Confusion Assessment Method for the ICU (CAM-ICU) screening tool was used to identify delirium (20). The CAM-ICU is administered by highly trained Mayo Clinic ICU nursing staff adept at both the administration and appropriate use of this tool. The CAM-ICU is administered every 8 hours or when a mental status change is noted. Positive and negative CAM-ICU results are documented in the electronic health record as events occurring during the following 4-hour windows: 0:00–4:00; 4:00–8:00; 8:00–12:00; 12:00–16:00; 16:00–20:00; 20:00–24:00. Surgical procedure performed subsequent to hospital admission, and prior to the onset of delirium when applicable, was defined as recent

surgery, and pertinent data are reported below. Vital signs and laboratories were collected during the first ICU day; worse values were abstracted. The Acute Physiology and Chronic Health Evaluation (APACHE) IV score (21), Sequential Organ Failure Assessment (SOFA) score (22), and predicted hospital mortality rates based on these scores were calculated using integrated electronic health record tools.

Serums samples were obtained within 12 hours of ICU admission from surplus blood collected for clinically indicated testing. Samples were either transported at 4°C and immediately analyzed or frozen at –80°C within 12 hours of collection for later analysis. Routine chemicals were obtained from Sigma-Aldrich (Saint-Louis, MO). C-C motif ligand 2 (CCL2), C-C motif ligand 3 (CCL3), C-X-C motif chemokine ligand 1 (CXCL1), C-X-C motif chemokine ligand 10 (CXCL10), and IL-8 were analyzed using a fluorescence-based capture sandwich immunoassay kit (MILLIPLEX Human Cytokine, Chemokine, Growth Factor Panel A; Millipore, Burlington, MA). The assay was performed in accordance with the manufacturer's instructions using a Luminex 200 System (Invitrogen, Carlsbad, CA) for reading fluorescence. Results were analyzed using xPONENT Software: (Version 4.3; Luminex Corporation, Austin, TX) software as previously described by Singh et al (23, 24).

Statistics

All data are summarized as median (interquartile range [IQR]) or percentages. Unpaired Student *t* test was used to compare continuous variables with normal distribution and the Wilcoxon rank test for skewed distribution. For comparison of categorical variables, chi-square test was used if the number of elements in each cell was greater than or equal to 5; Fisher exact test was used otherwise. For the assessment of independent predictors of delirium, we created a multiple logistic regression model by entering covariates that showed significant differences ($p \leq 0.05$) between those that developed and those that did not develop delirium. The model was refined with backwards stepwise regression, using both clinical and statistical criteria, considering collinearity and interaction terms. When appropriate, the odds ratio (OR) and 95% CIs were calculated. Multivariate models were created using standardized values. Model discrimination was assessed using receiving operator curves. Model fit (calibration) was assessed using the Hosmer-Lemeshow goodness-of-fit test. A Bonferroni correction was applied to the multivariate modeling of chemokines (Table 3) resulting in an adjustment of the *p* value significance threshold to less than or equal to 0.01. A *p* value of less than or equal to 0.05 was considered statistically significant in all other cases. Exploratory analysis of data was performed using JMP Statistical Software (Version 16.0.0; SAS Institute, Cary, NC).

RESULTS

Of the 119 patients in our study, 41 (34.5%) developed delirium while in the ICU. Delirium was associated with higher SOFA score, higher APACHE IV score, younger age, lower pH, higher glucose, lower serum albumin, higher WBC count, and higher BUN (**Table 1**). In the delirium group, hospital and ICU lengths of stay were longer, sepsis and COVID-19 more prevalent, Glasgow Coma Scale score lower, and total opioid, midazolam, and dexmedetomidine exposure was greater than in group of patients who did not develop delirium (Table 1). Surgery showed a negative correlation with delirium (1). Serum concentrations of CCL2, CCL3, CXCL1, CXCL10, and IL-8 were higher in the delirium group compared with the group without delirium (**Table 2** and **Fig. 1**). CCL2 was the only chemokine independently associated with the development of delirium on multivariate analysis including all the evaluated chemokines (**Table 3**). Shock was the only hemodynamic variable that showed a statistically significant relationship with the development of delirium (**Table 4**). The association of CCL2 with delirium remained robust across multiple multivariate models that included the following known precipitants of delirium: age, presence of Shock, sepsis, SOFA score, APACHE IV score, initial MAP, lowest MAP, and total opioid, midazolam, propofol, and dexmedetomidine exposure (**Table 5**; and **Supplemental Tables 1–4**, Supplementary Digital Content, http://links.lww.com/CCX/B27).

DISCUSSION

In this prospective exploratory study of critically ill patients treated in the ICU, we found that the serum concentrations of all chemokines investigated showed a statistically significant association with the development of delirium; however, only CCL2 was independently associated with delirium on multivariate analysis. The association of CCL2 with delirium was

TABLE 1.
Patient Characteristics, Labs, Vitals, and Hospital Course

Variables	No Delirium, *N* = 78	Delirium, *N* = 41	*p*	Total Cohort
Patient characteristics				
Age, yr, median (IQR)	66.6 (55.8–75)	55 (46.5–69.5)	**0.01**[a]	64 (50–75)
Female gender, *n* (%)	24 (30.8)	16 (39)	0.42	40 (33.6)
Sequential Organ Failure Assessment score, median (IQR)	6 (4–8)	9 (6–12)	**< 0.001**[a]	7 (5–9)
Acute Physiology And Chronic Health Evaluation IV, median (IQR)	53 (37.5–65.3)	79 (52–98.5)	**< 0.001**[a]	56 (39–75)
Glasgow Coma Scale, median (IQR)	15 (11.8–15)	11 (3–15)	**< 0.001**[a]	15 (10–15)
Prior history of cerebrovascular accident (ischemic stroke), *n* (%)	4 (5.1)	4 (9.8)	0.44	8 (6.7)
Prior history of hemorrhagic stroke, *n* (%)	1 (1.3)	2 (4.9)	0.27	3 (2.5)
Prior history of traumatic brain injury, *n* (%)	2 (2.6)	1 (2.4)	1.0	3 (2.5)
Preexisting cognitive impairment, *n* (%)	1 (1.3)	1 (2.4)	1.0	2 (1.7)
body mass index , median (IQR)	28.5 (24.9–33.8)	28.9 (25.7–32.7)	0.78	28.9 (25–33.5)
Vitals				
Temperature (°C), median (IQR)	37.5 (36.7–38.5)	37.3 (36.8–38.1)	0.46	37.5 (36.7–38.4)
Heart rate, median (IQR)	97.5 (86.8–108)	101 (90–118)	0.09	98 (88–111)
Respiration rate, median (IQR)	24 (20–29)	27 (22.5–32)	0.08	25 (20–29)
Laboratories				
Positive cultures, *n* (%)	15 (19.2)	12 (29.3)	0.25	27 (22.7)
Initial lactate (mmol/L), median (IQR)	1.4 (1.1–2.8)	1.7 (1.1–3.7)	0.32	1.5 (1.1–3)
Highest lactate (mmol/L), median (IQR)	1.7 (1.1–3.6)	1.9 (1.3–3.8)	0.34	1.8 (1.1–3.8)
Arterial pH, median (IQR)	7.4 (7.36–7.44)	7.36 (7.27–7.43)	**0.01**[a]	7.4 (7.34–7.43)
Na+ (mmol/L), median (IQR)	138.5 (135.6–141)	136 (132.5–140)	0.07	138 (134–141)
Urine output (mL/24H), median (IQR)	1,640.5 (1,178–2,392.5)	1,735 (977.5–2,387.5)	0.95	1,687 (1,160–2,385)
Creatinine (mg/dL), median (IQR)	1.1 (0.8–1.7)	1.2 (0.7–2)	0.49	1.1 (0.8–1.7)
Blood urea nitrogen (mg/dL), median (IQR)	16.6 (12–25.3)	24 (13.5–38)	**0.05**[a]	18.5 (13–28)
Glucose (mg/dL), median (IQR)	140.5 (110–174)	168 (137–259.5)	**0.002**[a]	151 (114–188)
Albumin (g/dL), median (IQR)	3.8 (3.2–4)	3.3 (2.6–3.7)	**0.004**[a]	3.5 (3–4)
Bilirubin (mg/dL), median (IQR)	0.7 (0.4–1)	0.6 (0.3–1.1)	0.53	0.7 (0.4–1)
Hct %, median (IQR)	33.8 (27.8–37.7)	32.2 (27.1–38.3)	0.79	33 (27.9–37.7)
WBC, median (IQR)	9.5 (6.7–13.1)	11.4 (8.8–16.3)	**0.03**[a]	10 (6.9–15)

(*Continued*)

TABLE 1. (*Continued*).
Patient Characteristics, Labs, Vitals, and Hospital Course

Variables	No Delirium, *N* = 78	Delirium, *N* = 41	*p*	Total Cohort
Hospital course				
ICU LOS, median (IQR)	2.2 (1.3–4.0)	14.5 (3.7–33.2)	**< 0.001**[a]	3.3 (1.9–10.4)
Hospital LOS, median (IQR)	7.1 (5.0–10.9)	23.2 (16.8–40.2)	**< 0.001**[a]	9.9 (1.1–10.4)
ICU mortality, *n* (%)	7 (9.0)	5 (12.2)	0.75	12 (10.1)
Hospital mortality, *n* (%)	7 (9.0)	6 (14.6)	0.37	13 (10.9)
Sepsis, *n* (%)	37 (47.4)	29 (70.7)	**0.02**[a]	66 (55.5)
COVID-19, *n* (%)	18 (23.1)	20 (48.8)	**0.007**[a]	38 (31.9)
Recent surgery, *n* (%)	41 (52.6)	11 (26.8)	**0.01**[a]	52 (43.7)
Total surgery blood loss (mL), median (IQR)	102.5 (100–500)	125 (100–300)	0.96	105 (100–450)
Total surgery time (min), median (IQR)	306 (250.5–396)	284 (225–486)	0.90	304 (246.8–408.3)
28-d mortality, *n* (%)	7 (9.0)	6 (14.6)	0.37	13 (10.9)
Total opioid dose (morphine equivalents, mg), median (IQR)	235 (71.5–380)	742 (151.8–3,700.3)	**0.002**[a]	249 (102.1–797.7)
Total midazolam dose (mg), median (IQR)	3.7 (2.5–6)	176.5 (7.5–1,049.4)	**< 0.001**[a]	5.5 (3–256)
Total propofol dose (mg), median (IQR)	260.9 (120–1,012)	1,000 (133.5–3,875)	0.28	453.8 (130.1–2,484.8)
Total dexmedetomidine dose (μg), median (IQR)	383 (158–806.2)	2,800 (987.2–7,637.9)	**< 0.001**[a]	774 (264.8–2,800)

Hct = hematocrit, IQR = interquartile range, LOS = length of stay.
[a]$p \leq 0.05$.

independent of other factors associated with delirium, such as SOFA score, APACHE IV score, shock, drug exposure, and age.

CCL2, also referred to as monocyte chemoattractant protein 1 (MCP1), is a proinflammatory chemokine that has been implicated in the pathophysiology of various

TABLE 2.
Univariate Analysis of Chemokines Associated With ICU Delirium

Variables	No Delirium, *N* = 78	Delirium, *N* = 41	*p*	Total Cohort
C-C motif ligand 2 (pg/mL), median (IQR)	636.05 (413.35–1,019.30)	1,295.60 (709.43–2,092.03)	**< 0.001**[a]	761.86 (447.83–1,358.52)
C-C motif ligand 3 (pg/mL), median (IQR)	0 (0–2.72)	1.36 (0–7.24)	**0.008**[a]	0 (0–3.57)
C-X-C motif chemokine ligand 1 (pg/mL), median (IQR)	23.45 (8.79–34.56)	29.64 (17.95–53.50)	**0.01**[a]	26.24 (10.82–47.33)
C-X-C motif chemokine ligand 10 (pg/mL), median (IQR)	269.95 (132.38–1,928.12)	1,159.90 (277.06–3,856.02)	**0.004**[a]	366.72 (149.05–2,834.38)
Interleukin-8 (pg/mL), median (IQR)	29.48 (19.17–48.24)	42.62 (24.56–92.87)	**0.02**[a]	33.37 (20.49–59.42)

IQR = interquartile range.
[a]$p \leq 0.05$.

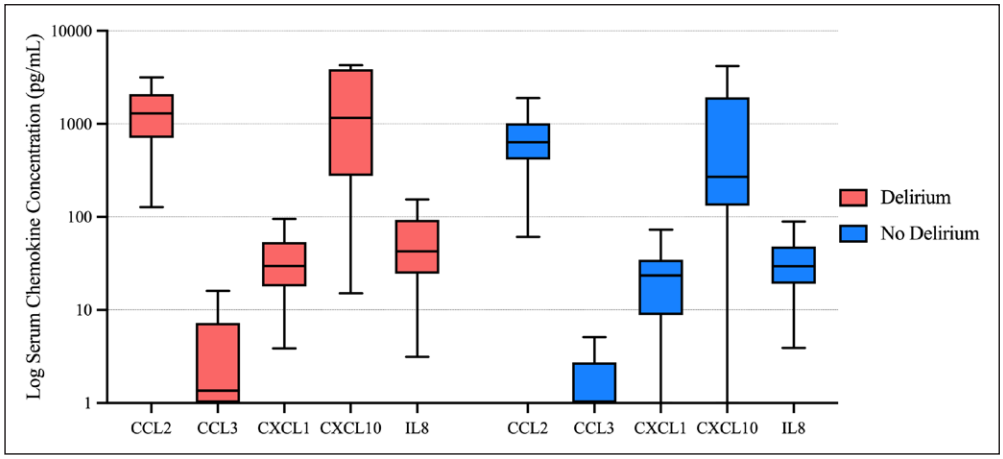

Figure 1. Univariate analysis of chemokines associated with ICU delirium. Chemokine levels by delirium: median, interquartile range, Tukey *whisker*. CCL2 = C-C motif ligand 2, CCL3 = C-C motif ligand 3, CXCL1 = C-X-C motif chemokine ligand 1, CXCL10 = C-X-C motif chemokine ligand 10, IL-8 = interleukin 8.

brain diseases with an inflammatory component, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, neurodegeneration secondary to status epilepticus, and stroke (25, 26). Elevated serum and cerebrospinal fluid levels of CCL2 have been previously associated with delirium (8). The exact mechanism by which elevated CCL2 contributes to, or results from, the cerebral dysfunction manifested as delirium has yet to be elucidated.

In vitro exposure of astrocytes to IL-1β and TNF-α results in increased production of CCL2 (17). Similarly, microglial cells exposed to TNF-α produce CCL2, which in turn contributes to monocyte chemotaxis and amplification of neuroinflammation (16). In addition to its known role as a chemotactic cytokine, CCL2 has been shown to affect the distribution of tight junction proteins, thereby increasing blood brain barrier permeability (17).

TABLE 3.

Multivariate Analysis by Chemokine (Receiving Operator Characteristic Area Under Curve = 0.71)

Variables	Unit OR	95% CI	*p*
C-C motif ligand 2	2.3	1.2–4.4	**0.007**[a]
C-X-C motif chemokine ligand 10	1.3	0.5–3.2	0.64
Interleukin-8	1.1	0.7–1.9	0.69
C-X-C motif chemokine ligand 1	1.0	0.6–1.6	0.94
C-C motif ligand 3	0.5	0.04–7.0	0.08

OR = odds ratio.

[a]$p \leq 0.01$. Bonferroni adjusted *p*. Variables standardized.

Therefore, it appears that CCL2 not only drives chemotaxis of monocytes to the blood brain barrier but also may facilitate their penetration into the brain (16). CCL2 is expressed constitutively in neurons as well as by glial cells, which suggests it may play an additional role in neuromodulation (26). In fact, CCL2 has been shown to increase dopamine release in the substantia nigra of rats resulting in neuroexcitation (27).

Septic shock, the archetypal condition associated with delirium, represents a state of profound inflammation (15) and, by definition, hypotension (18). Loss of the vascular reflex responsible for cerebral autoregulation, the means by which constant cerebral perfusion pressure is maintained despite variation in systemic blood pressure, has been shown to occur in critical illness (28). As a result of this, patients are more susceptible to cerebral hypoperfusion resulting from low peripheral blood pressure (28). Impaired cerebral autoregulation has been implicated as a possible mechanism to explain how hypotension results in delirium in the critically ill (29). In support of this contention, lactate has been found to be elevated in the cerebral spinal fluid of patients with delirium (30).

Our interest in including variables pertaining to hypotension in our analysis was to characterize the contribution of this component of shock to the development of delirium in our chemokine containing models. Other forms of shock, such as cardiogenic shock, can result in an uncontrolled inflammatory response as well (31). This sterile inflammatory response occurs secondary to, and further compounds, the organ failure that characterizes shock (31, 32). Interestingly, the proinflammatory cytokine profile of cardiogenic shock, which includes IL-6, TNF-α, and CCL2 (33), is similar to that seen in delirium. Cerebral hypoperfusion and inflammation may both play interlinked roles favoring the occurrence of delirium among patients with shock; however, this exploratory study provides preliminary evidence supporting the role of CCL2 in

TABLE 4.
Univariate Analysis of Hemodynamic Variables in ICU Delirium

Variables	No Delirium, *N* = 78	Delirium, *N* = 41	*p*	Total Cohort
Shock, *n* (%)	19 (24.4)	18 (43.9)	**0.04**[a]	37 (31.1)
Pressor requirement at ICU admission, *n* (%)	41 (52.3)	28 (68.3)	0.12	69 (58)
Initial ICU MAP, median (IQR)	78 (67.8–91)	83 (66–95)	0.52	80 (67–93)
Lowest ICU MAP, median (IQR)	55 (50–60.3)	53 (44.5–58)	0.11	54 (49–69)

IQR = interquartile range.
[a]$p \leq 0.05$.

TABLE 5.
Multivariate Models Containing C-C Motif Ligand 2

Variables	Unit OR	95% CI	*p*
Multivariate analysis by SOFA and initial ICU MAP (ROC AUC: 0.83)			
SOFA	4.0	2.1–7.7	**< 0.0001**[a]
CCL2	2.4	1.4–4.0	**0.0002**[a]
Initial ICU MAP	2.2	1.2–3.9	**0.004**[a]
Total opioid	1.1	0.7–1.6	0.76
Age	0.6	0.3–0.9	**0.02**[a]
Multivariate analysis by SOFA and lowest MAP (ROC AUC: 0.80)			
SOFA	3.2	1.7–6.1	**< 0.0001**[a]
CCL2	2.2	1.3–3.7	**0.0006**[a]
Lowest MAP	1.5	0.9–2.5	0.15
Total opioid	1.2	0.8–1.9	0.34
Age	0.5	0.3–0.9	**0.01**[a]
Multivariate analysis by SOFA and shock (ROC AUC: 0.80)			
SOFA	2.7	1.5–4.9	**0.0002**[a]
CCL2	2.1	1.3–3.5	**0.0008**[a]
Total opioid	1.1	0.7–1.7	0.56
Shock	0.9	0.6–1.5	0.74
Age	0.5	0.3–0.9	**0.01**[a]
Multivariate analysis by SOFA and sepsis (ROC AUC: 0.80)			
SOFA	2.6	1.5–4.4	**< 0.0001**[a]
CCL2	2.0	1.2–3.4	**0.003**[a]
Sepsis	1.2	0.7–1.9	0.54
Total opioid	1.1	0.7–1.7	0.64
Age	0.5	0.3–0.9	**0.01**[a]

CCL2 = C-C motif ligand 2, MAP = mean arterial pressure, OR = odds ratio, ROC AUC = receiving operator characteristic area under curve, SOFA = Sequential Organ Failure Assessment.
[a]$p \leq 0.05$. Variables standardized.

the development of delirium. Further research is necessary to elucidate the relative contribution of these mechanism to the pathogenesis of delirium.

Although most variables associated with delirium were expected, there were some unexpected findings in our analyses that deserve some discussion. On univariate analysis, age was inversely associated with the occurrence of delirium. Yet, this unexpected finding can be explained by the greater prevalence of older patients among those undergoing planned surgeries and a longer duration of ICU stay among younger patients in our cohort (in fact, age was no longer associated with delirium after we controlled for length of ICU stay). The inverse association of surgery with delirium may similarly be explained by the confounding effect of planned surgeries that in turn resulted in shorted ICU hospitalizations.

Our study has several limitations, notably including a modest sample size, performance at a single center, and measurement of chemokine levels at a single point in time. Subsequent research may benefit from trending chemokines over the ICU course in order to capture evolution of the inflammatory profile associated with ICU delirium. As chemokine samples were collected within 12 hours of ICU admission, this would allow us to better characterize the temporal relationship between chemokine elevation and delirium onset. Considering our limited sample size and the number of patients who experienced delirium, those models containing five variables are at risk of overfitting. However, Supplemental Table 1 (Supplementary Digital Content, http://links.lww.com/CCX/B23) demonstrates that our findings are unchanged in similar models containing only four variables. Our cohort included patients with heterogenous indications for ICU admission, which increases the representativeness of the findings but conversely may have obscure stronger associations of chemokines with delirium that could be seen in more homogeneous cohorts (e.g. solely patients with septic shock). Our cohort was not sufficiently large to evaluate differential associations in specific groups of patients, such as those with COVID infection. In addition, there are questions regarding thermal stability and the effect of freezing and thawing chemokine samples. A recent review performed by Simpson et al (34) found consensus regarding the stability of CCL2 at 4°C and at least five cycles of freezing and thawing. CCL3 is stable for up to six freeze thaw cycles; however, results are conflicting regarding stability at temperatures above freezing (34). Both CXCL10 and IL-8 were shown to be stable at 4°C and for several freeze-thaw cycles (34). Unfortunately, no data are available regarding the thermal stability of CXCL1 in serum. Future studies may benefit from freezing all samples immediately at –80°C in order to eliminate the risk of degradation when prompt analysis is not possible. Regardless, repeating the chemokine multivariate analysis excluding CCL3, CXCL1, and both CCL3 and CXCL1 did not alter our findings regarding the relationship between CCL2 and delirium. Finally, our study included patients admitted to the ICU for observation after planned major cardiac surgeries; we decided to include these patients because cardiac surgery has been associated with the development of delirium (8). Future studies with larger cohorts may be best conducted in more homogeneous populations.

In conclusion, we found that serum concentration of CCL2 was independently associated with the development of delirium in patients admitted to the ICU. Further research will be necessary to confirm the validity of this association in larger cohorts and to examine if this chemokine could represent a possible therapeutic target to prevent the occurrence or ameliorate the severity of delirium in critically ill patients.

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