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Association of Hypoactive and Hyperactive Delirium With Cognitive Function After Critical Illness

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Abstract

Objectives: Delirium, a heterogenous syndrome, is associated with worse long-term cognition after critical illness. We sought to determine if duration of motoric subtypes of delirium are associated with worse cognition.

Design: Secondary analysis of prospective multicenter cohort study.

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Setting: Academic, community, and Veteran Affairs hospitals. Patients: Five-hundred eighty-two survivors of respiratory failure or shock.

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Interventions: We assessed delirium and level of consciousness using the Confusion Assessment Method-ICU and Richmond Agitation Sedation Scale daily during hospitalization. We defined a day with hypoactive delirium as a day with positive Confusion Assessment Method-ICU and corresponding Richmond Agitation Sedation Scale score less than or equal to 0 and a day with hyperactive delirium as a day with positive Confusion Assessment Method-ICU and corresponding Richmond Agitation Sedation Scale score greater than 0. At 3 and 12 months, we assessed global cognition with the Repeatable Battery for the Assessment of Neurologic Status and executive function with the Trail Making Test Part B. We used multivariable regression to examine the associations between days of hypoactive and hyperactive delirium with cognition outcomes. We allowed for interaction between days of hypoactive and hyperactive delirium and adjusted for baseline and in-hospital covariates.

Measurements and Results: Hypoactive delirium was more common and persistent than hyperactive delirium (71% vs 17%; median 3 vs 1 d). Longer duration of hypoactive delirium was associated with worse global cognition at 3 (−5.13 [−8.75 to −1.51]; $p = 0.03$) but not 12 (−5.76 [−9.99 to −1.53]; $p = 0.08$) months and with worse executive functioning at 3 (−3.61 [−7.48 to 0.26]; $p = 0.03$) and 12 (−6.22 [−10.12 to −2.33]; $p = 0.004$) months; these associations were not modified by hyperactive delirium. Hyperactive delirium was not associated with global cognition or executive function in this cohort.

Conclusions: Longer duration of hypoactive delirium was independently associated with worse long-term cognition. Assessing motoric subtypes of delirium in the ICU might aid in prognosis and intervention allocation. Future studies should consider delineating motoric subtypes of delirium. (Crit Care Med 2020; 48:e480–e488)

Keywords

cognition; cognitive dysfunction; critical illness; delirium; executive function; survivors

Delirium is an acute form of brain dysfunction that is common in the critically ill and is associated with worse short- and long-term outcomes (1). Unfortunately, the prevalence of delirium in the critically ill is common, with around 35% of mechanically ventilated patients developing the syndrome (2). Patients who develop delirium in the ICU have increased ventilator days, longer lengths of stay, and greater costs of care. In the long-term, they suffer increased mortality and increased likelihood of institutionalization (1, 3, 4). Delirium in the ICU is also one of the strongest risk factors for worse long-term global cognition and executive function after discharge (4). Such impairments are often debilitating and negatively impact ICU survivor's ability to live a normal and productive life.

Delirium, however, is heterogeneous and can present with different motoric phenotypes (5). Hypoactive delirium is characterized by reduced activity, apathy, decreased amount or speed of speech, decreased alertness, unawareness, or hypersomnolence. Hyperactive delirium, alternatively, is characterized by increased activity levels, increased speed of actions or

speech, restlessness, abnormal content of verbal output, hyperalertness, irritability, and combativeness. In previous studies, subtypes that include hypoactive appear to be the most prevalent (6, 7). Specific subtypes of delirium also likely have different outcomes. In postoperative and hospital settings, patients with hypoactive delirium have greater risk for pressure ulcers and hospital-acquired infections, have prolonged length of stay, and have increased mortality compared with patients with hyperactive delirium (8–10). The association between motoric subtypes and outcomes in the critically ill, however, remains unknown, and the reasons for differences in outcomes between motoric subtypes are also unclear. It has previously been suggested that patients who develop hypoactive delirium have more frailty and more neuropathology and are, therefore, unable to exhibit the overt signs of hyperactivity. This increased vulnerability and disease burden could lead to worse long-term outcomes. It is not known if the motoric subtypes of delirium are associated with different cognitive outcomes after critical illness.

We hypothesized that hypoactive delirium, but not hyperactive delirium, in the ICU would be associated with long-term cognitive impairment. To test this hypothesis, we performed a post hoc analysis of a prospective cohort study of critically ill adults that assessed delirium in the ICU and global cognition and executive function at 3 and 12 months after discharge.

MATERIALS AND METHODS

This study is a post hoc analysis of the prospective multicenter cohort study—Bringing to Light the Risk Factors and Incidence of Neuropsychologic Dysfunction in ICU Survivors (BRAIN-ICU) study (NCT00392795) conducted from 2007 to 2010 at Vanderbilt University Medical Center and Saint Thomas Hospital (both Nashville, TN) and the parallel (identical protocol) MIND-ICU Study: Delirium and Dementia in Veterans Surviving ICU Care study (NCT00400062) conducted at the Tennessee Valley Healthcare System (Nashville, TN), George E. Wahlen Department of VA Medical Center in VA Salt Lake City Healthcare System (Salt Lake City, UT), and Seattle Division of the VA Puget Sound Healthcare System (Seattle, WA). Results from these studies have been previously reported (4, 11), but the hypotheses and findings presented are original and have not been published. Each institutional review board approved the protocol.

Adult medical and surgical ICU patients with respiratory failure or shock were eligible for inclusion if they were enrolled in the BRAIN-ICU and MIND-ICU studies as previously described (4, 12). We excluded patients with prolonged critical illness prior to evaluation, those who had been in the ICU greater than 5 days in the month prior to admission, mechanical ventilation in the past 2 months, unlikely to survive for 24 hours, or who had greater than 72 hours with organ dysfunction during the current ICU admission. We also excluded patients at high risk for preexisting cognitive deficits from neurodegenerative disease, cardiac surgery within the previous 3 months, suspected anoxic brain injury, or severe dementia. Patients who could not be reliably assessed for delirium or cognitive impairment, in whom it would be difficult to complete follow-up, and those without informed consent were excluded. We obtained written informed consent from all patients or their authorized surrogates; if consent was initially obtained from a surrogate, we obtained consent from the patient once deemed competent. We analyzed participants from the

BRAIN-ICU and Modifying the INcidence of Delirium (The MIND Study) studies who survived and completed follow-up assessments after hospital discharge.

Exposures

Trained research nurses evaluated each patient for delirium and level of consciousness bid using the Confusion Assessment Method for the ICU (CAM-ICU) (13) tool and Richmond Agitation Sedation Scale (RASS) (14). This included both sedated and nonsedated patients. Using previously published criteria (7, 15), we defined a day with hypoactive delirium as a day with a positive CAM-ICU and corresponding RASS less than or equal to 0 and a day with hyperactive delirium as a day with a positive CAM-ICU and corresponding RASS greater than 0. Each day was allowed to qualify for both hypoactive and hyperactive delirium if at least one of the assessments met the above criteria. We used these definitions to collect the most granular data on durations of hypoactive and hyperactive delirium, since sole hyperactive subtypes are rare. Similarly, a day with a RASS score of −4 or −5 was defined as a day with coma, and patients were allowed to have a day with coma and a day with delirium.

Outcomes

At 3 and 12 months after hospital discharge, trained psychology professionals assessed global cognition with the Repeatable Battery for the Assessment of Neurologic Status (RBANS) (16). This is a validated neuropsychologic battery that evaluates memory, attention, language, and visuospatial constructs to assess overall global cognition (16). The test is scored from 40 to 160, with 100 ± 15 representing the population age-adjusted mean and sd. Lower scores are worse. In addition to global cognition, executive function was assessed with the Trail Making Test, Part B (Trails B) (17), a validated tool that examines cognitive flexibility and set-shifting. The Trails B has an age-, sex-, and education-adjusted mean (sd) score of 50 ± 10 with lower scores indicating worse executive function.

Covariates

We collected demographic data upon enrollment and hospital course data from admission until discharge, death, or a maximum of 30 days after enrollment. Covariates were chosen a priori based on their potential to confound the association between duration of the motoric subtypes of delirium, cognitive impairment, and executive function. Baseline covariates included age, Charlson Comorbidity Index (18) as a measure of comorbid disease, years of education, and Short Form Informant Questionnaire On Cognitive Decline in the Elderly (IQCODE-SF) (19) for preadmission cognitive deficit. In-hospital covariates included mean modified Sequential Organ Failure Assessment (20) score (which excluded Glasgow Coma Scale since coma was adjusted for separately), days with coma, days of severe sepsis, and an interaction term between duration of hyperactive and hypoactive delirium. During study enrollment, severe sepsis was defined as presence of infection and greater than or equal to 2 systemic inflammatory response syndrome features, plus signs of organ dysfunction, including mechanical ventilation, cardiovascular or renal Sequential Organ Failure Assessment score greater than 2, or delirium or coma. We included exposure to medications that could affect motoric subtype of delirium including mean 24-hour benzodiazepine

(midazolam equivalents), propofol, dexmedetomidine, opioid (fentanyl equivalents), and haloperidol exposure.

Statistical Analysis

We performed multivariable linear regression, adjusted for covariates, to examine the independent association of days with hypoactive delirium and days with hyperactive delirium with global cognition and executive function at 3 and 12 months. With the exception of IQCODE-SF, years of education, haloperidol, and dexmedetomidine (which all had too little variability), continuous variables were initially allowed to have a nonlinear relationship with the outcomes using restricted cubic splines. We allowed for potential interactions between hypoactive and hyperactive delirium using separate cross-product terms to evaluate if fluctuation between subtypes affected outcomes.

To reduce bias from missing data, we used multiple imputation to account for missing covariates and outcomes among patients with at least partial outcomes data available. For the primary exposure, if a patient had no mental status assessment, we used single imputation to impute an overall status (normal, delirious, or comatose) based on the status on the days immediately prior to and after the missing day. If a missing study day was assigned a normal or comatose status during single imputation, we assumed no hypoactive or hyperactive delirium. For days assigned a delirious status, we imputed indicators for whether delirium was hypoactive or hyperactive based on overall mental status, coma, and motoric subtypes on the days immediately prior to and after the missing day. Overall, imputation of mental status occurred in less than 4% of patient days.

With our cohort of 582 patients, we could reliably fit a model with up to 38 degrees of freedom (21). We limited the number of covariates included to avoid overfitting. We used R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses. p values of less than 0.05 were considered significant

RESULTS

Patient Characteristics

We included 582 patients overall, including 561 patients assessed at 3 months and 464 assessed at 12 months (Fig. 1). Data regarding screened and excluded patients for cohort were previously reported (4, 22). The median (interquartile range) age was 61 years (52–70 yr). The cohort had a high severity of illness, with a median (interquartile range) Acute Physiology And Chronic Health Evaluation II score of 23 (17–29) at ICU admission and 88% requiring mechanical ventilation. The majority of patients (66%) were admitted to a medical ICU. Additional patient characteristics are presented in Table 1. The median RBANS score at 3 and 12 months was 80 (71–87) and 82 (72–90) respectively, approximately 1.5 sds below adjusted population mean, indicating a significant degree of cognitive impairment. The median Trails B was 40 (33–48) and 42 (35–50) at 3 and 12 months respectively, which are approximately one sd below the population norm.

Prevalence and Duration of Motoric Subtypes of Delirium

Within our cohort, 71% of patients (411/582) experienced hypoactive delirium for a median of 3 days (1–7 d), and 17% (100/582) experienced hyperactive delirium for a median of 1 day (1–2 d). In total, 8% (49/582) experienced a day with both hyperactive and hypoactive delirium, with a median duration of 1 day (1–2 d) of both subtypes during same day. Of those with delirium, 92% had a day with only hypoactive delirium, and 5% had a day with only hyperactive delirium. Patients with hyperactive delirium on average received higher daily doses of benzodiazepines, propofol, and antipsychotics (Table 1).

Association of Motoric Subtypes With Long-Term Cognitive Outcomes

After adjusting for potential confounders, a greater number of days with hypoactive delirium was significantly associated with worse global cognition at 3 months ($p = 0.03$) but not at 12 months ($p = 0.08$) (Fig. 2). For example, on average a patient with 5 days (75^{th} percentile of our cohort) with hypoactive delirium would have a RBANS global score approximately 5 points lower at 3 months (−5.13 [−8.75 to −1.51]) and 6 points lower at 12 months (−5.76 [−9.99 to −1.53]) than a patient with 0 days (25^{th} percentile of our cohort) with hypoactive delirium. These associations were not modified by duration of hyperactive delirium (p value for the interaction term = 0.62 at 3 mo and 0.68 at 12 mo).

Greater number of days of hypoactive delirium was also significantly associated with worse executive function at 3 ($p = 0.03$) and at 12 months ($p = 0.004$) (Fig. 3). For example, on average a patient with 5 days with hypoactive delirium would have a Trails B score approximately 4 points lower at 3 months (–3.61 [–7.48 to 0.26]) and 6 points lower at 12 months (–6.22 [–10.12 to –2.33]) than a patient with 0 days with hypoactive delirium.

There was no significant association between number of days with hyperactive delirium and global cognition at 3 ($p = 0.73$) or 12 months ($p = 0.47$) in our cohort (Fig. 4). There was also no association between days of hyperactive delirium and executive function at 3 ($p = 0.59$) or 12 months ($p = 0.99$) in our cohort (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/CCM/F376).

DISCUSSION

Our results show that a greater number of days with hypoactive delirium is independently associated with worse global cognition at 3 months and worse executive function at 3 and 12 months, after adjustment for relevant potential baseline and in-hospital confounders, including baseline cognition, days with hyperactive delirium, days with coma, and sedative medication exposure. Number of days with hyperactive delirium, in our cohort, was not associated with long-term global cognition or executive function.

Our results expand on previous literature demonstrating the association between delirium and long-term cognitive impairment (4, 22–25) and contribute to recent evidence suggesting outcomes differ between motoric subtypes of delirium. Our data builds on this evidence, showing for the first time that hypoactive delirium during critical illness is associated with worse long-term cognitive function in survivors. Understanding why one subtype manifests versus another will be important to help reduce the risk of poor outcomes. The etiology of

delirium associated with critical illness is likely multifactorial and still incompletely understood. Likewise, the underlying pathology causing the specific subtypes of delirium is not understood. Multiple hypotheses for delirium exist including neuroinflammation, central cholinergic deficiency, alterations in the dopaminergic pathways, or the result of deliriogenic medications. It is unclear if any of these factors are more likely than others to produce a specific subtype. Additionally, patient vulnerability factors and their innate physiologic reaction to insult likely contribute to different clinical presentations. To that end, there have been several hypotheses about the differences in outcomes.

One hypothesis is that the hyperactive subtype has higher detection rates, thus prompting more aggressive treatment, leading to improved outcomes (26). This was difficult to fully evaluate in our cohort, as all patients were equally screened for delirium twice daily. It is possible, however, that we missed short episodes of hyperactive delirium that were treated pharmacologically between our assessments. Patients with hyperactive delirium in our cohort did on average receive higher daily antipsychotic and sedative exposure compared with those with hypoactive delirium. Antipsychotics, however, have been shown ineffective at reducing the duration of hyperactive delirium (27). Whether this pharmacologic exposure contributed to a shorter duration of hyperactive delirium or converted hyperactive delirium to hypoactive delirium is unclear, although sedative exposure was accounted for in our cognitive outcomes analyses.

Another hypothesis is that hyperactive delirium is related to excess dopamine transmission and reduced central cholinergic activity whereas hypoactive delirium may be associated with more widespread CNS disturbances (28, 29). It is possible that patients with hyperactive delirium are more fit, and thus able act out, as opposed to those with hypoactive delirium (30), where there may be a sense of apathy or resignation (31) that predisposes them to worse outcomes. Further, patients with hypoactive delirium may have increased neuropathologic disease that limits their motoric activity and portends worse long-term outcomes. Future studies will hopefully help elucidate whether hypoactive delirium has worse outcomes due to its underlying etiology or whether it is a symptom of increased vulnerability (although we did adjust for vulnerability markers in our models).

Our results support the importance of routine delirium assessments in the ICU, as the majority of hypoactive delirium will go undiagnosed without routine screening (32) but is associated with worse outcomes. This has implications for targeted prevention and treatment strategies, recognizing that although hyperactive delirium is more disruptive, the outcomes associated with it are not as poor as outcomes from hypoactive delirium. Our results, in addition to those of prior studies, support the importance of appropriate and timely clinical evaluation of patients with hypoactive delirium, which could be a presentation of encephalopathy or neuropathology that has long-term consequences. Pharmacologic treatments have shown no benefit in hypoactive delirium (27, 33) although implementation of prevention strategies such as the ICU Liberation Bundle of interventions (ABCDEF) have been able to demonstrate reduction in delirium (including hypoactive delirium) and improve its associated deleterious outcomes (34–36). The results of our study further emphasize the need to pay close attention to hypoactive delirium among critically ill patients and to implement strategies to reduce its incidence and duration.

Our study has several notable strengths and weaknesses. Our large cohort consisted of critically ill patients with a wide range of diagnoses from an academic hospital, a community hospital, and three Veterans Affairs hospitals. We were able to adjust for important potential confounders of the association between delirium and cognitive and functional impairment, including age, education level, severity of illness, sepsis, and sedation exposure. We were likely better able to capture the episodes of hyperactive delirium than studies with patients labeled as mixed by accounting for motoric subtype per assessment and overall days with hyperactive delirium exposure. Further, we used duration of each subtype, as opposed to presence or absence, to provide increased statistical power. This allowed us to note that hypoactive delirium had a dose-response relationship with long-term cognitive outcomes. Despite efforts to increase our ability to detect possible associations between hyperactive delirium and outcomes, we had little hyperactive delirium (similar to the majority of delirium subtype studies) which eliminated our ability to draw conclusions about this rarer event. Additionally, we assessed delirium twice daily, but due to the fluctuating nature of delirium symptoms, we could have missed episodes of hyperactive delirium that were treated with sedatives and converted to hypoactive delirium or to coma. Although we were able to account for daily drug exposure, we were unable to account for the amount of early mobilization or sleep protocols the individual patients were exposed to, as the BRAIN-ICU study did not capture these data. The BRAIN-ICU study did not include the etiologic workup or neurologic examination other than CAM-ICU and RASS due to resource and scope of interest constraints. We were unable to perform extensive cognitive testing prior to hospitalization, but we did obtain information on patients' baseline cognitive functioning using the IQCODE-SF, which has high sensitivity to identify mild cognitive impairment and dementia (37–39), and adjusted for other characteristics associated with cognitive status (e.g., age, educational level). We only evaluated survivors since we were examining cognitive outcomes, and hence, the results are susceptible to survivor bias. Finally, observational studies cannot prove causation and are subject to unmeasured confounders; we were, however, able to adjust for a large number of confounders.

In conclusion, our results indicate that in our cohort, a longer duration of hypoactive delirium during critical illness is independently associated with worse global cognition at 3 months post discharge and worse executive function up to 12 months post discharge. Further, hyperactive delirium does not modify the association between hypoactive delirium and cognition after critical illness. Hyperactive delirium, while easily recognizable and disconcerting in the acute setting, was much less common and appeared to not be associated with worse long-term cognitive or functional outcomes in our cohort. This has implications for monitoring, preventing, and treating delirium motoric subtypes. Future studies of delirium should consider the motoric subtype when evaluating delirious patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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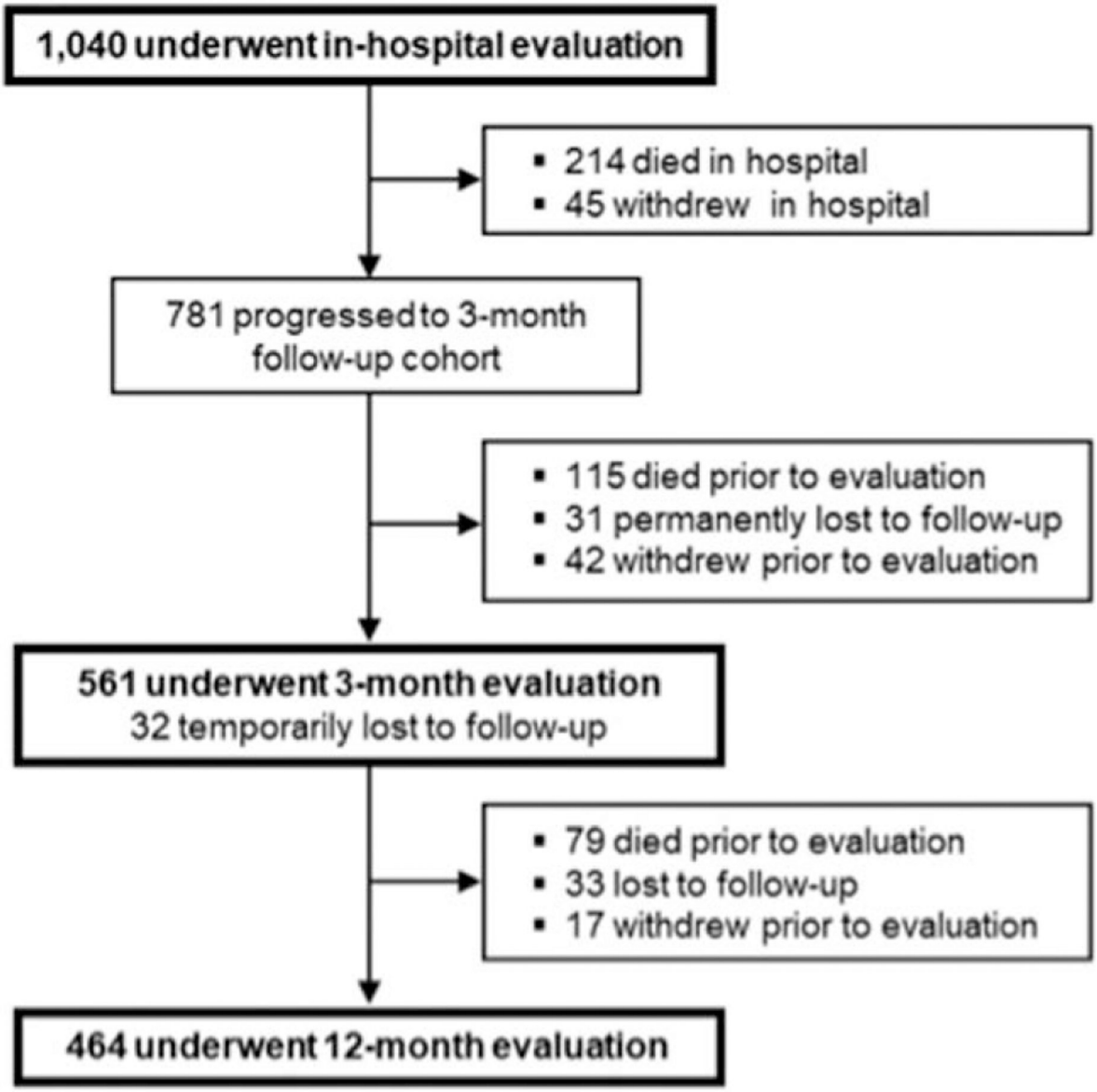

Figure 1.
Patient flow diagram.

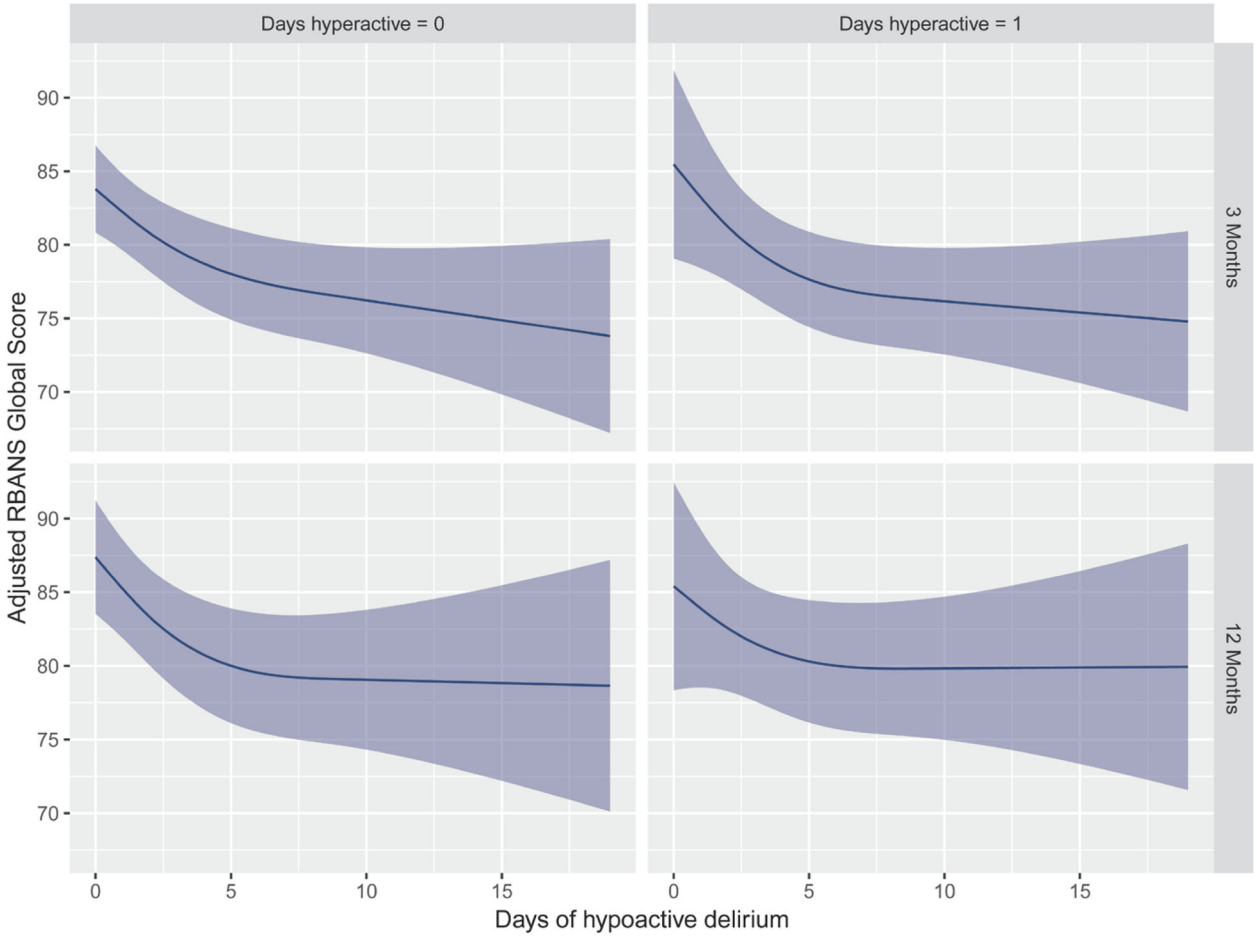

Figure 2.

Hypoactive delirium duration versus global cognition. The associations between days of hypoactive delirium and global cognition at 3 and 12 mo, as measured by the Repeatable Battery for the Assessment of Neurologic Status (RBANS) global score, are displayed for patients with and without hyperactive delirium. Increased duration of hypoactive delirium was independently associated with worse global cognition at 3 mo ($p = 0.03$) but not at 12 mo ($p = 0.08$). These associations were not significantly modified by hyperactive delirium. The *solid line* represents the point estimate of the association between duration of hypoactive delirium and global cognition, with the gray ribbon indicating the 95% CI.

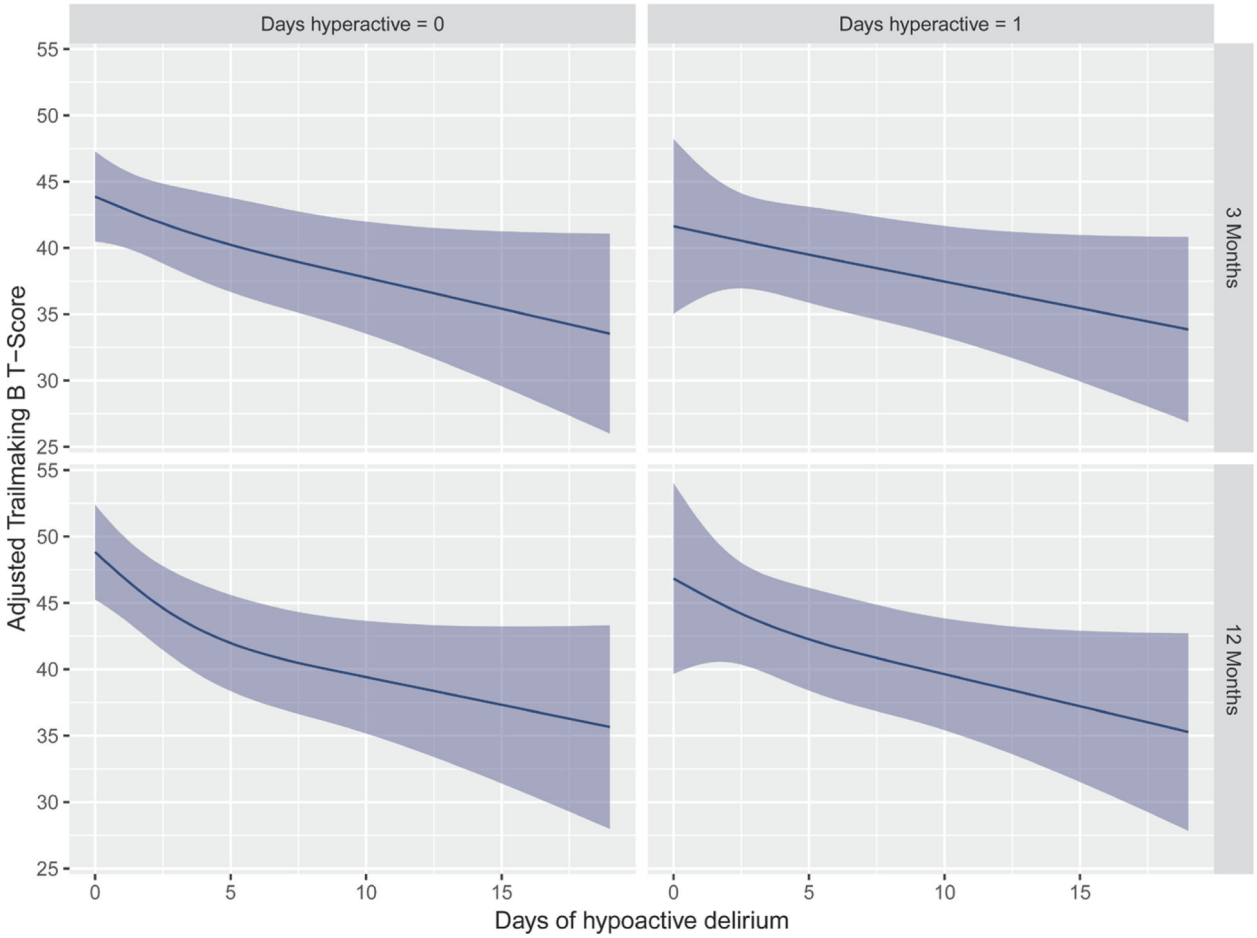

Figure 3.

Hypoactive delirium duration versus executive function. The associations between days of hypoactive delirium and executive function at 3 and 12 mo, as assessed by the Trail Making Test Part B, are displayed for patients with and without hyperactive delirium. Increased duration of hypoactive delirium was independently associated with worse executive function at 3 mo ($p = 0.03$) and at 12 mo ($p = 0.004$). The *solid line* represents the point estimate of the association between duration of hypoactive delirium and executive function, with the gray ribbon indicating the 95% CI.

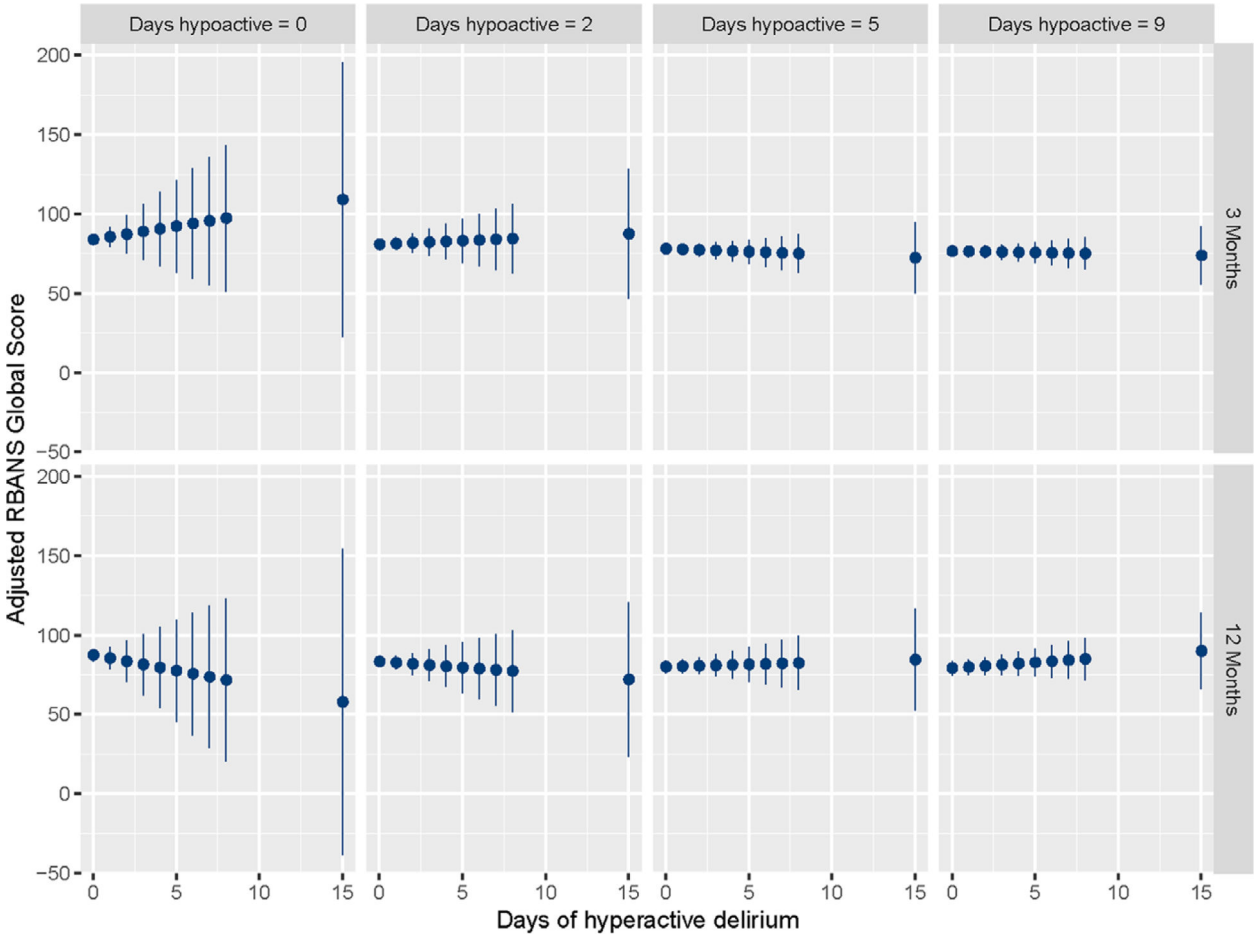

Figure 4.

Hyperactive delirium versus global cognition. The association of hyperactive delirium with global cognition at 3 ($p = 0.73$) and 12 mo ($p = 0.47$) by varying amounts of hypoactive delirium exposure. Number of days with hyperactive delirium was not associated with global cognition in our cohort, and number of days with hypoactive delirium did not modify this relationship (p for interaction = 0.62 and 0.68, respectively). RBANS = Repeatable Battery for the Assessment of Neurologic Status.

TABLE 1.

Patient Characteristics

Characteristics	All Patients (*n* = 582)	Hypoactive Delirium (*n* = 411)	Hyperactive Delirium (*n* = 100)
Age (yr), median (IQR)	61 (52–70)	62 (52–70)	63 (52–71)
Sex (%)			
Male	59	57	72
Female	41	43	28
Race (%)			
Caucasian	89	89	95
African American	10	11	5
Other	1	2	0
Education (yr), median (IQR)	12 (12–14)	12 (12–14)	12 (12–14)
Canadian Study of Health and Aging Frailty Index, % (*n*)			
Very fit	4 (22)	2 (16)	3 (3)
Well	16 (96)	18 (72)	19 (19)
Well with treated comorbid disease	35 (202)	35 (142)	38 (38)
Apparently vulnerable	22 (126)	21 (87)	25 (25)
Mildly frail	12 (70)	10 (43)	6 (6)
Moderately frail	9 (54)	10 (43)	8 (8)
Severely frail	2 (12)	2 (8)	1 (1)
Acute Physiology And Chronic Health Evaluation II at ICU admission, median (IQR)	23 (17–29)	25 (19–30)	22.5 (18.8–28)
Informant Questionnaire On Cognitive Decline in the Elderly at enrollment, median (IQR)	3 (3–3.12)	3 (3–3.12)	3 (3–3.19)
ICU type (%)			
Medical	66	64	61
Surgical	34	36	39
Mean Sequential Organ Failure Assessment in the ICU, median (IQR)	6.6 (5.3–8.5)	6.8 (5.6–8.7)	6.8 (5.7–8.3)
Charlson score, median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)
Ever received mechanical ventilation, *n* (%)	515 (88)	392 (95)	99 (99)
Length of time among those exposed (d), median (IQR)	2.22 (0.95–5.99)	3.16 (1.17–8.73)	3.77 (1.8–9.36)
Days severely septic in the ICU	2 (0–5)	3 (0–7)	4 (2–7)
Mean 24 hr dose of benzodiazepines in the ICU[a] (mg), median (IQR)	0.71 (0–6.94)	1.73 (0–11.21)	4.48 (0.64–16.61)

Characteristics	All Patients (*n* = 582)	Hypoactive Delirium (*n* = 411)	Hyperactive Delirium (*n* = 100)
Mean 24 hr dose of haloperidol in the ICU (mg), median (IQR)	0 (0–0)	0 (0–0.6)	0.71 (0–2.76)
Mean 24 hr dose of dexmedetomidine in the ICU (μg), median (IQR)	0 (0–0)	0 (0–0)	0 (0–14)
Mean 24 hr dose of propofol in the ICU (mg), median (IQR)	0 (0–582)	0 (24–737)	55 (0–794)
Mean 24 hr dose of opioids in the ICU[b], median (IQR)	292 (5–1,000)	441 (43–1,229)	576 (150–1,034)
ICU length of stay (d), median (IQR)	5 (2.7–10)	6 (3.1–12.0)	8 (4.1–16.9)
Hospital length of stay (d), median (IQR)	10 (6–18)	12 (7.3–21.2)	17.1 (9.7–27)

IQR = interquartile range.

Patient characteristics with all patients, those who had at least a day with hypoactive delirium, and those who had at least a day with hyperactive delirium. These categories are not exclusive.

[a]Measured in midazolam equivalents.

[b]Measured in fentanyl equivalents (fentanyl = morphine × 50 = hydromorphone × 7.5).