ORIGINAL ARTICLE

The Association between Acute Respiratory Distress Syndrome, Delirium, and In-Hospital Mortality in Intensive Care Unit Patients

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Abstract

Rationale: Both acute respiratory distress syndrome (ARDS) and intensive care unit (ICU) delirium are associated with significant morbidity and mortality. However, the risk of delirium and its impact on mortality in ARDS patients is unknown.

Objectives: To determine if ARDS is associated with a higher risk for delirium compared with respiratory failure without ARDS, and to determine the association between ARDS and in-hospital mortality after adjusting for delirium.

Methods: Prospective observational cohort study of adult ICU patients admitted to two urban academic hospitals.

Measurements and Main Results: Delirium was assessed daily using the Confusion Assessment Method for the ICU and Richmond Agitation and Sedation Scale. Of the 564 patients in our cohort, 48 had ARDS (9%). Intubated patients with ARDS had the highest prevalence of delirium compared with intubated patients without ARDS and nonintubated patients (73% vs. 52% vs. 21%, respectively; $P < 0.001$). After adjusting for common risk factors for delirium, ARDS was associated with a higher risk for delirium compared with mechanical ventilation without ARDS (odds ratio [OR], 6.55 [1.56–27.54]; $P = 0.01$ vs. OR, 1.98 [1.16–3.40]; $P < 0.013$); reference was nonintubated patients. Although ARDS was significantly associated with hospital mortality (OR, 10.44 [3.16–34.50]), the effect was largely reduced after adjusting for delirium and persistent coma (OR, 5.63 [1.55–20.45]).

Conclusions: Our findings suggest that ARDS is associated with a greater risk for ICU delirium than mechanical ventilation alone, and that the association between ARDS and in-hospital mortality is weakened after adjusting for delirium and coma. Future studies are needed to determine if prevention and reduction of delirium in ARDS patients can improve outcomes.

Keywords: delirium; acute respiratory distress syndrome; hospital mortality; coma

As mortality in patients with acute respiratory distress syndrome (ARDS) has decreased over time, it is becoming increasingly clear that up to 70% of survivors of ARDS develop new cognitive, physical, and functional impairments during their critical illness (1–3). These deficits can persist for years after hospital discharge and often translate into reduced health-related quality of life, inability to return to work, inability for self-care, and psychological morbidity (3–5). Given the severity of the cognitive and functional impairments, it is important to identify modifiable intra intensive care unit (ICU) factors that may contribute to these poor outcomes because they may represent therapeutic opportunities to improve late outcomes after ARDS.

Delirium is the most common organ dysfunction in medical and surgical ICU patients, with rates as high as 80% (6). Several of the physiologic derangements experienced by ARDS patients (e.g., hypoxemia, metabolic abnormalities), concomitant sepsis, and the treatments that they receive (e.g., invasive mechanical ventilation, sedation-induced coma, neuromuscular blockade, steroids) have

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At a Glance Commentary

Scientific Knowledge on the Subject: Intensive care unit (ICU) delirium is associated with poor short- and long-term outcomes. Patients with acute respiratory distress syndrome (ARDS) are exposed to many risk factors for ICU delirium and share similar poor outcomes with delirious patients. However, it is unclear if ARDS is associated with a higher risk for delirium when compared with mechanical ventilation without ARDS. Furthermore, the impact of delirium on the association between ARDS and in-hospital mortality is unknown.

What This Study Adds to the Field: ARDS was strongly associated with ICU delirium, independent of mechanical ventilation and other risk factors. Moreover, the association between ARDS and in-hospital mortality was attenuated after adjusting for delirium and persistent coma in a critically ill cohort. These findings identify ICU delirium as a novel risk factor for poor outcomes in ARDS patients. Future studies are needed to determine if prevention or reduction of delirium can improve outcomes in ARDS patients.

been identified as risk factors for ICU delirium (7–12). Likewise, survivors of ICU delirium and ARDS share similar poor long-term neuropsychiatric and functional outcomes (13–16). However, the impact of ICU delirium on outcomes of ARDS patients is poorly understood. This is an important gap in knowledge because studies suggest that ICU delirium can be reduced; hence, it may represent a potential target for improving long-term outcomes in ARDS survivors (17, 18).

In contrast to the growing literature on delirium in medical and surgical ICU patients, studies of the prevalence and impact of delirium in ARDS patients are sparse and estimates of in-hospital mortality in ARDS patients have not accounted for delirium (19, 20). Therefore, the goal of the present study is to investigate the prevalence of delirium in ARDS patients, to determine if ARDS is associated with a higher risk for delirium compared with respiratory failure without ARDS, and to determine the association between ARDS and in-hospital mortality after adjusting for delirium status. Some of the results of these studies have been previously reported in the form of an abstract (21).

Methods

The online supplement provides a more detailed description of study procedures.

Study Design and Patients

This prospective cohort study included consecutive adult patients admitted to five medical and surgical ICUs at two academic hospitals in Bronx, New York between May and September 2011. Patients who could not be assessed for delirium because of non-English or non-Spanish language, developmental delay, or end-stage dementia were excluded from analyses. This study was determined to be exempt from review by the Institutional Review Board of Albert Einstein College of Medicine–Montefiore Medical Center.

Delirium Assessment

As part of a quality initiative, delirium and level of consciousness was assessed once daily in the morning or afternoon by trained research staff for a maximum of 14 days or until ICU discharge or death, whichever occurred first. Delirium was assessed using the Confusion Assessment Method (CAM)-ICU (6, 22–25). Delirium prevalence was defined as any patient with at least one CAM-ICU positive assessment during the first 14 days of their ICU stay, regardless of the underlying etiology of delirium. Level of consciousness was assessed using the Richmond Agitation and Sedation Scale (26). Persistent coma was defined as Richmond Agitation and Sedation Scale scores of -4 or -5 at every evaluation until death, ICU discharge, or 14 days in ICU, whichever occurred first. Delirium- and coma-free days were defined as the number of days alive, CAM-ICU negative, and not comatose within 14 days after ICU admission (27).

ARDS Assessment

All patients were prospectively screened for ARDS on a daily basis during their ICU admission. ARDS was defined as acute respiratory failure requiring invasive mechanical ventilation with bilateral infiltrates on chest radiograph and $Pa_{O_2}/F_{I_{O_2}}$ less than or equal to 300 that was not fully explained by cardiac failure (28). Patients were classified into three mutually exclusive categories: (*1*) no invasive mechanical ventilation, (*2*) invasive mechanical ventilation without ARDS, and (*3*) invasive mechanical ventilation with ARDS.

Statistical Methods

Multivariable logistic regression was performed to determine the association between ARDS status and ICU delirium. Multivariable logistic regression was also used to determine if the association between ARDS and hospital mortality is altered after adjusting for delirium and persistent coma. For this analysis, delirium and coma status was classified into three mutually exclusive categories: (*1*) never delirious, (*2*) ever delirious, and (*3*) persistently comatose. We analyzed the data in this manner for two reasons: because patients with persistent coma would not be assessable for delirium, and because we considered it biologically plausible that patients with persistent coma would have worse outcomes than patients who were delirious. For both regression models, covariates that were risk factors for the outcomes were selected *a priori* based on prior studies, and additional risk factors identified to be associated with the outcome on bivariate analyses ($P < 0.05$) that were scientifically plausible were also included in the multivariate model. All covariates were included in the regression models, regardless of statistical significance. In the model testing the association between ARDS and delirium, benzodiazepine and propofol use were entered as binary covariates because the median (interquartile range) daily dose for both sedatives was 0 (0–0) in nondelirious patients. To ease interpretation, fentanyl use was also entered as a binary covariate because estimates were similar with fentanyl expressed as a binary and continuous covariate.

Multivariable regression model fit was assessed with the Hosmer-Lemeshow test. The likelihood ratio test was used to determine if the addition of delirium and coma to the in-hospital mortality model improved model fit. All statistical tests were two-tailed, with P less than or equal to 0.05 defined as statistical significance.

Statistical analyses were performed with STATA/MP 11 (Statacorp, College Station, Texas).

Results

From July to September 2011, 580 adult patients were admitted to medical and surgical ICUs at the two hospitals; 4 patients were not assessed for delirium, 11 patients did not speak English or Spanish, and 1 patient was not assessable for delirium because of developmental delay. The remaining 564 patients were included in the analyses.

Characteristics of Study Participants

The mean age of the cohort was 61 (SD, 15); 43% were delirious for at least 1 day during their ICU stay, with a median delirium duration of 2 days (interquartile range [IQR], 1–4). Six percent of the cohort remained persistently comatose (n = 32). Table 1 describes baseline characteristics of study subjects stratified by delirium status. Delirium was associated with older age, higher comorbidity burden, history of dementia, higher severity of illness, alcohol and drug abuse before ICU admission, and preferred non-English language ($P < 0.01$). Delirious patients received benzodiazepines, opiates, propofol, and steroids more often than nondelirious patients during their ICU stay ($P < 0.05$). Patients with persistent coma had more severe sepsis and received opiates more often than delirious patients ($P < 0.05$) (*see* Table E1 in the online supplement).

Among the 564 patients in the cohort, 318 patients were intubated without ARDS (56%) and 48 were intubated with ARDS (9%). Patients with ARDS had a higher prevalence of dementia and alcohol abuse at baseline, and more severe sepsis, and

Table 1. Baseline Demographics and Clinical Characteristics (n = 532)*

Clinical Characteristic	Never Delirious (*n = 291*)	Ever Delirious† (*n = 241*)	*P* Value
Age, mean ± SD	59 ± 15	63 ± 15	0.006
Female sex	145 (50)	107 (44)	0.21
Race			0.42
White	96 (33)	65 (27)	
Black	105 (36)	86 (36)	
Multiracial	67 (23)	60 (25)	
Other	23 (8)	30 (12)	
Hispanic ethnicity	95 (33)	92 (38)	0.18
Preferred non-English language	37 (13)	55 (23)	0.002
Charlson Comorbidity Index, median (IQR)	4 (2–8)	6 (3–9)	<0.001
Dementia	7 (2)	32 (13)	<0.001
Alcohol abuse	15 (5)	32 (13)	0.001
Drug abuse	8 (3)	21 (9)	0.003
APACHE IV, median (IQR)	47 (39–53)	57 (45–71)	<0.001
ICU type			<0.001
Medical	87 (30)	124 (51)	
Surgical	204 (70)	117 (49)	
Primary admitting diagnosis to ICU			<0.001
Sepsis	58 (20)	62 (26)	
Respiratory failure	33 (11)	71 (29)	
Neurologic	53 (18)	43 (18)	
Cardiac	79 (27)	32 (13)	
Surgery	32 (11)	11 (5)	
Other	36 (12)	22 (9)	
Severe sepsis	34 (12)	73 (30)	<0.001
Respiratory failure			<0.001
Not intubated	156 (54)	41 (17)	
Intubated, no ARDS	131 (45)	165 (68)	
Intubated with ARDS	4 (1)	35 (15)	
Tidal volume, ml/kg PBW, mean ± SD‡	8.3 ± 1.3	8.4 ± 1.4	0.34
Ever given during first 14 d in ICU			
Midazolam	41 (14)	112 (46)	<0.001
Opiates	63 (21)	130 (54)	<0.001
Propofol	27 (9)	106 (44)	<0.001
Steroids	59 (20)	89 (37)	<0.001
Daily dose, median (IQR)			
Midazolam, mg	0 (0–0)	0 (0–5)	<0.001
Opiates, μg§	71 (3–208)	228 (15–788)	0.002
Propofol, mg	0 (0–0)	4 (0–335)	<0.001

Definition of abbreviations: APACHE IV = Acute Physiology and Chronic Health Evaluation IV; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; PBW = predicted body weight.
Data are reported as number (percent) unless otherwise specified.
*Patients with persistent coma (n = 32) were excluded from this analysis because delirium cannot be assessed in comatose patients.
†Defined as more than one episode of delirium within the first 14 ICU days.
‡Defined as maximum tidal volume (milliliters) on first day of mechanical ventilation divided by kilograms; excludes nonintubated patients (n = 135 and 200, respectively).
§Expressed in fentanyl equivalents.

a higher severity of illness at the time of ICU admission ($P < 0.05$) (*see* Table E2). During the ICU admission, patients with ARDS received benzodiazepines, opiates, propofol, and steroids more often than patients who were intubated without ARDS and nonintubated patients ($P < 0.05$).

Association between ARDS and Delirium

Patients with ARDS had the highest prevalence of delirium (73% vs. 52% vs. 21%) and persistent coma (19% vs. 7% vs. 0.5%) compared with intubated non-ARDS and nonintubated patients, respectively ($P < 0.001$) (Table 2). Patients with ARDS also spent a significantly smaller proportion of their ICU stay without delirium and coma, with a median of 0% ICU days (IQR, 0–14) compared with 25% (IQR, 0–56) in intubated patients without ARDS and 50% in nonintubated patients (IQR, 33–75). Neither the severity of hypoxemia at the time of ARDS diagnosis, nor the maximum tidal volume on the first day of invasive mechanical ventilation were associated with the prevalence and duration of delirium and coma (*see* Table E3).

After adjusting for age, dementia, alcohol abuse, Charlson Comorbidity Index, Acute Physiology and Chronic Health Evaluation IV, severe sepsis, sedative and steroid use, and preferred non-English language, patients with ARDS had a higher odds for developing delirium compared with intubated patients without ARDS (odds ratio [OR], 6.55 [95% CI, 1.56–27.54]; $P = 0.010$ vs. OR, 1.98 [95% CI, 1.16–3.40]; $P = 0.013$); reference was nonintubated patients (Table 3).

Association between ARDS and In-Hospital Mortality after Adjusting for Delirium and Persistent Coma

Patients with ARDS had the highest in-hospital mortality compared with intubated patients and nonintubated patients (43% vs. 16% and 7%; $P < 0.001$). Although patients with delirium had greater in-hospital mortality compared with patients without delirium (20% vs. 5%), patients with persistent coma had the highest in-hospital mortality (75%; $P < 0.001$). All ARDS patients with persistent coma died during their hospitalization (n = 9).

In multivariate analyses adjusting for age, comorbidity burden, severity of illness, severe sepsis, and alcohol abuse, the odds of in-hospital mortality were appreciably higher in ARDS patients (OR, 10.44 [95% confidence interval (CI), 3.16–34.50]; $P < 0.001$) than intubated patients without ARDS (OR, 6.78 [95% CI, 2.62–17.57]; $P < 0.001$) when compared with nonintubated patients (reference OR) (Table 4). After additional adjustment for delirium and persistent coma, model fit significantly improved (likelihood ratio test, $P < 0.001$) and the association between ARDS and in-hospital mortality was greatly reduced (OR, 5.63 [95% CI, 1.55–20.45]; $P = 0.009$). Delirium was associated with increased in-hospital mortality, although the estimate was not statistically significant (OR, 1.95 [95% CI, 0.97–3.92]; $P = 0.062$). Of the covariates, persistent coma had the strongest association with in-hospital mortality (OR, 22.15 [95% CI, 7.68–63.89]; $P < 0.001$).

Discussion

This multicenter prospective cohort study of medical and surgical ICU patients is the first investigation to show that ARDS is independently associated with a higher odds for delirium compared with mechanical ventilation without ARDS, even after adjusting for such factors as severity of illness and sedative and steroid use. In addition, we found that ICU delirium and persistent coma attenuates the association between ARDS and in-hospital mortality. Our results indicate that ARDS patients are at high risk for developing ICU delirium and that delirium and persistent coma may either contribute to or may be markers of poor short-term outcomes in ARDS patients. These data raise important questions regarding the pathogenesis of poor outcomes in ARDS patients and identify delirium as a novel and potentially modifiable target for future interventional studies.

The long term physical and neuropsychiatric impairments suffered by ARDS survivors are well established (1, 3, 4). However, the etiology of these impairments is unclear, and interventions for reducing these impairments have yet to be identified. Although multiple epidemiologic studies have shown a strong and independent association between delirium and neuropsychiatric and functional morbidity (13–16), to our knowledge, none of the published studies on long-term outcomes of ARDS patients have concurrently assessed for delirium. The high prevalence and longer duration of delirium found in ARDS patients in this study highlight the need for future studies

Table 2. Prevalence and Duration of Delirium and Coma in Patients with and without ARDS (n = 564)

Outcome	Not Intubated (*n = 198*)	Intubated, No ARDS (*n = 318*)	Intubated with ARDS (*n = 48*)	*P* Value
Delirium and coma status, n (%)				<0.001
Never delirious	156 (79)	131 (41)	4 (8)	
Ever delirious	41 (21)	165 (52)	35 (73)	
Persistently comatose*	1 (0.5)	22 (7)	9 (19)	
Delirium days in ICU (max 14), median (IQR)	0 (0–0)	1 (0–2)	2 (0–4)	<0.001
Delirium and coma-free days (max 14), median (IQR)†	14 (13–14)	12 (3–14)	2 (0–9)	0.0001
% ICU days free of delirium and coma, median (IQR)‡	50 (33–75)	25 (0–56)	0 (0–14)	0.0001

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range.
*Defined as Richmond Agitation and Sedation Scale −4 or −5 until ICU discharge, death, or ICU Day 14 (whichever is first).
†Defined as the number of days alive and free of delirium and coma over first 14 days in ICU.
‡Defined as percentage of days in ICU without delirium and coma before ICU discharge, death, or ICU Day 14 (whichever is first).

Table 3. Association between ARDS Status and Odds of Developing ICU Delirium (n = 532)*

Risk Factor	Multivariate OR (95% CI)	*P* Value
ARDS status		
Not intubated, no ARDS	Reference	
Intubated, no ARDS	1.98 (1.16–3.40)	0.013
Intubated, with ARDS	6.55 (1.56–27.54)	0.010
Age	1.00 (0.99–1.02)	0.89
Charlson Comorbidity Index	1.21 (0.78–1.89)	0.40
APACHE IV†	1.22 (1.08–1.37)	0.002
Dementia	6.76 (2.57–17.75)	<0.001
Non-English language	2.20 (1.26–3.84)	0.005
Alcohol abuse	2.42 (1.09–5.37)	0.03
Illicit drug use	1.97 (0.73–5.32)	0.18
Severe sepsis	1.11 (0.58–2.13)	0.76
Any benzodiazepine	1.93 (1.09–3.41)	0.024
Any opiate	1.14 (0.64–2.01)	0.66
Any propofol	4.16 (2.41–7.20)	<0.001
Any steroid	1.06 (0.63–1.79)	0.83

Definition of abbreviations: APACHE IV = Acute Physiology and Chronic Health Evaluation IV; ARDS = acute respiratory distress syndrome; CI = confidence interval; ICU = intensive care unit; OR = odds ratio.
*Patients with persistent coma were excluded from this analysis (n = 32).
†OR per 10-point increase.

to determine whether delirium mediates the association between ARDS and these long-term outcomes, and if preventing and reducing delirium in ARDS patients can improve long-term outcomes.

Despite concerted efforts, identification of effective treatments to reduce in-hospital mortality in ARDS patients has had limited success in recent years and mortality in ARDS patients has plateaued at approximately 40% (19, 20). Our findings that delirium and persistent coma attenuate the association between ARDS and in-hospital mortality identify new risk factors for poor short-term outcomes that, to our knowledge, have not been accounted for in prior outcome studies of ARDS. Although persistent coma may be less easily modifiable, studies have demonstrated that delirium can be effectively reduced with concurrent improvements in short-term outcomes, such as decreased duration of mechanical ventilation, improved functional mobility, and decreased ICU and hospital length of stay (17, 18, 29, 30). In contrast, a recent metaanalysis of randomized clinical trials found no association between delirium reduction interventions and improved short-term mortality; however, study heterogeneity and the lack of power to test for mortality may have limited the analyses (31). Therefore, our findings raise the possibility that delirium may represent a novel and potentially modifiable risk factor for poor short-term outcomes in ARDS patients. Future studies are needed to determine if preventing and reducing delirium in ARDS patients can improve short-term outcomes.

In previous studies, mechanical ventilation has been variably reported as a risk factor for ICU delirium and no distinction has been made between patients with and without ARDS (32–34). We found that both mechanical ventilation and ARDS are independently associated with ICU delirium, and that the strength of association between ARDS and delirium is above and beyond that of mechanical ventilation and delirium, even after adjusting for common confounders. Although the pathophysiology for the association between mechanical ventilation and delirium has yet to be determined, a recent study proposes an intriguing mechanism by demonstrating that positive-pressure mechanical ventilation selectively induces neuronal apoptosis in the hippocampus via a dopamine-mediated pathway, and not through inflammatory

Table 4. Multivariate Regression Model of Association between ARDS and In-Hospital Mortality

	Adjusted Odds Ratio (95% CI) for In-Hospital Mortality			
Risk Factor	Omitting Delirium and Coma	*P* Value	Including Delirium and Coma	*P* Value
Respiratory status				
Not Intubated	Reference		Reference	
Intubated, no ARDS	6.78 (2.62–17.57)	<0.001	4.44 (1.65–11.94)	0.003
Intubated with ARDS	10.44 (3.16–34.50)	<0.001	5.63 (1.55–20.45)	0.009
Delirium and coma status				
Not delirious	*		Reference	
Ever delirious	*		1.95 (0.97–3.92)	0.062
Persistent coma	*		22.15 (7.68–63.89)	<0.001
Age	0.99 (0.98–1.01)	0.47	0.99 (0.97–1.01)	0.43
Charlson Comorbidity Index	1.00 (0.94–1.08)	0.92	1.03 (0.96–1.11)	0.43
Alcohol abuse	1.38 (0.62–3.05)	0.43	1.12 (0.47–2.67)	0.79
APACHE IV†	1.36 (1.21–1.53)	<0.001	1.32 (1.16–1.50)	<0.001
Severe sepsis	2.19 (1.12–4.29)	0.022	1.96 (0.97–3.98)	0.062

Definition of abbreviations: CI = confidence interval; APACHE IV = Acute Physiology and Chronic Health Evaluation IV; ARDS = acute respiratory distress syndrome.
*Omitted from model.
†Odds ratio per 10-point increase.

or hypoxemia-mediated pathways (35). Although tidal volume did not differ between delirious and nondelirious patients in our cohort, other potential contributors to ventilator-induced lung injury, such as plateau pressure and insufficient positive end-expiratory pressure, were not measured.

In addition, several factors related to the pathophysiology and treatment of ARDS may account for the additional risk that ARDS patients have for developing delirium, compared with intubated patients without ARDS. First, hypoxemia has been suggested to be a risk factor for short-term cognitive impairment (3). Although we found no relationship between severity of hypoxemia at the time of ARDS diagnosis and delirium in ARDS patients, our findings may have been limited by the lack of daily hypoxemia data. Second, to improve oxygenation through ventilator synchrony, ARDS patients can experience sedative-induced coma and prolonged immobility through administration of higher sedative doses and neuromuscular blockade. Sedative-induced coma and prolonged immobility have both been identified as risk factors for ICU delirium (7, 34). Third, systemic corticosteroid use has been identified as a risk factor for delirium in ARDS patients in a recent study (11). Although steroid use was greater in our cohort's ARDS patients, it was not significantly associated with delirium in our model. Our results may have differed from the prior study because of our smaller sample size.

Finally, there may be other risk factors for delirium that are more prevalent in ARDS patients but were unaccounted for in this study (e.g., increased circulating inflammatory mediators) (36). For example, inflammation has recently been shown to be an important contributor to delirium and long-term cognitive dysfunction (37–40). Indeed, all ARDS patients in our cohort had severe sepsis at the time of ICU admission. Our findings highlight the importance of delirium detection and early and aggressive efforts to reduce modifiable risk factors for delirium in inflammatory conditions, such as ARDS and sepsis, as soon as it is clinically safe to do so (41). These interventions can be accomplished feasibly, even in patients with ARDS, as demonstrated by a recent quality initiative study, which showed that a reduction in deep sedation in ARDS patients was associated with a decrease in delirium duration (42).

This study had several notable strengths including its prospective assessment of consecutive ICU patients at multiple hospitals and medical and surgical ICUs, and being the first study to concurrently and rigorously assess ICU delirium and ARDS status. In addition, sedative medications were included in the multivariate model for delirium and a robust modeling approach was used in which all covariates were included, regardless of statistical significance.

There were also several limitations. The sample size of patients with ARDS was small, and future studies in a larger cohort are needed to confirm our findings. Patients with rapidly reversible delirium in the setting of sedative discontinuation have been found to have similar outcomes as patients with no delirium (43). We did not assess for this small but important subgroup of delirious patients (12% in the published study) because this project was conducted before the publication of those findings. Notwithstanding this limitation, inclusion of rapid reversers with other delirious patients would have biased our findings toward the null, and suggests that our estimates might have been even stronger if rapid resolvers were accounted for. Prolonged immobilization has also been identified as a modifiable risk factor for delirium and several barriers to early initiation of physical therapy have been identified in ARDS patients (44, 45). Although outside of the scope of this study, the feasibility and safety of early initiation of physical therapy needs to be evaluated in ARDS patients. Dementia, another potentially important confounder, was assessed by ICD9 code and medical record review, and therefore the sensitivity of our assessment may be lower than surrogate interview. Finally, additional potential confounders of the association between ARDS and ICU delirium with in-hospital mortality were not measured, such as plateau pressure, pulmonary dead-space fraction, and other physiologic, laboratory, and biomarker parameters.

Conclusions

In this multicenter observational study, we found that patients with ARDS have a higher risk of delirium above and beyond that of mechanically ventilated patients even after adjusting for multiple risk factors for delirium and severity of illness, and that ICU delirium and coma substantially weakens the association between ARDS and in-hospital mortality. Future studies are needed to determine if delirium is associated with poorer long-term cognitive and functional outcomes in ARDS survivors, and if prevention or reduction of delirium can improve outcomes in this high-risk patient population. ■

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