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Sedation/Delirium

Post-ICU psychological morbidity in very long ICU stay patients with ARDS and delirium☆

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ABSTRACT

Purpose: We investigated the impact of delirium on illness severity, psychological state, and memory in acute respiratory distress syndrome patients with very long ICU stay.
Materials and methods: Prospective cohort study in the medical-surgical ICUs of 2 teaching hospitals. Very long ICU stay (>75 days) and prolonged delirium (≥40 days) thresholds were determined by ROC analysis. Subjects were ≥18 years, full-code, and provided informed consent. Illness severity was assessed using Acute Physiology and Chronic Health Evaluation IV, Simplified Acute Physiology Score-3, and Sequential Organ Failure Assessment scores. Psychological impact was assessed using the Hospital Anxiety and Depression Scale, Impact of Event Scale-Revised, and the 14-question Post-Traumatic Stress Syndrome (PTSS-14). Memory was assessed using the ICU Memory Tool survey.
Results: 181 subjects were included. Illness severity did not correlate with delirium duration. On logistic regression, only PTSS-14 < 49 correlated with delirium ($p = 0.001$; 95% CI 1.011, 1.041). 49% remembered their ICU stay clearly. 47% had delusional memories, 50% reported intrusive memories, and 44% reported unexplained feelings of panic or apprehension.
Conclusion: Delirium was associated with memory impairment and PTSS-14 scores suggestive of PTSD, but not illness severity.

1. Background

Delirium is a transient global disorder of cognition associated with increased morbidity and mortality [1,2]. Early diagnosis and symptom resolution is correlated with favorable outcomes [3]. Delirium may occur at any age, but is more common in the elderly and persons with compromised mental status [4]. The mechanism remains unclear. No diagnostic laboratory or radiographic test is available, and diagnosis may be particularly difficult in patients with dementia.

Ten to 31% of new hospital admissions meet diagnostic criteria, with a probability of transitioning into delirium as high as 29% [5]. In general intensive care unit (ICU) patients, delirium prevalence may reach as high as 80% [6], with a daily probability of transitioning into delirium

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as high as 14% [7]. Additionally, subsyndromal delirium (intermediate between delirium and normal cognition) may occur in up to 1/3 of ICU patients [8]. Moreover, ARDS is associated with a greater delirium risk than mechanical ventilation alone [2,9]. ICU delirium may be also a predictor of prolonged ICU stay and increased morbidity [10]. The hospital mortality of ARDS patients with delirium ranges from 22 to 56% [11-14]. Additionally, delirium may prolong hospital stays [15-17], increase complications, hospital costs [18], long-term disability [19], long-term cognitive impairment [20,21], and odds of discharge to a nursing home [22-25].

In the general ICU population, the presence and duration of delirium has been associated with development of long-term cognitive impairment [20] and post-traumatic stress disorder (PTSD) [26,27]. Although cognitive and psychiatric symptoms are among the most common comorbidities that ARDS survivors experience, very little is known about the role that delirium plays in short or long-term outcomes. Even less is known on how these factors impact the very long ICU-stay cohort.

The purpose of this study was to examine the impact of delirium on ARDS patients with very long ICU-stay including effects on patient mortality, illness severity, memory, and development of anxiety, depression, PTSD, or memory impairment. As prior studies have focused on patients with ICU stays of short or typical length, we chose those with very long ICU stays as this vulnerable group represents a unique and understudied population at risk for mood and psychiatric comorbidity.

2. Materials and methods

2.1. Study design and setting

We conducted a prospective longitudinal cohort study. The study was conducted in the mixed medical-surgical ICUs of 2 academic teaching hospitals in Tehran, Iran. Subjects were enrolled between June 1, 2007 and October 31, 2015. All ARDS patients presenting during this period were screened for enrollment. All study parts were reviewed according to the Strengthening the Reporting of Observational Studies in Epidemiology for Respondent-Driven Sampling Studies: 'STROBE-RDS' Statement [28].

2.2. Participants

ARDS patients with very-long ICU stay were included. No standard exists for what length-of-time determines a prolonged length-of-stay (LOS). Prior ICU studies have reported >10 days [29,30], >14 days [31,32], ≥21 days [33-37], >1 month [38-43], >60 days [44], the 85th percentile [45], or as determined by ROC analysis [46,47]. We chose delirium duration as the preferred severity marker. Consensus threshold values for what constitute very-long ICU LOS or delirium duration haven't been described to date. In this study, optimal thresholds were selected by ROC analysis of a database of 4200 ICU patients. To achieve a sensitivity of 95% and a specificity of 90%, a threshold of >75 ICU days and ≥40 delirium days was observed to have the best ROC characteristics. Threshold selection was discussed in a qualitative panel of 12 members including one psychiatrist, one psychologist, three intensivists, one neurologist, two internists, two anesthesiologists, and two ICU nurses. Consensus agreement was achieved that based on the available data, an ICU stay >75 days constitutes a very-long ICU stay in this region of Iran. The inclusion criteria were: (1) age ≥ 18 years, (2) ICU LOS > 75 days, (3) full-code status, and if (4) occurrence of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and Confusion Assessment Method for the ICU (CAM-ICU) during the hospitalization period [48-50], and (5) informed consent obtained from the patient, legal guardian, or healthcare surrogate. Patients with pre-ICU psychiatric comorbidity, and those admitted for a primary psychiatric diagnosis were excluded.

2.3. Sample size

The sample size was calculated for having delusional memory from the ICU LOS. By considering a delirium prevalence of 0.5, 95% confidence interval level, 80% power, and absolute error 10%, the necessary sample size was calculated to be 196 patients. Sample size calculation was performed using G-Power 3.1.2 software (available at http://www.gpower.hhu.de/) [51].

2.4. Data collection

Semi-structured interviews lasting 45–90 min were conducted in a private room to gather in-depth data at an early time post-ICU discharge (3–21 days). During these interviews four different questionnaires were administered including the Post-traumatic Stress Syndrome 14-question (PTSS-14), Impact of Event Scale Revised (IES-R), Hospital Anxiety and Depression Scale (HADS), and the ICU Memory Tool (ICU-MT). Interviews were conducted by teams of 3 investigators (including 1 ICU nurse), all of whom were experienced in doing qualitative interviews. Recall bias was limited by the aforementioned selection of interview participants as well as by as well as the choice of evaluation tools that were either designed or previously validated for use in the ICU and Delirium populations.

2.5. Research instruments

Severity of medical illness was measured on ICU days 1 (admission), 14 and 28 using validated illness severity scales: (1) Acute Physiology and Chronic Health Evaluation (APACHE) IV, (2) Simplified Acute Physiology Score (SAPS) 3, and (3) Sequential Organ Failure Assessment score (SOFA).

The APACHE IV tool uses variables derived from the worst values from the initial 24 h of ICU admission [52,53].

The Simplified Acute Physiology (SAPS) 3 admission score is one model used to predict hospital mortality from admission data taken within the first hour of the patient's admission [54].

The SOFA score was initially designed to sequentially assess the severity of organ dysfunction in critically ill sepsis patients. SOFA uses simple measurements of major organ function to calculate a severity score. The scores are calculated 24 h after ICU admission, and every 48 h thereafter. The mean and highest scores are most predictive of mortality. In addition, scores that increase by about 30% are associated with a mortality of at least 50% [55].

Delirium was assessed during each shift (three times daily) by the bedside nurse and researcher (Kappa agreement coefficient 0.801–0.902), using the CAM-ICU screening tool and DSM-IV-TR criteria. Delirium duration high (≥40) vs. low (<40) was determined by the number of days with at least 1 positive delirium screen.

The 14-item Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depression levels in hospitalized patients. Seven of the items relate to anxiety and seven relate to depression. Items are scored from 0 to 3 (total score 0–21; 0–7 normal, 8–10 borderline, and 11–21 abnormal) [56,57].

The 22-item Impact of Event Scale-Revised (IES-R) has 3 subscales: intrusion, avoidance, and hyperarousal. Items are scored on a five-Likert scale ranging 0 (*not at all*) to 4 (*extremely*) [58]. The total score ranges from 0 to 88 (≥30 signifies distress), and subscale scores can also be calculated for the Intrusion, Avoidance, and Hyperarousal subscales [56,59]. Generally, the IES-R is not used to diagnosis PTSD, however, cutoff scores for a preliminary diagnosis have been reported [60,61].

After confirming delirium resolution, three tools were used to further explore the psychological impact of these factors and patients' readiness to resume their previous state of living after a 15-day period of psychiatrist-psychologist counseling (5–7 sessions). The three assessment tools were the HADS, IES-R, and PTSS-14. Each was administered two months post-ICU discharge.

The PTSS-14 consists of 18 questions divided into two sections. Part A consists of four dichotomous (yes/no) questions about the patient's memory of his/her ICU stay. Part B consists of 14 statements about the patient's current health state. Responses are scored from 1 to 7 (never-to-always), with a total range 14–98 [56]. When utilized along with the ICU-MT, a threshold of ≥49 is related to an increased potential risk for not remembering ICU admission, delusional memories, and unexplained feelings of panic or apprehension (Table 1) [56,62,63].

2.6. Data analysis

All analyses were performed using IBM® SPSS® 23.0 (IBM Corp., Armonk, NY) [64] and GraphPad Prism 5© (GraphPad Software Inc., La Jolla, CA). Descriptive statistics were calculated for all variables. Normality was assessed by the Shapiro-Wilk test. Normally distributed continuous variables were compared using the *t*-test, with non-normally distributed variables compared using the Mann-Whitney *U* test. Categorical variables were compared using the Chi-Square and Fisher's Exact test, as appropriate. Univariate and multivariate logistic regression were used to identify those factors exerting a statistically significant effect on the delirium levels. In the univariate model, each variable was entered in the model. In the multivariate model, all variables with enter method were entered in the model. Significance was determined as an alpha of 0.05. No interim analysis was planned or conducted.

3. Results

A total of 209 ARDS patients consented to participate; 181 were included in the final analysis. Twenty-eight patients were excluded due to incomplete data (n = 6), logistical impediment to data collection (n = 7), revoked consent (n = 9), and death (n = 6). Demographic and clinical features are summarized in Table 2. The mean age was 65 years with a female predominance (66%). Admission diagnoses were similar between the high vs. low delirium groups: Trauma (11 vs. 13; p = 0.67), Cardiovascular (8 vs. 11; p = 0.32), Neurological (14 vs. 12; 0.45), Renal (9 vs. 6; 0.34), GI-abdominal (10 vs. 11; 0.19), Cancer (15 vs. 16; 0.87), Respiratory (14 vs. 15; 0.91), Toxicological (7 vs. 9; 0.33). The mean delirium duration was 40.53 ± 4.18 days. The mean hospital length-of-stay (LOS) was 116.3 ± 22.9 days, with a mean ICU LOS of 77 ± 11.6 days. The mean intubation duration was 851 ± 127.5 h. The incidence of multiple organ failure was 80.7%. Patients had similar comorbidities (data not presented) and Chi-square testing revealed no significant relationship between comorbidities and delirium duration (p = 0.675). The relationship of delirium duration (high ≥ 40 days) to Illness severity (SAPS-3, SOFA, APACHE IV) is depicted in Table 3. Illness severity did not correlate with delirium duration, and was similar in the low and high delirium groups (Table 3). Overall In-hospital mortality was 27.8%, with ICU mortality of 17.3%, and non-ICU mortality of 10.5%. Seventy-two percent were discharged home, whereas 29% were referred to nursing or rehabilitation facilities. Table 4 shows the crude and adjusted logistic regression model for LOS and illness severity variables according to low and high delirium groups.

The mean HADS anxiety (HADS-A) score was 11.28 ± 2.39: normal (n = 5; 2.8%), suggestive (n = 58; 32%), and probable (n = 118; 65.2%) for anxiety. The mean HADS depression (HADS-D) score was 10.24 ± 1.94: normal (n = 18; 9.9%), suggestive (n = 89; 49.2%), and probable (n = 74; 40.9%) for depression. The mean IES-R score was 70.1 ± 4.8 (≥30 signifies distress), with 100% (n = 181) of patients scoring ≥ 30. Mean PTSS-14 scores were 69.16 ± 3.93 (<49 = decreased likelihood of PTSD), with 46% (n = 83) of patients scoring ≥ 49. Moreover, illness severity as measured by APACHE IV score trended toward correlation with the PTSS-14 score on days 1 (p = 0.059) and 14 (p = 0.04), but not day 28 (p = 0.28). Thirteen percent (n = 23) of the respondents could not remember their admission to hospital, 23% (n = 41) did not remember the time in the hospital before ICU admission, 49% (n = 88) did not remember being transferred from the ICU to the general ward, and only 49% (n = 89) remembered their ICU stay clearly (Table 1). Forty-four percent (n = 79) had factual memories, and 47% (n = 85) had delusional memories from their ICU stay. Nearly 44% (n = 80) of respondents stated that they have had unexplained feelings of panic or apprehension and 50% reported intrusive memories from their time in hospital or of the event that led up to the admission. Most of the patients talked with family, friends, or other staff about their experience.

Table 1
The ICU Memory Tool.

Question	Response	N (%)
1. Do you remember being admitted to hospital?	Clearly	39 (21.5)
	Hazily	119 (65.7)
	Not at all	23 (12.7)
2. Can you remember the time inhospital before you were admitted to ICU?	All of it	26 (14.4)
	Something	114 (63)
	Nothing	41 (22.7)
3. Do you remember being in ICU?	No	93 (51.4)
	Yes	88 (48.6)
4. Do you remember all the stay clearly?	No	92 (50.8)
	Yes	89 (49.2)
4.1 Factual memories	No	102 (56.4)
	Yes	79 (43.6)
4.2 Delusional memories	No	96 (53)
	Yes	85 (47)
5. Do you remember being transferred from ICU to the general wards?	Clearly	26 (14.4)
	Hazily	107 (59.1)
	Not at all	48 (26.5)
6. Have you had any unexplained feelings of panic or apprehension?	No	101 (55.8)
	Yes	80 (44.2)
7. Have you had any intrusive memories from your time inhospital or of the event that lead up to your admission?	No	91 (50.3)
	Yes	90 (49.7)
8. Have you talked about what happened to you in ICU with:		
8.1. A member of family	No	81 (44.8)
	Yes	100 (55.2)
8.2. A friend	No	79 (43.6)
	Yes	102 (56.4)
8.3. A doctor on the ward	No	76 (42)
	Yes	105 (58)
8.4. A nurse on the ward	No	79 (43.6)
	Yes	102 (56.4)
8.5. A family doctor	No	86 (47.5)
	Yes	95 (52.5)

Table 2
Patient demographics and illness severity stratified by delirium severity.

Variable	Delirium (all)	Delirium (low)	Delirium (high)	p – Value
Sex, female n (%)	120 (66.3)	61 (64.2)	59 (68.6)	0.28[a]
Multi-organ failure n (%)	146 (80.7)	77 (81.1)	69 (80.2)	0.58[a]
Age (years)				
Median (Q1–Q3)	65 (62–68)	64 (62–67)	65 (62–69)	0.07[b]
Mean ± SD	64.9 ± 5.2	64.3 ± 5.1	65.7 ± 5.2	
ICU LOS (days)				
Median (Q1–Q3)	75 (71–79)	73 (71–78)	75 (72–80)	0.13[b]
Mean ± SD	77.4 ± 11.6	76.2 ± 10.5	78.8 ± 12.6	
Hospital LOS (days)				
Median (Q1–Q3)	110 (105–120)	108 (104–120)	111.5 (107–121)	0.14[b]
Mean ± SD	116.3 ± 22.9	113.9 ± 20.6	866.7 ± 138.5	
Duration of intubation (hours)				
Median (Q1–Q3)	825 (781–869)	803 (781–858)	825 (792–880)	0.13[b]
Mean ± SD	851.5 ± 127.5	837.7 ± 115.7	866.7 ± 138.5	
SAPS-3 score, median (Q1–Q3)				
Day 1	30 (28–34)	29 (28–33)	30 (28–34)	0.35[b]
Day 14	41 (38–49)	40 (37–45)	43 (38–50)	0.02[b]
Day 28	36 (33–40)	36 (33–39)	37 (33–40)	0.52[b]
SOFA score, median (Q1-Q3)				
Day 1	15 (13–17)	15 (14–17)	15 (13–17)	0.48[b]
Day 14	15 (13–17)	14 (13–16)	15 (13–18)	0.23[b]
Day 28	15 (13–17)	15 (13–17)	15 (13–18)	0.63[b]
APACHE IV score, median (Q1-Q3)				
Day 1	24 (23–25.5)	24 (23–26)	24 (23–25.3)	0.84[b]
Day 14	35 (32–38)	35 (32–38)	35 (32–39.3)	0.47[b]
Day 28	26 (22–28.5)	26 (22–29)	25 (21–28)	0.38[b]

ICU means intensive care unit; Q1-Q3 means first through third interquartile range; SD means standard deviation, LOS means length-of-stay; SAPS means Simplified Acute Physiology Score; SOFA means Sequential Organ Failure Assessment; APACHE means Acute Physiology and Chronic Health Evaluation.
[a] Chi-square.
[b] Independent sample *t*-test.

With univariate logistic regression, only PTSS-14 was significantly correlated with delirium duration, whereas IES-R total, IES-R Intrusion, IES-R Avoidance, IES-R Hyperarousal, ICU-MT, HADS-A, and HADS-D did not correlate significantly. With multivariate logistic regression, the only variable significantly associated with delirium was PTSS-14 < 49. Or in other words, PTSS-14 ≥ 49 was significantly correlated with prolonged delirium duration (>40 days).

4. Discussion

ARDS is associated with a high mortality and morbidity. The hospital mortality in our ARDS cohort (27.8%) is consistent with prior reports including multi-national (34.9%–46.1%) [12], Pakistan (56%) [13], Taiwan (24%) [11], and a US trauma cohort (22%) [14]. Among the most common, but least characterized, comorbidities that ARDS survivors experience are psychiatric and neuro-cognitive. In one study of ARDS survivors (n = 406), long-term cognitive impairment was present in 55% of those completing cognitive testing [65]. Depression, PTSD, or anxiety was present in 36%, 39%, and 62% of one-year survivors. The extent to which delirium influences short or long-term outcomes remains unclear, however it is known that ARDS and delirium are linked to each other and outcomes [9].

A number of techniques exist to identify delirium in critically ill patients. The CAM-ICU allows the clinician to screen for presence (not severity) of delirium in critically ill patients, including those on mechanical ventilation (sensitivity 75.5%, specificity 95.8%) [66]. It makes use of non-verbal assessments to evaluate important features of delirium and is one of the most specific bedside tools to diagnose delirium in critically ill patients. Other tools include the delirium symptom interview (DSI), intensive care delirium screening checklist (ICDSC), delirium detection scale (DDS), and CAM short form [67].

Poor mental health and functional disability is common in ARDS patients. The incidence of anxiety experienced by ICU patients remains unclear, however one Iranian study (n = 104) reported that 63% of patients reported anxiety (HADS-A > 11) on ICU discharge [68]. This is in keeping with our results in which 65% of patients exhibited a HADS-A score in the *probable* anxiety range (>11). The prevalence at 2–3 months post-ICU has been reported at 27–38% [69]. Among ICU admissions fitting the outdated acute lung injury (ALI) definition, defined as a partial pressure of oxygen to the inspired fraction of oxygen (P/F ratio) of 201 to 300 [70], the prevalence of delirium is as high as 38–44% at two-year follow-up [71]. Furthermore, it has been reported that a more consistent or stable *trait* anxiety, but not the temporary or situational *state* anxiety, may be associated with subsequent post-traumatic stress symptoms [72].

Table 3
The relationship of illness severity and delirium duration: high > 40 days.

Variable	Day	Sub-group	Mean ± SD	p – Value[*]	p-Value within low delirium group[†]	p-Value within high delirium group[†]	p-Value between two groups[†]
SAPS-3 score	1	Low	32.20 ± 6.84	0.35			
		High	33.19 ± 7.40				
	14	Low	42.61 ± 8.22	0.02	Before adjustment: <0.0001	Before adjustment: <0.0001	Before adjustment: 0.104
		High	45.40 ± 8.21		After adjustment: 0.66[a]	After adjustment: 0.67[a]	After adjustment: 0.11[a]
	28	Low	38.02 ± 7.08	0.52			
		High	38.72 ± 7.66				
SOFA score	1	Low	14.96 ± 3.13	0.48			
		High	15.30 ± 3.46				
	14	Low	14.42 ± 3.10	0.23	Before adjustment: <0.0001	Before adjustment: 0.17	Before adjustment: 0.42
		High	15.00 ± 3.41		After adjustment: 0.52[a]	After adjustment: 0.41[a]	After adjustment: 0.42[a]
	28	Low	14.82 ± 3.31	0.63			
		High	15.07 ± 3.58				
APACHE IV score	1	Low	24.69 ± 2.32	0.84			
		High	24.63 ± 2.06				
	14	Low	35.03 ± 4.25	0.47	Before adjustment: <0.0001	Before adjustment: <0.0001	Before adjustment: 0.84
		High	35.50 ± 4.54		After adjustment: 0.39[a]	After adjustment: 0.38[a]	After adjustment: 0.76[a]
	28	Low	25.36 ± 4.72	0.38			
		High	24.76 ± 4.53				

SAPS means Simplified Acute Physiology Score; SOFA means Sequential Organ Failure Assessment; APACHE means Acute Physiology and Chronic Health Evaluation.
[*] p-Value based on Independent samples *t*-test.
[†] p-Value based on repeated measures ANOVA. Dependent on the results of Mauchly's test, p-values presented are based on the Sphericity assumed test.
[a] Adjusted cofactors: heart rate, systolic blood pressure, diastolic blood pressure, temperature, respiratory rate, P_aO_2/F_IO_2 ratio, and P_aO_2/P_AO_2 ratio.

Table 4
The results of crude and adjusted logistic regression models on length-of-stay variables and illness severity scores.

Variable	Simple logistic model		Adjusted logistic model	
	Crude OR (CI 95%)	p-Value	Adjusted OR (CI 95%)	p-Value
Age	1.06 (0.995–1.119)	0.07		
Sex				
- Male	Base	0.53		
- Female	1.22 (0.656–2.262)			
MOF				
- No	Base	0.89		
- Yes	1.054 (2.205–0.504)			
P_aO_2/F_iO_2	0.995 (0.987–1.003)	0.21		
A-a gradient	0.001 (0.000–1.598)	0.07		
Duration of intubation	1.00 (0.999–1.004)	0.14	1.00 (0.999–1.004)	0.37
ICU LOS	1.02 (0.993–1.050)	0.14	1.01 (0.984–1.044)	0.37
Hospital LOS	1.02 (0.992–1.048)	0.16	1.01 (0.983–1.042)	0.40
SAPS-3 score				
- Day 1	1.02 (0.979–1.063)	0.35	1.02 (0.975–1.065)	0.41
- Day 14	1.04 (1.005–1.081)	0.03	1.05 (1.009–1.088)	0.02
- Day 28	1.01 (0.974–1.054)	0.52	1.01 (0.968–1.052)	0.68
SOFA score				
- Day 1	1.03 (0.944–1.129)	0.48	1.04 (0.950–1.143)	0.39
- Day 14	1.06 (0.965–1.157)	0.23	1.06 (0.967–1.169)	0.21
- Day 28	1.02 (0.938–1.112)	0.63	1.03 (0.946–1.129)	0.46
APACHE IV score				
- Day 1	0.99 (0.863–1.127)	0.84	0.98 (0.851–1.127)	0.77
- Day 14	1.03 (0.958–1.096)	0.47	1.04 (0.964–1.110)	0.35
- Day 28	0.97 (0.912–1.036)	0.38	0.96 (0.900–1.028)	0.25

OR means odds ratio; CI means confidence interval; MOF means multiple organ failure; P_aO_2/F_iO_2 means the ratio of partial pressure arterial oxygen and fraction of inspired oxygen; A-a gradient means the alveolar to arterial oxygen gradient; LOS means length of stay; SAPS means Simplified Acute Physiology Score; SOFA means Sequential Organ Failure Assessment; APACHE means Acute Physiology and Chronic Health Evaluation.

Depression is five times more common than is PTSD after critical illness [27]. In one Iranian study (n = 104), 58.7% of patients reported depression (HADS-D > 11) on ICU discharge [68]. This corroborates our findings (HADS-D > 11), with 40.9% of patients scoring *probable*. Moreover, evidence suggests that depressive symptoms may be lasting. Up to one-third of ICU survivors note depressive symptoms at 12-month follow-up [73], and 26–33% of ALI patients (retired criteria) reporting depressive symptoms at two-year follow-up [70,71]. Data for ARDS patients remains unclear.

Delirious patients may have less factual recall than non-delirious patients, and may report lower [74,75] or unchanged [76] healthcare-related QoL following discharge. This corroborates our findings of impaired factual recall in ICU patients who experienced delirium. In our cohort, fewer than half of patients remembered their ICU stay clearly, 44% had factual memories, and 47% had delusional memories.

To date, no significant relationship has been noted between illness severity, delirium severity or duration, and PTSD symptoms [77]. Although rates in ARDS patients are not well described, studies have reported that up to 27% of ICU survivors suffer from PTSD [27,75]. Rates are higher in patients diagnosed with ALI (retired criteria) or ARDS [70,71]. This corroborates our findings, with 46% of very-long ICU stay patients scoring ≥49 on the PTSS-14, consistent with PTSD. The observed correlation between illness severity and PTSD (not statistically significant) warrants further investigation as this study was not designed to assess this. In this analysis of patients with very-long ICU stay, we studied whether delirium duration correlated to psychiatric outcomes: depression, anxiety, PTSD. In doing this assessment, the patient population was characterized in a number of ways, including illness severity. Illness severity was similar between groups based on delirium duration. This was important to show that the study groups were balanced because the development of PTSD is known to relate to markers of critical illness including duration of mechanical ventilation, sedation duration, and benzodiazepine use [78]. Thus, since illness severity was balanced between study groups, one would not expect to find a significant link to delirium duration. Patient stratification by illness severity is needed to better study the relationship between illness severity and delirium or PTSD. The incidence of PTSD observed in this study is likely higher than prior reports due to cohort selection. Consistent predictors of post-ICU PTSD include prior psychopathology, sex (female), younger age, and post-ICU memories of in-ICU frightening and/or psychotic experiences [75]. There is also increasing evidence that duration of mechanical ventilation, sedation duration, benzodiazepine use, fear, stress and delirium may be PTSD risk factors [75,77-79]. It has been noted that 88% of ICU delirium patients have intrusive memories (hallucinatory or delusional) [80]. These memories merge realistic events (involving intensive care staff, environment, medical procedures and unpleasant physical experiences) with delusions and frightening hallucinations. They found that such patients were more traumatized by frightening hallucinations/delusions than real events, suggesting they may have post-psychosis PTSD rather than classic PTSD [80]. To decrease the stress of critical illness, every attempt must be made to ensure that the environment is as hospitable as reasonably possible. Post-ICU follow-up should include filling in the 'missing gaps', particularly for delirious patients. Ongoing explanations and a caring environment may assist the patient in making a complete recovery both physically and mentally [74]. Future investigations may consider prospectively evaluating the impact of continuing or withholding outpatient psychotropic medications on ICU delirium. Additionally, the impact of provider-patient communication on ICU delirium remains a question in need of investigation.

5. Conclusions

In this study delirium was associated with memory impairment and decreased memory quality. Delirium also correlated with PTSS-14 scores ≥ 49, suggestive of PTSD. No correlation between illness severity and delirium presence or severity was observed. The extent to which ICU delirium impacts long-term health, and the optimal means to prevent or treat it requires further study.

Declarations

List of abbreviations

ICU	intensive care unit
DSM	Diagnostic and Statistical Manual of Mental Disorders
ARDS	acute respiratory distress syndrome
ALI	acute lung injury
PTSD	post-traumatic stress disorder
PHP	prolonged hospitalization patients
PTSS-14	14-question posttraumatic stress syndrome survey
IES-R	impact event scale revised
HADS	hospital anxiety and depression scale
HADS-A	HADS-anxiety
HADS-D	HADS-depression
APACHE	acute physiology and chronic health evaluation
SAPS	simplified acute physiology score
SOFA	sequential organ failure assessment
LOS	length-of-stay
DSI	delirium symptom interview
ICDSC	intensive care delirium screening checklist
DDS	delirium detection scale

Ethical approval and consent to participate

The study was approved by the Investigative Review Board at the two participating academic medical centers: Baqiyatallah Hospital of Baqiyatallah University of Medical Sciences (Tehran, Iran), and Shariati Hospital of Tehran University of Medical Sciences (Tehran, Iran). Study participation was optional for respondents. Informed consent was obtained from the patient, legal guardian or healthcare surrogate or designated healthcare proxy.

Consent for publication

Informed consent was obtained from the patient, legal guardian or healthcare surrogate and allowed for both study participation and publication of de-identified aggregate results. There is no data contained within the manuscript from which individual patients or participants may be identified.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to disclose.

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References

[1] Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ Jun 03 2015;350:h2538.
[2] Pisani MA, Murphy TE, Araujo KL, Van Ness PH. Factors associated with persistent delirium after intensive care unit admission in an older medical patient population. J Crit Care 2010;25(3):540.e541–7.
[3] Vahedian Azimi A, Ebadi A, Ahmadi F, Saadat S. Delirium in prolonged hospitalized patients in the intensive care unit. Trauma Mon May 2015;20(2):e17874.
[4] Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, Van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA 2010;304(4):443–51.
[5] Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing Jul 2006;35(4):350–64.
[6] Kalabalik J, Brunetti L, El-Srougy R. Intensive care unit delirium: a review of the literature. J Pharm Pract Apr 2014;27(2):195–207.
[7] Schreiber MP, Colantuoni E, Bienvenu OJ, et al. Corticosteroids and transition to delirium in patients with acute lung injury. Crit Care Med Jun 2014;42(6):1480–6.
[8] Serafim RB, Soares M, Bozza FA, et al. Outcomes of subsyndromal delirium in ICU: a systematic review and meta-analysis. Crit Care Jul 12 2017;21(1):179.
[9] Hsieh SJ, Soto GJ, Hope AA, Ponea A, Gong MN. The association between acute respiratory distress syndrome, delirium, and in-hospital mortality in intensive care unit patients. Am J Respir Crit Care Med Jan 1 2015;191(1):71–8.
[10] Yamaguchi T, Tsukioka E, Kishi Y. Outcomes after delirium in a Japanese intensive care unit. Gen Hosp Psychiatry Nov–Dec 2014;36(6):634–6.
[11] Wang CY, Calfee CS, Paul DW, et al. One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. Intensive Care Med Mar 2014;40(3):388–96.
[12] Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA Feb 23 2016;315(8):788–800.
[13] Sharif N, Irfan M, Hussain J, Khan J. Factors associated within 28 days in-hospital mortality of patients with acute respiratory distress syndrome. Biomed Res Int 2013;2013:564547.
[14] Fahr M, Jones G, O'Neal H, Duchesne J, Tatum D. Acute respiratory distress syndrome incidence, but not mortality, has decreased nationwide: a national trauma data bank study. Am Surg Apr 01 2017;83(4):323–31.
[15] Al-Qadheeb NS, Skrobik Y, Schumaker G, et al. Preventing ICU subsyndromal delirium conversion to delirium with low-dose IV haloperidol: a double-blind, placebo-controlled pilot study. Crit Care Med 2015.
[16] Mehta S, Cook D, Devlin JW, et al. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults*. Crit Care Med 2015;43(3):557–66.
[17] Trogrlić Z, van der Jagt M, Bakker J, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care 2015;19(1):1–17.
[18] Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of delirium and other major complications on outcomes after elective surgery in older adults. JAMA Surg 2015; 150(12):1134–40.
[19] Marcantonio ER, Kiely DK, Simon SE, et al. Outcomes of older people admitted to postacute facilities with delirium. J Am Geriatr Soc Jun 2005;53(6):963–9.
[20] Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med Oct 3 2013;369(14):1306–16.
[21] Sukantarat KT, Burgess PW, Williamson RC, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. Anaesthesia Sep 2005;60(9):847–53.
[22] Devlin JW, Al-Qadhee NS, Skrobik Y. Pharmacologic prevention and treatment of delirium in critically ill and non-critically ill hospitalised patients: a review of data from prospective, randomised studies. Best Pract Res Clin Anaesthesiol 2012; 26(3):289–309.
[23] Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients*. Crit Care Med 2010;38(12):2311–8.
[24] Shehabi Y, Riker R, Bokesch P, Wisemandle W, Shintani A, Ely E. SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) study group: delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010;38(12):2311–8.
[25] Tsuruta R, Nakahara T, Miyauchi T, et al. Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit. Gen Hosp Psychiatry 2010;32(6):607–11.
[26] Nouwen MJ, Klijn FA, van den Broek BT, Slooter AJ. Emotional consequences of intensive care unit delirium and delusional memories after intensive care unit admission: a systematic review. J Crit Care 2012;27(2):199–211.
[27] Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med May 2014;2(5):369–79.
[28] White RG, Hakim AJ, Salganik MJ, et al. Strengthening the reporting of observational studies in epidemiology for respondent-driven sampling studies: "STROBE-RDS" statement. J Clin Epidemiol Dec 2015;68(12):1463–71.
[29] Chan CL, Ting HW, Huang HT. The definition of a prolonged intensive care unit stay for spontaneous intracerebral hemorrhage patients: an application with national health insurance research database. Biomed Res Int 2014;2014:891725.
[30] Rimachi R, Vincent JL, Brimioulle S. Survival and quality of life after prolonged intensive care unit stay. Anaesth Intensive Care Feb 2007;35(1):62–7.
[31] Zampieri FG, Colombari F, de Batista Lovatto Pastore C, Santoro C, Haib D, Ladeira JP. Factors associated with prolonged ICU stay: a retrospective analysis. Crit Care 2013; 17(Suppl. 3):P9.
[32] Arabi Y, Venkatesh S, Haddad S, Al-Shimemeri A, Al-Malik S. A prospective study of prolonged stay in the intensive care unit: predictors and impact on resource utilization. International J Qual Health Care 2002;14(5):403–10.
[33] A G, T M. Characteristics, outcomes and costs of prolonged stay icu patients. Turk J Intensive Care Med 2011;3:53–8.

[34] Martin CM, Hill AD, Burns K, Chen LM. Characteristics and outcomes for critically ill patients with prolonged intensive care unit stays. Crit Care Med Sep 2005;33(9):1922–7 [quiz 1936].
[35] Teno JM, Fisher E, Hamel MB, et al. Decision-making and outcomes of prolonged ICU stays in seriously ill patients. J Am Geriatr Soc May 2000;48(Suppl. 5):S70–74.
[36] Arabi Y, Venkatesh S, Haddad S, Al Shimemeri A, Al Malik S. A prospective study of prolonged stay in the intensive care unit: predictors and impact on resource utilization. International J Qual Health Care Oct 2002;14(5):403–10.
[37] Laupland KB, Kirkpatrick AW, Kortbeek JB, Zuege DJ. Long-term mortality outcome associated with prolonged admission to the ICU. Chest Apr 2006;129(4):954–9.
[38] Yu PJ, Cassiere HA, Fishbein J, Esposito RA, Hartman AR. Outcomes of patients with prolonged intensive care unit length of stay after cardiac surgery. J Cardiothorac Vasc Anesth Mar 23 2016.
[39] Ong AW, Omert LA, Vido D, et al. Characteristics and outcomes of trauma patients with ICU lengths of stay 30 days and greater: a seven-year retrospective study. Crit Care 2009;13(5):R154.
[40] Naghib S, van der Starre C, Gischler SJ, Joosten KF, Tibboel D. Mortality in very long-stay pediatric intensive care unit patients and incidence of withdrawal of treatment. Intensive Care Med Jan 2010;36(1):131–6.
[41] Goins WA, Reynolds HN, Nyanjom D, Dunham CM. Outcome following prolonged intensive care unit stay in multiple trauma patients. Crit Care Med Mar 1991;19(3):339–45.
[42] Friedrich JO, Wilson G, Chant C. Long-term outcomes and clinical predictors of hospital mortality in very long stay intensive care unit patients: a cohort study. Crit Care 2006;10(2):R59.
[43] Trottier V, McKenney MG, Beninati M, Manning R, Schulman CI. Survival after prolonged length of stay in a trauma intensive care unit. J Trauma Jan 2007;62(1):147–50.
[44] Venker J, Miedema M, Strack van Schijndel RJ, Girbes AR, Groeneveld AB. Long-term outcome after 60 days of intensive care. Anaesthesia Jun 2005;60(6):541–6.
[45] Studdert DM, Mello MM, Burns JP, et al. Conflict in the care of patients with prolonged stay in the ICU: types, sources, and predictors. Intensive Care Med Sep 2003;29(9):1489–97.
[46] Ettema RG, Peelen LM, Kalkman CJ, Nierich AP, Moons KG, Schuurmans MJ. Predicting prolonged intensive care unit stays in older cardiac surgery patients: a validation study. Intensive Care Med Sep 2011;37(9):1480–7.
[47] Koseoglu Z, Ozdogan M, Kuvvetli A, et al. Increased nutritional risk in major trauma: correlation with complications and prolonged length of stay. Ulus Travma Acil Cerrahi Derg Nov 2011;17(6):521–4.
[48] Smith H, Gangopadhyay M, Goben CM, et al. The preschool confusion assessment method for the ICU: valid and reliable delirium monitoring for critically ill infants and children. Crit Care Med 2015.
[49] Schieveld J, van Zwieten JJ. From pediatrics to geriatrics: toward a unified standardized screening tool for delirium: a thought experiment. Crit Care Med 2016;44(9):1778–80.
[50] Bruno JJ, Warren ML. Intensive care unit delirium. Crit Care Nurs Clin North Am 2010;22(2):161–78.
[51] Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods Nov 2009;41(4):1149–60.
[52] Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med May 2006;34(5):1297–310.
[53] Keegan MT, Gajic O, Afessa B. Comparison of APACHE III, APACHE IV, SAPS 3, and MPM0III and influence of resuscitation status on model performance. Chest Oct 2012;142(4):851–8.
[54] Hernandez AM, Palo JE. Performance of the SAPS 3 admission score as a predictor of ICU mortality in a Philippine private tertiary medical center intensive care unit. J Intensive Care 2014;2(1):29.
[55] Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA Oct 10 2001;286(14):1754–8.
[56] Mishra RK, Alalawi R, Raj R, Nugent KM. Prolonged acute care in a 52-year-old man with respiratory failure: lessons learned from 70-day intensive care unit hospitalization. J Crit Care 2011;26(5) [532.e539–532.e516].
[57] Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes Aug 01 2003;1:29.
[58] Weiss DS, Marmar CR. The impact of event scale - revised. In: Wilson J, Keane TM, editors. Assessing psychological trauma and PTSD. New York: Guilford; 1996. p. 399–411.
[59] Derogatis LR. SCL-90-R: symptom checklist-90-R: administration, scoring & procedures manual. 3rd ed. Minneapolis, MN: National Computer Systems, Inc.; 1994.
[60] Asukai N, Kato H, Kawamura N, et al. Reliability and validity of the Japanese-language version of the impact of event scale-revised (IES-R-J): four studies of different traumatic events. J Nerv Ment Dis Mar 2002;190(3):175–82.
[61] Creamer M, Bell R, Failla S. Psychometric properties of the impact of event scale - revised. Behav Res Ther Dec 2003;41(12):1489–96.
[62] Granja C, Gomes E, Amaro A, et al. Understanding posttraumatic stress disorder-related symptoms after critical care: the early illness amnesia hypothesis. Crit Care Med Oct 2008;36(10):2801–9.
[63] Jones C, Humphris G, Griffiths RD. Preliminary validation of the ICUM tool: a tool for assessing memory of the intensive care experience. Clin Intensive Care 2011;11(5):251–5.
[64] Kline RB. Software programs for structural equation modeling: AMOS, EQS, and LISREL. J Psychoeduc Assess 1998;16(4):343–64.
[65] Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med Jun 15 2012;185(12):1307–15.
[66] Neto AS, Nassar Jr AP, Cardoso SO, et al. Delirium screening in critically ill patients: a systematic review and meta-analysis. Crit Care Med Jun 2012;40(6):1946–51.
[67] Inouye SK, Kosar CM, Tommet D, et al. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. Ann Intern Med Apr 15 2014;160(8):526–33.
[68] Momennasab M, Ghahramani T, Yektatalab S, Zand F. Physical and mental health of patients immediately after discharge from intensive care unit and 24 hours later. Trauma Mon Feb 2016;21(1):e29231.
[69] Nikayin S, Rabiee A, Hashem MD, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. Gen Hosp Psychiatry Nov–Dec 2016;43:23–9.
[70] Costa EL, Amato MB. The new definition for acute lung injury and acute respiratory distress syndrome: is there room for improvement? Curr Opin Crit Care Feb 2013;19(1):16–23.
[71] Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, et al. Cooccurrence of and remission from general anxiety, depression, and posttraumatic stress disorder symptoms after acute lung injury: a 2-year longitudinal study. Crit Care Med Mar 2015;43(3):642–53.
[72] Castillo MI, Cooke ML, Macfarlane B, Aitken LM. In ICU state anxiety is not associated with posttraumatic stress symptoms over six months after ICU discharge: a prospective study. Aust Crit Care Aug 2016;29(3):158–64.
[73] Rabiee A, Nikayin S, Hashem MD, et al. Depressive symptoms after critical illness: a systematic review and meta-analysis. Crit Care Med Sep 2016;44(9):1744–53.
[74] Roberts BL, Rickard CM, Rajbhandari D, Reynolds P. Factual memories of ICU: recall at two years post-discharge and comparison with delirium status during ICU admission–a multicentre cohort study. J Clin Nurs Sep 2007;16(9):1669–77.
[75] Davydow DS, Gifford JM, Desai SV, Needham DM, Bienvenu OJ. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. Gen Hosp Psychiatry Sep–Oct 2008;30(5):421–34.
[76] Wolters AE, van Dijk D, Pasma W, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: a prospective cohort study. Crit Care Jun 18 2014;18(3):R125.
[77] Girard TD, Shintani AK, Jackson JC, et al. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care 2007;11(1):R28.
[78] Caiuby AV, Andreoli PB, Andreoli SB. Post-traumatic stress disorder in intensive care unit patients. Rev Bras Ter Intensiva Mar 2010;22(1):77–84.
[79] Wade D, Hardy R, Howell D, Mythen M. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. Minerva Anestesiol Aug 2013;79(8):944–63.
[80] Wade DM, Brewin CR, Howell DC, White E, Mythen MG, Weinman JA. Intrusive memories of hallucinations and delusions in traumatized intensive care patients: an interview study. Br J Health Psychol Sep 2015;20(3):613–31.