



# Impact of Religiosity on Delirium Severity Among Critically Ill Shi'a Muslims: A Prospective Multi-Center Observational Study

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## Abstract

This study assesses the impact of religiosity on delirium severity and patient outcomes among Shi'a Muslim intensive care unit (ICU) patients. We conducted a prospective observational cohort study in 21 ICUs from 6 Iranian academic medical centers. Delirium was assessed using the Confusion Assessment Method for the ICU (CAM-ICU) tool. Eligible patients were intubated, receiving mechanical ventilation (MV) for  $\geq 48$  h. Illness severity was assessed using Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. A total of 4200 patients were enrolled. Patient religiosity was categorized as more (40.6%), moderate (42.3%), or less (17.1%) based on responses to patient and surrogate questionnaires. The findings suggest that lower pre-illness religiosity may be associated with greater delirium severity, MV duration, and ICU and hospital LOS. The lower mortality in the *less religiosity* group may be related in part to a greater proportion of female patients, but it remains unclear whether and to what extent greater religiosity impacted treatment decisions by patients and families. Further investigation is needed to validate and clarify the mechanism of the mortality findings.

**Keywords** Delirium · Intensive care unit · Critical care · Religion · Religiosity

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## Introduction

Delirium is a transient global disorder of cognition associated with increased morbidity and mortality (Pisani et al. 2010). Early recognition, treatment, and symptoms resolution are correlated with favorable outcomes (Vahedian-Azimi et al. 2015). The mechanism remains unclear, and no diagnostic test is available. In intensive care unit (ICU) patients, the prevalence may reach as high as 80% (Kalabalik et al. 2014), with a daily probability of transitioning into delirium as high as 14% (Schreiber et al. 2014). ICU delirium may also be a predictor of increased mortality and prolonged ICU length of stay (LOS) (Yamaguchi et al. 2014), prolonged hospital LOS (Al-Qadheeb et al. 2016; Mehta et al. 2015; Trogrlic et al. 2015), increased complications, hospital costs (Gleason et al. 2015), long-term disability (Marcantonio et al. 2005), long-term cognitive impairment (Pandharipande et al. 2013; Sukantarat et al. 2005), and decreased odds of discharge home (Devlin et al. 2012; Shehabi et al. 2010; Tsuruta et al. 2010).

The American Psychiatric Association's Diagnostic and Statistical Manual, 5th edition (DSM-V) defines delirium by: disturbances of (1) attention, (2) cognition, (3) that develops over a short period, (4) that is a change from baseline, (5) that fluctuates, (5) not otherwise explained by another neurocognitive disorder, (6) with evidence suggesting a potential cause in the history, physical examination, or laboratory findings (American Psychiatry Association 2013).

Despite the high incidence, delirium remains understudied. Furthermore, it remains unclear what role pre-illness beliefs and practices, including religiosity and spirituality (R/S), may play in delirium development or recovery.

The WHO definition of health comprises physical, psychological, and spiritual factors as well as social well-being (World Health Organization 1998). The potential for both positive and negative effects of R/S on health, combined with the high levels of engagement, suggests that this area is ripe for research as evidenced by the marked increase in R/S health research over the past decade (Bagiella et al. 2005; Ellison and Levin 1998; Park et al. 2016; Pereira et al. 2010; Powell et al. 2003). For many patients who face life-threatening illness, R/S and associated resources may be particularly relevant and important determinant factors of their quality of life (QoL) (Atef-Vahid et al. 2011; Balboni et al. 2013; Bonelli et al. 2012; Bulow et al. 2012; Darviri et al. 2016; Ironson et al. 2016). Religious participation is related to better outcomes for persons who are recovering from physical and mental illness and is correlated with improved mental and physical health and longevity (Alves et al. 2010).

Research has consistently linked indices of religious coping to measures of health and well-being, a major source of support and hope, among diverse groups recovering from physical and mental illness or facing critical life events (Alves et al. 2010; Marcantonio et al. 2005; Mardiyono et al. 2011; Saisunantarom et al. 2015; Shehabi et al. 2010). Hence, these are factors of vital importance to many ICU and their families (Shinall et al. 2014; Wall et al. 2007). Although some literature assessing the relationship between R/S and ICU outcomes does exist, there is a paucity of data regarding the interplay of R/S and delirium. The

objective of this study was to investigate whether pre-admission religiosity correlated with delirium severity, or patient outcomes including survival, illness severity, and hospital and ICU LOS.

## Methods

### Study Design and Setting

We conducted a prospective observational cohort study in 21 ICUs (10 mixed, 5 surgical, 6 medical) from 6 academic medical centers across 4 Iranian provinces from October 1, 2007, to May 30, 2015. All 7750 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* “STROBE” (von Elm et al. 2007).

### Participants

The inclusion criteria were: (1) age  $\geq 18$  years, (2) endotracheally intubated and on mechanical ventilation (MV) for  $\geq 48$  h, (3) full-code status, and (4) informed consent obtained from the patient, legal guardian, or healthcare surrogate.

Patients were excluded for: (1) no consent, (2) death while on ventilator, (3) permanent ventilator dependence, (4) tracheostomy placement for long-term weaning, (5) discrepancy between patient and his/her surrogate opinion about the patient’s religious degree, (6) copious excessive/secretions precluding wean, and (7) incomplete data.

### Delirium

Delirium was assessed during each shift (three times daily) by the bedside nurse and researcher (kappa agreement coefficient 0.801–0.902), using the Confusion Assessment Method for the ICU (CAM-ICU) screening tool. The CAM-ICU allows the clinician to screen for the presence (not severity) of delirium in critically ill patients, including those on MV (sensitivity 75.5%, specificity 95.8%) (Ely et al. 2001a, b; Neto et al. 2012). It makes use of nonverbal assessments to evaluate important features of delirium and is one of the most specific bedside tools to diagnose delirium in critically ill patients. Delirium severity was determined using the delirium rating scale-revised-98 (DRS-R-98) (Trzepacz et al. 2001). Investigators also recorded the number of *shifts* during which patients were noted to have a delirious episode. Delirium was further subcategorized into binary low/high groups and stratified into low, moderate, and high for additional analysis. Optimal thresholds were selected by receiver operating curve (ROC) analysis of a database of 16,000 ICU patients. To achieve a sensitivity of 95% and a specificity of 95%, binary and ordinal categorizations were observed to have the best ROC characteristics. Thresholds selection was discussed in a qualitative panel of 31 members including two psychiatrists, three

psychologists, five intensivists, three neurologists, three internists, five anesthesiologists, and ten ICU nurses. Consensus agreement was achieved based on the available data.

### Religiosity Grouping

Upon screening positive for delirium, the patient's designated surrogate was asked about the patient's baseline level of religiosity. When available, patients were asked the same questions upon their clinical improvement. A kappa agreement coefficient was determined between patients and their surrogates (0.923;  $p < 0.0001$ ). The components of religiosity determination included: (i) 5 obligatory daily prayers (*Salaat*) or 17 *rakats* per day; (ii) *Nafilah* prayers (34 *rakats*); (iii) fasting (*Sawm*) during Ramadan and other recommended days; (iv) reading one or more pages of Qur'an daily; (v) performance of additional optional acts of faith including following the example (*Sunnah*) of the prophet Muhammad, making additional supplications (*Dua*), and reading sermons of notable Imams. The *high* religiosity category was defined as always fulfilling criteria (i) through (v). The *moderate* religiosity group was defined as always meeting criteria (i) and (iii), and sometimes (ii), (iv), and (v). The *less* religiosity group was defined as meeting not more than criteria (i) and (iii). Assignment of categorization was done using the 3-round Delphi technique.

### Ethical Considerations

The study was approved by the investigational review board at Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1394.451), whose approval was accepted by each enrolling site. Surrogate consent from the patient's legal guardian or designated health proxy was permitted in cases where the patient did not have decision-making capacity. All patients that survived and regained their faculties were informed of the project.

### Sample Size

The sample size was calculated for the occurrence of ICU delirium. 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 4200 patients. Sample size calculation was performed using G-Power 3.1.2 software (available at <http://www.gpower.hhu.de/>) (Faul et al. 2009).

### Data Collection

Baseline demographics (age, sex, marital status, smoking status), hospital data (diagnosis, ICU LOS, hospital LOS, MV duration, comorbidities, sedation, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and mortality), delirium presence and severity, and religiosity level were collected for each patient. The primary outcome was to determine whether religiosity correlated with delirium

severity. Secondary outcomes were to determine whether religiosity correlated with patient outcomes including survival, illness severity, and hospital and ICU length of stay.

### Availability of Data and Materials

This study was part of a much larger project, and not all data are published in this manuscript. De-identified individual subject data may be available from the corresponding author on reasonable request for researchers who meet the criteria for access to confidential data.

### Statistical Analysis

Continuous variables were expressed as the mean  $\pm$  SD and median (interquartile range), and the categorical variables were expressed as a number (percentage). Continuous variables were checked for normality by using Shapiro–Wilk test. Independent samples Student’s *t* test was used to compare between two groups of normally distributed variables. One-way ANOVA test was used to compare between more than two groups of normally distributed variables. Percent of categorical variables were compared using Pearson’s Chi-square ( $\chi^2$ ) test or Fisher’s exact test when was appropriate. Trend of change in distribution of relative frequencies between ordinal data was compared using  $\chi^2$  test for trend. To determine predictors for high delirium, univariate logistic regression was done. Backward multivariate logistic regression analysis model was done using any predictor with *p* value  $< 0.2$  in univariate analysis. All tests were two-sided. *p* Value  $< 0.05$  was considered significant. Lastly, a multivariate analysis was performed to identify variables associated with mortality. All statistics were performed using IBM® SPSS® 22.0 (IBM Corp., Armonk, NY) and MedCalc® (MedCalc Software bvba 13, Ostend, Belgium).

### Results

A total of 7750 potential patients were approached to participate. A total of 199 declined to participate. A total of 4200 were included in the final analysis, and 3351 patients were excluded for reasons including: patient death before weaning ( $n = 616$ ); permanent ventilator dependence ( $n = 167$ ); tracheostomy placement for long-term weaning ( $n = 489$ ); copious secretions precluding wean ( $n = 1494$ ); discrepancy between patient and surrogate precluding classification ( $n = 475$ ); insufficient data gathered ( $n = 110$ ; Fig. 1). Demographic and clinical features are summarized in Table 1. All patients were Shi’a Muslims. The mean age was  $67 \pm 11.5$  years with a female predominance (58%). Patients were categorized by religiosity into *high* (40.6%), *moderate* (42.3%), or *less* (17.1%) religiosity groups. Overall, patients were admitted for sepsis (29.9%), acute respiratory distress syndrome (ARDS; 19.6%), trauma (17.5%), abdominal surgery (15.9%), pneumonia (10.2%), COPD (8.6%), pulmonary edema (5.8%), and

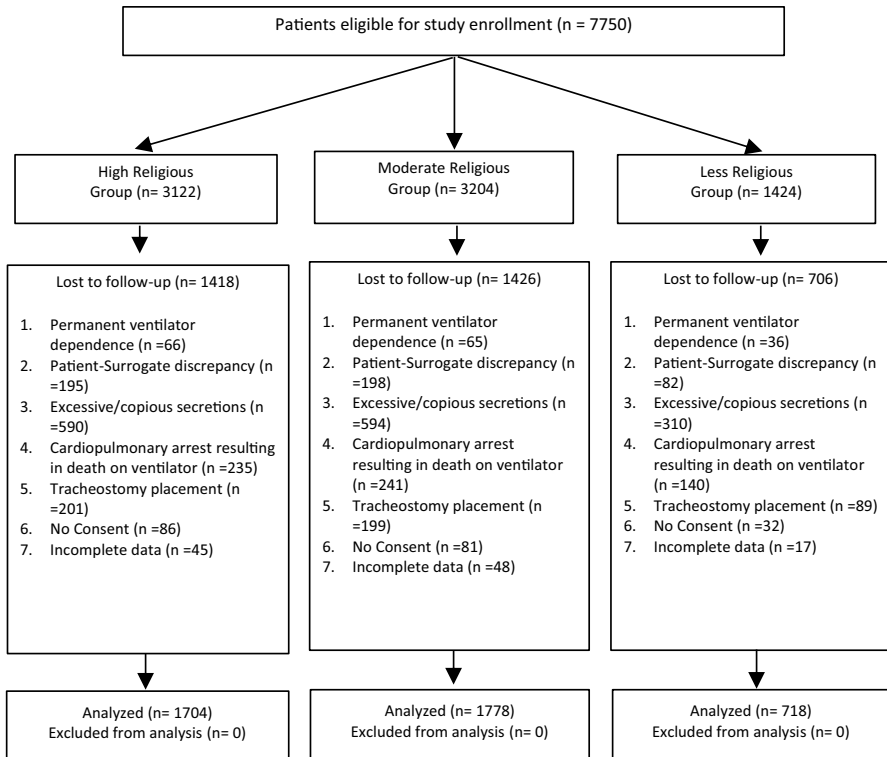


Fig. 1 CONSORT 2010 flow diagram

miscellaneous other (1.3%). Admission diagnoses were similar between groups as shown in Table 2. The overall mean delirium duration was  $23.32 \pm 7.88$  days. The mean hospital length of stay (LOS) was  $19.6 \pm 10.9$  days (range 8–98), with a mean ICU LOS of  $16.8 \pm 10.9$  days (range 9–93). The mean intubation duration was  $326.5 \pm 110.3$  h (range 140–602). The mean APACHE II score was  $15 \pm 2.4$  (range 11–22), and the mortality rate was 27.8%.

Increasing age directly correlated with both degree of religiosity (Table 3), delirium severity (Table 4), and greater in-hospital mortality. Although statistically significant, the (mean difference  $\pm$  standard deviation) differences in age relative to sedation dose were not clinically significant: high versus moderate ( $1.48 \pm 0.46$  years;  $p = 0.003$ ), high versus low ( $2.40 \pm 0.53$ ;  $p < 0.001$ ), moderate versus low ( $0.92 \pm 0.43$  years;  $p = 0.08$ ).

Religiosity, however, correlated inversely with delirium severity (Table 5). A description of comorbidities is provided in Table 6. Patients differed in comorbidities when stratified by religiosity ( $p < 0.001$ ), and  $\chi^2$  testing revealed significant relationship between comorbidities and delirium duration ( $p = 0.042$ ). Moreover, increasing comorbidities correlated significantly with patient mortality (Table 7).

**Table 1** Patient demographics, illness severity, and delirium severity

Characteristics	All studied patients ( <i>N</i> = 4200)		Characteristics	All studied patients ( <i>N</i> = 4200)	
	Number	%		Number	%
Age (year)			Disease		
Mean $\pm$ SD	67.25 $\pm$ 11.57		COPD	363	8.6
Median (range)	65 (50–93)		ARDS	830	19.6
Sex			Sepsis	876	20.9
Male	1761	41.9	Multiple trauma	737	17.5
Female	2439	58.1	Abdominal surgery	668	15.9
Marital status			Pneumonia	430	10.2
Unmarried	489	11.6	Pulmonary edema	242	5.8
Married	3360	80	Miscellaneous	54	1.3
Divorced	351	8.4			
Smoking			APACHE II		
Current and ex-smoker	2734	65.1	Mean $\pm$ SD	15.60 $\pm$ 2.41	
Never smoking	1466	34.9	Median (range)	15 (11–22)	
			Survival		
			Death	1169	27.8
			Alive	3031	72.2
Religious status			Shifts with delirious episode		
More religious	1704	40.6	Mean $\pm$ SD	23.32 $\pm$ 7.88	
Medium religious	1778	42.3	Median (range)	24 (10–43)	
Less religious	718	17.1	Delirium* (binary)		
Hospital length of stay (days)			Less delirium (10–23)	2030	48.3
Mean $\pm$ SD	19.64 $\pm$ 10.93		High delirium (24–43)	2170	51.7
Median (range)	17 (8–98)		Delirium* (ordinal)		
ICU length of stay (days)			Less delirium (10–20)	1403	33.4
Mean $\pm$ SD	16.77 $\pm$ 10.89		Moderate delirium (21–28)	1364	32.5
Median (range)	13 (9–93)		High delirium (29–43)	1433	34.1
MV duration (days)			Physical restraints		
Mean $\pm$ SD	326.49 $\pm$ 110.33		Yes	1763	42
Median (range)	336 (140–602)		No	2437	58
Sedation <sup>†</sup>			Acute nursing care <sup>‡</sup>		
High dose	891	21.2	High	854	20.3
Moderate	2254	53.7	Moderate	2098	50
Low dose	1055	25.1	Low	1248	29.7

Continuous variables were expressed as the mean  $\pm$  SD and median (range); categorical variables were expressed as a number (percentage)

\*Score according to the CAM-ICU scale

<sup>†</sup>Sedation levels determined in accordance with published recommendations (Miller et al. 2014; Nagaraj et al. 2016; Nagaraj et al. 2017)

<sup>‡</sup>Determined based on number of nursing hours needed per shift: high ( $\geq 8$  h), moderate (4–8 h), low (< 4 h)

**Table 2** Association between study variables, delirium, and degree of religiosity (univariate analysis)

Study variables	More religious ( <i>n</i> = 1704)	Moderate religious ( <i>n</i> = 1778)	Less religious ( <i>n</i> = 718)	<i>p</i> Value
Age (years)				
Mean ± SD	66.82 ± 9.23	63.84 ± 11.75	76.71 ± 10.98	< 0.001*
Median (range)	65 (51–92)	60 (50–93)	78 (51–93)	
Sex (female)	909 (53.3%)	1060 (59.6%)	470 (65.5%)	< 0.001 <sup>†</sup>
Marital status				
Unmarried	243 (14.3%)	174 (9.8%)	72 (10%)	< 0.001 <sup>†</sup>
Married	1389 (81.5%)	1427 (80.3%)	544 (75.8%)	
Divorced	72 (4.2%)	177 (10%)	102 (14.2%)	
Smoking status				
Current and former	1185 (69.5%)	1061 (59.7%)	488 (68%)	< 0.001 <sup>†</sup>
Never	519 (30.5%)	717 (40.3%)	230 (32%)	
Hospital LOS (days)				
Mean ± SD	18.95 ± 7.74	20.04 ± 13.21	20.28 ± 11.10	0.003*
Median (range)	17 (8–56)	16 (8–98)	17 (9–85)	
ICU LOS (days)				
Mean ± SD	16.04 ± 7.74	17.21 ± 13.13	17.41 ± 11.10	0.001*
Median (range)	14 (9–53)	13 (9–93)	13 (9–78)	
MV duration (hours)				
Mean ± SD	220.80 ± 67.44	378.32 ± 66.94	448.95 ± 33.98	< 0.001*
Median (range)	196 (140–490)	364 (280–602)	448 (378–560)	
Illness				
COPD	139 (8.2%)	162 (9.1%)	60 (8.6%)	0.001 <sup>†</sup>
Pneumonia	175 (10.3%)	179 (10.1%)	76 (10.6%)	
Sepsis	355 (20.8%)	372 (20.9%)	149 (20.8%)	
ARDS	342 (20.1%)	350 (19.7%)	138 (19.2%)	
Pulmonary edema/ CHF	98 (5.8%)	101 (5.7%)	43 (6%)	
Trauma	301 (17.7%)	311 (17.5%)	125 (17.4%)	
Abdominal surgery	273 (16%)	281 (15.8%)	114 (15.9%)	
Other	21 (1.2%)	22 (1.2%)	11 (1.5%)	
APACHE II				
Mean ± SD	15.64 ± 2.45	15.61 ± 2.42	15.45 ± 2.30	0.194*
Median (range)	15 (11–22)	15 (11–22)	15 (11–22)	
Physical restraints				
Yes	642 (37.7%)	777 (43.7%)	344 (47.9%)	0.001 <sup>†</sup>
No	1062 (62.3%)	1001 (56.3%)	374 (52.1%)	
Sedation dose <sup>‡</sup>				
High	286 (16.8%)	396 (22.3%)	209 (29.1%)	< 0.001 <sup>†</sup>
Moderate	972 (57%)	915 (51.5%)	367 (51.1)	
Low	446 (26.2%)	467 (26.3%)	142 (19.8)	



**Table 2** (continued)

Study variables	More religious ( <i>n</i> = 1704)	Moderate religious ( <i>n</i> = 1778)	Less religious ( <i>n</i> = 718)	<i>p</i> Value
<b>Acute nursing care**</b>				
High	434 (25.5%)	336 (18.9%)	84 (11.7%)	< 0.001 <sup>†</sup>
Moderate	876 (51.4)	859 (48.3%)	363 (50.6%)	
Low	394 (23.1%)	583 (32.8%)	271 (37.7%)	
<b>Shifts with delirious episode</b>				
Mean ± SD	15.77 ± 4.81	27.02 ± 4.78	32.06 ± 2.42	< 0.001*
Median (range)	14 (10–35)	26 (20–43)	32 (27–40)	
<b>Delirium (binary)††</b>				
High	192 (11.3%)	1260 (70.9%)	718 (100%)	< 0.001 <sup>†</sup>
Less	1512 (88.7%)	518 (29.1%)	0	
<b>Delirium (ordinal)††</b>				
High	18 (1.1%)	721 (40.6%)	694 (96.7%)	< 0.001 <sup>†</sup>
Moderate	319 (18.7%)	1021 (57.4%)	34 (3.3%)	
Less	1367 (80.2%)	36 (2%)	0	
Inpatient mortality	495 (29%)	503 (28.3%)	171 (23.8%)	0.027 <sup>†</sup>

**APACHE Acute Physiology and Chronic Health Evaluation**

Continuous variables were expressed as the mean ± SD and median (range); categorical variables were expressed as number (percentage); *p* < 0.05 is significant

\*One-way ANOVA test

†Chi-square test

‡Sedation levels determined in accordance with published recommendations (Miller et. al. 2015; Nagaraj et al. 2016, 2017)

\*\*Determined based on number of nursing hours needed per 8-h shift: high (≥ 8 h), moderate (4–8 h), low (< 4 h)

††Score according to the CAM-ICU scale

**Table 3** Tukey highly significant difference comparison tests for age (dependent variable) and degree of religiosity: high, moderate, or less

Tukey test	Mean difference (SE)	95% confidence interval		<i>p</i> Value	Inference
		Lower bound	Upper bound		
High versus moderate	2.98 (0.36)	2.13	3.82	< 0.001	Significant
High versus less	− 9.89 (0.47)	− 11.0	− 8.78	< 0.001	Significant
Moderate versus high	− 2.98 (0.36)	− 3.82	− 2.13	< 0.001	Significant
Moderate versus less	− 12.86 (0.47)	− 13.97	− 11.76	< 0.001	Significant
Less versus high	9.89 (0.47)	8.78	11.0	< 0.001	Significant
Less versus moderate	12.86 (0.47)	11.76	13.97	< 0.001	Significant

**Table 4** Tukey highly significant difference comparison tests for age (dependent variable) and degree of delirium: high (29–43), moderate (21–28), less (10–20)

Tukey test	Mean difference (SE)	95% confidence interval		p Value	Inference
		Lower bound	Upper bound		
Less versus moderate	-5.22 (0.43)	-6.23	-4.20	<0.001	Significant
Less versus high	-3.78 (0.43)	-4.78	-2.78	<0.001	Significant
Moderate versus less	5.21 (0.43)	4.20	6.23	<0.001	Significant
Moderate versus high	1.44 (0.43)	0.43	2.45	0.002	Significant
High versus less	3.78 (0.43)	2.78	4.78	<0.001	Significant
High versus moderate	-1.44 (0.43)	-2.45	-0.43	0.002	Significant

**Table 5** Relationship between religiosity degree and delirium severity (binary categorization)

Religiosity	Delirium (binary categorization)		Total	p Value
	Less delirium (10–23)	High delirium [24–43]		
Greater	1512	192	1704	<0.001 <sup>a</sup>
Moderate	518	1260	1778	
Less	0	718	718	
Total	2030	2170	4200	

<sup>a</sup> Pearson  $\chi^2$ 

In a multivariate analysis, variables significantly associated with mortality included: age ( $p=0.003$ ), sex ( $p<0.001$ ), comorbidities ( $p<0.001$ ), APACHE II score ( $p=0.015$ ), ICU LOS ( $p<0.001$ ), and hospital LOS ( $p<0.001$ ). Sedation level did not correlate with mortality (Table 8).

The delirium score was transformed in a binary scoring factor with *less delirium* indicating a delirium rating score of 10–23, and *high delirium* by a score of 24–43. A total of 51.7% ( $N=2170$ ) of patients scored as high delirium. Upon performing binary logistic regression with degree of religiosity as a fixed variable, *delirium (binary)* was not a predictor of death in any group (Table 9). However, with binary logistic regression making the delirium a fixed variable, degree of religiosity was found to be a predictor of death in the *high religiosity* group (Table 10;  $p=0.003$ ).

Comparison of various parameters between the three degree of religiosity groups with delirium is shown in Table 2. In comparison with the other two groups, the *less religiosity* group had significantly higher delirium scores ( $p<0.001$ ) and more shifts with delirious episodes ( $p<0.001$ ). The increased incidence of severe delirium in the *less religiosity* group correlated with a concomitant increase in high dose sedation and physical restraint use. Univariate analysis showed that the less religious group had a significantly longer hospital LOS ( $p=0.003$ ), ICU LOS ( $p=0.001$ ), and duration of MV ( $p<0.001$ ), but lower in-hospital mortality (23.8% vs. 29%,  $p=0.027$ ).

**Table 6** Patient comorbidities with reference to prevalence in Iran

		Comorbidities <sup>a</sup>									
None	CV disease	CHF/CM	Diabetes	CKD stage 4 and 5	Chronic respiratory disease	Chronic liver disease	Liver cancer	GI cancer	Primary CNS cancer	Rheumatoid arthritis	
Death, <i>N</i> (%)	58 (5.0)	85 (7.3)	87 (7.4)	92 (7.9)	62 (5.3)	78 (6.7)	45 (3.8)	32 (3)	47 (4.0)	8 (0.7)	
Alive, <i>N</i> (%)	2725 (90)	42 (1.4)	34 (1.1)	53 (1.7)	22 (0.7)	51 (1.7)	21 (<1)	21 (0.7)	17 (0.6)	8 (0.3)	
Total, <i>N</i> (%)	3289 (78)	127 (3.0)	121 (2.9)	145 (3.5)	84 (2.0)	129 (3.1)	66 (2)	53 (1.3)	64 (1.5)	16 (0.4)	
Prevalence in Iran, %	1.2	0.3	3.6–6.7	0.5	N/A <sup>b</sup>	N/A <sup>b</sup>	<0.01	0.04	<0.01	0.3	
Citation, author (year)	Talaei et al. (2013)	Calender et al. (2014)	Azimi-Nezhad et al. (2008), Sadeghi et al. (2007)	Safarinejad (2009)	N/A <sup>b</sup>	N/A <sup>b</sup>	Ganji et al. (2009)	Ganji et al. (2009)	Jazayeri et al. (2013)	Forghanizadeh et al. (1995)	

*HTN* Hypertension; *CV* cardiovascular; *CHF* congestive heart failure; *CM* cardiomyopathy; *CKD* chronic kidney disease; *GI* gastrointestinal; *CNS* central nervous system; *Rheum* rheumatologic arthritis; *NA* not available

<sup>a</sup>Total number of patients was 4200

<sup>b</sup>Prevalence data for combined causes not available

**Table 7** Relationship between the presence of comorbidities and patient mortality

Mortality	Comorbidities		Total, <i>n</i> (%)	<i>p</i> Value
	Yes	No		
Dead	605	564	1169 (27.8)	<0.001 <sup>a</sup>
Alive	306	2725	3031 (72.2)	
Total	911	3289	4200 (100)	

<sup>a</sup>Pearson  $\chi^2$

**Table 8** Relationship between sedation dose and patient mortality

Mortality	High dose <i>N</i> (%)	Moderate dose <i>N</i> (%)	Low dose <i>N</i> (%)	Total, <i>n</i> (%)	<i>p</i> Value
Dead	256 (28.7%)	607 (26.9%)	306 (29%)	1169 (27.8%)	0.369 <sup>a</sup>
Alive	635 (71.3%)	1647 (73.1%)	749 (71%)	3031 (72.2%)	
Total	891 (100%)	2254 (100%)	1055 (100%)	4200 (100%)	

<sup>a</sup>Pearson  $\chi^2$

**Table 9** Delirium (binary) as a mortality predictor, with religious status as fixed variable

Religious status/Delirium (binary)	All studied patients ( <i>N</i> =4200) No. (%)	Outcome		<i>p</i> Value
		Death ( <i>N</i> =1169) No. (%)	Alive ( <i>N</i> =3031) No. (%)	
More religious group	1704 (40.6%)	495 (29%)	1209 (71%)	0.223 <sup>a</sup>
Less delirium	1512 (88.7%)	432 (28.6%)	1080 (71.4%)	
High delirium	192 (11.3%)	63 (32.8%)	129 (67.2%)	
Moderate religious group	1778 (42.3%)	503 (28.3%)	1275 (71.7%)	0.222 <sup>a</sup>
Less delirium	518 (29.1%)	136 (26.3%)	382 (73.7%)	
High delirium	1260 (70.9%)	367 (29.1%)	893 (70.9%)	
Less religious group	718 (17.1%)	171 (23.8%)	547 (76.2%)	1.000 <sup>a</sup>
High delirium	718 (100%)	171 (23.8%)	547 (76.2%)	

<sup>a</sup>Chi square ( $\chi^2$ ) test

## Discussion

### Delirium

The incidence and prevalence of delirium are high in ICU patients, with higher rates among mechanically ventilated patients (Bashar et al. 2018). The incidence and prevalence among ICU patients have been reported at 45–87% and 32%, respectively (Ely et al. 2001a, b; Roberts et al. 2005; Salluh et al. 2010; Thomason et al. 2005), rates considerably higher than those reported for general medical

**Table 10** Religious status as a mortality predictor, with delirium (binary) as fixed variable

Delirium (binary)/religious status	All studied patients ( <i>N</i> = 4200) No. (%)	Outcome		<i>p</i> Value
		Death ( <i>N</i> = 1169)	Alive ( <i>N</i> = 3031)	
		No. (%)	No. (%)	
Less delirium group	2030 (48.3%)	568 (28%)	1462 (72%)	0.311 <sup>a</sup>
More religious	1512 (74.5%)	432 (28.6%)	1080 (71.4%)	
Moderate religious	518 (25.5%)	136 (26.3%)	382 (73.7%)	
High delirium group	2170 (51.7%)	601 (27.7%)	1569 (72.3%)	0.003 <sup>b</sup>
More religious	192 (8.8%)	63 (32.8%)	129 (67.2%)	
Moderate religious	1260 (58.1%)	367 (29.1%)	893 (70.9%)	
Less religious	718 (33.1%)	171 (23.8%)	547 (76.2%)	

*p* < 0.05 is significant

<sup>a</sup>Chi-square ( $\chi^2$ ) test

<sup>b</sup> $\chi^2$  test for trend

patients (incidence 29–31%; prevalence 11–25%) (Francis et al. 1990; Levkoff et al. 1991, 1992; O’Keeffe and Lavan 1997).

Delirium significantly impacts the morbidity and mortality of patients. Short-term implications include prolonged ICU and hospital LOS, and increased likelihood of functional decline, hospital-acquired complications, and admission to long-term care (O’Keeffe and Lavan 1997). ICU delirium has been linked to increased MV duration, higher rates of self-extubation, and increased mortality (Ely et al. 2004). Longer-term complications include chronic cognitive impairment and functional disability. Moreover, delirium exacts a high financial cost. It is estimated that delirium is responsible for up to \$64,000 of additional healthcare costs per patient with delirium per year; thus, total direct 1-year healthcare costs attributable to delirium might range from \$38 billion to up to \$152 billion nationally (Leslie et al. 2008). The cost associated with delirium in mechanically ventilated patients in the US is around 4–16 billion dollars per year (Milbrandt et al. 2004).

A systematic review of six observational studies evaluated risk factors for ICU delirium and identified twenty-five risk factors, four of which were recognized as predisposing, whereas twenty-one were considered precipitating. The predisposing risk factors included respiratory disease, older age, alcohol abuse, and dementia; the precipitating factors included electrolyte abnormalities, fever, vasopressor requirement, increasing opiate dose, and metabolic acidosis (Van Rompaey et al. 2008). Besides opiates, the other classes of medications commonly associated with delirium include anti-cholinergic agents and benzodiazepines (Alagiakrishnan and Wiens 2004).

### Religiosity and Spirituality

R/S are broadly defined as feelings, thoughts, experiences, and behaviors that arise from searching for the “sacred,” with the former implying group or social practices

and doctrines, and the latter referring to personal experiences and beliefs (Chida et al. 2009). It has been reported that approximately 90% of Iranians (USA 84%) report a religious affiliation, and 96% of Iranians (USA 82%) report religion as at least somewhat or very important in their lives (Hajiesmaeili et al. 2016; The Pew Research Center 2008). Several systematic reviews of the literature support a relationship between religiosity promoting improved health behaviors (Oji et al. 2017; Saad and Medeiros 2017) and lower all-cause mortality (Hatah et al. 2015; McCullough et al. 2000; Powell et al. 2003; Saad and Medeiros 2017). Emerging evidence suggests that R/S are correlated with improved mental and physical health outcomes, including decreased rates of depression (Bonelli et al. 2012; El-Hady and Kandeel 2017; Frih et al. 2017; Kazemi and Baharami 2014; Saisunantararom et al. 2015), anxiety, post-traumatic stress disorder, suicide, and coronary heart disease (Bashar et al. 2018).

Additionally, research in Muslim populations suggests that religious practice may generate physiologic changes that are clinically evident. Recitations of Qur'an verses and the 99 names of *Allah* (God) to ill patients, for example, are practiced by many Muslims as a form of healing and worship (Ariff et al. 2013; Yadak et al. 2019). This practice has been reported to decrease perioperative pain (Avazeh et al. 2011; Mirzaeian et al. 2017) and anxiety (Atari et al. 2000; Avazeh et al. 2011; Hassan and Othman 2013; Hosseini et al. 2013; Majidi 2004; Tajvidi et al. 2001). The mechanism may in part be due to alpha wave generation as demonstrated on electroencephalogram (Hassan and Othman 2013; Abdullah and Omar 2011). The effects of Qur'anic recitation or *Zikr* meditation on heart rate, blood pressure, mean arterial pressure, respiratory rate, and peripheral capillary oxygen saturation have been mixed (Abu Bakr 2014; Ajorpaz and Aghajani 2011; El-Hady and Kandeel 2017; Mansouri et al. 2017; Mirzaeian et al. 2017; Ariff et al. 2013; Sitepu 2009), although it has been suggested that repeated exposure may result in changes that are not evident the first time (Ildar et al. 2003; Mansouri et al. 2017).

## Morbidity and Mortality

In this study, we found that the less religious group (self- or family reported) had more delirious shifts, higher delirium scores, longer MV duration, longer ICU and hospital LOS, and lower mortality. These findings warrant further discussion considering the literature, especially as it pertains to mortality.

Like prior reports, we found that greater delirium severity was associated with longer ICU and hospital LOS (Ely et al. 2004; Ouimet et al. 2007). However, ICU LOS has not been shown to be an independent risk factor for in-hospital mortality (Williams et al. 2010). Reports on the impact of delirium on mortality have been mixed, suggesting other confounding factors may be at play as well (Ely et al. 2004; Ouimet et al. 2007). As delirium-associated mortality has not previously been described in Iranian cohorts, the current study is the first to provide insight into this understudied aspect of delirium in Iranian ICUs.

Based on the literature, potential confounding factors that may be associated with delirium severity and/or mortality include: sex, age, smoking status, comorbidities,

illness severity, sedation, restraints, duration of MV, ICU LOS, hospital LOS, nurse-to-patient ratio, and physician-to-patient ratio.

In this cohort, the percentage of female patients was higher in the less religious group. Whereas some have reported that male sex may contribute to higher ICU mortality (Reinikainen et al. 2005), others have reported that values converge beyond 50 years of age (Mahmood et al. 2012). As the mean age in each group far exceeded this, it remains unclear whether sex contributed to the observed mortality differences.

In the multivariate analysis, tobacco use was also associated with mortality. Numerous studies estimate the smoking prevalence in Iran to be 10.5–22.9% (Ghouri et al. 2006; Meysamie et al. 2010; Moosazadeh et al. 2013; Moosazadeh 2013). Data regarding the accuracy of self versus proxy reporting of smoking in Iran are lacking. Moreover, whether smoking is viewed as prohibited (*haram*) or simply discouraged (*makruh*) varies greatly by region and sect (Ghouri et al. 2006). Further discussion of origins and types of Islamic moral law (*shari'ah*) that allow for these divergent interpretations is outside the scope of this manuscript; however, we have previously outlined the basics of Islamic jurisprudence elsewhere (Miller et al. 2014; Miller 2016). As the numbers observed in this cohort were higher than prior reports of regional and national prevalence, coupled with the fact that the data were gathered in a de-identified fashion, we believe the tobacco use measurements in this cohort to be accurate. In one US report, the discrepancy between proxy report and self-report has been reported to be 4.3%, with the greatest discrepancy when the self-respondent reported non-daily smoking or recent quitting (Gilpin et al. 1994).

Similarly, advanced age has been correlated with delirium incidence and patient mortality. In a multivariate analysis, we similarly found increasing age to correlate significantly with greater delirium severity, greater sedation doses, and greater in-hospital mortality. However, some have suggested that the nature of the admission and severity of illness, but not age, are determinants of ICU survival (Ryan et al. 2008). Illness severity can be recorded in many ways; one commonly used and validated means is by reporting the APACHE II score. An increase in APACHE II score is associated with increased mortality (Barie et al. 1995; Capuzzo et al. 2000; Del Bufalo et al. 1995; Ho et al. 2006; Katsaragakis et al. 2000; Khwannimit and Geater 2007; Naved et al. 2011; Ratanarat et al. 2005). Moreover, the APACHE II score has been reported to outperform both the Sequential Organ Failure Assessment (SOFA) score and Charlson Comorbidity Index (CCI) in predicting in-hospital mortality in ICU patients (Ho et al. 2007; Quach et al. 2009). In a multivariate analysis, we similarly found APACHE II score to correlate with patient mortality; however, as scores were similar across groups, this variable is unlikely to account for the mortality difference. Although we did not calculate the CCI, a listing of the most frequent comorbidities is provided (Table 6). It is known that with each chronic comorbidity, mortality increases (de Groot et al. 2003; Librero et al. 1999), and in a multivariate analysis, we similarly found that the number of comorbidities correlated with mortality.

The role that sedatives and physical restraints play in both precipitating and treating delirium while maintaining patient safety represents a confluence of intersecting and often opposing forces. The higher sedation doses in the *less religiosity* group

are likely in response to the greater severity of delirium observed in this group. In a within-group analysis of delirium (binary categorization), it was observed that patients that died had less delirium and required less sedation. We hypothesize that this may in part be due to a decline in neurologic status necessitating lower sedation requirements prior to death.

Like the use of sedation, the use of physical restraints also corresponded to delirium severity, and thus, rates were higher in the *less religiosity* group. It is unclear whether other factors may have contributed to the discrepancy in physical restraint use, as the psychological effects of physical restraints may include anxiety, panic, increased agitation, fear, anger, depression, lethargy, and withdrawal (Kapp 1996; Martin 2002; Reigle 1996). The use of physical restraints for delirium is not a heavily researched topic in Iran. In two reports by the same group, Moradimajd et al. reported that adherence to routine restraint standards and guidelines ranged from 47.6 to 56.7% but rose to 73.3% following an educational intervention (Moradimajd et al. 2015, 2016). Although suboptimal, this is less an Iranian issue and more a reflection of the dismal state of education and documentation regarding physical restraints that has similarly been reported in other regions including Asia, Oceania, and the USA, where one study showed that nurses were lacking in their knowledge of restraints and that education changed their perception, leading to a 60% reduction in their use (Choi and Song 2003; Swauger and Tomlin 2000; Whitehead et al. 1997).

ICU staffing has also been shown to impact patient mortality. It has been reported that a high nurse-to-patient ratio (e.g., greater than 1:1.5) is independently associated with a lower risk of in-hospital death (Cho et al. 2008; Sakr et al. 2015). For instance, every additional patient per nurse may increase the odds of patient mortality by 9% (Cho et al. 2008). In the current study sites, the nurse-to-patient ratio was 1:2. Although this was equal between groups and would not have affected inter-group comparisons, it could have increased overall mortality within the study. Moreover, physician staffing may be a significant factor contributing to patient mortality. A meta-analysis found that high-intensity staffing (mandatory intensivists consultation or closed ICU) was associated with lower ICU mortality in 14 of 15 studies (93%) and lower hospital mortality in 16 of 17 studies (94%) (Pronovost et al. 2002). High-intensity staffing also reduced ICU and hospital LOS (Pronovost et al. 2002). This is not the case in the current study due to healthcare system and logistical impediments. Although a high-intensity staffing model was used at the study sites, the outpatient and subacute rehabilitation industries are less developed than in many Western nations. Therefore, much of what might be outpatient rehab in Western nations is shifted to the inpatient setting in Iran, thereby prolonging the overall hospital LOS.

Next, the role of family members in the care of critically ill patients with delirium in Iran warrants examination. Family members in Iran have been described as an enthusiastic unpaid volunteer labor force that works to improve the quality of care for their family members (Vahedian-Azimi et al. 2015). Patients receive significant unskilled and non-professional nursing care from their family members (Khosravan et al. 2014). Moreover, most nurses and families believe that family participation is both voluntary and compulsory (Khosravan et al. 2014). There is an emphasis on



communication between staff and family members allowing staff to better understand the patient's habits and mannerisms so as to speed up patient-related affairs and enable better management of the patient's condition (Khosravan et al. 2014; Vahedian-Azimi et al. 2015). There is no evidence that the patient's level of religiosity impacts the level of family participation, and thus, any impact on delirium severity would have been equal across each tertile of religiosity.

It remains unclear whether and to what degree patient/family religiosity influenced their choice to pursue given treatment paths (e.g., life sustaining therapies). What constitutes a "good death" differs greatly between regions, cultures, religions, and personal beliefs (Tayeb et al. 2010). Not surprisingly, aspects of a *good death* may differ significantly between Muslim majority regions and the West (Tayeb et al. 2010). Data from Iran are not available, but in a study of patients in Saudi Arabia, one aspect of a good death was "to be able to leave when it is time to go, and not to have life prolonged pointlessly" (Tayeb et al. 2010). The potential interaction of faith and end-of-life treatment choices in Iran warrants further investigation.

Lastly, one's ability to cope with stress may be an important factor when assessing delirium. Unfortunately, the ability to cope with stress was not one of the defined study endpoints. Resiliency is a complex psychometric construct describing a person's ability to positively adapt to a stressful or traumatic situation and is composed of traits including optimism, cognitive flexibility, and adaptive coping mechanisms. Established survey instruments such as the COPE, Brief COPE, and the Utrecht Coping List (UCL) are lengthy, designed for the general population, and have not been validated in the critically ill. The validated, short, critical care focused survey instrument developed by Boezeman and colleagues entitled the Sickness Insight in Coping Questionnaire (SICQ) was published after this study was conducted (Boezeman et al. 2016). This tool will be considered for future studies.

## Conclusion

Patients with high religiosity had fewer delirious shifts, lower delirium scores, shorter duration of mechanical ventilation, shorter hospital and ICU length of stays, but higher mortality when compared to patients with *less religiosity*. In multivariate analysis factors associated with increased mortality included male sex, age, smoking status, comorbidities, illness severity, sedation, restraints, duration of MV, ICU LOS, hospital LOS, nurse-to-patient ratio, and physician-to-patient ratio. The lower mortality in the *less religiosity* group may be related in part to a greater proportion of female patients, but it remains unclear whether and to what extent greater religiosity impacted decisions by patients and families to initiate or continue life prolonging treatments rather than accepting a more natural death.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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