

Risk factors for delirium: are therapeutic interventions part of it?

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Background: Delirium is associated with increased morbidity and mortality in critically ill patients. Research on risk factors for delirium allows clinicians to identify high-risk patients, which is the basis for early prevention and diagnosis. Besides the risk factors for delirium that are commonly studied, here we more focused on the less-studied therapeutic interventions for critically ill patients which are potentially modifiable.

Materials and methods: A total of 320 non-comatose patients admitted to the ICU for more than 24 hrs during 9 months were eligible for the study. Delirium was screened once daily using the CAM-ICU. Demographics, admission clinical data, and daily interventions were collected.

Results: Ninety-two patients (28.75%) experienced delirium at least once. Delirious patients were more likely to have longer duration of mechanical ventilation, ICU stay, and hospital stay. Most of the less-studied therapeutic interventions were linked to delirium in the univariate analysis, including gastric tube, artificial airway, deep intravenous catheter, arterial line, urinary catheter, use of vasoactive drugs, and sedative medication. After adjusting with age and ICU length of stay, mechanical ventilation (OR: 5.123; 95% CI: 2.501–10.494), Acute Physiology and Chronic Health Evaluation (APACHE) II score \geq 20 at admission (OR: 1.897; 95% CI: 1.045–3.441), and gastric tube (OR: 1.935, 95% CI: 1.012–3.698) were associated with increased risk of delirium in multivariate analysis.

Conclusion: Delirium was associated with prolonged mechanical ventilation, ICU stay, and hospital stay. Multivariate risk factors were gastric tube, mechanical ventilation, and APACHE II score. Although being a preliminary study, this study suggests the necessity of earliest removal of tubes and catheters when no longer needed.

Keywords: delirium, critical care, intensive care unit, risk factors, prevention

Introduction

Delirium is an acute fluctuating change in mental status with attentional deficits and disorganized behavior. The prevalence of delirium ranges from 20% to 80% in critical ill patients in the intensive care unit (ICU).^{1,2} Delirium is related with higher mortality, prolonged hospitalization, larger hospital costs, cognitive decline, and potential functional disability.^{3–8}

Effective treatment for delirium is difficult. Thus, preventions of delirium are of great value in the ICU setting.^{9–11} The study of risk factors for delirium allows clinicians to identify patients at high risk of delirium, thereby enabling clinicians to implement delirium preventions in advance and/or increases delirium screening frequency for earlier diagnosis in this group of patients. Early prevention and diagnosis can also benefit critically ill patients in many ways, such as reducing the incidence of

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delirium and achieving timely and effective management, which ultimately reduce the risk of delirium, and reduce the burden on patients and the medical system.

The risk factors for delirium can be divided into predisposing factors and precipitating factors. Generally, predisposing factors are defined as baseline vulnerability factors exist prior to admission and are difficult to change. Harmful insults or hospitalization-related factors occurring during the course of illness are defined as precipitating factors, including factors related to therapeutic interventions and other factors related to the critical illness.¹² Precipitating factors are potentially modifiable, allowing clinicians to improve local practices and carry out preventive measures. A systematic review of 33 cohort studies or randomized controlled studies has reported only 11 putative risk factors for delirium in critically ill adults.¹³ Among them, only 3 are potentially modifiable including use of dexmedetomidine, length of mechanical ventilation, and coma.¹⁴

Till now, among all the modifiable therapeutic interventions, only the mechanical ventilation and sedative medication are the most widely studied risk factors for delirium.^{13,15,16} To our knowledge, little is known about the effect of other commonly used therapeutic interventions such as artificial airway, deep intravenous catheter, drainage tube, arterial line, gastric tube, urinary catheter, use of vasoactive drugs, and sedative medication on the development of delirium. Therefore, we conducted a prospective observational study to evaluate less-studied modifiable therapeutic interventions as well as other commonly studied risk factors for delirium in a critical care setting in China.

Methods

Study design and participants

From January 2017 to September 2017, we conducted a prospective observational study in medical and surgical ICU with 24 beds in the Affiliated Hospital of Qingdao University in China. Non-comatose patients aged 15 years or more and admitted for over 24 hrs were included. Patients were excluded if they met the following criteria: 1) RASS score <-3; 2) patients had cognitive dysfunction and were unable to cooperate; 3) patients with severe dementia or abuse of psychoactive drugs. All patients were treated according to ABCDE bundle (Assess, prevent, and manage pain; Both Spontaneous Awakening Trials (SATs) and Spontaneous Breathing Trials (SBTs); Choice of analgesia and sedation; Delirium assess, prevent, and manage; Early mobility and exercise; and Family engagement and

empowerment.).^{17,18} Fentanyl, morphine, midazolam, propofol, dexmedetomidine, or their combination were used for sedation; vasoactive drugs were norepinephrine, dobutamine, and epinephrine. The choice of drugs, dosage, and the duration of administration were determined by the physicians. The study was approved by the Affiliated Hospital of Qingdao University Ethics Committee, and written informed consent was obtained from patients or their guardian, in accordance with the declaration of Helsinki.

Delirium screening

Delirium was screened prospectively by a specific trained practitioner for all enrolled patients to ensure standardization. Delirium screening was carried out once daily during 8:00 AM–10:00 AM using the Confusion Assessment Method for the ICU (CAM-ICU). All patients were evaluated for delirium until discharging from ICU or death. Delirious patients were defined as any patient with at least once positive CAM-ICU assessment during our assessment.

Data collection

Demographics and admission clinical data were collected at the enrollment of each patient, including age, sex, education background, medical insurance, APACHE (Acute Physiology and Chronic Health Evaluation) II¹⁹ score at enrollment, admission diagnosis, and medical history (diabetes, hypertension, and malignant tumors, and impaired renal function).

We also prospectively collected daily recorded data during ICU stays of each patient, including mechanical ventilation, artificial airway (tracheal intubation or tracheotomy), deep intravenous catheter, drainage tube, arterial line, gastric tube, urinary catheter, use of sedatives medication, use of vasoactive drugs, and private room (environmental factors).

Statistics

Demographic and clinical variables were summarized using descriptive statistics. Non-normal distributed continuous variables were described using median and interquartile range (IQR). The comparison of these continuous variables was done using Wilcoxon rank-sum test for nonparametric data. For categorical variables, descriptions were used frequencies and proportions, and Pearson's chi-square (χ^2 test) was used for comparisons between the delirious and non-delirium group. Multivariate logistic regression analysis was used to assess the association of potential covariates with delirium. All analyses were performed using Stata 12.1 (Stata Corporation, College Station, Texas, USA).

Results

Characteristics of study participants

We recruited 320 patients over the study period, with male patients accounted for 58.44%. Characteristics of all patients are shown in Table 1. The median age of patients was 61 years, with interquartile range (IQR) from 46 to 71 years. As high as 30.63% had degree of senior high school or above, and 80.63% had medical insurance. Only 2.81% ($n=9$) of patients were with alcohol abuse.²⁰ The median of APACHE II scores at enrollment was 20 (IQR, 15 to 23). The median days of ICU length of stay and hospital length of stay were 4 days (IQR, 1 to 9) and 7 days (IQR, 3 to 13), respectively. One hundred and ninety-six patients (61.3%) underwent mechanical ventilation, and the median duration of mechanical ventilation was 1 day (IQR, 1 to 3).

All cases were assessed for delirium daily during the ICU stay, with a median of 2 assessments (IQR, 1–7) per patient. A total of 92 patients (28.75%) experienced delirium at least once during ICU stay. The median duration of delirium was 3 days, with IQR from 1 to 7 days.

Univariate analysis

To identify the possible risk factors of delirium during the ICU stay, univariate analysis was performed. We first analyzed routine risk factors associated with delirium including the patients' characteristics, underlying comorbidities and environmental factors, and identified 4 possible risk factors for delirium among our patient population. As shown in Table 2, patients with delirium may more frequently above 65 years of age, and with APACHE II score ≥ 20 . They also more frequently have a history of diabetes and impaired renal function.

Besides these routine widely studied risk factors, we also evaluated daily interventions, including mechanical ventilation, artificial airway, deep intravenous catheter, drainage tube, arterial line, gastric tube, urinary catheter, use of vasoactive drugs, and sedative medications (Table 3). Surprisingly, significant differences between the delirium and non-delirium group were observed in most of these interventions, with mechanical ventilation ($P<0.001$), artificial airway ($P<0.001$), deep intravenous catheter ($P=0.01$), arterial line ($P=0.007$), gastric tube ($P<0.001$), urinary catheter ($P=0.006$), use of vasoactive drugs ($P=0.003$), and sedative medication ($P<0.001$).

Table 1 Demographics and characteristics of study participants

Characteristics	All patients (n=320)
Age (years), median (IQR)	61 (46–71)
Sex (male), n (%)	187 (58.44)
Education background (senior high school or above), n (%)	98 (30.63)
Medical insurance, n (%)	258 (80.63)
APACHE II at enrollment, median (IQR)	20 (15–23)
Alcohol abuse, n (%)	9 (2.81)
Pre-ICU conditions, n (%)	
Cancer	33 (10.31)
Hypertension	95 (29.69)
Diabetes	34 (10.63)
Impaired renal function	20 (6.25)
Type of admission, n (%)	
Medical patients	130 (40.63)
Surgical patients	190 (59.38)
Admission diagnoses, n (%)	
Asthma/COPD/respiratory failure/ARDS	97 (30.31)
Sepsis	146 (45.63)
MODS	51 (15.94)
CHF, myocardial infarction, arrhythmia	38 (11.88)
Complex trauma	30 (9.38)
Severe acute pancreatitis	29 (9.06)
Cerebrovascular disease	24 (7.50)
Acute renal failure	23 (7.19)
Hypovolemic shock	18 (5.63)
Combined liver failure	17 (5.31)
Acute diffuse peritonitis/gastrointestinal perforation	15 (4.69)
Chronic progressive renal failure	13 (4.06)
Septic shock	12 (3.75)
Eclampsia, amniotic fluid embolism, placental abruption, etc	11 (3.44)
Poisoning	10 (3.12)
Neurologic (status epilepticus, other)	6 (1.88)
Upper airway obstruction	1 (0.31)
Duration of mechanical ventilation (days) median (IQR)	1 (0–3)
ICU length of stay (days), median (IQR)	4 (1–9)
Hospital length of stay (days), median (IQR)	7 (3–13)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, adult respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; CHF, congestive heart failure.

Taken together, univariate analysis showed that sex, education, medical insurance, hypertension, cancer, drainage tube, and private room were not significantly different between patients with delirium and patients never delirious (Tables 2 and 3).

Table 2 Comparison of routine risk factors associated with delirium

Variables	No delirium (n=228)	Delirium [#] (n=92)	P
Demographics, n (%)			
Age, ≥65 years	79 (34.65)	45 (48.91)	0.018
Male	136 (59.6)	51 (55.4)	0.532
Senior high school or above	70 (30.7)	26 (28.3)	0.666
Medical insurance	186 (81.6)	72 (78.3)	0.497
Pre-existing medical condition, n (%)			
APACHE II score ≥20 at admission	104 (45.61)	62 (67.39)	<0.001
Hypertension	63 (27.6)	32 (34.8)	0.205
Diabetes	19 (8.33)	15 (16.3)	0.036
Cancer	26 (11.4)	7 (7.61)	0.312
Impaired renal function	8 (3.51)	12 (13.0)	0.001
Private room	122 (53.5)	58 (63.0)	0.12

Notes: [#]Defined as >1 episode of delirium within the ICU days with delirium screening.

Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 3 Comparison between delirium group and non-delirium group in terms of interventions

Interventions	No delirium (n=228)	Delirium [#] (n=92)	P
Mechanical ventilation	116 (50.9)	80 (87.0)	<0.001
Artificial airway			<0.001
Not use	112 (49.1)	12 (13.0)	
Tracheal intubation	107 (46.9)	67 (72.8)	
Tracheotomy	9 (3.95)	13 (14.1)	
Deep intravenous catheter	63 (27.6)	39 (42.4)	0.01
Drainage tube	100 (43.9)	33 (35.9)	0.189
Invasive artery	137 (60.1)	70 (76.1)	0.007
Gastric tube	105 (46.1)	73 (79.3)	<0.001
Urinary catheter	189 (82.9)	87 (94.6)	0.006
Use of vasoactive drugs	12 (5.26)	14 (15.2)	0.003
Sedative medications	149 (65.4)	85 (92.4)	<0.001

Notes: [#]Defined as >1 episode of delirium within the ICU days with delirium screening. $P<0.05$, significant difference between the delirium group and non-delirium group.

Multivariate analysis

Multi-logistic regression analysis (Table 4) revealed 3 factors that were retained in the optimized multivariate model after adjusting with age and ICU length of stay.

Table 4 Multivariate analysis

Variables	Odds ratio	95% confidence interval (CI)	P
Age, ≥65 years	1.664	0.919–3.014	0.093
ICU length of stay	1.067	1.035–1.099	<0.001
Mechanical ventilation	5.123	2.501–10.494	<0.001
Gastric tube	1.935	1.012–3.698	0.046
APACHE II score (≥20)*	1.897	1.045–3.441	0.035
Sedative medications			0.093
Use of vasoactive drugs			0.890
Artificial airway			
Not use			
Tracheal intubation			0.248
Tracheotomy			0.248
Deep intravenous catheter			0.567
Arterial line			0.801
Urinary catheter			0.355
Diabetes			0.419
Impaired renal function			0.170

Notes: *APACHE II score was calculated as categorical variable including: APACHE II score <20 and APACHE II score ≥20. The analyses were adjusted for age and ICU length of stay.

Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II.

Mechanical ventilation increased the risk of delirium by odds ratio of 5.123 (95% CI: 2.501–10.494, $P<0.001$). APACHE II score ≥20 at admission is the only predisposing factors that associated with increased risk of delirium (OR 1.897; 95% CI: 1.045–3.441, $P=0.035$). Gastric tube was the other precipitating risk factor that was associated with delirium (OR 1.935, 95% CI: 1.012–3.698, $P=0.046$).

Consequences of delirium

The median duration of mechanical ventilation of patients who developed delirium was 3.5 (IQR: 1–7.75) days, and those who did not develop delirium was 1 (IQR: 0–2). There was a significant difference ($P<0.001$) in the duration of mechanical ventilation between the two groups.

The median duration of ICU stay and hospital stay of patients who developed delirium were 10 (IQR: 5–24) days and 12 (IQR: 6.25–27.25) days, respectively. For patients who did not develop delirium, the median duration of ICU stay and hospital stay were 2 (IQR: 1–6) and 5.5 (IQR: 2–10) days, respectively. Patients with delirium

Table 5 Outcomes of delirium

Items	No delirium (n=228)	Delirium# (n=92)	P
Duration of mechanical ventilation, days, median (IQR)	1 (0–2)	3.5 (1–7.75)	<0.001
ICU length of stay, days, median (IQR)	2 (1–6)	10 (5–24)	<0.001
Hospital length of stay, days, median (IQR)	5.5 (2–10)	12 (6.25–27.25)	<0.001

Notes: #Defined as >1 episode of delirium within the ICU days with delirium screening. $P < 0.05$, significant difference between the delirium group and non-delirium group.

Abbreviation: IQR, interquartile range.

had significantly longer duration of ICU stay ($P < 0.001$) and hospital stay ($P < 0.001$) (Table 5).

Discussion

ICU patients present a high incidence rate of delirium, ranging from 20% to 80%.^{4,21,22} The relative huge variation is probably associated with many factors, such as patient populations, screening instruments for delirium (CAM-ICU vs ICDSC), and diagnosis and treatment habits. Risk factors for delirium have gradually drawn the clinicians and researchers' attention in China. Therefore, relative reports increase obviously in recent years.^{23–26} The prevalence of delirium reported in these publications ranges from 24% to 42%.^{23–26} In the present study, the incidence of delirium was 28.75% (92 in 320 patients), which is generally consistent with these reports enrolling Chinese populations.^{23–26}

Consistent with previous studies, the patients with delirium may more frequently above 65 years of age, and with APACHE II score ≥ 20 .^{23,27,28} Moreover, delirious patients are more likely to have worse outcomes with longer duration of mechanical ventilation, ICU stay, and hospital stay.^{5,29–32}

Older age is one of the most basic predisposing risk factors for ICU delirium.^{33,34} In the univariate analysis, we found that patients with delirium may more frequently above 65 years of age. Although hypertension has been identified as a risk factor of ICU delirium in a systematic review, 5 of the 7 studies included in the meta-analysis did not find association between hypertension and delirium in univariate analysis.¹³ Hypertension is not associated with delirium even in univariate analysis in our study cohort. Consistently, Yang et al had reported that hypertension is

not a risk factor for delirium in univariate analysis in their Chinese patients' cohort.²⁴ Further studies should carry out to clarify the association of hypertension and delirium in Chinese critically ill patients.

Alcohol abuse is one of the most commonly identified risk factors for delirium in western countries.^{31,35,36} However, in our study cohort, only 9 of the 320 patients (2.81%) had alcohol abuse habits. Such differences existing in living habits may attribute to the difference of risk factors for ICU delirium between China and Western countries. Similarly, Yang and colleges also did not find that alcohol abuse history affected the development of delirium in sequential sedation critically ill patients.²⁴ Thus, more studies identifying risk factors for the China population are necessary in order to identify Chinese-specific delirium risk factors.

A meta-analysis reported that patients with mechanical ventilation were more likely to develop delirium in the ICU setting than those without mechanical ventilation with an odds ratio of 4.51 (95% CI: 1.41–14.39).³⁷ Our results revealed that mechanical ventilation increased the risk of delirium with an odds ratio of 5.123. Mechanical ventilation is a widely studied risk factor associated with delirium and strong evidences suggesting that minimizing the duration of mechanical ventilation could reduce delirium in critically ill patients.^{38–43} In addition, our results also showed that patient with delirium had prolonged mechanical ventilation compared with those without delirium. The association between delirium and prolonged mechanical ventilation have also been reported by a meta-analysis.⁴⁴ Based on current evidence, it is difficult to distinguish the causal relationship between these factors, but we believe that mechanical ventilation and prolonged ventilation in the ICU may interact and aggravate the severity of the disease. Mechanically ventilated ICU patients are susceptible to inhalation, a possible cause of hypoxemia and lung infections, which increase their risk for developing delirium.⁴⁵ In addition, the prolonged mechanical ventilation may further lead to sleep disorders due to noise, patient care interventions, disease severity, and the use of sedatives.⁴¹

Furthermore, many patients in the ICU have a large chance to receive a more invasive treatment, including artificial airway, deep intravenous catheter, drainage tube, arterial line, gastric tube, urinary catheter, use of vasoactive drugs, and sedative medication.³⁶ However, the relationship between these interventions and delirium has been less elucidated. Here, we found that artificial airway, deep

intravenous catheter, arterial line, urinary catheter, use of vasoactive drugs, and sedatives medication were linked to delirium in the univariate analysis. Gastric tube was a significant factor associated with delirium both in univariate analysis and multivariate analysis. Although the mentioned factors are related to the severity of the disease and even the necessary treatments, our results still suggest the necessity of earliest removal of tubes and catheters when no longer needed. At the meantime, it is necessary to increase the number of delirium screening in the more severely ill patients or the higher risk patients.

Our study has several limitations. First, we only screened patients once daily due to limited professional personnel, and mild temporary and fluctuated delirium might be missed. Second, we screened all patients during their stay in the ICU. This may inevitably cause time bias. A longer ICU stay could expose patients to a greater exposure to the risk factors, and increasing times of assessment may also increase the chance of delirium diagnosis due to the fluctuating characteristics of delirium. To minimize this time effect, we have adjusted with the duration of ICU stay in multivariate analysis. This problem exists extensively in the studies on risk factors for delirium; further research should focus more on improving the study design in the first step other than use of better statistical methods. Third, we did not evaluate the severity or motor type of delirium which may be another important factor when examining delirium. In addition, we only preliminarily evaluated the effects of specific interventions on delirium, such as vasoactive drugs and sedation. There is no specific drug and dose analysis, partially due to the limited sample size. In the univariate analysis, we found that patients with vasoactive drugs/sedative medications are more likely to develop delirium than patients without vasoactive drugs/sedative medications, respectively. Due to the complexity of medications for patients in the ICU setting, in the future, a well-designed study on specific drugs and doses with larger sample size should be carried out.

Conclusion

Delirium was associated with a longer duration of mechanical ventilation, ICU stay, and hospital stay. Most of the less-studied therapeutic interventions for critically ill patients were associated with delirium in univariate analysis, including gastric tube, artificial airway, deep intravenous catheter, invasive artery, urinary catheter, use of vasoactive drugs, and sedative medication. Mechanical ventilation, APACHE II score ≥ 20 at admission, and gastric

tube were multivariate factors associated with increased risk of delirium after adjusting with age and ICU length of stay. Although being a preliminary study, this study suggests the necessity of earliest removal of tubes and catheters when no longer needed. We are currently conducting an in-depth multi-center study on the impact of therapeutic interventions on delirium.

Disclosure

The authors report no conflicts of interest in this work.

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