The Impact of Delirium on Clinical Outcomes in Multi-Center Thai Surgical Intensive Care Units: A Prospective Cohort Study

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Objective: *Delirium in intensive care units (ICU) increases risks in prolonged mechanical ventilation, hospitalization, and mortality rate. The purpose of this study is to determine if delirium in the surgical intensive care units (SICU) is an independent predictor of clinical outcomes during hospitalization.*

Material and Method: *A multi-center, prospective cohort study was conducted between April 2011 and January 2013. All patients who were admitted to nine university-based SICU were enrolled. Delirium was diagnosed by using the Intensive Care Delirium Screening Checklists. The clinical outcomes of study included length of mechanical ventilation, length of hospital stay, ICU and 28 day mortality. Cox proportional hazard regression model was used to assess the effects of delirium on ICU and 28 day mortality.*

Results: *A total of 4,652 patients were included. One hundred and sixty-three patients were diagnosed delirium (3.5%, 163 of 4,652). Patients who experienced delirium during ICU admission were significantly older (65.0±15.8 years versus 61.6±17.3 years, p = 0.013), had higher American Society of Anesthesiologists physical status (24.3% versus 12.2%, p<0.001), higher Acute Physiology and Chronic Health Evaluation II score (16 (12-23) versus 10 (7-15), p<0.001), and higher Sequential Organ Failure Assessment score (5 (2-8) versus 2 (1-5), p<0.001) compared to non-delirium. Delirious patients also had higher ventilator days (7 (4-17) versus 2 (1-4), p<0.001, longer length of hospital stay (22 (14-34) versus 15 (9-26), p<0.001) and higher ICU mortality (24% versus 9%, p<0.001), and 28-day mortality (28% versus 13%, p<0.001). Patients who developed delirium in the intensive care unit were associated with increased 28-day mortality (adjusted HR = 2.47, 95% CI: 1.13-5.41, p = 0.023).*

Conclusion: *Delirium in an ICU was a major predictor of hospital mortality after adjusted for relevant covariates. Routine monitoring of delirium, early detection, and implementation of preventive strategy are recommended.*

Keywords: *Delirium, Surgical intensive care unit, Clinical outcome, Mortality*

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Delirium is defined as an acute disturbance of consciousness, cognition, attention, and perception and these symptoms tend to fluctuate over the course of the day[1]. The incidences of delirium vary among patient settings or diagnostic tools for delirium from 10-70%[2-5]. Surgical patients may be exposed to predisposing risk factors of delirium including various types of surgery, anesthetic techniques, pain, or exposure to sedative or analgesic medication, which are different from medical patients[5-9].

Previous studies reported that delirium in ICUs was associated with poor clinical outcomes including longer mechanical ventilation support, prolonged duration of ICU stays and hospital stays, increased ICU and hospital mortality as well as long-term cognitive impairment[2,6,10-12]. However, few studies reported that there was no difference in ICU mortality and length of ICU stays[13,14]. The THAI-Surgical

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Intensive Care Unit (SICU), a large multi-center study, reported multiple adverse outcomes including delirium occurring in SICU. The purpose of this study is to determine whether delirium in SICU is an independent predictor of clinical outcomes during hospitalization.

Material and Method

The prospective cohort study included patients of nine university-based surgical intensive care units in Thailand. These university SICUs were across all regions of Thailand (Siriraj, Ramathibodi, King Chulalongkorn, Phramongkutklao, Sirinthorn Medical Center, Vajira, Maharaj Nakorn Chiang Mai, Srinakharinwirot, and Prince of Songkhla)[15]. The recruitment process began after approval was received from the Thai Joint Research Ethics Committee (JREC, No. 001/2011) and each institution's Ethic Committee. All surgical patients with an age greater than 18 years old, who were admitted in an SICU between April, 2011 and January, 2013 were recruited in the study. Patients who had a sustained coma during admission, and required cardiopulmonary resuscitation with no return of spontaneous circulation, and patients who stayed in the ICU for less than 24 hours were excluded from the study. In addition, neurosurgical patients and cardiac patients were also excluded because these patients were not admitted in most sites of SICUs. Patients or their surrogates who met the inclusion criteria were informed about the study in order to obtain their consents. Data collections were divided into three phases including "on admission", "daily recording data", and "at discharge". The criteria for the diagnosis of delirium based on the Intensive Care Delirium Screening Checklists (ICDSC) were discussed by all primary investigators. These diagnostic symptoms include alteration in the level of consciousness, inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation, inappropriate speech and mood, disturbance in the sleep and wake cycle, and fluctuation symptoms. Patients who developed four or more of the above-mentioned symptoms were diagnosed as suffering from delirium. The assigned intensive care nurses of all sites were trained using ICDSC and completed the scale based on the information from the previous 24 hours. All the patients who were included in the study were followed up until being discharged from the ICU. If patients were admitted in the ICU for longer than 28 days, they were followed up until day 28 of the ICU admission. Sedative and analgesic medications were prescribed by the ICU physicians and titrated to achieve the target sedation and analgesic level by bedside nurses. The main outcome of this study was the determination short-term outcomes of delirium, which included unplanned extubation, reintubation, days of mechanical ventilation, length of stays in ICU and hospital, and all-cause ICU and 28-day hospital mortality after ICU admission. All case record forms and documents were further assessed and verified by the Central Data Monitoring Unit. Demographic variables included age, gender, co-morbidity, American Society of Anesthesiologists physical status (ASA PS), smoking status, emergency surgery, sites of surgery, and the amount of blood and blood products administration. The sequential organ failure assessment score (SOFA score) and the Acute Physiology and Chronic Health Evaluation II score (APACHE II score) were determined in order to assess the severity of the disease and the patient status, respectively. Other information included presence of sepsis, requirement of mechanical ventilation, laboratory investigation, and exposure to sedative and analgesic medications, types of sedative and analgesic medications and route of drug administration, duration of ICU stay, hospital stay, and mortality rate.

The statistical analyses were analyzed using STATA, version 11.0 (STATA Inc., College Station, TX, USA). The descriptive data are presented as the number and percent for categorical data, and mean $\pm$ standard deviation (SD), median and interquartile range (IQR) for continuous data according to their distribution. Unpaired t-test, Mann-Whitney U test, Chi-square test, and Fisher exact probability test were used to detect the difference between the groups in the univariable analysis, as appropriate. Hospital mortality and ICU mortality were analyzed using time-to event analyses. Kaplan Meier Survival Curve was used to present time to hospital mortality and log rank test was used to detect different of delirious and non-delirious patients. Cox proportional hazard model was used to obtain hazard ratio (HR) and 95% confident interval. Multivariable Cox regression model was used to determine an effect of ICU delirium after adjusting for all potential confounders. The p-value <0.05 was considered statistically significant.

Results

A total of 4,652 patients were included and presented in Table 1. One hundred and sixty-three patients were diagnosed delirium (3.5%, 163 of 4,652). Patients who diagnosed delirium were significantly older (65.5$\pm$15.8 years versus 61.6$\pm$17.3 years, p<0.001),

had higher APACHE II score (16 (12-23) versus 10 (7-15), $p<0.001$), and required higher percentage of emergency surgery (66.7% versus 30.3%, $p<0.001$). Delirious patients also had higher incidence of sepsis (67.3% versus 18.2%, $p<0.001$), required higher percentage of mechanical ventilation (87% versus 62%, $p<0.001$), and higher exposure to sedative medication (67.5% versus 21.1%, $p<0.001$). Midazolam and propofol were commonly used to control agitation in ICU about 16.2% (755 of 4,652) and 5.2% (243 of 4,652), respectively. Table 2 showed the association of delirium in SICU and its clinical outcomes. Delirious patients also had significant longer ventilator days (7 (4-17) versus 2 (1-4), $p<0.001$), significant longer ICU stay (8 (5-19) versus 2 (1-4), $p<0.001$), and longer hospital stay (22 (14-34) versus 15 (9-26), $p<0.001$). Delirious patients had significantly higher ICU mortality (24% versus 9.1%, $p<0.001$) and higher 28-day mortality (28.2% versus 13.3%, $p<0.001$) than non-delirious patients. The relationship between duration of delirium and ICU and 28-day mortality was presented in Table 3. Patients who experienced delirium equal or more than 3 days had significantly higher ICU and 28-day mortality. Kaplan Meier plot presented for the probability of 28-day hospital stay between delirious and non-delirious patients (Fig. 1). The univariable Cox proportional hazard showed that delirium was associated with increased 28-day mortality (crude HR = 2.05, 95% CI: 1.40-2.98, $p<0.001$), but not increased ICU mortality (crude HR = 0.81, 95% CI: 0.57- 1.14, $p = 0.221$). After adjusting for age, gender, APACHE II score, SOFA score, sepsis, and mechanical ventilation support, delirium was an independent predictor of 28-day mortality after ICU admission (adjusted HR = 2.47, 95% CI: 1.13-5.41, $p = 0.023$).

Discussion

The overall incidence of delirium in this study

Table 1. Baseline characteristics of patients

Variables	Delirium (n = 163)	Non-delirium (n = 4,489)	*p*-value
Age (year) (mean ± SD)	65.5±15.8	61.6±17.3	0.013
Male (n, %)	103 (63.2)	2,626 (58.5)	0.232
Body mass index (kg/m^2) (mean ± SD)	22.0±4.6	23.0±5.7	0.027
ASA PS (n, %)			<0.001
I-II	26 (23.4)	1,340 (38.8)	
III	58 (52.3)	1,690 (49.0)	
IV-VI	27 (24.3)	422 (12.2)	
Co-morbidity (%)			
Hypertension	75 (46.0)	2,193 (48.8)	0.476
Diabetes mellitus	33 (20.2)	985 (22.0)	0.607
Coronary artery disease	15 (9.2)	445 (10.0)	0.765
Congestive heart failure	11 (6.7)	96 (2.1)	<0.001
COPD	21 (12.9)	191 (4.3)	<0.001
Chronic renal failure	25 (15.3)	417 (9.3)	0.010
Current smoking	34 (22.1)	533 (12.6)	0.001
Type of surgery			
Emergency surgery (%)	80 (66.7)	1,068 (30.3)	<0.001
Elective surgery (n, %)	40 (33.3)	2,461 (69.7)	
APACHE II Median (IQR)	16 (12-23)	10 (7-15)	<0.001
SOFA Median (IQR)	5 (2-8)	2 (1-5)	<0.001
Sepsis (n, %)	109 (67.3)	779 (18.2)	<0.001
Mechanical ventilation (%)	141 (87.0)	2,635 (61.8)	<0.001
Exposure to sedative drugs (n, %)	110 (67.5)	952 (21.2)	<0.001
Exposure to analgesic drugs (%)	135 (82.8)	3,830 (85.3)	0.377

ASAPS = American Society of Anesthesiologists physical status; COPD = Chronic Obstructive Pulmonary Disease; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; IQR = Interquartile range

Table 2. Clinical outcomes of patients with and without delirium

Outcomes	Delirium	Non-delirium	*p*-value
Unplanned extubation (n, %)	11 (6.75)	46 (1.06)	<0.001
Reintubation (n, %)	22 (13.5)	119 (2.60)	<0.001
Ventilator days (days) median (IQR)	7 (4-17)	2 (1-4)	<0.001
Length of ICU stay (days) median (IQR)	8 (5-19)	2 (1-4)	<0.001
Length of hospital stay (days) median (IQR)	22 (14-34)	15 (9-26)	<0.001
ICU mortality (n,%)	39 (24)	408 (9.1)	<0.001
28-day hospital mortality (n, %)	46 (28.2)	596 (13.3)	<0.001

IQR = interquartile range

Table 3. The relationship between duration of delirium and ICU and 28-day all-cause mortality

Outcomes	Survive	Dead	*p*-value
ICU mortality			
Duration of delirium	Total n = 124	Total n = 39	
1 day (n = 56)	47 (37.9)	9 (23.1)	0.015
2 day (n = 17)	16 (12.9)	1 (2.6)	
≥3 days (n = 90)	61 (49.2)	29 (74.4)	
28-day mortality			
Duration of delirium	Total n = 117	Total n = 36	
1 day (n = 56)	42 (35.9)	14 (30.4)	0.045
2 day (n = 17)	16 (13.7)	1 (2.2)	
≥3 days (n = 90)	59 (50.4)	31 (67.4)	

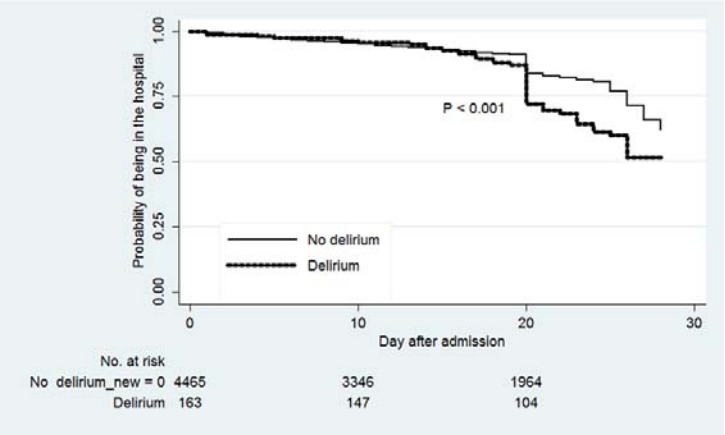

Fig. 1 Kaplan Meier Survival Curve comparing 28 day hospital mortality between patients with and without delirium. Patients with delirium were at significantly higher risk of death than patients with no delirium.

was 3.5%, which was commonly found in elderly patients, patients with higher severity of medical conditions, or higher exposure to sedative medication. This study also found that delirium was an independent predictor of hospital mortality, which was consistent with those of previous studies[2-4,6,10,16,17]. However, some of these studies did not find any association of delirium with hospital mortality[5,12,18-20]. A prospective cohort study concluded that the higher ICU mortality in delirious patients could be related to an increase in

length of ICU stay rather than direct influence of delirium[11]. Few reasons could be explained why there were inconsistent findings among studies. These differences included types of patients being studied such as medical or surgical patients, numbers of study population, various degree of disease severity, follow-up time period (28 days versus 6 month), and types of statistical analysis[12,19].

Several previous studies reported that several risk factors of ICU delirium included elderly, higher APACHE II score, higher SOFA score, sepsis, and the use of mechanical ventilation[2,7,17,21,22]. Advanced age is commonly associated with greater risk of pre-operative cognitive function, greater use of several medications, and increased risk of confusion[23]. Higher APACHE scores represent higher severity of disease and high risk patients. During sepsis, there was an increase in level of inflammatory cytokines and increased permeability of blood brain barrier and this process can lead to acute brain dysfunction[9]. Delirium was also highly associated with mortality in mechanical ventilated patients[20]. These prognostic factors had been adjusted for mortality related to ICU delirium in this study.

The present study found that delirium increased 28-day hospital mortality about 2 times after adjusting for potential confounders. Duration of delirium was significantly associated with ICU and 28-day mortality, which was consistent with a prospective cohort study[24]. Delirious patients also had higher incidences of unplanned extubation and reintubation, which was corresponded with the other study[10]. However, this study could not demonstrate that delirium was an independent prognostic factor for ICU mortality. This could be possible that most of delirious and non-delirious patients had shorter length of ICU stays. While delirious patients had significantly higher mortality rate than non-delirious patients after day 15 of ICU admission (Fig. 1), which patients were supposed to be already discharged from ICU. Routine delirium monitoring is encouraged to allow early detection for high risk patients. In addition, an identification and treat possible causes of delirium may reduce severity of diseases. Further studies are required to address whether some preventive measures and treatment can improve an outcome of delirium.

This study was a large multi-center study for determination an impact of delirium and clinical outcomes in SICU in Thailand. There were some limitations in the study. Firstly, the incidence of delirium was low compared to other studies and there were some heterogeneity among severity of diseases of patients among surgical institutions. Secondly, CAM-ICU is currently considered as the gold standard for diagnosis of delirium in ICU[25]. However, the investigators could not use this tool before conducting this study because we had not finished testing the validity and reliability of Thai-version of CAM-ICU. Therefore, the ICDSC was chosen for as a diagnostic tool of delirium instead during the study. Nevertheless, the investigators did not perform inter or intra-rater reliability for ICDSC among nurses and this factor could also affect on the incidence of delirium. Thirdly, the follow-up time period was relatively short and might not demonstrate long-term negative clinical outcomes of delirium such as mortality rate or cognitive impairment. Finally, although this study could demonstrate an association of delirium with short-term clinical outcomes, the authors could not address their causal relationship.

Conclusion

Delirium in ICU was a major predictor of hospital mortality after adjusted for relevant covariates in both patients with and without mechanical ventilation. Early detection, finding of the preventive strategy for reducing an incidence of delirium are recommended in order to improve the clinical outcomes of delirium.

What is already known on this topic?

The authors determined the incidence of delirium in SICU and compared characteristic of delirious patients and non-delirious patients.

What this study adds?

Clinical outcomes related to delirium in ICU had been presented. The authors could demonstrate the relationship between ICU delirium and hospital mortality.

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Potential conflicts of interest

None.

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การศึกษาผลของภาวะเพ้อต่อผลลัพธ์ทางคลินิกในหออภิบาลผู้ป่วยภาวะวิกฤตทางศัลยกรรม

ตันหยง พิพานเมฆาภรณ์, กวีศักดิ์ จิตตวัฒนรัตน์, อรอุมา ชัยวัฒน์, ธรรมศักดิ์ ทวิชศรี, เพชร วัชรสินธุ์, สุณีรัตน์ คงเสรีพงศ์, Thai SICU study group

วัตถุประสงค์: *เพื่อศึกษาผลกระทบของภาวะเพ้อต่อการผลลัพธ์ทางคลินิกในหออภิบาลผู้ป่วยภาวะวิกฤตทางศัลยกรรม*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงวิเคราะห์แบบไปข้างหน้า โดยทำการเก็บรวบรวมข้อมูลในผู้ป่วยที่เข้ารับการรักษาในหออภิบาลผู้ป่วยภาวะวิกฤตทางศัลยกรรมของคณะแพทยศาสตร์ 9 สถาบันในประเทศไทยตั้งแต่ เดือนเมษายน พ.ศ. 2554 ถึง เดือนมกราคม พ.ศ. 2556 การวินิจฉัยภาวะเพ้อโดยการใช้เครื่องมือ intensive care screening checklist ผลลัพธ์ทางคลินิกที่ศึกษา ได้แก่ ระยะเวลาของการใช้เครื่องช่วยหายใจ ระยะเวลาการนอนในโรงพยาบาล อัตราการเสียชีวิตในหออภิบาลผู้ป่วยภาวะวิกฤตทางศัลยกรรมและอัตราการเสียชีวิตในโรงพยาบาลภายในระยะเวลา 28 วัน หลังจากเข้ารักษาในหออภิบาลผู้ป่วยภาวะวิกฤต การวิเคราะห์ความสัมพันธ์ของภาวะเพ้อและอัตราการเสียชีวิตในโรงพยาบาลใช้สถิติ Cox proportional hazard*

ผลการศึกษา: *ได้ทำการศึกษาในผู้ป่วยหนักทางศัลยกรรมจำนวน 4,652 ราย โดยพบผู้ป่วยที่มีภาวะเพ้อจำนวน 163 ราย หรือ คิดเป็นร้อยละ 3.5 พบว่าผู้ป่วยที่มีภาวะเพ้อมีอายุมากกว่า มี ASAPS สูงกว่า มีความรุนแรงของโรคมากกว่า โดยพิจารณาจากคะแนน APACHE II score และ SOFA score ที่สูงกว่า เมื่อเปรียบเทียบกับผู้ป่วยที่ไม่มีภาวะเพ้อ นอกจากนี้ผู้ป่วยที่มีภาวะเพ้อมีจำนวนวันของการใช้เครื่องช่วยใจมากกว่าจำนวนวันในการพักรักษาในหออภิบาลผู้ป่วยภาวะวิกฤตและในโรงพยาบาลที่นานกว่า โดยมีอัตราการเสียชีวิตในหอในหออภิบาลผู้ป่วยภาวะวิกฤตคิดเป็นร้อยละ 24 และอัตราการเสียชีวิตภายใน 28 วัน ร้อยละ 28 ตามลำดับ ซึ่งสูงกว่าผู้ป่วยที่ไม่มีภาวะเพ้อ อย่างไรก็ตามพบว่าภาวะเพ้อสัมพันธ์กับการเพิ่มความเสี่ยงของการเสียชีวิตผู้ป่วยภาวะใน 28 วัน มากกว่าผู้ป่วยที่ไม่มีภาวะเพ้อ 2.47 เท่า*

สรุป: *ภาวะเพ้อเป็นปัจจัยเสี่ยงที่สำคัญที่เพิ่มโอกาสการเสียชีวิตในโรงพยาบาลการคัดกรองผู้ป่วยที่มีความเสี่ยง เพื่อจะวินิจฉัยผู้ป่วยที่มีภาวะเพ้อตั้งแต่ระยะแรก การป้องกันการเกิดภาวะเพ้อโดยวิธีต่าง ๆ ควรที่จะได้รับการสนับสนุนให้ทำเป็นประจำในระหว่างการดูแลผู้ป่วยที่มารับการรักษาในหออภิบาลผู้ป่วยวิกฤตศัลยกรรม*