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Delirium and coma evaluated in mechanically ventilated patients in the intensive care unit in Japan: A multi-institutional prospective observational study ☆

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ABSTRACT

Purpose: The object of this study is to evaluate the prevalence and effects of delirium on 28-day mortality in critically ill patients on mechanical ventilation in Japan.
Materials and methods: Prospective cohort study was conducted in medical and surgical intensive care units (ICUs) of 24 medical centers. Patients were followed up daily for delirium during ICU stay after enrollment. Coma was defined with the Richmond Agitation Sedation Scale score of −4 or −5. Delirium was diagnosed using the Confusion Assessment Method for the ICU. The Cox proportional hazards regression model was used to assess the effects of delirium and coma on 28-day mortality, time to extubation, and time to ICU discharge; delirium and coma were included as time-varying covariates after controlling for age, Acute Physiology and Chronic Health Evaluation II score, ventilator-associated pneumonia, and the reason for intubation with infection.
Results: Of 180 patients, 115 patients (64%) developed delirium. Moreover, 15 patients (8%) died within 28 days after ICU admission, including 7 patients who experienced coma and 8 patients who experienced both coma and delirium. There were no deaths among patients who did not experience coma. Delirium was associated with a shorter time to extubation (hazard ratio [HR], 2.52; 95% confidence interval [CI], 1.65-3.85; $P < .001$) and a shorter ICU length of stay in comatose patients (HR, 1.59; 95% CI, 1.04-2.44; $P = .034$), whereas delirium appeared with prolonged time to ICU discharge among patients without coma, although statistical significance was not detected due to limited analytical power (HR, 0.62; 95% CI, 0.34-1.12; $P = .114$). Delirium during ICU stay was not associated with higher mortality.
Conclusions: Further study is needed to investigate the discrepancy between these and previous data.

1. Introduction

Delirium, coma, or acute brain dysfunction due to both delirium and coma is a significant complication that affects the time to extubation in mechanically ventilated patients [1] and length of stay in the intensive care unit (ICU-LOS) [2] and the hospital [3] as well as mortality of critically ill patients in the intensive care unit (ICU) [4]. Although the gravity of ICU delirium has been recognized, the use of validated tools such as the Confusion Assessment Method for the ICU (CAM-ICU) [5] and the Intensive Care Delirium Checklist [6] to detect hypoactive delirium is often overlooked [7]. Thus, delirium assessment is an important routine task in the ICU. Guidelines established by the Society of Critical Care Medicine regarding management and care of delirium in ICU settings have expanded over recent years, with particular emphasis on the relationship between the onset of delirium and post-ICU cognitive impairment [8].

The incidence of delirium in ICU is an event that has been relatively underrecognized in Japanese hospitals, with only a few reported instances from a single medical institution [9], and there are

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mechanically ventilated patients not only in ICUs but also in general wards in Japanese hospitals. Thus, we explored the mechanically ventilated patients in the ICU certified by the Japanese Society of Intensive Care Medicine (JSICM). The purposes of this prospective observational study were to describe the incidence of delirium and coma and to evaluate association between delirium and coma with clinical outcomes of patients who were mechanically ventilated from ICUs (over a certain standard) throughout Japan.

2. Materials and methods

The study population included adult ICU patients on mechanical ventilation (≥48 hours), who were admitted within the 2-month period from June 1 to July 31, 2011, or from October 1 to November 30, 2011, in the medical and surgical ICUs of 24 Japanese medical centers. This study, Japanese Epidemiology of Delirium in ICUs (JEDI), was approved by the JSICM (no. 0001). A total of 24 of 219 ICUs certified by the JSICM applied for the JEDI study. A study representative at each ICU was identified, and instruction of diagnosing delirium was shared among them. Assessments were done by nurses at each site who were trained by the representative at each site. The institutional review board of each ICU approved this study, and an informed consent was waived considering that the noninterventional nature of the study posed no added risk to subjects. For this study, the following a priori selected exclusion criteria were included: (*a*) patients younger than 19 years; (*b*) patients with a "do not resuscitate" order; (*c*) patients with expected persistent disturbed consciousness (eg, due to anoxic encephalopathy, brain stem hemorrhage, or head trauma); (*d*) neurosurgical patients; (*e*) patients with history of chronic dementia, psychosis, mental retardation, or neuromuscular disease; (*f*) patients with a visual or hearing disturbance; and (*g*) patients unable to understand Japanese language.

All patients were assessed daily for signs of developing delirium during their ICU stay after enrollment in the study. Coma was defined in accordance with the Richmond Agitation Sedation Scale (RASS) score [10] of −4 or −5. Delirium was diagnosed using CAM-ICU [11] and defined as RASS scores from −3 to +4 along with positive results for CAM-ICU. Patients with no delirium or coma were classified as being normal.

2.1. Data collection and study design

Information collected prospectively at the time of enrollment included patient demographics and Acute Physiology and Chronic Health Evaluation (APACHE) II score [12]. Patients were followed up for 28 days from the day of the first intubation in ICU. Ventilator-associated pneumonia (VAP), the reason for intubation, maximum serum C-reactive protein (CRP) levels during ICU stay, duration of mechanical ventilation, sedative and analgesic agents used, ICU-LOS, and ICU mortality were recorded. The primary outcome for this cohort analysis was all-cause 28-day mortality, which is defined as death occurring up to 28 days after study enrollment. Secondary outcomes included time to the first successful extubation (defined as no reintubation or death within 48 hours postextubation) and time to ICU discharge (ICU-LOS) for all patients in the 28 days of enrollment. Thus, we included extubation even when it occurred in the general ward.

2.2. Statistical analysis

Baseline characteristics were described using median and interquartile range for continuous variables and frequency and percentage for categorical variables. Time-to-event analyses were used for all outcomes of 28-day mortality, ICU-LOS, and time to extubation. For the 28-day mortality analysis, patients were censored at hospital discharge or 28 days from the initiation of the study, whichever came earlier. For assessment of ICU-LOS and time to the first successful extubation, patients were censored at the time of death; time of hospital discharge; or 28 days after study enrollment, whichever came earlier.

The delirium incidence was analyzed as a "time-varying" exposure variable in the time-to-event analysis [13]. All patients were coded as delirium negative until the first positive episode of delirium was assessed in the study, and then, these patients were switched to an exposure category for days after the first onset of delirium. A similar method was used to create a binary, time-dependent, comatose variable. The primary analysis for these time-to-event outcomes was a time-varying Cox proportional hazards multivariable regression model with the following 4 baseline a priori covariates that were selected because of their clinical relevance: age, baseline APACHE II score, VAP, reason for intubation, and dexmedetomidine (DEX) used more than and equal to 24 hours. For analysis of mortality, because the number of events was small, age, APACHE II, and reason for intubation were included as a covariate to avoid overfitting [14]. Furthermore, to assess whether the effects of delirium are modified by the presence or absence of coma, a cross product term between delirium and comatose variables was included in the Cox regression (ie, interaction) analysis. Because there were no deaths in patients without coma, hazard ratio (HR) for death reached infinite values; thus, we reported *P* value for the association between death and delirium or coma. For all analyses, a robust covariance matrix (sandwich) estimator was used to accurately compute SE and *P* value of the effects of coma and delirium.

The time-varying Kaplan-Meier curves were obtained using the method described by Simons and Makuch [15] comparing 4 exposure groups (delirium only, delirium-coma, coma-normal, normal) along with a significance test using Mantel-Byar estimators [16]. All data analyses were performed using Statistical Analysis Software 9.1 (SAS Institute, Cary, NC) and R version statistical software 2.15.0. A 2-sided significance level of 0.05 was used for all statistical inferences.

3. Results

During the study period, 329 patients were admitted, of whom 192 (58%) were enrolled in the study (Fig. 1); of these patients, 12 were excluded because of persistent coma. The demographic data of 180 patients are presented in Table 1. A total of 66 patients (37%) were intubated for major surgery, 33 (18%) for cardiovascular disease and 32 (18%) for respiratory disease. Propofol, DEX used 24 hours or more, and midazolam were commonly administered as sedative agents. Fifteen patients (8%) were dead in 28 days after intubation. One hundred fifteen patients (64%) and 137 patients (76%) developed delirium and coma, respectively. Median (interquartile range) of

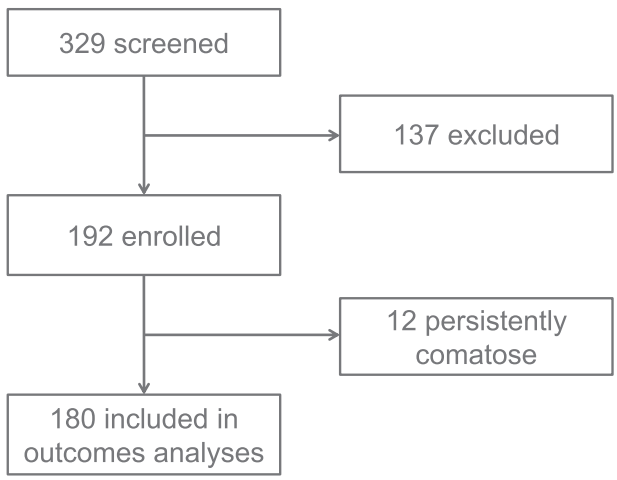

Fig. 1. Flow of patients in study cohort.