Asian Nursing Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Asian Nursing Research

journal homepage: www.asian-nursingresearch.com

Research Article

Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study

Jeong Mi Hwang,[1] Su Jung Choi[2,*]

[1] Department of Nursing, Samsung Medical Center, Republic of Korea
[2] Graduate School of Clinical Nursing Science, Sungkyunkwan University, Republic of Korea

ARTICLE INFO

Article history:
Received 4 July 2022
Received in revised form
20 December 2022
Accepted 26 December 2022

Keywords:
deep sedation
intensive care units
mortality

SUMMARY

Purpose: This study aimed to identify the early sedation depth in the first 48 hours of mechanical ventilation and its relationship to clinical outcomes to promote the transition to light sedation.
Methods: This retrospective single-center cohort study was conducted in two medical intensive care units (MICUs) at a general tertiary hospital, using a standardized sedation protocol. To investigate the early sedation depth, the Sedation Index was used, which can indicate changes over the first 48 hours. Patients were divided into three groups based on tertiles of Sedation Index. The primary outcome was mortality at 30, 90, and 180 days. The secondary outcomes included length of stay in the ICU and ventilator-free days. Kaplan-Meier analysis and multivariable Cox regression were conducted to compare factors influencing mortality.
Results: This study included 394 patients. The deepest sedation group showed more severe illness, delirium, and deeper sedation at admission ($p < .001$). The survival curve decreased as sedation increased, even within the light sedation levels. In the deepest sedation group, 30-day mortality (hazard ratio [HR] 2.11, 95% confidence interval [CI] 1.33–3.34), 90-day mortality (HR 2.00, 95% CI 1.31–3.06), and 180-day mortality (HR 1.77, 95% CI 1.17–2.67) increased. The length of stay in the ICU and ventilator-free days did not show statistical differences.
Conclusions: These results indicate that early deep sedation is a modifiable factor that can potentially affect mortality. The protocol for inducing the transition into light sedation must comply with recommendations to improve clinical outcomes.

Introduction

Sedating a patient under mechanical ventilation is important for promoting stability and safety to aid in managing pain, agitation, and delirium, as well as preventing increased oxygen consumption due to desynchronization with mechanical ventilation [1–3]. However, the appropriateness of sedation therapy is being questioned after reports of negative outcomes due to the prolonged application of mechanical ventilation under deep sedation [4–6]. Thus, the practice guidelines for sedation of critical patients under mechanical ventilation released by the U.S. Society of Critical Care Medicine advise maintaining light sedation, which is sufficient to facilitate treatment [7,8].

It has recently been reported that deep sedation within the first 48 hours of mechanical ventilation is a major factor that increases mortality in hospitals, even considering the patient's characteristics, such as severity of illness [1,9–11]. Furthermore, deeply sedated patients tend to experience less pain [1], but more subsequent delirium [9] and have an increased length of stay in the intensive care unit (ICU) [1,10] and longer ventilation times [1,10,11]. Although this modifiable factor can improve clinical outcomes [1], many patients still undergo deep sedation at the beginning of their treatment [12,13]. In Korea, efforts have been made to comply with the sedation protocol [14] and adjust medication use [15,16] to transition to light sedation. Nevertheless, >50% of patients remain under deep sedation for the first 5 days under mechanical ventilation [16]. There is a lack of data on the association between sedation level and clinical outcomes such as early sedation depth and mortality.

Jeong Mi Hwang: https://orcid.org/0000-0002-8457-5252; Su Jung Choi: https://orcid.org/0000-0003-2171-7441
* Correspondence to:
E-mail address: sujungchoi@skku.edu

https://doi.org/10.1016/j.anr.2022.12.002
p1976-1317 e2093-7482/

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002

Deep sedation, as defined by the Richmond Agitation–Sedation Scale (RASS), an instrument for measuring sedation depth [17], is typically classified as a RASS score of ≤ -3 points [13]. However, the RASS score of the patient varies considerably over time [4] and has positive and negative values. Thus, calculating the sedation depth in the first 48 hours following mechanical ventilation is difficult [9]. To deal with methodological problems, the Sedation Index was regarded as a representative value of early sedation depth to reflect changes over the first 48 hours of ventilation instead of a single point in time [9]. To ascertain the current situation in this study, the Sedation Index was investigated in patients admitted to two medical ICUs (MICUs) at a general tertiary hospital in Korea that followed a standardized sedation protocol. In addition, the association of Sedation Index with clinical outcomes, including mortality, was analyzed. This study was aimed to examine the recent practice of sedating critically ill patients and provide basic data for transitioning to a light sedation protocol.

Methods

Study design

This retrospective cohort study used data from the electronic medical records of an university-affiliated hospital Seoul, South Korea. To identify the effects of early deep sedation on the clinically important outcomes of patients under mechanical ventilation, all patients in the database were admitted to two MICUs and received mechanical ventilation from July 2018 to December 2019. This hospital follows a standardized sedation protocol (the Pain, Agitation, and Delirium [PAD] Protocol) [14], with the nursing staff periodically measuring the patients' sedation depth using the RASS [17].

Participants

Patients aged older than 18 years old who underwent endotracheal intubation followed by mechanical ventilation were included. Endotracheal intubation was performed in the emergency room, general ward, operating room, radiology room, or ICU of the study hospital. The criteria for initiation of mechanical ventilation were based on the actual time of intubation. The exclusion criteria were as follows: mechanical ventilation lasting less than 48 hours, not consenting to provide personal information, history of endotracheal intubation at another hospital, fewer than three RASS assessments during the first 48 hours under mechanical ventilation, reduced consciousness due to separate sedation or neurological injury from cardiovascular resuscitation, stroke, or other reasons; receiving extracorporeal membrane oxygenation (ECMO) for the heart or lungs; and history of ICU admission twice or more.

Demographics and clinical characteristics

Age, sex, admission route, patient diagnosis, and Simplified Acute Physiology Score (SAPS) III [18] were collected. The SAPS III is a validated scoring system for predicting hospital mortality that considers patient characteristics before ICU admission, reasons for ICU admission, and existence of physiologic derangement at ICU admission [18]. After admittance to the ICU, the doctor recorded the patient's unique SAPS III score.

Sedation depth

Early sedation depth refers to the Sedation Index in the first 48 hours of mechanical ventilation: the higher the Sedation Index, the deeper the early sedation depth. The Sedation Index is the sum of negative RASS scores divided by the total number of RASS measurements [9]. The RASS is reliable instrument for assessing the quality and degree of sedation and agitation in adult ICU patients [7,17] and has a high quality of psychometric evidence such as interrater reliability, convergent or discriminant validation [7]. The individual RASS values, indicating the sedation depth at a specific time, were the data that the nurse measured every shift or, additionally, if changed. The participants were divided into three groups based on the tertiles of Sedation Index: the first tertile indicates the group with the lightest sedation level, whereas the third tertile indicates the group with the deepest sedation level. Under the central limit theorem, when the number of participants in each group was greater than 30, the normal approximation was regarded adequate [19]. However, the individual RASS score at the point of admission could not be expressed by the Sedation Index; a single RASS of -3 or lower was categorically classified as deep sedation, from -2 to $+1$ as light sedation, and $+2$ and higher as agitation [20].

Prevalence of pain and delirium

During the first 48 hours of mechanical ventilation, the presence of pain and delirium was recorded. Pain and delirium in critically ill adults are recommended to measure by using reliable and valid assessment method [7,8]. For patients who can express pain, the Numeric Rating Scale (NRS) is a valid and feasible pain scale [7,8,21]. For whom unable to report pain, the Critical Care Pain Observation Tool (CPOT) is useful because it has high interrater reliability and discriminant and criterion validity for all ICU adults except patients with brain injury [7,22]. Pain was recorded as yes in the presence of the NRS score ≥ 4, or the CPOT score ≥ 3 at least once during the early phase of ventilation. Delirium was assessed using the Confusion Assessment Method-ICU (CAM-ICU), which has very good psychometric properties of validity and high interrater reliability [7]. The presence of at least one positive result was considered delirium during the first 48 hours of ventilation. But RASS scores of -4 or lower and $+3$ or higher were excluded because they could not be assessed in the CAM-ICU. Pain and delirium data were assessed by the bedside ICU nurse every shift or, additionally, if changed.

Sedative variables

Information on medications administered as analgesics and sedatives during the first 48 hours of ventilation was also collected. They were sorted by type (analgesics or sedatives) and infusion method (intermittent or continuous administration).

Outcome

Clinical outcomes related to early sedation depth included the following. The primary outcome was mortality over 30, 90, and 180 days. Patients were followed-up until hospital day 180 or death. Secondary outcomes included length of stay in the ICU and ventilator-free days [23]. Length of stay in the ICU refers to the total period from admission to discharge from ICU. Ventilator-free days are defined as the number of days in which spontaneous breathing is possible continuously for more than 48 hours without mechanical ventilation assistance [23]. If the patient is successfully weaned from mechanical ventilation within 28 days, ventilator-free days are calculated by subtracting the number of days applied to the mechanical ventilation from 28 days [23]. If the patient died before 28 days or required mechanical ventilation for 28 days or more, ventilator-free days are zero [23].

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002

Ethical consideration

This study was approved by the Institutional Review Board of the Samsung Medical Center (Approval no. 2020-XX-099). The need for informed patient consent was waived because of the study's retrospective nature. This study was performed in accordance with the relevant guidelines and regulations of the IRB. One researcher then examined and collected electronic medical records.

Statistical analysis

The collected data were analyzed using SPSS WIN 25.0 (SPSS Inc., Chicago, IL, USA), with a significance level of .05, and a 95% confidence interval as follows: continuous variables were presented as average and standard deviation, and categorical variables as frequency and percentage. The patient demographics, clinical characteristics, sedative variables, and clinical outcomes according to the Sedation Index were analyzed using one-way analysis of variance, chi-squared test, or Fisher exact test. A post-hoc test was performed using Bonferroni correction. Kaplan–Meier analysis was conducted to compare the survival period according to the early sedation depth. To analyze the factors influencing mortality, a multivariable Cox regression analysis was conducted (backward likelihood ratio test was used to select variables). The confounding variables were age, sex, admission route, SAPS III, patient diagnosis, RASS at admission, Sedation Index, prevalence of pain and delirium, and analgesics and sedatives with intermittent or continuous administration. To account for numerous confounding variables, multivariable Cox regression included covariates with a p value 0.05 in univariable Cox regression. Significant predictors were defined as covariates with a multivariable Cox regression p value 0.05.

Results

Demographics, clinical characteristics, and sedative variables according to Sedation Index

Among the 1,287 patients who were aged more than 18 years and received mechanical ventilation via endotracheal intubation, 970 received mechanical ventilation for ≥48 hours. Of these, 28 patients refused to provide their personal information, 84 had undergone endotracheal intubation in other hospitals, 2 had fewer than three RASS assessments during the first 48 hours under mechanical ventilation, 124 had reduced consciousness due to separate sedation or neurological injury from seizures, cardiovascular resuscitation, stroke, or other reasons, 43 were under ECMO for the heart or lung, and 295 patients had been admitted to the ICU for two or more reasons. After excluding these 576 patients, data from 394 patients were used for analysis. The mean early sedation depth in the entire cohort was 1.35. Dividing this into three groups based on tertiles, the Sedation Index of the first tertile with the lightest sedation ranged from 0.00 to 0.83, with 130 patients (0.54 ± 0.23); the second tertile's Sedation Index ranged from 0.84 to 1.50, with 136 patients (1.13 ± 0.20); and the Sedation Index of the third tertile with the deepest sedation ranged from 1.51 to 5.00, with 128 patients (2.40 ± 0.77) (Figure 1).

The demographics, clinical characteristics, and sedative variables of the patients in the early phase of ventilation in terms of Sedation Index are shown in Table 1. Age, sex (male), ICU admission route, and patient diagnosis did not differ significantly between the groups. More than 50% of patients admitted to ICU had cancer, followed by respiratory, neurological, and digestive system diseases. The SAPS III was 58.64 ± 14.62 points in the first tertile, 62.13 ± 15.53 points in the second tertile, and 68.25 ± 15.94 points in the third tertile, increasing as the sedation deepened; there were significant differences between the third tertile and first and second tertile groups ($p < .001$); 73.8% of the first tertile group was lightly sedated at admission, and only 17.7% were deeply sedated. On the other hand, 50.8% of the third tertile group showed light sedation at admission, and 43.8% showed deep sedation ($p < .001$).

Pain prevalence decreased from the first to the third tertile (30.8 vs. 18.8%, $p = .021$). Delirium prevalence was 65.4% in the first tertile, 83.8% in the second tertile, and 89.8% in the third tertile, increasing as sedation deepened, showing significant differences ($p < .001$).

Intermittent analgesics were most frequently used in the second tertile (92.6%, $p = .033$). Fentanyl was used the most in all groups and showed significant differences among the three groups ($p = .022$). Continuous analgesic prescribed most was remifentanil in all three groups, but statistically significant difference between groups was only shown in hydromorphone among continuous analgesics ($p = .004$). No significant differences were found between the three groups in the use of intermittent sedatives, and ketamine was used the most. The use of midazolam showed significant differences among the three groups ($p = .011$). Continuous sedatives were used by 60.2% of the third tertile, with a significantly higher usage rate than the first tertile (38.5%) and the second tertile (39.0%) ($p < .001$). Although the continuous infusion of midazolam, ketamine, and propofol showed significant differences among the groups per medication, there were no significant differences in the use of dexmedetomidine among the three groups.

Clinical outcomes according to Sedation Index

The clinical outcomes of patients in the first 48 hours of ventilation in accordance with the Sedation Index are shown in Table 2. The primary outcome was the mortality rate. The 30-day mortality ($p < .001$), 90-day mortality ($p = .004$), and 180-day mortality ($p = .013$) increased as sedation deepened, indicating statistical differences. The results of the Kaplan–Meier analysis of 30-, 90-, and 180-day mortality are shown in Figure 2. Throughout all periods, the survival curve indicated a significant difference between the first tertile and the second and third tertiles, and the survival curve between the second and third tertiles was not statistically significant. The secondary outcome was length of stay in the ICU and ventilator-free days, neither of which revealed statistically significant differences within the groups (Table 2).

Relationship between factors influencing mortality

To analyze the factors influencing mortality and how the Sedation Index predicted mortality, multivariable Cox regression was performed, and the results are shown in Table 3. Multivariable Cox regression incorporated factors with a p value of 0.05 in univariable Cox regression to account for various confounding variables of age, sex, admission route, SAPS III, patient diagnosis, RASS at admission, Sedation Index, prevalence of pain and delirium, and analgesics and sedatives with intermittent or continuous administration. The admission route, SAPS III, use of intermittent morphine, delirium prevalence, and Sedation Index were the variables associated with 30-day mortality in univariable Cox regression. Addition to variables above, patient's diagnosis and use of intermittent ketamine were plus added for predicting the 90- and 180-day periods, and use of continuous fentanyl for the 180-day mortality in univariable Cox regression. Significant predictors were determined to be variables with a multivariable Cox regression p value of 0.05. Delirium prevalence and use of continuous fentanyl among the initial covariates in the univariable cox analysis were excluded from the final model to predict all period of mortality.

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002

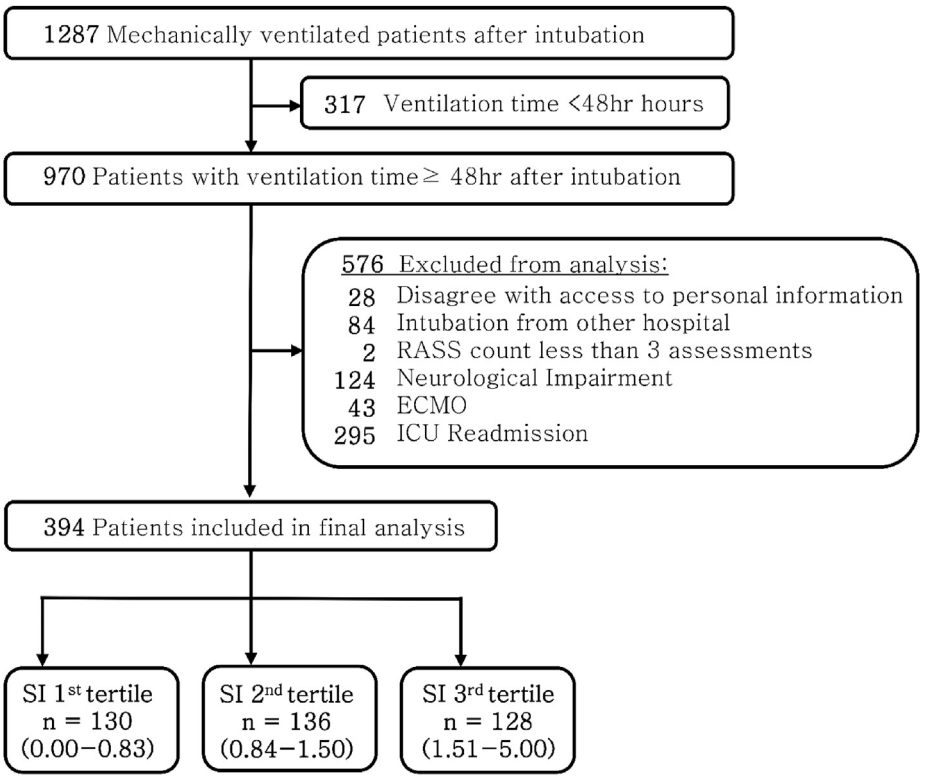

Figure 1. Patient Inclusion Flow Diagram.
Note: RASS = Richmond Agitation Sedation Scale; ECMO = extracorporeal membrane oxygenation; SI=Sedation Index.

The Sedation Index tertiles were identified as independent predictors of mortality. In the second tertile group, compared to the first one, the risk of death increased by 1.73 times at 30 days ($p = .018$), 1.61 times at 90 days ($p = .020$), and 1.46 times at 180 days ($p = .052$). In the third tertile group, mortality was 2.11 times higher than the first tertile at 30 days, 2.00 times at 90 days, and 1.77 times at 180 days ($p < .01$). As the SAPS III increased, all types of mortality increased ($p < .01$). While intermittent ketamine usage only increased the risk of death by 1.47 times at 90 days, intermittent morphine usage more than doubled the mortality rate across all time periods. When patient was admitted to the intensive care unit via the general ward compared to the emergency room, mortality at 90 and 180 days increased higher by 1.53 times ($p < .05$) and 1.61 times ($p < .01$), respectively. The risk of death at 90 and 180 days decreased, however, when the patient had a neurological diagnosis compared to a respiratory diagnostic by 0.35 times and 0.28 times, respectively ($p < .05$).

Discussion

This retrospective cohort study attempted to improve early sedation strategies in critical patients by analyzing early sedation depth, which has been reported to be related to mortality in patients under mechanical ventilation.

The average Sedation Index of the entire patient cohort was 1.35 points, with two-thirds of the participants scoring 0.00−1.50 points. The patients in this study maintained a lighter sedation depth overall compared with the results of other study where the average Sedation Index was 2.42 points and the distribution of two-thirds of the participants ranged from 0.00 to 3.25 [9].

Also, the participants in this study showed less pain prevalence, about 30% or less. According to previous studies, 40−70% of patients admitted to ICU are known to experience moderate to severe pain [24,25]. More than 30% of patients complained of pain even during rest, and this number was more than 50% during various nursing treatments [26]. The use of the standardized sedation protocol (PAD Protocol) is cited as the reason for maintaining light sedation while controlling pain properly. It is estimated that pain in mechanically ventilated patients was properly controlled by assessing pain every shift and administering analgesic first. In all groups, intermittent analgesic fentanyl was used in at least 80% of cases. The benefit of fentanyl-based analgosedation is that it is known to help the transition to light sedation by reducing pain and unnecessary use of sedatives [27]. The continuous analgesic remifentanil is chiefly used, which is also effective for maintaining light sedation [28]. The frequent use of ketamine, a sedative with analgesic effects, could have led to lower pain as the sedation deepened, even though the analgesic dosage decreased [29,30]. In particular, benzodiazepine midazolam usage was substantially lower in all groups, regardless of Sedation Index. This low use could have influenced the fact that there was no difference in the length of stay in the ICU and ventilator-free days among the three groups in this study [20,31].

However, despite the low use of benzodiazepine, delirium occurred frequently in this study's patients, even in the first tertile, with the lowest occurrence (65.4%) compared with 38.8% in previous study [9], and it was the highest in the deepest sedation (third tertile). Delirium is assumed to occur due to various risk factors, including the use of mechanical ventilation, age, emergency room admission, and medical history of dementia [8]. The risk of delirium increased 6.27 times when under mechanical ventilation [32]. This study targeted only patients undergoing mechanical ventilation. In contrast with the previous study [9], the admission rate in the emergency rooms and the average age in this study showed higher,

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002

Table 1 *Demographics, Clinical Characteristics and Sedative Variables of Patients in the First 48 Hours of Ventilation according to Sedation Index (N = 394).*

Variable	SI 1st tertile[a] (n = 130)	SI 2nd tertile[b] (n = 136)	SI 3rd tertile[c] (n = 128)	X^2 or F	*p*	Post-hoc
	N (%)/M±SD	N (%)/M±SD	N (%)/M±SD			
Age(y)	63.61 ± 14.19	63.67 ± 15.90	65.50 ± 14.22	0.68	.506	
Gender, Men	87 (66.9)	92 (67.6)	85 (66.4)	0.05	.977	
Admission route						
ER	53 (40.8)	56 (41.2)	52 (40.6)	4.18	.375†	
Ward	71 (54.6)	78 (57.4)	75 (58.6)			
Other	6 (4.6)	2 (1.5)	1 (0.8)			
SAPS III (n = 354)	58.64 ± 14.62	62.13 ± 15.53	68.25 ± 15.94	11.54	<.001**	a,b < c
Patient diagnosis						
Respiratory	19 (14.6)	19 (14.0)	13 (10.2)	6.91	.547	
Cancer	73 (56.2)	73 (53.7)	76 (59.4)			
Neurology	7 (5.4)	8 (5.9)	13 (10.2)			
Gastrointestinal	6 (4.6)	8 (5.9)	9 (7.0)			
Other	25 (19.2)	28 (20.6)	17 (13.3)			
RASS at admission						
Light sedation	96 (73.8)	83 (61.0)	65 (50.8)	20.57	<.001**	
Deep sedation	23 (17.7)	43 (31.6)	56 (43.8)			
Agitation	11 (8.5)	10 (7.4)	7 (5.5)			
Pain prevalence‡	40 (30.8)	45 (33.1)	24 (18.8)	7.71	.021*	
Delirium prevalence§	85 (65.4)	114 (83.8)	115 (89.8)	26.03	<.001**	
Analgesic, intermittent	114 (87.7)	126 (92.6)	105 (82.0)	6.83	.033*	
Fentanyl	114 (87.7)	126 (91.9)	103 (80.5)	7.67	.022*	
Morphine	5 (3.8)	5 (3.7)	5 (3.9)		1.000	
Pethidine	4 (3.1)	6 (4.4)	2 (1.6)		.442	
Hydromorphone	1 (0.8)	0 (0.0)	1 (0.8)		.547	
Analgesic, continuous	118 (90.8)	120 (88.2)	108 (84.4)	2.50	.287	
Remifentanil	110 (84.6)	112 (82.4)	94 (73.4)	5.68	.058	
Fentanyl	21 (16.2)	21 (15.4)	21 (16.4)	0.05	.976	
Hydromorphone	6 (4.6)	11 (8.1)	21 (16.4)	10.87	.004**	
Sedative, intermittent	89 (68.5)	85 (62.5)	86 (67.2)	1.17	.556	
Ketamine	85 (65.4)	79 (58.1)	70 (54.7)	3.21	.201	
Propofol	3 (2.3)	2 (1.5)	3 (2.3)		.824	
Midazolam	1 (0.8)	0 (0.0)	5 (3.9)		.011*	
Sedative, continuous	50 (38.5)	53 (39.0)	77 (60.2)	16.01	<.001**	
Ketamine	30 (23.1)	30 (22.1)	50 (39.1)	11.73	.003**	
Dexmedetomidine	24 (18.5)	28 (20.6)	22 (17.2)	0.51	.774	
Propofol	4 (3.1)	2 (1.5)	25 (19.5)	35.82	<.001**	
Midazolam	0 (0.0)	0 (0.0)	5 (3.9)		.003**	

Note: ER = emergency room; RASS = Richmond Agitation–Sedation Scale; SAPS III = Simplified Acute Physiology Score III; SI = Sedation Index.
* $p < .01$.
** $p < .001$.
[a] SI 1st tertile group.
[b] SI 2nd tertile group.
[c] SI 3rd tertile group
† Fisher exact test.
‡ Pain was recorded as yes in the presence of the Numeric Rating Scale (NRS) score ≥4, or the Critical Care Pain Observation Tool (CPOT) score ≥3 at least once.
§ Delirium was recorded as yes when at least one Confusion Assessment Method-ICU (CAM-ICU) was positive.

40.0% vs. 27.9% and 64.0 vs. 58.4 years, respectively, and could thus represent risk factors for the occurrence of delirium. Moreover, unlike a previous study that only investigated a patient's delirium between −2 and + 1 of RASS [9], this study included all patients between −3 and +2 of RASS. It is assumed that this inclusion reflects hypoactive delirium, the primary subtype of delirium occurring in the ICU [33,34]. According to a systematic literature review of subtypes of delirium [34], the prevalence of hypoactive delirium is high in groups with increased severity of disease or mechanical ventilation. Considering that patients in the third tertile group had high severity of illness with a ventilator, it is estimated that the incidence of delirium was the highest since hypoactive type delirium was reflected more than the others.

Although RASS at admission did not affect mortality, it showed a tendency to affect early sedation depth during the first 48 hours. Patients with deep sedation in early phase of mechanical ventilation were more subsequently deeply sedated during the first 2 ICU days [12]. Hence, medical staff must accurately assess and constantly monitor early sedation depth to prevent unnecessary

Table 2 *Clinical Outcomes of Patients in the First 48 Hours of Ventilation according to Sedation Index (N = 394).*

Variable	SI 1st tertile (n = 130)	SI 2nd tertile (n = 136)	SI 3rd tertile (n = 128)	X^2 or F	*p*
	N (%)/M±SD	N (%)/M±SD	N (%)/M±SD		
Mortality					
30-day mortality	32 (24.6)	58 (42.6)	67 (52.3)	21.37	<.001**
90-day mortality	48 (36.9)	70 (51.5)	73 (57.0)	11.19	.004**
180-day mortality	56 (43.1)	75 (55.1)	78 (60.9)	8.63	.013*
Length of stay, ICU	11.65 ± 9.68	13.58 ± 13.63	12.42 ± 8.69	1.06	.349
Ventilator-free days	19.59 ± 7.75	18.72 ± 7.63	18.59 ± 6.99	0.68	.507

Note: SI = Sedation Index.
* $p < .01$.
** $p < .001$.

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002

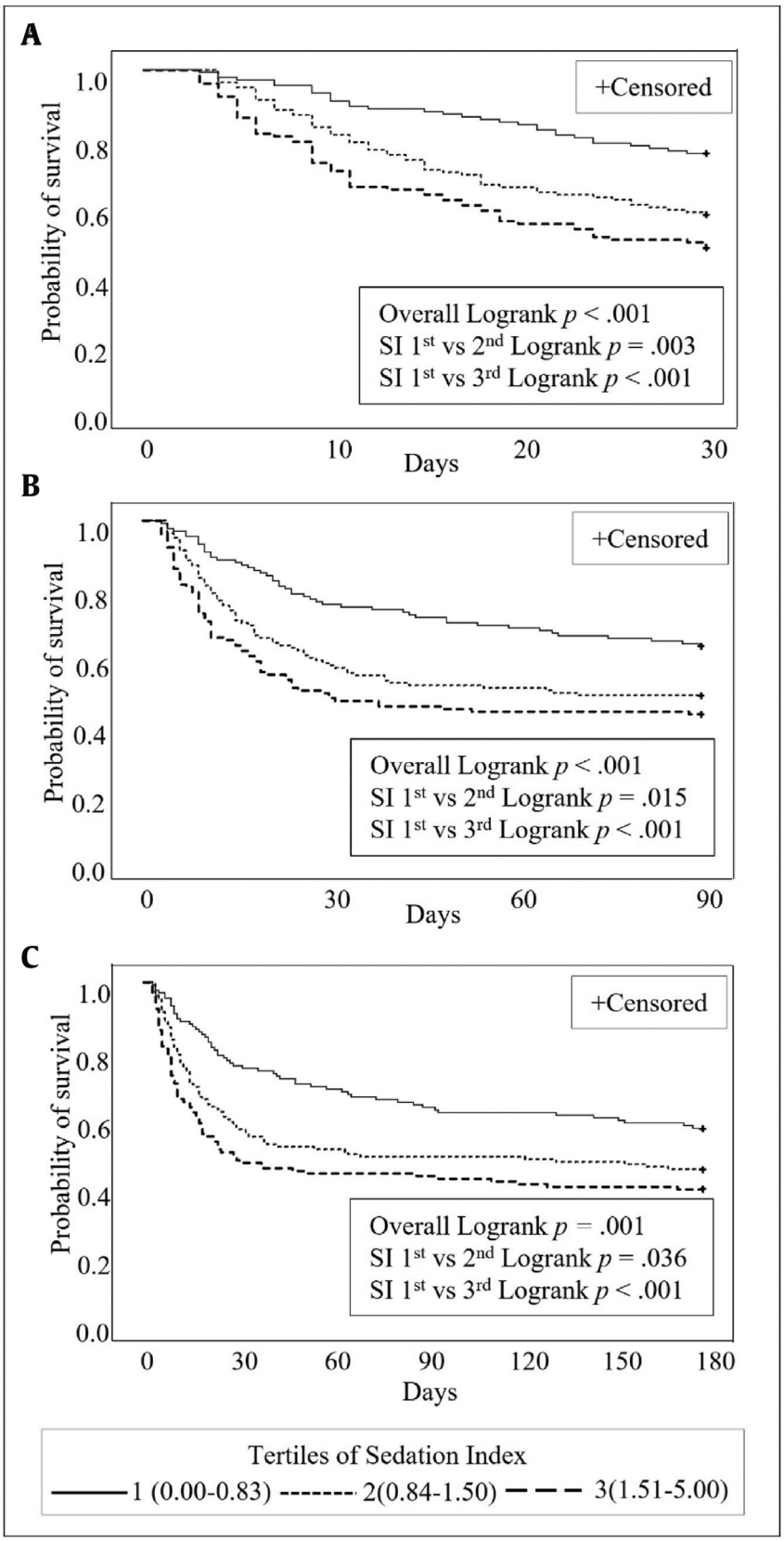

Figure 2. Tertiles of Sedation Index Kaplan–Meier 30-, 90-, and 180-day survival curve.
Note: The log rank p values of comparing with groups are values applied with Bonferroni correction.

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002

Table 3 *Multivariable Cox Regression Analysis of Relationship Between Factors Influencing 30-, 90-, and 180-day Mortality (N = 354).*

Variable	30-day			90-day			180-day		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Sedation Index									
1st tertile (=Ref)	1.0			1.0			1.0		
2nd tertile	1.73	1.10–2.72	.018*	1.61	1.08–2.39	.020*	1.46	1.00–2.14	.052
3rd tertile	2.11	1.33–3.34	.001**	2.00	1.31–3.06	.001**	1.77	1.17–2.67	.007**
SAPS III	1.02	1.01–1.03	<.001**	1.02	1.00–1.03	.006**	1.02	1.01–1.03	.004**
Admission route									
ER (=Ref)				1.0			1.0		
Ward				1.53	1.09–2.16	.015*	1.61	1.16–2.24	.005**
Other				1.97	0.70–5.59	.201	1.73	0.61–4.88	.302
Patient diagnosis									
Respiratory (=Ref)				1.0			1.0		
Cancer				1.24	0.75–2.07	.403	1.12	0.70–1.81	.631
Neurology				0.35	0.13–0.95	.039*	0.28	0.10–0.74	.010*
Gastrointestinal				0.88	0.38–2.03	.762	0.71	0.31–1.61	.411
Other				0.81	0.43–1.51	.499	0.69	0.39–1.25	.226
Morphine, intermittent	2.37	1.14–4.89	.020*	2.17	1.09–4.31	.028*	2.28	1.19–4.40	.013*
Ketamine, intermittent				1.47	1.05–2.05	.025*	1.35	0.99–1.85	.062
Delirium prevalence							1.40	0.94–2.08	.100

Note: CI = confidence interval; ER = emergency room; HR = hazard ratio; Ref = reference.
Multivariable Cox regression incorporated factors with a p value of 0.05 in univariable Cox regression of 30, 90, and 180 days to account for various confounding variables of age, sex, admission route, SAPS III, patient diagnosis, RASS at admission, Sedation Index, prevalence of pain and delirium, and analgesics and sedatives with intermittent or continuous administration.
* $p < .01$.
** $p < .001$.

deep sedation. Admission route was not associated with the Sedation Index, but, in line with previous research [9,35], the patients in this study also showed increased 90- and 180-day mortality when admitted from a ward compared to emergency room. Patients who remained in the ward for a longer period may have an opportunity to be exposed to infection, nutritional deficiencies, and other conditions [35]. Therefore, it is necessary to consider the possibility that patient characteristics may vary depending on the source of admission, which may have an impact on mortality. Even though patient's diagnosis was mainly cancer and morphine administration was less observed in this study, there was association between morphine use and morality in all period. Morphine can increase mortality for patients with acute heart failure [36] or ARDS [37], and its evidence remains controversial [36,37]. Thus, it is necessary to use morphine carefully in consideration of each patient's disease.

The 30-, 90-, and 180-day mortality rates tended to significantly increase as the sedation deepened, and this tendency was identical to a previous study [9]. However, the participants in this study differed in that there was a decrease in the survival curve even in the first and second tertile groups with light sedation although the difference in SAPS III that affected the mortality between the two groups was not statistically significant. In the current circumstances, in which the definition of light sedation and deep sedation is not clear [8] unless deep sedation is required for therapeutic purposes, it suggests that maintaining the patient in a lighter sedation may play a role in improving mortality of patients with mechanical ventilation. However, no statistical significance was confirmed in the survival curve between the second and third tertile. This lack of significance could have been due to a difference in SAPS III scores, strongly affecting mortality between the two groups.

A limitation of this study is that there could be other factors that influenced the clinical outcomes during the early phase of ventilation. For example, there were no data on the reason for mechanical ventilation at the time of hospitalization or the setting value of the ventilator. In addition, the medication administration dosages were not considered and medication administration during intubation was not excluded from total medication usage during the first 48 hours of ventilation. Furthermore, it is difficult to state that this research is representative of treatment in Korea, given that it was conducted in only one tertiary general hospital that already had a standardized sedation protocol. The details of protocols may vary from hospital to hospital, and inconsistent protocols may affect the transition of the patient to light sedation, which may be another bias in evaluating the effect of sedation status on clinical outcomes. Therefore, a study was conducted in a single hospital where standardized sedation protocols were applied. In the future, it will be necessary to conduct the study in multiple institutions with a uniform sedation protocol.

Despite these limitations, the results from this study are consistent with the previous study [9] and indicate that early deep sedation in critically ill patients on mechanical ventilation is associated with mortality. It should be noted that early sedation depth is a modifiable variable among those known to be related to mortality [1,9,11]. Compared with the general treatment as directed by the doctor, nurses play a crucial role in reducing mortality in the ICU and mitigating sedation-related adverse effects by maintaining an appropriate sedation depth for the patient [38,39]. Since the early stage of mechanical ventilation is a phase when a doctor diagnoses a patient and determines the treatment direction, the patients' sedation depth may be considered relatively less important. The patient's target sedation level should be set. The nurse at the bedside can adjust the sedative medication dose without delay [38] and make a faster clinical decision to guarantee a light sedation in keeping with the patient's condition during the early phase of ventilation. Also, the nurse' protocol management skills can be improved with adequate educational intervention [39]. Thus, nurses must endeavor to accomplish early light sedation by performing a standardized sedation protocol.

Conclusion

This study confirmed that early sedation depth during the first 48 hours of mechanical ventilation is a modifiable factor that can potentially affect the mortality of patients. Considering bedside

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002

nurses play a leading role in controlling the sedation depth of critical patients, the protocol for inducing the transition into light sedation must be geared toward improving clinical outcomes of patients with mechanical ventilation. Additional studies on enhancing sedation depth in the first 48 hours are warranted.

Funding

This study was based on the first author's thesis and was supported by the Seoul Nurse Association. (No. 519).

Conflict of interest

The authors have declared no competing interests.

References

1. Balzer F, Weiss B, Kumpf O, Treskatsch S, Spies C, Wernecke KD, et al. Early deep sedation is associated with decreased in-hospital and two-year follow-up survival. Crit Care. 2015;19:197. https://doi.org/10.1186/s13054-015-0929-2
2. Lee JM, Lee SH, Kwak SH, Kang HH, Lee SH, Lim JM, et al. Comparison of morphine and remifentanil on the duration of weaning from mechanical ventilation. Korean J Crit Care Med. 2016;31(4):381. https://doi.org/10.4266/kjccm.2014.29.4.281.e01
3. Park CS. The current state of sedation outside the operating room. J Korean Med Assoc. 2013;56(4):264–70.
4. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med. 2012;186(8):724–31. https://doi.org/10.1164/rccm.201203-0522OC
5. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375(9713):475–80. https://doi.org/10.1016/s0140-6736(09)62072-9
6. Treggiari MM, Romand JA, Yanez ND, Deem SA, Goldberg J, Hudson L, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37(9):2527–34. https://doi.org/10.1097/CCM.0b013e3181a5689f
7. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306. https://doi.org/10.1097/CCM.0b013e3182783b72
8. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–73. https://doi.org/10.1097/m.0000000000003299
9. Shehabi Y, Bellomo R, Kadiman S, Ti LK, Howe B, Reade MC, et al. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a multinational prospective longitudinal cohort study. Crit Care Med. 2018;46(6):850–9. https://doi.org/10.1097/ccm.0000000000003071
10. Stephens RJ, Evans EM, Pajor MJ, Pappal RD, Egan HM, Wei M, et al. A dual-center cohort study on the association between early deep sedation and clinical outcomes in mechanically ventilated patients during the COVID-19 pandemic: the COVID-SED Study. Res Sq [Preprint]. 2022 [cited 2022 May 1]. Available from: https://doi.org/10.21203/rs.3.rs-1389892/v1.
11. Tanaka LM, Azevedo LC, Park M, Schettino G, Nassar AP, Rea-Neto A, et al. Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study. Crit Care. 2014;18(4):R156. https://doi.org/10.1186/cc13995
12. Fuller BM, Roberts BW, Mohr NM, Knight Iv WA, Adeoye O, Pappal RD, et al. The ED-SED study: a multicenter, prospective cohort study of practice patterns and clinical outcomes associated with emergency department sedation for mechanically ventilated patients. Crit Care Med. 2019;47(11):1539–48. https://doi.org/10.1097/CCM.0000000000003928
13. Stephens RJ, Dettmer MR, Roberts BW, Ablordeppey E, Fowler SA, Kollef MH, et al. Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review and meta-analysis. Crit Care Med. 2018;46(3):471–9. https://doi.org/10.1097/ccm.0000000000002885
14. Ko JY, Park HJ, In YW, Lee YM, Kim JM, Lee SY. Effect of pharmacist's intervention and management of pain and sedation protocol on clinical outcomes in medical ICU. J Korean Soc Health-Syst Pharm. 2018;35(3):268–80.
15. Kim HH, Choi SC, Ahn JH, Chae MK, Heo J, Min YG. Analysis of trends in usage of analgesics and sedatives in intensive care units of South Korea: a retrospective nationwide population-based study. Medicine (Baltim). 2018;97(35):e12126. https://doi.org/10.1097/md.0000000000012126
16. Sim JK, Lee SM, Kang HK, Kim KC, Kim YS, Kim YS, et al. Change in management and outcome of mechanical ventilation in Korea: a prospective observational study. Korean J Intern Med. 2022;37(3):618–30. https://doi.org/10.3904/kjim.2020.285
17. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44. https://doi.org/10.1164/rccm.2107138
18. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3–From evaluation of the patient to evaluation of the intensive care unit. part 2: development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med. 2015;31(10):1345–55. https://doi.org/10.1007/s00134-005-2763-5
19. Johnson RA, Bhattacharyya GK. Statistics: principles and methods. In: Chapter 7, Variation in repeated samples-sampling distributions. 6th ed. United States of America: John Wiley & Sons; 2019. p. 276–7.
20. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489–99. https://doi.org/10.1001/jama.2009.56
21. Puntillo K, Pasero C, Li D, Mularski RA, Grap MJ, Erstad BL, et al. Evaluation of pain in ICU patients. Chest. 2009;135(4):1069–74. https://doi.org/10.1378/chest.08-2369
22. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–7. https://doi.org/10.4037/ajcc2006.15.4.420
23. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002;30(8):1772–7. https://doi.org/10.1097/00003246-200208000-00016
24. Desbiens NA, Wu AW. Pain and suffering in seriously ill hospitalized patients. J Am Geriatr Soc. 2000;48(S1):S183–6. https://doi.org/10.1111/j.1532-5415.2000.tb03130.x
25. Li DT, Puntillo K. A pilot study on coexisting symptoms in intensive care patients. Appl Nurs Res. 2006;19(4):216–9. https://doi.org/10.1016/j.apnr.2006.01.003
26. Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S. A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. Anesthesiology. 2007;107(5):858–60. https://doi.org/10.1097/01.anes.0000287211.98642.51
27. Faust AC, Rajan P, Sheperd LA, Alvarez CA, McCorstin P, Doebele RL. Impact of an analgesia-based sedation protocol on mechanically ventilated patients in a medical intensive care unit. Anesth Analg. 2016;123(4):903–9. https://doi.org/10.1213/ane.0000000000001393
28. Aoki Y, Niwa T, Shiko Y, Kawasaki Y, Mimuro S, Doi M, et al. Remifentanil provides an increased proportion of time under light sedation than fentanyl when combined with dexmedetomidine for mechanical ventilation. J Int Med Res. 2021;49(3):3000605211002683. https://doi.org/10.1177/03000605211002683
29. Chan K, Burry LD, Tse C, Wunsch H, De Castro C, Williamson DR. Impact of ketamine on analgosedative consumption in critically ill patients: a systematic review and meta-analysis. Ann Pharmacother. 2022. https://doi.org/10.1177/10600280211069617
30. Patanwala AE, Martin JR, Erstad BL. Ketamine for analgosedation in the intensive care unit: a systematic review. J Intensive Care Med. 2017;32(6):387–95. https://doi.org/10.1177/0885066615620592
31. Wang H, Wang C, Wang Y, Tong H, Feng Y, Li M, et al. Sedative drugs used for mechanically ventilated patients in intensive care units: a systematic review and network meta-analysis. Curr Med Res Opin. 2019;35(3):435–46. https://doi.org/10.1080/03007995.2018.1509573
32. Choi SJ, Cho YA. Prevalence and related risk factors of delirium in intensive care units as detected by the CAM-ICU. J Korean Clin Nurs Res. 2014;20(3):406–16. https://doi.org/10.22650/JKCNR.2014.20.3.406
33. Pun BT, Ely EW. The importance of diagnosing and managing ICU delirium. Chest. 2007;132(2):624–36. https://doi.org/10.1378/chest.06-1795
34. Krewulak KD, Stelfox HT, Leigh JP, Ely EW, Fiest KM. Incidence and prevalence of delirium subtypes in an adult ICU: a systematic review and meta-analysis. Crit Care Med. 2018;46(12):2029–35. https://doi.org/10.1097/ccm.0000000000003402
35. Motzkus CA, Chrysanthopoulou SA, Luckmann R, Rincon TA, Lapane KL, Lilly CM. ICU admission source as a predictor of mortality for patients with sepsis. J Intensive Care Med. 2018;33(9):510–6. https://doi.org/10.1177/0885066617701904
36. Caspi O, Naami R, Halfin E, Aronson D. Adverse dose-dependent effects of morphine therapy in acute heart failure. Int J Cardiol. 2019;293:131–6. https://doi.org/10.1016/j.ijcard.2019.06.015
37. Hu AM, Shan ZM, Zhang ZJ, Li HP. Comparative efficacy of fentanyl and morphine in patients with or at risk for acute respiratory distress syndrome: a propensity score-matched cohort study. Drugs R&D. 2021;21(2):149–55. https://doi.org/10.1007/s40268-021-00338-3
38. Qi Z, Yang S, Qu J, Li M, Zheng J, Huang R, et al. Effects of nurse-led sedation protocols on mechanically ventilated intensive care adults: a systematic review and meta-analysis. Austral Crit Care. 2020. https://doi.org/10.1016/j.aucc.2020.07.013
39. Ramoo V, Abdullah KL, Tan PS, Wong LP, Chua YP, Tang LY. Sedation scoring and managing abilities of intensive care nurses post educational intervention. Nurs Crit Care. 2017;22(3):141–9. https://doi.org/10.1111/nicc.12180

Please cite this article as: Hwang JM, Choi SJ, Early Sedation Depth and Clinical Outcomes in Mechanically Ventilated Patients in a Hospital: Retrospective Cohort Study, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.12.002