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Longitudinal trajectories of sedation level and clinical outcomes in mechanically ventilated patients: a prospective, multicenter, longitudinal, observational study

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ABSTRACT

Objectives: Although low sedation depth level is recommended for intensive care unit (ICU) patients, actual sedation often deviates from this recommendation due to prolonged ICU stay. Therefore, we investigated changes in sedation levels over time and their association with clinical outcomes in a national cohort of mechanically ventilated patients.

Design: This was a multicenter, prospective, longitudinal, observational study.

Setting: Twenty ICUs spanning several medical institutions in Korea.

Participants: Patients who received mechanical ventilation and sedatives in the ICU within 48 h of admission between April 2020 and July 2021.

Primary and secondary outcome measures: The primary objective of this study was to identify the pattern of sedation practice. Also, we analyzed associations of trajectory groups with clinical outcomes as the secondary outcome.

Results: Sedation depth was monitored using the Richmond agitation-sedation scale. A group-based trajectory model was used to classify 631 patients into four trajectories based on sedation depth: persistent suboptimal (13.2%), delayed lightening (13.9%), early lightening (38.4%), and persistent optimal (34.6%). The "persistent suboptimal" trajectory was associated with delayed extubation (hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.16–0.32, $p < 0.001$), longer ICU stay (HR 0.36, 95% CI 0.26–0.51, $p < 0.001$), and hospital mortality (HR 13.62, 95% CI 5.99–30.95, $p < 0.001$) compared with the "persistent optimal". The "delayed lightening" and "early lightening" trajectories showed lower extubation probability (HR 0.30, 95% CI 0.23–0.41, $p < 0.001$; HR 0.72, 95% CI 0.59–0.87, $p < 0.001$, respectively) and ICU discharge (HR 0.44, 95% CI 0.33–0.59; $p < 0.001$ and HR 0.80, 95%CI 0.65–0.97; $p = 0.024$) compated to "persistently optimal".

Conclusions: Among the four trajectories describing longitudinal sedation depth, "persistent suboptimal" trajectory was associated with higher mortality.

Keywords: deep sedation; intensive care units; mortality; critical care; mechanical ventilators

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large national data from 20 ICUs in Korea representing real-world practice.

⇒ A Unique investigation into the level of long-term sedation in mechanically ventilated patients.

⇒ A group-based trajectory model identifying patterns of sedation over time.

⇒ Misclassification of nondifferential group as inherent restriction of group-based trajectory models with limited generalizability.

⇒ Unclear causal relationship between trajectory and outcome.

INTRODUCTION

Sedation is cruical to promote tolerance in patients during mechanical ventilation in the intensive care unit (ICU).[1] Previously, ICU patients were considered unnecessarily over-sedated, and the tools to assess the depth of sedation varied widely.[2] Inappropriate sedation was associated with adverse outcomes, such as prolonged ventilation, longer ICU stay, and higher post-ICU psychological concerns.[3-6] Over-sedation also predicted long-term mortality in critically ill patients.[7] Considering its essential role in the care of mechanically ventilated patients, international guidelines guide to improve sedation practice for favorable outcomes in ICU patients.[8-10]

Currently, sedation monitoring in the ICU is clinically recommended to achieve low levels of sedation,[11] though real-world implementation is debated.[12] Longitudinal studies on the level of sedation over long time are limited. Previous national surveys mainly focused on the type of sedatives and assessment tools.[13-16] Moreover, most studies are cross-sectional, evaluating the association between the sedation level for the first 2–3 days and clinical outcomes.[17 18] Therefore, we aimed to investigate long-term sedation levels in a national cohort of mechanically ventilated patients by classifying them into different longitudinal patterns. We further assessed the association between these patterns and clinical outcomes.

METHODS

Study design

We conducted a multicenter, prospective, longitudinal, and observational, cohort study in 20 ICUs in Korea between April 2020 and July 2021, which was sponsored by Pfizer Korea Pharmaceuticals Ltd. and involved 30 investigators (table S1). We designed a harmonized electric case report form that was centrally managed and combined into one database for data entry, day queries, and analysis. During the study period, patients were recruited according to

the number of available patients at each ICU. Principal investigators, research staff, and nurses at each participating center were trained in the study procedures. The decisions regarding a patient's care were at the discretion of the attending medical staff. Our inclusion criteria were as follows: patients aged >19 years, who had undergone mechanical ventilation and sedation in the ICU within 48 h, and were expected to remain sedated and on mechanical ventilation for >48 h. We excluded patients with a disease that was likely to cause death within 90 days, those whose treatment had been discontinued due to imminent death or non-effective therapy, and who needed non-selective deep sedation due to medical conditions, including brain damage and hemorrhage, spinal cord injury, drug overdose, burns, and nerve root block.

Monitoring of sedation and measurement of outcome

We monitored sedation depth using the Richmond agitation-sedation scale (RASS), ranging from −5 to +4 every 8 h until ICU discharge or day 30.[19] The daily depth of sedation was calculated as the median RASS value for 1 day. The primary objective of this study was to identify the pattern of sedation practice. Group-based trajectory models have been widely employed for analyzing developmental trajectories.[20] They can address the dynamic profile of sedation by classifying patients into different trajectories of sedation level over time. We used a group-based trajectory model analyzing a scale form of RASS over the first 30 days after enrollment. To characterize each trajectory group, an analysis between the trajectory groups and the patients' characteristics was also performed. The secondary objective included associations of trajectory groups with clinical outcomes by adjusting for covariates.

Covariates

Demographic, clinical, and laboratory data, including age, gender, reason for ICU admission, type of ICU admission, comorbidities, and illness severity (acute physiology and

chronic health evaluation [APACHE] Ⅱ score), were collected. Severe to moderate liver disease was defined as cirrhosis and portal hypertension with or without variceal bleeding history. Severe to moderate chronic kidney disease was defined as serum creatinine >3 mg/dL or on dialysis or post-kidney transplant status or uremia status. The need for vasopressors, renal replacement therapy, and neuromuscular blockade was also recorded. We collected and calculated the daily cumulative dose and the number of days prescribed for the sedatives and analgesics administered to patients during their ICU stay. Patients were followed up until hospital discharge, death, or day 30 in the ICU. Clinical outcomes, including ICU discharge, ventilator days, and survival status, were recorded.

Patient and public involvement

Patient and the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Statistical analysis

The pattern of sedation over time was described using a group-based trajectory model, which identified differential patterns of individual change in the populations. The final model was selected based on a combination of the Bayesian information criterion and the estimated trajectory group proportions that were sufficiently large. In this study, four-group solutions that best characterized the cohort were identified.

Data are presented as numbers and proportions for categorical variables and as means ± standard deviations or medians (interquartile range) for continuous variables. Differences between groups were analyzed using the χ^2 test or Fisher's exact test and the independent two-sample t-test or Mann–Whitney *U* test with a normal or non-normal distribution, as appropriate. The normality of the data was assessed by inspecting histograms. For time-to-event analysis,

the Kaplan–Meier method was used to estimate survival curves, whereas a log-rank test was used to test the significance of the differences. Univariable and multivariable Cox proportional hazards regression models were used to identify associations with clinical outcomes by adjusting known prognostic covariates, including age, gender, type of admission, type of ICU, vasopressor, and neuromuscular blockade. The results are presented as hazard ratios (HR) with 95% confidence interval (CI). Two-sided *p*-values <0.05 indicated significance. All analyses were performed using SAS (Statistical Analysis System) software version 9.4 (SAS Institute, Cary, NC).

RESULTS

In 20 participating centers, 676 patients were recruited from April 2020 to July 2021 (figure S1). Of them, 45 were excluded because of missing data, an RASS date before mechanical ventilation, or were enrolled ≥48 h after mechanical ventilation. The final cohort included 631 patients. The profile of sedatives and analgesics administered within the first 48 h was summarized in Table S2. Dexmedetomidine was the most frequently used sedative (38.2%), followed by propofol (26.1%) and midazolam (19.2%). The most commonly used analgesic was remifentanil (73.5%).

A four-group model was chosen for the cohort based on specified selection criteria: trajectory 1 (persistent suboptimal; 13.2% of patients, RASS level ≤ −3 throughout the 30 days), trajectory 2 (delayed lightening; 13.9% of patients, RASS level ≥ −2 after the first 15 days), trajectory 3 (early lightening; 38.4% of patients, RASS level ≥ −2 after the first 7 days), trajectory 4 (persistent optimal: 34.6%, RASS level ≥ −2 during the first 30 days) (figure 1).

A large number of patients in the "persistent suboptimal" group were older, with 35.82% in the >80 age group (*p*-value = 0.002) (table 1). Conversely, 39.24% and 40.46% of patients in the "early lightening" and "persistent optimal" groups, respectively, were aged between 50–

69 years. Gender and body weight did not significantly differ between the trajectories. Considering the comorbidities, there was a significant difference in dementia between patients of different trajectories (p-value = 0.010). Although no significant difference was found, the "persistent suboptimal" group had the highest percentage of solid tumor and cerebrovascular disease (38.00%, p-value = 0.278; 28.00%, p-value = 0.101, respectively), whereas the "delayed lightening" group had the lowest percentage of moderate to severe chronic kidney disease (4.61%, p-value = 0.375). The "persistent suboptimal" and "delayed lightening" groups were more likely to be admitted to a medical ICU (52.24% and 48.81% versus 34.72% and 31.63%, respectively) with a medical illness (61.19% and 58.33% versus 46.79% and 43.26%, respectively) and less likely to be admitted to a surgical ICU (44.78% and 50.00% versus 59.25% and 66.05%, respectively; p-value = 0.023) for scheduled surgery (10.45% and 11.90% versus 23.77% and 23.72%, respectively; p-value = 0.001). The most common cause for ICU admission was respiratory (56.8%) in all the groups, and the "delayed lightening" group had the highest proportion for respiratory-related admissions (67.86%), whereas the "early lightening" group had the lowest (51.32%, p-value = 0.030). Cardiovascular-related ICU admissions were most common in the "early lightening" group (25.66%, p-value = 0.610), although there was no statistical significance. The APACHE Ⅱ score was significantly different among the four trajectories (27.82, 25.28, 21.39, and 24.07 for "persistent suboptimal," "delayed lightening," "early lightening," and "persistent optimal" groups, respectively; p-value <0.001). As a part of ICU support within the first 48 h, the "delayed lightening" group received the largest number of vasopressor infusions (91.67%, p-value < 0.001), renal replacement therapy (26.19%, p-value = 0.078), and neuromuscular blockade use (46.43%, p-value < 0.001). In-hospital death occurred in 12.2% patients in the entire cohort. By trajectory, in-hospital mortality was 49.52% in the "persistent suboptimal" group, 21.43% in the "delayed lightening" group, 6.79% in the "early lightening" group, and 3.72% in the

"persistent optimal" group (p-value < 0.001). Similarly, differences according to the trajectories were observed for ICU discharge and extubation. The proportion of ICU discharge was 67.16%, 79.76%, 92.45%, and 92.09%, respectively (p-value < 0.001); rate of extubation was 68.16%, 78.57%, 95.47%, and 95.81%, respectively (p-value < 0.001). Moreover, differences in time to extubation (p-value < 0.001), ICU discharge (p-value < 0.001), and in-hospital mortality (p-value < 0.001) were observed among the four trajectories (figure 2). Table 2 summarizes the representative phenotypes of each trajectory.

In adjusted Cox proportional hazard analyses, the "persistent suboptimal" (HR 13.62, 95% CI 5.99–30.95, p-value < 0.001) and "delayed lightening" groups (HR 5.62, 95% CI 2.36–13.38, p-value < 0.001) had a significantly higher risk of death than the "persistent optimal" group (table 3). The "persistent suboptimal" (HR 0.23, 95% CI 0.16–0.32, p-value < 0.001), "delayed lightening" (HR 0.30, 95% CI 0.23–0.41, p-value < 0.001), and "early lightening" groups (HR 0.72, 95% CI 0.59–0.87, p-value < 0.001) showed a reduced probability of extubation and were less likely to discharge from the ICU (HR 0.36, 95% CI 0.26–0.51, p-value < 0.001; HR 0.44, 95% CI 0.33–0.59, p-value < 0.001; HR 0.80, 95% CI 0.65–0.97, p-value = 0.024, respectively) than the "persistent optimal" group. Patients undergoing scheduled surgery showed a higher probability of extubation (HR 2.13, 95% CI 1.64–2.78, p-value < 0.001) and ICU discharge (HR 2.10, 95% CI 1.59–2.78, p-value < 0.001) than outpatient admissions. Patients in the surgical ICU had a lower risk of death (HR 0.45, 95% CI 0.23–0.89, p-value = 0.021) than medical ICU patients. No additional significant differences were found with respect to age, gender, vasopressor infusions, or neuromuscular blockade.

DISCUSSION

To the best of our knowledge, this is the first study to characterize the longitudinal pattern of sedation level over time in mechanically ventilated patients. We identified four

distinct trajectories of sedation depth over the first 30 days after mechanical ventilation in our subjects. Only 34.6% patients were in an optimal depth of sedation during this period, whereas 13.2% were in the suboptimal range of RASS for most of this time, and the remaining patients achieved adequate depth of sedation 7 (early lightening: 38.4%) or 15 (delayed lightening: 13.9%) days after initiation. Patients who were at suboptimal levels of sedation throughout this period had a higher risk of mortality and lower probabilities of extubation and ICU discharge than those who were in consistently optimal level of sedation.

Group-based trajectory modeling is useful for characterizing longitudinal courses over time to identify distinct subgroups.[21 22] This trajectory model is used in different domains of clinical research, such as nonadherence spectrum in newly-diagnosed juvenile epilepsy, health status in outpatients with heart failure, neurologic postinjury recovery, and symptom burden nuances of patients with metastatic cancer.[20] Therefore, group-based trajectory modeling is a specialized method for sorting individuals into meaningful subgroups that show statistically similar trajectories.

There were several significant differences in characteristics between the four trajectory groups. Patients in trajectory 1 (persistent suboptimal) experienced deep sedation throughout the study period, with RASS ranging from −3 to −5. This group was mainly characterized by elderly patients with cognitive impairment, admitted to a medical ICU for treating illnesses, such as respiratory problems, with the worst condition at admission. Conversely, patients in trajectory 2 (delayed lightening) experienced initial deep sedation, which improved to a light depth of RASS −2 after 15 days. This group was characterized by elderly patients with dementia with respiratory failure, receiving vasopressors, neuromuscular blockade, and renal replacement therapy. Interestingly, although the two trajectories had relatively similar characteristics and the “delayed lightening” group even required more ICU support within the first 48 h, the “persistent suboptimal” group had worse time to extubation, ICU discharge, and

hospital mortality. These findings suggest that the longitudinal course of sedation depth in our subjects was not associated with the severity of illness; the difference in sedation practice between the two trajectories might have resulted into different outcomes.

A prospective multicenter study, conducted across 42 international ICUs, demonstrated that the time to extubation and mortality increased with the sedation intensity.[18] In observational, matched-pair analyses based on the APACHE II score and the type of admission, early deep sedation during the first 48 h of ICU stay was associated with worse outcomes, including long-term mortality.[7] We report similar findings in our study upon comparing trajectories 3 and 4 with the earlier trajectories. Patients in trajectory 3 (early lightening) experienced early deep sedation, which became lighter after 7 days, whereas those in trajectory 4 (persistent optimal) experienced light sedation throughout. Patients in these groups were younger, had fewer medical conditions, and were mostly admitted to surgical ICUs than those in the other two groups. They also had lower APACHE Ⅱ scores and needed lesser ICU support within the first 48 h. Patients in the "early lightening" group, especially, had the lowest APACHE score, the lowest proportion of renal replacement therapy, and the fewest respiratory problems. Nevertheless, multivariable Cox proportional hazard analysis showed that patients in this group had a lower probability of extubation and ICU discharge than those in the "persistent optimal" group. The early practice of inadequate sedation in the "early lightening" group might have induced this relatively worse prognosis in these patients. A recent meta-analysis assessing the literature on early sedation suggested that interventions targeting the depth of early sedation, starting with ICU admission, could improve patient outcomes.[23] Appropriate sedation is a critical aspect in the management of mechanically ventilated patients.

We observed that 65.9% patients in our study were deeply sedated for at least the first week after mechanical ventilation, whereas only 34.07% patients received consistent light sedation throughout the sedation period. This finding is consistent with previous data

describing the sedation depth. A multinational survey among intensivists reported that 74% patients monitored using a validated sedation tool were deeply sedated.[24] A survey in Germany found that the actual depth of sedation was significantly deeper (39.5%–62.4%) than the desired depth in all categories of sedation.[25] A Swedish study investigating the relationship between memory and sedation showed that only 39% of ventilated patients achieved their target sedation goal.[26] A previous systematic review estimated the incidence of over-sedation in ICUs at 40%–60%, despite the poor quality of epidemiologic data.[2] In a recent study conducted in the emergency department, the incidence of deep sedation was 52.8%.[27] These data suggest that deep sedation remains a common real-world ICU practice. To improve the quality of patient care, further research is warranted focusing on the longitudinal profile in addition to the binary concept of sedation, light versus deep.

Our study has a few limitations. First, information bias may exist because only patients visiting tertiary or university-affiliated hospitals were included in our study. Second, unmeasured confounders could have affected the trajectories, despite many relevant variables in our study. Moreover, nondifferential group of patients may have been misclassified. This restriction is inherent to group-based trajectory models with limited generalizability. Third, the causal relationship between trajectory and outcome could not be established in this study. For example, it is unclear whether a prolonged duration of extubation reflected the effects of sedative overdose, or whether more sedation was needed because of longer mechanical ventilation. Thus, prospective and randomized controlled studies are required to investigate the interaction of two parameters (depth and duration) of sedation to better define the optimal practice. Finally, we were unable to examine the long-term complications in the trajectory groups. Further nationwide studies should evaluate long-term complications after sedation to comprehensively understand its socioeconomic and clinical burden.

In conclusion, this study captured the four trajectories of sedation level over time in

mechanically ventilated patients. The patterns were significantly associated with time to extubation, ICU discharge, and hospital mortality. Our findings suggest sedation strategy in ICU patient needs to incorporate a longitudinal pattern of sedation level.

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Contributors

CML, HYG, JHA have contributed to the study conception and design. Material preparation was performed by HYG. Data collection was performed DH, JHA, CML. Statistical analysis were performed by CMN and CY. The first draft of the manuscript was written by DH and JHA, and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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Competing Interests

Ha-Yeong Gil is an employee of Pfizer Korea. The other authors declare that they have no competing interests.

Patient consent for publication

Not applicable.

Ethic approval

The study protocol was approved by the Institutional Review Boards of all participating medical centers (B-1911/577-405, AJIRB-MED-OBS-19-372, AJIRB-MED-OBS-19-373, 1908-156-1058, 1908-157-1058, 1910-003-083, 2019-1624, 2019-1039, 2019-10-0321, 2019-09-040, 2019-10-162, GCIRB2019-366, DSMC 2019-08-018, HALLYM 2019-08-021, HALLYM 2019-08-022, 2019-09-010, 2019-08-082, DAUHIRB-19-166, 4-2019-0821, 4-2019-0820, 2019-09-011-002, 2019-07-038-002, CR-19-117-L, 2019AN0376, 2019AN0478, 20-2019-92, 20-2019-91, 2019GR0461, 2020GR0103, 2020AS0054). All patients (or patient representatives) provided their written informed consent. Some participating centers' local review boards waived the need for informed consent considering the observational nature of the study. This study was conducted per the amended Declaration of Helsinki.

Data Availability statement

Data are available on request

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Figure Legends

Figure 1 Trajectories of longitudinal Richmond Agitation Sedation Scale in the first 30 days of sedation for mechanical ventilation. The percentage of patients included in each trajectory were presented in central illustration. Outcome of y-axis indicates the score of richmond agitation sedation scale and T of x-axis represents day after the initiation of sedation.

Figure 2 Kaplan-Meier of clinical outcomes from admission according to the trajectory groups. (a) time to extubation in the intensive care unit, (b) length of stay in the intensive care unit, (c) in-hospital mortality.

Table 1 Baseline Characteristics and Clinical Outcomes for the Total Cohort and for Each Trajectory of the Richmond Agitation-Sedation Scale

		Trajectory group				
Characteristic	All (N = 631)	1 (N = 67)	2 (N = 84)	3 (N = 265)	4 (N = 215)	*p*-value
Age						0.002
20–29	11 (1.74%)	0 (0.00%)	2 (2.38%)	6 (2.26%)	3 (1.40%)	
30–39	34 (5.39%)	0 (0.00%)	2 (2.38%)	12 (4.53%)	20 (9.30%)	
40–49	44 (6.97%)	3 (4.48%)	11 (13.10%)	13 (4.91%)	17 (7.91%)	
50–59	92 (14.58%)	6 (8.96%)	6 (7.14%)	44 (16.60%)	36 (16.74%)	
60–69	140 (22.19%)	12 (17.91%)	17 (20.24%)	60 (22.64%)	51 (23.72%)	
70–79	177 (28.05%)	22 (32.84%)	23 (27.38%)	80 (30.19%)	52 (24.19%)	
≥80	133 (21.08%)	24 (35.82%)	23 (27.38%)	50 (18.87%)	36 (16.74%)	
Male gender	404 (64.0)	44 (65.67)	57 (67.86)	165 (62.26)	138 (64.19)	0.807
Body weight, kg*	62.0 (53.0-71.0)	62.25 ± 10.69	62.81 ± 13.31	62.51 ± 13.01	63.79 ± 17.62	0.785
Comorbidity	448 (71.00)	50 (74.62)	65 (77.38)	183 (69.05)	150 (69.76)	0.434
Diabetes with end-organ damage	30 (4.31)	2 (4.00)	2 (3.07)	14 (7.65)	12 (8.00)	0.573
COPD	60 (8.6)	7 (14.00)	8 (12.30)	25 (13.66)	20 (13.33)	0.994
Congestive heart failure	49 (7.0)	3 (6.00)	7 (10.76)	19 (10.38)	20 (13.33)	0.596
Moderate-to-severe liver disease**	27 (3.8)	3 (6.00)	3 (4.61)	9 (4.91)	12 (8.00)	0.681
Moderate-to-severe CKD**	46 (6.6)	5 (10.00)	3 (4.61)	18 (9.83)	20 (13.33)	0.375
Solid tumor	127 (18.2)	19 (38.00)	15 (23.07)	48 (26.22)	45 (30.00)	0.278
Dementia	35 (5.0)	6 (12.00)	9 (13.84)	16 (8.74)	4 (3.00)	0.010
Cerebrovascular disease/TIA	82 (11.7)	14 (28.00)	14 (21.53)	28 (15.30)	26 (17.33)	0.101
Type of admission						0.023
Medical	307 (48.6)	41 (61.19)	49 (58.33)	124 (46.79)	93 (43.26)	
Emergency surgery	193 (30.5)	19 (28.36)	25 (29.76)	78 (29.43)	71 (33.02)	
Scheduled surgery	131 (20.7)	7 (10.45)	10 (11.90)	63 (23.77)	51 (23.72)	
Type of ICU						0.001
Medical ICU	236 (37.4)	35 (52.24)	41 (48.81)	92 (34.72)	68 (31.63)	
Surgical ICU	371 (58.8)	30 (44.78)	42 (50.00)	157 (59.25)	142 (66.05)	
Others	24 (3.8)	2 (2.99)	1 (1.19)	16 (6.04)	5 (2.33)	

Reason for ICU admission***						
Renal	16 (2.5)	1 (1.49)	0 (0.00)	7 (2.64)	8 (3.72)	0.294
Digestive	83 (13.1)	10 (14.93)	12 (14.29)	28 (10.57)	33 (15.35)	0.434
Cardiovascular	147 (23.3)	15 (22.39)	16 (19.05)	68 (25.66)	48 (22.33)	0.610
Hematologic	14 (2.2)	2 (2.99%)	3 (3.57%)	4 (1.51%)	5 (2.33%)	0.679
Respiratory	359 (56.8)	43 (64.18%)	57 (67.86%)	136 (51.32%)	123 (57.21%)	0.030
Miscellaneous	67 (10.6)	3 (4.48%)	11 (13.10%)	34 (12.83%)	19 (8.84%)	0.152
Neurologic	12 (1.9)	3 (4.48%)	1 (1.19%)	4 (1.51%)	4 (1.86%)	0.418
Others	105 (16.6)	11 (16.42%)	13 (15.48%)	42 (15.85%)	39 (18.14%)	0.907
APACHE Ⅱ, score*	23.4 ± 10.0	27.82 ± 9.73	25.28 ± 11.45	21.39 ± 9.59	24.07 ± 9.56	< 0.001
ICU support within first 48 hours						
Vasopressor infusions	486 (77.02)	57 (85.07)	77 (91.67)	199 (75.09)	153 (71.16)	< 0.001
Renal replacement	107 (16.9)	11 (16.42)	22 (26.19)	37 (13.96)	37 (17.21)	0.078
Neuromuscular blockade	171 (27.1)	27 (40.30)	39 (46.43)	69 (26.04)	36 (16.74)	< 0.001
Clinical outcomes						
In-hospital mortality	77 (12.2)	33 (49.52)	18 (21.43)	18 (6.79)	8 (3.72)	< 0.001
ICU discharge	555 (87.9)	45 (67.16)	67 (79.76)	245 (92.45)	198 (92.09)	< 0.001
Extubation	571 (90.4)	46 (68.66)	66 (78.57)	253 (95.47)	206 (95.81)	< 0.001
Length of ventilator support, days	5 (3–11)	11 (20–NE)	11.5 (7–23.5)	5 (3–8)	3 (2–5)	< 0.001
ICU length of stay, days	10 (5–18)	20 (12–NE)	18 (10–26)	9 (6–14)	4 (6–10)	< 0.001

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and number (percentage) for categorical variables.
*Data on body weight are presented for all 605 patients, excluding 26 patients with missing data (4 in the light sedation group and 22 in the deep sedation group). Data on APACHE Ⅱ are presented for all 577 patients, excluding 54 patients with missing data (15 in the light sedation group and 39 in the deep sedation group).
**Severe to moderate liver disease are defined as cirrhosis and portal hypertension with or without variceal bleeding history. Severe to moderate CKD are defined as serum creatinine > 3 mg/dL or on dialysis or post-kidney transplant status or uremia status.
***172 patients had multiple reasons for ICU admission.
ICU = intensive care unit; SMD = standardized mean difference; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; TIA = transient ischemic attack; APACHE Ⅱ = acute physiology and chronic health evaluation Ⅱ; NE = not estimated

Table 2 Summary of the demographics of the trajectories and the trajectory ranks for characteristics

	Trajectory 1	**Trajectory 2**	**Trajectory 3**	**Trajectory 4**
Demographics				
Age	70–79 & ≥80	70–79 & ≥80	60–69 & 70–-79	60–69 & 70–-79
Gender	Male	Male	Male	Male
Comorbidity	Solid tumor, CVD/TIA, COPD	Solid tumor, CVD/TIA, Dementia	Solid tumor, CVD/TIA, COPD	Solid tumor, CVD/TIA, COPD
Type of ICU	Medical ICU	Surgical ICU	Surgical ICU	Surgical ICU
Reason for ICU admission	Respiratory & Cardiovascular	Respiratory & Cardiovascular	Respiratory & Cardiovascular	Respiratory & Cardiovascular
Ranks for characteristics				
Medical admission	1st	2nd	3rd	4th
Scheduled surgery	4th	3rd	2nd	1st
APACHE Ⅱ	1st	2nd	4th	3rd
Vasopressor infusions	2nd	1st	3rd	4th
Renal replacement therapy	3rd	1st	4th	2nd
Neuromuscular blockade	2nd	1st	3rd	4th

Representative demographics with more than half of the patients on each trajectory, except age on trajectory 4, are shown in the table. Rank-order of trajectories was determined by the comparison of proportion of variable within each trajectory. Trajectories are ordered from lowest (4th) to highest (1st) rank values.

ICU = intensive care unit; APACHE Ⅱ = acute physiology and chronic health evaluation Ⅱ; CVD = cardiovascular disease; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

Table 3 Multivariable Cox Proportional Hazard regression models of time to event

	Time to extubation			Time to ICU discharge			Time to in-hospital death	
	HR (95% CI)	***p*-value**		**HR (95% CI)**	***p*-value**		**HR (95% CI)**	***p*-value**
Trajectory group								
Group 1	0.23 (0.16–0.32)	< 0.001		0.36 (0.26–0.51)	< 0.001		13.62 (5.99–30.95)	< 0.001
Group 2	0.30 (0.23–0.41)	< 0.001		0.44 (0.33–0.59)	< 0.001		5.62 (2.36–13.38)	< 0.001
Group 3	0.72 (0.59–0.87)	< 0.001		0.80 (0.65–0.97)	0.024		1.76 (0.76–4.08)	0.185
Group 4	Reference			Reference			Reference	
Age								
20–29	Reference			Reference			Reference	
30–39	1.08 (0.53–2.21)	0.825		0.70 (0.35–1.42)	0.334		0.69 (0.06–7.72)	0.765
40–49	0.89 (0.43–1.81)	0.748		0.63 (0.31–1.25)	0.188		0.59 (0.06–5.28)	0.641
50–59	1.04 (0.53–2.03)	0.893		0.65 (0.34–1.23)	0.192		0.41 (0.04–3.46)	0.414
60–69	1.00 (0.52–1.93)	0.987		0.79 (0.42–1.48)	0.469		0.88 (0.11–6.75)	0.905
70–79	1.04 (0.54–1.99)	0.893		0.64 (0.34–1.20)	0.170		0.47 (0.06–3.65)	0.473
≥80	0.85 (0.44–1.64)	0.632		0.53 (0.28–1.00)	0.052		0.82 (0.10–6.26)	0.850
Female	0.85 (0.71–1.01)	0.075		0.98 (0.81–1.17)	0.848		1.17 (0.73–1.89)	0.50
Type of admission								
Medical	Reference			Reference			Reference	
Emergency surgery	1.02 (0.79–1.32)	0.839		1.17 (0.90–1.53)	0.234		1.35 (0.62–2.91)	0.444
Scheduled surgery	2.13 (1.64–2.78)	< 0.001		2.10 (1.59–2.78)	< 0.001		1.91 (0.87–4.16)	0.102
Type of ICU								
Medical ICU	Reference			Reference			Reference	
Surgical ICU	1.05 (0.83–1.33)	0.629		0.87 (0.68–1.12)	0.299		0.45 (0.23–0.89)	0.021
Others	1.53 (0.96–2.40)	0.068		1.28 (0.80–2.06)	0.289		0.55 (0.12–2.47)	0.441
Vasopressor infusions	0.85 (0.69–1.04)	0.116		0.85 (0.69–1.04)	0.122		1.25 (0.62–2.51)	0.529
Neuromuscular blockade	1.05 (0.86–1.28)	0.586		0.88 (0.72–1.07)	0.217		1.42 (0.88–2.29)	0.148

Hazard ratio > 1 indicates a higher probability of event than reference.
ICU = intensive care unit; HR hazard ratio = CI confidence interval.

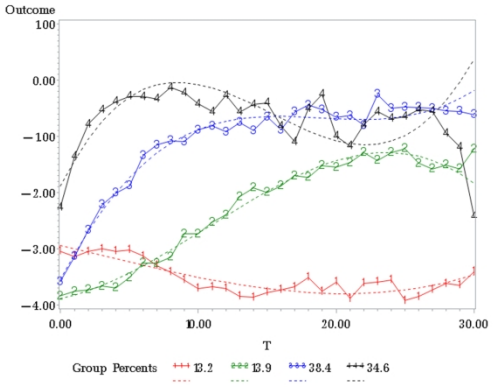

Figure 1 Trajectories of longitudinal Richmond Agitation Sedation Scale in the first 30 days of sedation for mechanical ventilation. The percentage of patients included in each trajectory were presented in central illustration. Outcome of y-axis indicates the score of richmond agitation sedation scale and T of x-axis represents day after the initiation of sedation.

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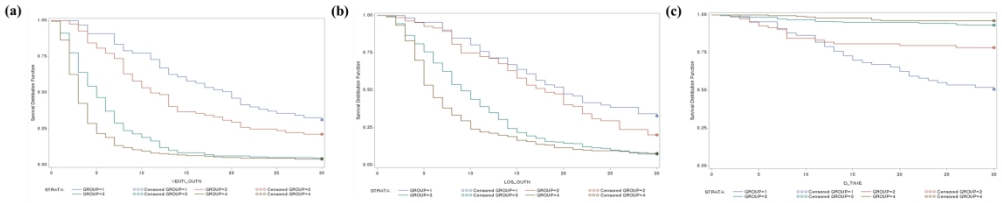

Figure 2 Kaplan-Meier of clinical outcomes from admission according to the trajectory groups. (a) time to extubation in the intensive care unit, (b) length of stay in the intensive care unit, (c) in-hospital mortality.

338x190mm (200 x 200 DPI)

Longitudinal trajectories of sedation level and clinical outcomes in mechanically ventilated patients: a prospective, multicenter, longitudinal, observational study

Dong-gon Hyun, M.D.[1], Jee Hwan Ahn, M.D.[1], Ha-Yeong Gil, M.S.[2], Chung Mo Nam, Ph.D.[3], Choa Yun, M.S.[4], Chae-Man Lim, M.D., Ph.D.[1]*

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Table S1. Participating intensive care units

City	Participating hospitals	Investigators
Seoul	Asan Medical Center	Dong-gon Hyun, Jee Hwan Ahn, Suk-Kyung Hong, Chae-Man Lim
Seoul	Seoul National University Hospital	Sang-Min Lee, Ho-Geol Ryu
Seoul	Samsung Medical Center	Gee Young Suh, Chi Min Park
Seoul	Severance Hospital	Su Hwan Lee, Jeoung Min Kim
Seoul	Seoul St. Mary's Hospital	Seok Chan Kim
Seoul	Korea University Anam Hospital	Won Jai Jung, Jae-Myeong Lee
Seoul	Korea University Guro Hospital	Young-Seok Lee, Nak-Jun Choi
Seoul	Seoul National University Boramae Medical Center	Taeyun Park
Seongnam	Seoul National University Bundang Hospital	Dong Jung Kim
Suwon	Ajou University School of Medicine	Keu Sung Lee, Young-Gi Min
Busan	Pusan National University Hospital	Jae Hun Kim
Busan	Dong-A University Hospital	Dong-Hyun Lee
Busan	Inje University Haeundae Paik Hospital	Hang-Jea Jang, Ki Hoon Kim
Wonju	Yonsei University Wonju College of Medicine	Seok Jeong Lee
Incheon	Gachon University Gil Medical Center	Woo-Sung Choi
Daegu	Keimyung University School of Medicine	Jae-Bum Kim
Daegu	Yeungnam University Medical Center	Eun Young Choi, Jong-Hyun Baek
Daegu	Daegu Catholic University Medical Center	Eun Jin Kim
Anyang	Hallym University Sacred Heart Hospital	Sunghoon Park, Hyung Won Kim
Ansan	Korea University Ansan Hospital	Je Hyeong Kim

Table S2. Profile of analgesic and sedative within the first 48 hours

Type of Sedatives	N = 662
Diazepam	1 (0.2)
Cumulative dose (µg)	2000.0
Midazolam	127 (19.2)
Cumulative dose (µg)	64253.9 ± 133338.1
Lorazepam	14 (2.1)
Cumulative dose (µg)	2750 ± 1868.3
Other benzodiazepine	19 (2.9)
Cumulative dose (µg)	34294.7 ± 53960.7
Propofol	173 (26.1)
Cumulative dose (µg)	3444220.1 ± 2752320.0
Ketamine	53 (8.0)
Cumulative dose (µg)	1450147.2 ± 1830958.4
Haloperidol	1 (0.2)
Cumulative dose (µg)	5000.0
Dexmedetomidine	253 (38.2)
Cumulative dose (µg)	4080.2 ± 38325.4
Other non-benzodiazepine	21 (3.2)
Cumulative dose (µg)	75659.5 ± 133078.2
Type of analgesics	N = 528
Fentanyl	119 (22.5)
Cumulative dose (µg)	30861.1 ± 315168.1
Remifentanil	388 (73.5)
Cumulative dose (µg)	13227.8 ± 10971.7
Morphine	6 (1.1)
Cumulative dose (µg)	24000.0 ± 38740.2
Sufentanil	15 (2.8)
Cumulative dose (µg)	285.4 ± 280.6

Data are reported as means ± standard deviation for continuous variables and numbers (percentage) for categorical variables.
RASS = Richmond agitation-sedation scale

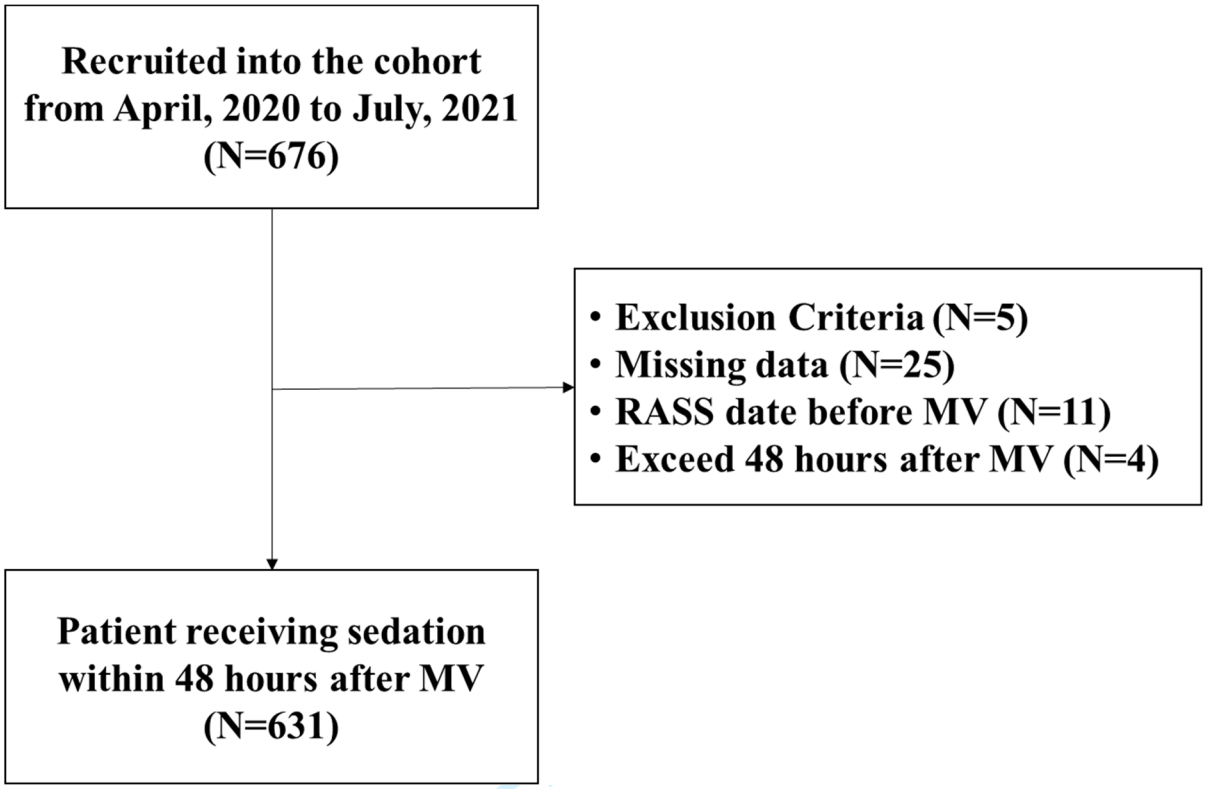

Figure S1. Flow diagram of patients in the present study.
MV = mechanical ventilation; RASS = Richmond agitation-sedation scale

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Longitudinal trajectories of sedation level and clinical outcomes in mechanically ventilated patients based on a group-based trajectory model: a prospective, multicenter, longitudinal, observational study in Korea

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Word Count: 2995

ABSTRACT

Objectives: Changes in sedation levels over long time in mechanically ventilated patients are unknown. Therefore, we investigated long-term sedation levels of mechanically ventilated patients by classifying them into different longitudinal patterns.

Design: This was a multicenter, prospective, longitudinal, observational study.

Setting: Twenty ICUs spanning several medical institutions in Korea.

Participants: Patients who received mechanical ventilation and sedatives in the ICU within 48 h of admission between April 2020 and July 2021.

Primary and secondary outcome measures: The primary objective of this study was to identify the pattern of sedation practice. Also, we analyzed associations of trajectory groups with clinical outcomes as the secondary outcome.

Results: Sedation depth was monitored using the Richmond agitation-sedation scale (RASS). A group-based trajectory model was used to classify 631 patients into four trajectories based on sedation depth: persistent suboptimal (13.2%, RASS ≤ −3 throughout the first 30 days), delayed lightening (13.9%, RASS ≥ −2 after the first 15 days), early lightening (38.4%, RASS ≥ −2 after the first 7 days), and persistent optimal (34.6%, RASS ≥ −2 during the first 30 days). The "persistent suboptimal" trajectory was associated with delayed extubation (hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.16–0.32, $p < 0.001$), longer ICU stay (HR 0.36, 95% CI 0.26–0.51, $p < 0.001$), and hospital mortality (HR 13.62, 95% CI 5.99–30.95, $p < 0.001$) compared with the "persistent optimal". The "delayed lightening" and "early lightening" trajectories showed lower extubation probability (HR 0.30, 95% CI 0.23–0.41, $p < 0.001$; HR 0.72, 95% CI 0.59–0.87, $p < 0.001$, respectively) and ICU discharge (HR 0.44, 95% CI 0.33–0.59; $p < 0.001$ and HR 0.80, 95%CI 0.65–0.97; $p = 0.024$) compated to "persistently optimal".

Conclusions: Among the four trajectories describing longitudinal sedation depth, "persistent

suboptimal" trajectory was associated with higher mortality.

Keywords: deep sedation; intensive care units; mortality; critical care; mechanical ventilators

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large national data from 20 ICUs in Korea representing real-world practice.

⇒ An investigation into the level of long-term sedation in mechanically ventilated patients.

⇒ A group-based trajectory model identifying patterns of sedation over time.

⇒ Misclassification of nondifferential group as inherent restriction of group-based trajectory models with limited generalizability.

⇒ Unclear causal relationship between trajectory and outcome.

INTRODUCTION

Sedation is cruical to promote tolerance in patients during mechanical ventilation in the intensive care unit (ICU).[1] Previously, ICU patients were considered unnecessarily over-sedated, and the tools to assess the depth of sedation varied widely.[2] Inappropriate sedation was associated with adverse outcomes, such as prolonged ventilation, longer ICU stay, and higher post-ICU psychological concerns.[3-6] Over-sedation also predicted long-term mortality in critically ill patients.[7] Considering its essential role in the care of mechanically ventilated patients, international guidelines guide to improve sedation practice for favorable outcomes in ICU patients.[8-10]

Currently, sedation monitoring in the ICU is clinically recommended to achieve low levels of sedation,[11] though real-world implementation is debated.[12] Longitudinal studies on the level of sedation over long time are limited. Previous national surveys mainly focused on the type of sedatives and assessment tools.[13-16] Moreover, most studies are cross-sectional, evaluating the association between the sedation level for the first 2–3 days and clinical outcomes.[17 18] Therefore, we aimed to investigate long-term sedation levels in a national cohort of mechanically ventilated patients by classifying them into different longitudinal patterns. We further assessed the association between these patterns and clinical outcomes.

METHODS

Study design

We conducted a multicenter, prospective, longitudinal, and observational, cohort study in 20 ICUs in Korea between April 2020 and July 2021, which was sponsored by Pfizer Korea Pharmaceuticals Ltd. and involved 30 investigators (table S1). We designed a harmonized electric case report form that was centrally managed and combined into one database for data

entry, day queries, and analysis. During the study period, patients were recruited according to the number of available patients at each ICU. Principal investigators, research staff, and nurses at each participating center were trained in the study procedures. The decisions regarding a patient's care were at the discretion of the attending medical staff. Our inclusion criteria were as follows: patients aged >19 years, who had undergone mechanical ventilation and sedation in the ICU within 48 h, and were expected to remain sedated and on mechanical ventilation for >48 h. We excluded patients with a disease that was likely to cause death within 90 days, those whose treatment had been discontinued due to imminent death or non-effective therapy, and who needed non-selective deep sedation due to medical conditions, including brain damage and hemorrhage, spinal cord injury, drug overdose, burns, and nerve root block.

Monitoring of sedation and measurement of outcome

We monitored sedation depth using the Richmond agitation-sedation scale (RASS), ranging from −5 to +4 every 8 h until ICU discharge or day 30.[19] The daily depth of sedation was calculated as the median RASS value for 1 day. The primary objective of this study was to identify the pattern of sedation practice. Group-based trajectory models have been widely employed for analyzing developmental trajectories.[20] They can address the dynamic profile of sedation by classifying patients into different trajectories of sedation level over time. We used a group-based trajectory model analyzing a scale form of RASS over the first 30 days after enrollment. To characterize each trajectory group, an analysis between the trajectory groups and the patients' characteristics was also performed. The secondary objective included associations of trajectory groups with clinical outcomes by adjusting for covariates.

Covariates

Demographic, clinical, and laboratory data, including age, gender, reason for ICU admission, type of ICU admission, comorbidities, and illness severity (acute physiology and chronic health evaluation [APACHE] Ⅱ score), were collected. Severe to moderate liver disease was defined as cirrhosis and portal hypertension with or without variceal bleeding history. Severe to moderate chronic kidney disease was defined as serum creatinine >3 mg/dL or on dialysis or post-kidney transplant status or uremia status. The need for vasopressors, renal replacement therapy, and neuromuscular blockade was also recorded. We collected and calculated the daily cumulative dose and the number of days prescribed for the sedatives and analgesics administered to patients during their ICU stay. Patients were followed up until hospital discharge, death, or day 30 in the ICU. Clinical outcomes, including ICU discharge, ventilator days, and survival status, were recorded.

Patient and public involvement

Patient and the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Statistical analysis

The pattern of sedation over time was described using a group-based trajectory model, which identified differential patterns of individual change in the populations. The parameters of GBTM are generated by maximum likelihood estimation (MLE). The ultimate objective is to estimate a set of parameters, Ω, that maximize the probability of $Y_i = (y_{i1},...,y_{it})$. The equation describing the likelihood of an individual's observed repeated measures is composed of two elements: (1) the probability of group membership and (2) the probability of the observed data given group membership. The finite mixture model is defined by

$$P(Y_i) = \sum_k \pi_k P^k(Y_i),$$

where k: trajectory group, $i\ (=1,...,N)$: subject, and $j\ (=1,...,T)$: measurement time. The group membership probabilities,

$$\pi_k = e^{\theta_k} / \sum_k e^{\theta_k}$$

, $k = 1,...,K$, are not observed, so estimated by a multinomial logit function. For given k, conditional independence is assumed for the sequential realizations of the elements of Y_i, y_{ij}, over the T periods of measurement. This assumption implies that for each individual within a given trajectory group k, the distribution of y_{ij} for period T is independent of the realized level of the outcome in prior periods. The likelihood function is $L = \prod_{i=1}^{N} P(y_i|z_i, w_i)$ where $p(y_i|z_i, w_i) = \sum_{k=1}^{K} p(C_i = k \,|\, Z_i = z_i) p(Y_i = y_i \,|\, C_i = k, W_i = w_i)$ that the first term is the probability of group membership and second term is the probability of the observed data given group membership. $Y_i = (Y_{i1},...,Y_{iT}), Z_i = (Z_{i1},...,Z_{iR}), W_i = (W_{i1},...,W_{iT}), p = \frac{\exp(\theta_k + \lambda_k' z_i)}{\sum_{k=1}^{K} \exp(\theta_k + \lambda_k' z_i)}, and\ p(Y_i = y_i \,|\, C_i = k, W_i = w_i)$ which is specified by distribution of Y_i. For count data, it is specified as the zero-inflated Poisson distribution, for censored data, the censored normal distribution and for binary data, it is specified as the binary logit distribution. In this study, we use censored normal model. The final model was selected based on a combination of the Bayesian information criterion and the estimated trajectory group proportions that were sufficiently large.

Data are presented as numbers and proportions for categorical variables and as means ± standard deviations or medians (interquartile range) for continuous variables. Differences between groups were analyzed using the χ^2 test or Fisher's exact test and the independent two-sample t-test or Mann–Whitney *U* test with a normal or non-normal distribution, as appropriate.

The normality of the data was assessed by inspecting histograms. For time-to-event analysis, the Kaplan–Meier method was used to estimate survival curves, whereas a log-rank test was used to test the significance of the differences. Univariable and multivariable Cox proportional hazards regression models were used to identify associations with clinical outcomes by adjusting known prognostic covariates, including age, gender, type of admission, type of ICU, vasopressor, and neuromuscular blockade. The results are presented as hazard ratios (HR) with 95% confidence interval (CI). Two-sided *p*-values <0.05 indicated significance. All analyses were performed using SAS (Statistical Analysis System) software version 9.4 (SAS Institute, Cary, NC).

RESULTS

In 20 participating centers, 676 patients were recruited from April 2020 to July 2021 (figure S1). Of them, 45 were excluded because of missing data, an RASS date before mechanical ventilation, or were enrolled ≥48 h after mechanical ventilation. The final cohort included 631 patients. In this study, four-group solutions that best characterized the cohort were identified. A four-group model was chosen for the cohort based on specified selection criteria: trajectory 1 (persistent suboptimal; 13.2% of patients, RASS level ≤ −3 throughout the 30 days), trajectory 2 (delayed lightening; 13.9% of patients, RASS level ≥ −2 after the first 15 days), trajectory 3 (early lightening; 38.4% of patients, RASS level ≥ −2 after the first 7 days), trajectory 4 (persistent optimal: 34.6%, RASS level ≥ −2 during the first 30 days) (figure 1). A large number of patients in the "persistent suboptimal" group were older, with 35.82% in the >80 age group (*p*-value = 0.002) (table 1). Conversely, 39.24% and 40.46% of patients in the "early lightening" and "persistent optimal" groups, respectively, were aged between 50–69 years. Gender and body weight did not significantly differ between the trajectories.

Considering the comorbidities, there was a significant difference in dementia between patients of different trajectories (p-value = 0.010). Although no significant difference was found, the "persistent suboptimal" group had the highest percentage of solid tumor and cerebrovascular disease (38.00%, p-value = 0.278; 28.00%, p-value = 0.101, respectively), whereas the "delayed lightening" group had the lowest percentage of moderate to severe chronic kidney disease (4.61%, p-value = 0.375). The "persistent suboptimal" and "delayed lightening" groups were more likely to be admitted to a medical ICU (52.24% and 48.81% versus 34.72% and 31.63%, respectively) with a medical illness (61.19% and 58.33% versus 46.79% and 43.26%, respectively) and less likely to be admitted to a surgical ICU (44.78% and 50.00% versus 59.25% and 66.05%, respectively; p-value = 0.023) for scheduled surgery (10.45% and 11.90% versus 23.77% and 23.72%, respectively; p-value = 0.001). The most common cause for ICU admission was respiratory (56.8%) in all the groups, and the "delayed lightening" group had the highest proportion for respiratory-related admissions (67.86%), whereas the "early lightening" group had the lowest (51.32%, p-value = 0.030). Cardiovascular-related ICU admissions were most common in the "early lightening" group (25.66%, p-value = 0.610), although there was no statistical significance. The APACHE Ⅱ score was significantly different among the four trajectories (27.82, 25.28, 21.39, and 24.07 for "persistent suboptimal," "delayed lightening," "early lightening," and "persistent optimal" groups, respectively; p-value <0.001). As a part of ICU support within the first 48 h, the "delayed lightening" group received the largest number of vasopressor infusions (91.67%, p-value < 0.001), renal replacement therapy (26.19%, p-value = 0.078), and neuromuscular blockade use (46.43%, p-value < 0.001). In-hospital death occurred in 12.2% patients in the entire cohort. By trajectory, in-hospital mortality was 49.52% in the "persistent suboptimal" group, 21.43% in the "delayed lightening" group, 6.79% in the "early lightening" group, and 3.72% in the

"persistent optimal" group (p-value < 0.001). Similarly, differences according to the trajectories were observed for ICU discharge and extubation. The proportion of ICU discharge was 67.16%, 79.76%, 92.45%, and 92.09%, respectively (p-value < 0.001); rate of extubation was 68.16%, 78.57%, 95.47%, and 95.81%, respectively (p-value < 0.001). Moreover, differences in time to extubation (p-value < 0.001), ICU discharge (p-value < 0.001), and in-hospital mortality (p-value < 0.001) were observed among the four trajectories (figure 2). Table 2 summarizes the representative phenotypes of each trajectory.

In adjusted Cox proportional hazard analyses, the "persistent suboptimal" (HR 13.62, 95% CI 5.99–30.95, p-value < 0.001) and "delayed lightening" groups (HR 5.62, 95% CI 2.36–13.38, p-value < 0.001) had a significantly higher risk of death than the "persistent optimal" group (table 3). The "persistent suboptimal" (HR 0.23, 95% CI 0.16–0.32, p-value < 0.001), "delayed lightening" (HR 0.30, 95% CI 0.23–0.41, p-value < 0.001), and "early lightening" groups (HR 0.72, 95% CI 0.59–0.87, p-value < 0.001) showed a reduced probability of extubation and were less likely to discharge from the ICU (HR 0.36, 95% CI 0.26–0.51, p-value < 0.001; HR 0.44, 95% CI 0.33–0.59, p-value < 0.001; HR 0.80, 95% CI 0.65–0.97, p-value = 0.024, respectively) than the "persistent optimal" group. Patients undergoing scheduled surgery showed a higher probability of extubation (HR 2.13, 95% CI 1.64–2.78, p-value < 0.001) and ICU discharge (HR 2.10, 95% CI 1.59–2.78, p-value < 0.001) than outpatient admissions. Patients in the surgical ICU had a lower risk of death (HR 0.45, 95% CI 0.23–0.89, p-value = 0.021) than medical ICU patients. No additional significant differences were found with respect to age, gender, vasopressor infusions, or neuromuscular blockade.

DISCUSSION

To the best of our knowledge, this is the first study to characterize the longitudinal

pattern of sedation level over time in mechanically ventilated patients. We identified four distinct trajectories of sedation depth over the first 30 days after mechanical ventilation in our subjects. Only 34.6% patients were in an optimal depth of sedation during this period, whereas 13.2% were in the suboptimal range of RASS for most of this time, and the remaining patients achieved adequate depth of sedation 7 (early lightening: 38.4%) or 15 (delayed lightening: 13.9%) days after initiation. Patients who were at suboptimal levels of sedation throughout this period had a higher risk of mortality and lower probabilities of extubation and ICU discharge than those who were in consistently optimal level of sedation.

Group-based trajectory modeling is useful for characterizing longitudinal courses over time to identify distinct subgroups.[21 22] This trajectory model is used in different domains of clinical research, such as nonadherence spectrum in newly-diagnosed juvenile epilepsy, health status in outpatients with heart failure, neurologic postinjury recovery, and symptom burden nuances of patients with metastatic cancer.[20] Therefore, group-based trajectory modeling is a specialized method for sorting individuals into meaningful subgroups that show statistically similar trajectories.

There were several significant differences in characteristics between the four trajectory groups. Patients in trajectory 1 (persistent suboptimal) experienced deep sedation throughout the study period, with RASS ranging from −3 to −5. This group was mainly characterized by elderly patients with cognitive impairment, admitted to a medical ICU for treating illnesses, such as respiratory problems, with the worst condition at admission. Conversely, patients in trajectory 2 (delayed lightening) experienced initial deep sedation, which improved to a light depth of RASS −2 after 15 days. This group was characterized by elderly patients with dementia with respiratory failure, receiving vasopressors, neuromuscular blockade, and renal replacement therapy. Interestingly, although the two trajectories had relatively similar

characteristics and the "delayed lightening" group even required more ICU support within the first 48 h, the "persistent suboptimal" group had worse time to extubation, ICU discharge, and hospital mortality. These findings suggest that the longitudinal course of sedation depth in our subjects was not associated with the severity of illness; the difference in sedation practice between the two trajectories might have resulted into different outcomes.

A prospective multicenter study, conducted across 42 international ICUs, demonstrated that the time to extubation and mortality increased with the sedation intensity.[18] In observational, matched-pair analyses based on the APACHE II score and the type of admission, early deep sedation during the first 48 h of ICU stay was associated with worse outcomes, including long-term mortality.[7] We report similar findings in our study upon comparing trajectories 3 and 4 with the earlier trajectories. Patients in trajectory 3 (early lightening) experienced early deep sedation, which became lighter after 7 days, whereas those in trajectory 4 (persistent optimal) experienced light sedation throughout. Patients in these groups were younger, had fewer medical conditions, and were mostly admitted to surgical ICUs than those in the other two groups. They also had lower APACHE Ⅱ scores and needed lesser ICU support within the first 48 h. Patients in the "early lightening" group, especially, had the lowest APACHE score, the lowest proportion of renal replacement therapy, and the fewest respiratory problems. Nevertheless, multivariable Cox proportional hazard analysis showed that patients in this group had a lower probability of extubation and ICU discharge than those in the "persistent optimal" group. The early practice of inadequate sedation in the "early lightening" group might have induced this relatively worse prognosis in these patients. A recent meta-analysis assessing the literature on early sedation suggested that interventions targeting the depth of early sedation, starting with ICU admission, could improve patient outcomes.[23] Appropriate sedation is a critical aspect in the management of mechanically ventilated patients.

We observed that 65.9% patients in our study were deeply sedated for at least the first week after mechanical ventilation, whereas only 34.07% patients received consistent light sedation throughout the sedation period. This finding is consistent with previous data describing the sedation depth. A multinational survey among intensivists reported that 74% patients monitored using a validated sedation tool were deeply sedated.[24] A survey in Germany found that the actual depth of sedation was significantly deeper (39.5%–62.4%) than the desired depth in all categories of sedation.[25] A Swedish study investigating the relationship between memory and sedation showed that only 39% of ventilated patients achieved their target sedation goal.[26] A previous systematic review estimated the incidence of over-sedation in ICUs at 40%–60%, despite the poor quality of epidemiologic data.[2] In a recent study conducted in the emergency department, the incidence of deep sedation was 52.8%.[27] These data suggest that deep sedation remains a common real-world ICU practice. To improve the quality of patient care, further research is warranted focusing on the longitudinal profile in addition to the binary concept of sedation, light versus deep.

Our study has a few limitations. First, information bias may exist because only patients visiting tertiary or university-affiliated hospitals were included in our study. Second, unmeasured confounders could have affected the trajectories, despite many relevant variables in our study. Moreover, nondifferential group of patients may have been misclassified. This restriction is inherent to group-based trajectory models with limited generalizability. Third, the causal relationship between trajectory and outcome could not be established in this study. For example, it is unclear whether a prolonged duration of extubation reflected the effects of sedative overdose, or whether more sedation was needed because of longer mechanical ventilation. However, the strength, consistency, temporal precedence of the association and agreement with existing evidence of this study suggested the possibility of causal

relationship.[28] Thus, prospective and randomized controlled studies are required to investigate the interaction of two parameters (depth and duration) of sedation to better define the optimal practice. Fourth, there was a restriction on recruiting patients due to corona-19 crisis. Although the number of patients with mechanical ventilation increased in the corona-19 era, the lack of man-power in the ICU led to a low rate of registration. Finally, we were unable to examine the long-term complications in the trajectory groups. Further nationwide studies should evaluate long-term complications after sedation to comprehensively understand its socioeconomic and clinical burden.

In conclusion, this study captured the four trajectories of sedation level over time in mechanically ventilated patients. The patterns were significantly associated with time to extubation, ICU discharge, and hospital mortality. Our findings suggest sedation strategy in ICU patient needs to incorporate a longitudinal pattern of sedation level.

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Contributors

CML, HYG, JHA have contributed to the study conception and design. Material preparation was performed by HYG. Data collection was performed DH, JHA, CML. Statistical analysis were performed by CMN and CY. The first draft of the manuscript was written by DH and JHA, and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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Competing Interests

Ha-Yeong Gil is an employee of Pfizer Korea. The other authors declare that they have no competing interests. The Pfizer Korea, sponsor of the present study, made no influence on study design, data collection and analysis, and writing.

Patient consent for publication

Not applicable.

Ethic approval

The study protocol was approved by the Institutional Review Boards of all participating medical centers (B-1911/577-405, AJIRB-MED-OBS-19-372, AJIRB-MED-OBS-19-373, 1908-156-1058, 1908-157-1058, 1910-003-083, 2019-1624, 2019-1039, 2019-10-0321, 2019-09-040, 2019-10-162, GCIRB2019-366, DSMC 2019-08-018, HALLYM 2019-08-021, HALLYM 2019-08-022, 2019-09-010, 2019-08-082, DAUHIRB-19-166, 4-2019-0821, 4-2019-0820, 2019-09-011-002, 2019-07-038-002, CR-19-117-L, 2019AN0376, 2019AN0478, 20-2019-92, 20-2019-91, 2019GR0461, 2020GR0103, 2020AS0054). All patients (or patient representatives) provided their written informed consent. Some participating centers' local review boards waived the need for informed consent considering the observational nature of the study. This study was conducted per the amended Declaration of Helsinki.

Data Availability statement

Data are available on request

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Figure Legends

Figure 1 Trajectories of longitudinal Richmond Agitation Sedation Scale in the first 30 days of sedation for mechanical ventilation. The percentage of patients included in each trajectory were presented in central illustration. Outcome of y-axis indicates the score of richmond agitation sedation scale and T of x-axis represents day after the initiation of sedation.

Figure 2 Kaplan-Meier of clinical outcomes from admission according to the trajectory groups. (a) time to extubation in the intensive care unit, (b) length of stay in the intensive care unit, (c) in-hospital mortality.

Table 1 Baseline Characteristics and Clinical Outcomes for the Total Cohort and for Each Trajectory of the Richmond Agitation-Sedation Scale

		Trajectory group				
Characteristic	All (N = 631)	1 (N = 67)	2 (N = 84)	3 (N = 265)	4 (N = 215)	*p*-value
Age						0.002
20–29	11 (1.74%)	0 (0.00%)	2 (2.38%)	6 (2.26%)	3 (1.40%)	
30–39	34 (5.39%)	0 (0.00%)	2 (2.38%)	12 (4.53%)	20 (9.30%)	
40–49	44 (6.97%)	3 (4.48%)	11 (13.10%)	13 (4.91%)	17 (7.91%)	
50–59	92 (14.58%)	6 (8.96%)	6 (7.14%)	44 (16.60%)	36 (16.74%)	
60–69	140 (22.19%)	12 (17.91%)	17 (20.24%)	60 (22.64%)	51 (23.72%)	
70–79	177 (28.05%)	22 (32.84%)	23 (27.38%)	80 (30.19%)	52 (24.19%)	
≥80	133 (21.08%)	24 (35.82%)	23 (27.38%)	50 (18.87%)	36 (16.74%)	
Male gender	404 (64.0)	44 (65.67)	57 (67.86)	165 (62.26)	138 (64.19)	0.807
Body weight, kg*	62.0 (53.0-71.0)	62.25 ± 10.69	62.81 ± 13.31	62.51 ± 13.01	63.79 ± 17.62	0.785
Comorbidity	448 (71.00)	50 (74.62)	65 (77.38)	183 (69.05)	150 (69.76)	0.434
Diabetes with end-organ damage	30 (4.31)	2 (4.00)	2 (3.07)	14 (7.65)	12 (8.00)	0.573
COPD	60 (8.6)	7 (14.00)	8 (12.30)	25 (13.66)	20 (13.33)	0.994
Congestive heart failure	49 (7.0)	3 (6.00)	7 (10.76)	19 (10.38)	20 (13.33)	0.596
Moderate-to-severe liver disease**	27 (3.8)	3 (6.00)	3 (4.61)	9 (4.91)	12 (8.00)	0.681
Moderate-to-severe CKD**	46 (6.6)	5 (10.00)	3 (4.61)	18 (9.83)	20 (13.33)	0.375
Solid tumor	127 (18.2)	19 (38.00)	15 (23.07)	48 (26.22)	45 (30.00)	0.278
Dementia	35 (5.0)	6 (12.00)	9 (13.84)	16 (8.74)	4 (3.00)	0.010
Cerebrovascular disease/TIA	82 (11.7)	14 (28.00)	14 (21.53)	28 (15.30)	26 (17.33)	0.101
Type of admission						0.023
Medical	307 (48.6)	41 (61.19)	49 (58.33)	124 (46.79)	93 (43.26)	
Emergency surgery	193 (30.5)	19 (28.36)	25 (29.76)	78 (29.43)	71 (33.02)	
Scheduled surgery	131 (20.7)	7 (10.45)	10 (11.90)	63 (23.77)	51 (23.72)	
Type of ICU						0.001
Medical ICU	236 (37.4)	35 (52.24)	41 (48.81)	92 (34.72)	68 (31.63)	
Surgical ICU	371 (58.8)	30 (44.78)	42 (50.00)	157 (59.25)	142 (66.05)	

Others	24 (3.8)	2 (2.99)	1 (1.19)	16 (6.04)	5 (2.33)	
Reason for ICU admission***						
Renal	16 (2.5)	1 (1.49)	0 (0.00)	7 (2.64)	8 (3.72)	0.294
Digestive	83 (13.1)	10 (14.93)	12 (14.29)	28 (10.57)	33 (15.35)	0.434
Cardiovascular	147 (23.3)	15 (22.39)	16 (19.05)	68 (25.66)	48 (22.33)	0.610
Hematologic	14 (2.2)	2 (2.99%)	3 (3.57%)	4 (1.51%)	5 (2.33%)	0.679
Respiratory	359 (56.8)	43 (64.18%)	57 (67.86%)	136 (51.32%)	123 (57.21%)	0.030
Miscellaneous	67 (10.6)	3 (4.48%)	11 (13.10%)	34 (12.83%)	19 (8.84%)	0.152
Neurologic	12 (1.9)	3 (4.48%)	1 (1.19%)	4 (1.51%)	4 (1.86%)	0.418
Others	105 (16.6)	11 (16.42%)	13 (15.48%)	42 (15.85%)	39 (18.14%)	0.907
APACHE Ⅱ, score*	23.4 ± 10.0	27.82 ± 9.73	25.28 ± 11.45	21.39 ± 9.59	24.07 ± 9.56	< 0.001
ICU support within first 48 hours						
Vasopressor infusions	486 (77.02)	57 (85.07)	77 (91.67)	199 (75.09)	153 (71.16)	< 0.001
Renal replacement	107 (16.9)	11 (16.42)	22 (26.19)	37 (13.96)	37 (17.21)	0.078
Neuromuscular blockade	171 (27.1)	27 (40.30)	39 (46.43)	69 (26.04)	36 (16.74)	< 0.001
Clinical outcomes						
In-hospital mortality	77 (12.2)	33 (49.52)	18 (21.43)	18 (6.79)	8 (3.72)	< 0.001
ICU discharge	555 (87.9)	45 (67.16)	67 (79.76)	245 (92.45)	198 (92.09)	< 0.001
Extubation	571 (90.4)	46 (68.66)	66 (78.57)	253 (95.47)	206 (95.81)	< 0.001
Length of ventilator support, days	5 (3–11)	11 (20–NE)	11.5 (7–23.5)	5 (3–8)	3 (2–5)	< 0.001
ICU length of stay, days	10 (5–18)	20 (12–NE)	18 (10–26)	9 (6–14)	4 (6–10)	< 0.001

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and number (percentage) for categorical variables.
*Data on body weight are presented for all 605 patients, excluding 26 patients with missing data (4 in the light sedation group and 22 in the deep sedation group). Data on APACHE Ⅱ are presented for all 577 patients, excluding 54 patients with missing data (15 in the light sedation group and 39 in the deep sedation group).
**Severe to moderate liver disease are defined as cirrhosis and portal hypertension with or without variceal bleeding history. Severe to moderate CKD are defined as serum creatinine > 3 mg/dL or on dialysis or post-kidney transplant status or uremia status.
***172 patients had multiple reasons for ICU admission.
ICU = intensive care unit; SMD = standardized mean difference; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; TIA = transient ischemic attack; APACHE Ⅱ = acute physiology and chronic health evaluation Ⅱ; NE = not estimated

Table 2 Summary of the demographics of the trajectories and the trajectory ranks for characteristics

	Trajectory 1	**Trajectory 2**	**Trajectory 3**	**Trajectory 4**
Demographics				
Age	70–79 & ≥80	70–79 & ≥80	60–69 & 70–-79	60–69 & 70–-79
Gender	Male	Male	Male	Male
Comorbidity	Solid tumor, CVD/TIA, COPD	Solid tumor, CVD/TIA, Dementia	Solid tumor, CVD/TIA, COPD	Solid tumor, CVD/TIA, COPD
Type of ICU	Medical ICU	Surgical ICU	Surgical ICU	Surgical ICU
Reason for ICU admission	Respiratory & Cardiovascular	Respiratory & Cardiovascular	Respiratory & Cardiovascular	Respiratory & Cardiovascular
Ranks for characteristics				
Medical admission	1st	2nd	3rd	4th
Scheduled surgery	4th	3rd	2nd	1st
APACHE Ⅱ	1st	2nd	4th	3rd
Vasopressor infusions	2nd	1st	3rd	4th
Renal replacement therapy	3rd	1st	4th	2nd
Neuromuscular blockade	2nd	1st	3rd	4th

Representative demographics with more than half of the patients on each trajectory, except age on trajectory 4, are shown in the table. Rank-order of trajectories was determined by the comparison of proportion of variable within each trajectory. Trajectories are ordered from lowest (4th) to highest (1st) rank values.
ICU = intensive care unit; APACHE Ⅱ = acute physiology and chronic health evaluation Ⅱ; CVD = cardiovascular disease; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

Table 3 Multivariable Cox Proportional Hazard regression models of time to event

	Time to extubation		Time to ICU discharge		Time to in-hospital death	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Trajectory group						
Group 1	0.23 (0.16–0.32)	< 0.001	0.36 (0.26–0.51)	< 0.001	13.62 (5.99–30.95)	< 0.001
Group 2	0.30 (0.23–0.41)	< 0.001	0.44 (0.33–0.59)	< 0.001	5.62 (2.36–13.38)	< 0.001
Group 3	0.72 (0.59–0.87)	< 0.001	0.80 (0.65–0.97)	0.024	1.76 (0.76–4.08)	0.185
Group 4	Reference		Reference		Reference	
Age						
20–29	Reference		Reference		Reference	
30–39	1.08 (0.53–2.21)	0.825	0.70 (0.35–1.42)	0.334	0.69 (0.06–7.72)	0.765
40–49	0.89 (0.43–1.81)	0.748	0.63 (0.31–1.25)	0.188	0.59 (0.06–5.28)	0.641
50–59	1.04 (0.53–2.03)	0.893	0.65 (0.34–1.23)	0.192	0.41 (0.04–3.46)	0.414
60–69	1.00 (0.52–1.93)	0.987	0.79 (0.42–1.48)	0.469	0.88 (0.11–6.75)	0.905
70–79	1.04 (0.54–1.99)	0.893	0.64 (0.34–1.20)	0.170	0.47 (0.06–3.65)	0.473
≥80	0.85 (0.44–1.64)	0.632	0.53 (0.28–1.00)	0.052	0.82 (0.10–6.26)	0.850
Female	0.85 (0.71–1.01)	0.075	0.98 (0.81–1.17)	0.848	1.17 (0.73–1.89)	0.50
Type of admission						
Medical	Reference		Reference		Reference	
Emergency surgery	1.02 (0.79–1.32)	0.839	1.17 (0.90–1.53)	0.234	1.35 (0.62–2.91)	0.444
Scheduled surgery	2.13 (1.64–2.78)	< 0.001	2.10 (1.59–2.78)	< 0.001	1.91 (0.87–4.16)	0.102
Type of ICU						
Medical ICU	Reference		Reference		Reference	
Surgical ICU	1.05 (0.83–1.33)	0.629	0.87 (0.68–1.12)	0.299	0.45 (0.23–0.89)	0.021
Others	1.53 (0.96–2.40)	0.068	1.28 (0.80–2.06)	0.289	0.55 (0.12–2.47)	0.441
Vasopressor infusions	0.85 (0.69–1.04)	0.116	0.85 (0.69–1.04)	0.122	1.25 (0.62–2.51)	0.529
Neuromuscular blockade	1.05 (0.86–1.28)	0.586	0.88 (0.72–1.07)	0.217	1.42 (0.88–2.29)	0.148

Hazard ratio > 1 indicates a higher probability of event than reference.

ICU = intensive care unit; HR hazard ratio = CI confidence interval.

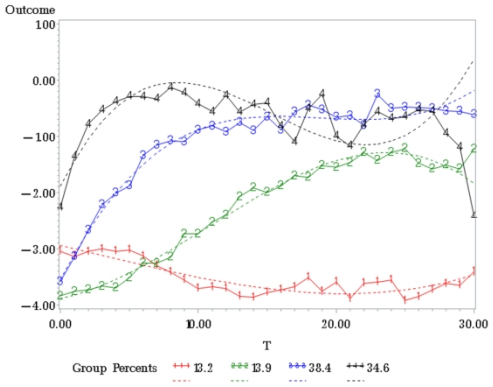

Figure 1 Trajectories of longitudinal Richmond Agitation Sedation Scale in the first 30 days of sedation for mechanical ventilation. The percentage of patients included in each trajectory were presented in central illustration. Outcome of y-axis indicates the score of richmond agitation sedation scale and T of x-axis represents day after the initiation of sedation.

338x190mm (200 x 200 DPI)

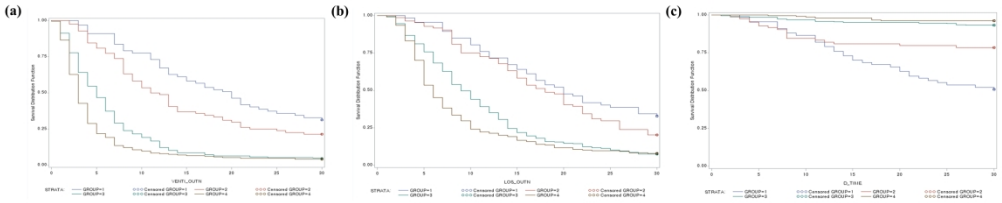

Figure 2 Kaplan-Meier of clinical outcomes from admission according to the trajectory groups. (a) time to extubation in the intensive care unit, (b) length of stay in the intensive care unit, (c) in-hospital mortality.

338x190mm (200 x 200 DPI)

Longitudinal trajectories of sedation level and clinical outcomes in mechanically ventilated patients: a prospective, multicenter, longitudinal, observational study

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Table S1. Participating intensive care units

City	Participating hospitals	Investigators
Seoul	Asan Medical Center	Dong-gon Hyun, Jee Hwan Ahn, Suk-Kyung Hong, Chae-Man Lim
Seoul	Seoul National University Hospital	Sang-Min Lee, Ho-Geol Ryu
Seoul	Samsung Medical Center	Gee Young Suh, Chi Min Park
Seoul	Severance Hospital	Su Hwan Lee, Jeoung Min Kim
Seoul	Seoul St. Mary's Hospital	Seok Chan Kim
Seoul	Korea University Anam Hospital	Won Jai Jung, Jae-Myeong Lee
Seoul	Korea University Guro Hospital	Young-Seok Lee, Nak-Jun Choi
Seoul	Seoul National University Boramae Medical Center	Taeyun Park
Seongnam	Seoul National University Bundang Hospital	Dong Jung Kim
Suwon	Ajou University School of Medicine	Keu Sung Lee, Young-Gi Min
Busan	Pusan National University Hospital	Jae Hun Kim
Busan	Dong-A University Hospital	Dong-Hyun Lee
Busan	Inje University Haeundae Paik Hospital	Hang-Jea Jang, Ki Hoon Kim
Wonju	Yonsei University Wonju College of Medicine	Seok Jeong Lee
Incheon	Gachon University Gil Medical Center	Woo-Sung Choi
Daegu	Keimyung University School of Medicine	Jae-Bum Kim
Daegu	Yeungnam University Medical Center	Eun Young Choi, Jong-Hyun Baek
Daegu	Daegu Catholic University Medical Center	Eun Jin Kim
Anyang	Hallym University Sacred Heart Hospital	Sunghoon Park, Hyung Won Kim
Ansan	Korea University Ansan Hospital	Je Hyeong Kim

Table S2. Profile of analgesic and sedative within the first 48 hours

Type of Sedatives	N = 662
Diazepam	1 (0.2)
Cumulative dose (µg)	2000.0
Midazolam	127 (19.2)
Cumulative dose (µg)	64253.9 ± 133338.1
Lorazepam	14 (2.1)
Cumulative dose (µg)	2750 ± 1868.3
Other benzodiazepine	19 (2.9)
Cumulative dose (µg)	34294.7 ± 53960.7
Propofol	173 (26.1)
Cumulative dose (µg)	3444220.1 ± 2752320.0
Ketamine	53 (8.0)
Cumulative dose (µg)	1450147.2 ± 1830958.4
Haloperidol	1 (0.2)
Cumulative dose (µg)	5000.0
Dexmedetomidine	253 (38.2)
Cumulative dose (µg)	4080.2 ± 38325.4
Other non-benzodiazepine	21 (3.2)
Cumulative dose (µg)	75659.5 ± 133078.2
Type of analgesics	N = 528
Fentanyl	119 (22.5)
Cumulative dose (µg)	30861.1 ± 315168.1
Remifentanil	388 (73.5)
Cumulative dose (µg)	13227.8 ± 10971.7
Morphine	6 (1.1)
Cumulative dose (µg)	24000.0 ± 38740.2
Sufentanil	15 (2.8)
Cumulative dose (µg)	285.4 ± 280.6

Data are reported as means ± standard deviation for continuous variables and numbers (percentage) for categorical variables.
RASS = Richmond agitation-sedation scale

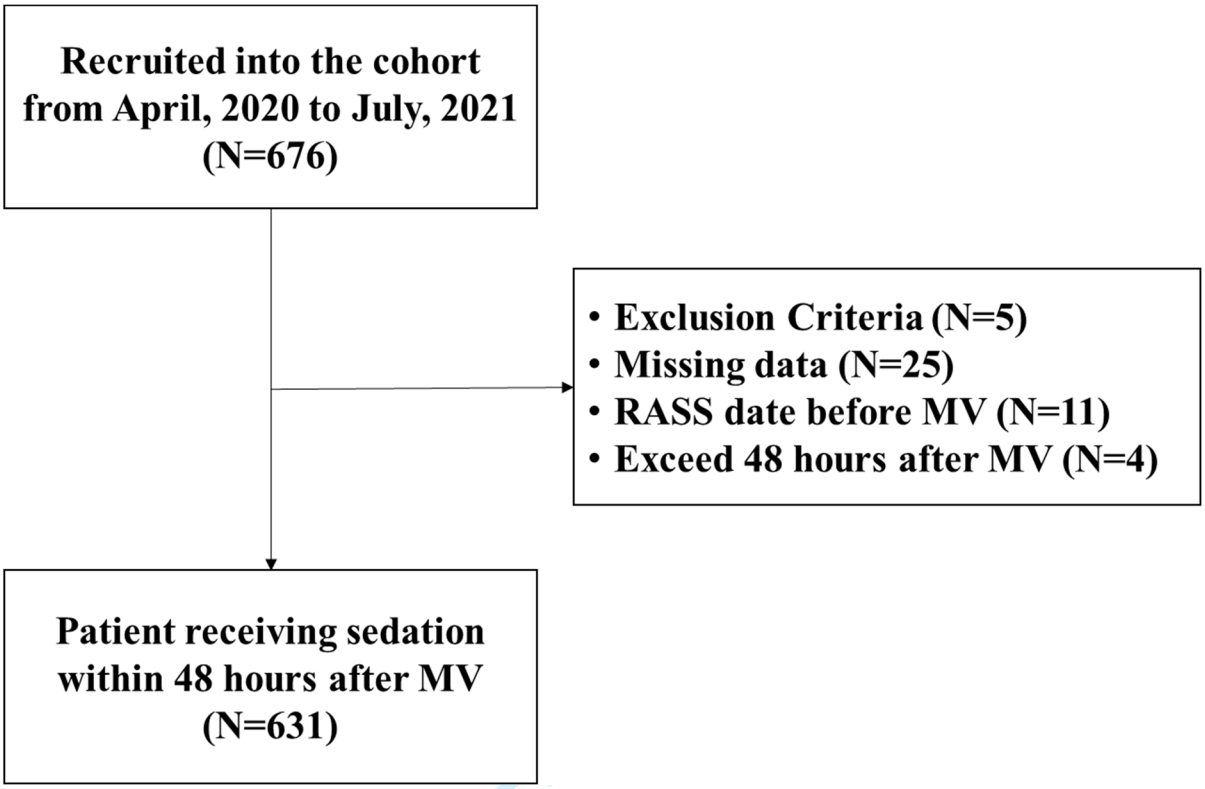

Figure S1. Flow diagram of patients in the present study.
MV = mechanical ventilation; RASS = Richmond agitation-sedation scale

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Longitudinal trajectories of sedation level and clinical outcomes in patients who are mechanically ventilated based on a group-based trajectory model: a prospective, multicenter, longitudinal, and observational study in Korea

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Word Count: 3201

ABSTRACT

Objectives: Changes in sedation levels over a long time in patients who are mechanically ventilated are unknown. Therefore, we investigated the long-term sedation levels of these patients by classifying them into different longitudinal patterns.

Design: This was a multicenter, prospective, longitudinal, and observational study.

Setting: Twenty intensive care units (ICUs) spanning several medical institutions in Korea.

Participants: Patients who received mechanical ventilation and sedatives in ICU within 48 h of admission between April 2020 and July 2021.

Primary and secondary outcome measures: The primary objective of this study was to identify the pattern of sedation practice. Additionally, we analyzed the associations of trajectory groups with clinical outcomes as the secondary outcome.

Results: Sedation depth was monitored using Richmond agitation-sedation scale (RASS). A group-based trajectory model was used to classify 631 patients into four trajectories based on sedation depth: persistent suboptimal (13.2%, RASS ≤ −3 throughout the first 30 days), delayed lightening (13.9%, RASS ≥ −2 after the first 15 days), early lightening (38.4%, RASS ≥ −2 after the first 7 days), and persistent optimal (34.6%, RASS ≥ −2 during the first 30 days). “Persistent suboptimal” trajectory was associated with delayed extubation (hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.16–0.32, $p < 0.001$), longer ICU stay (HR 0.36, 95% CI 0.26–0.51, $p < 0.001$), and hospital mortality (HR 13.62, 95% CI 5.99–30.95, $p < 0.001$) compared with “persistent optimal”. The “delayed lightening” and “early lightening” trajectories showed lower extubation probability (HR 0.30, 95% CI 0.23–0.41, $p < 0.001$; HR 0.72, 95% CI 0.59–0.87, $p < 0.001$, respectively) and ICU discharge (HR 0.44, 95% CI 0.33–0.59; $p < 0.001$ and HR 0.80, 95%CI 0.65–0.97; $p = 0.024$) compared with “persistently optimal.”

Conclusions: Among the four trajectories, "persistent suboptimal" trajectory was associated with higher mortality.

Keywords: deep sedation; intensive care units; mortality; critical care; mechanical ventilators

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large national data from 20 ICUs in Korea representing real-world practice

⇒ An investigation into the long-term sedation level in patients who are mechanically ventilated

⇒ A group-based trajectory model identifying patterns of sedation over time

⇒ Misclassification of nondifferential group as inherent restriction of group-based trajectory models with limited generalizability

⇒ Unclear causal relationship between trajectory and outcome

INTRODUCTION

Sedation is crucial to promote tolerance in patients during mechanical ventilation in the intensive care unit (ICU).[1] Previously, ICU patients were considered unnecessarily oversedated, and the tools to assess the depth of sedation varied widely.[2] Inappropriate sedation was associated with adverse outcomes, such as prolonged ventilation, longer ICU stay, and higher post-ICU psychological concerns.[3-6] Over-sedation also predicted long-term mortality in critically ill patients.[7] Considering its essential role in the care of patients who were mechanically ventilated, international guidelines guide to improve sedation practice for favorable outcomes in ICU patients.[8-10]

Currently, sedation monitoring in the ICU is clinically recommended to achieve low levels of sedation,[11] though real-world implementation is debated.[12] Longitudinal studies on the level of sedation over a long time are limited. Previous national surveys mainly focused on the type of sedatives and assessment tools.[13-16] Moreover, most studies are cross-sectional, evaluating the association between the sedation levels for the first 2–3 days and clinical outcomes.[17 18] Therefore, we aimed to investigate long-term sedation levels in a national cohort of patients who were mechanically ventilated by classifying them into different longitudinal patterns. We further assessed the association between these patterns and clinical outcomes.

METHODS AND ANALYSIS

Study design

We conducted a multicenter, prospective, longitudinal, and observational cohort study in 20 ICUs in Korea between April 2020 and July 2021, sponsored by Pfizer Korea Pharmaceuticals Ltd. and involved 30 investigators (Table S1). We designed a harmonized

electric case report form that was centrally managed and combined into one database for data entry, day queries, and analysis. During the study period, patients were recruited according to the number of available patients at each ICU. Principal investigators, research staff, and nurses at each participating center were trained in the study procedures. The decisions regarding a patient's care were at the discretion of the attending medical staff. Our inclusion criteria were as follows: patients >19 years of age, who had undergone mechanical ventilation and sedation in the ICU within 48 h and were expected to remain sedated and on mechanical ventilation for >48 h. We excluded patients with a disease that was likely to cause death within 90 days, those whose treatment had been discontinued owing to imminent death or noneffective therapy, and those who needed nonselective deep sedation owing to medical conditions, including brain damage and hemorrhage, spinal cord injury, drug overdose, burns, and nerve root block.

Monitoring of sedation and measurement of outcome

We monitored sedation depth using the Richmond agitation-sedation scale (RASS), ranging from −5 to +4 every 8 h until ICU discharge or day 30.[19] The daily depth of sedation was calculated as the median RASS value for 1 day. The primary objective of this study was to identify the pattern of sedation practice. Group-based trajectory models have been widely used for analyzing developmental trajectories.[20] They can address the dynamic profile of sedation by classifying patients into different trajectories of sedation level over time. We used a group-based trajectory model analyzing a scale form of RASS over the first 30 days after enrollment. To characterize each trajectory group, an analysis between the trajectory groups and the patients' characteristics was also performed. The secondary objective included associations of trajectory groups with clinical outcomes by adjusting for covariates.

Covariates

Demographic, clinical, and laboratory data, including age, gender, reason for ICU admission, type of ICU admission, comorbidities, and illness severity (acute physiology and chronic health evaluation [APACHE] Ⅱ score), were collected. Moderate-to-severe liver disease was defined as cirrhosis and portal hypertension with or without variceal bleeding history. Moderate-to-severe chronic kidney disease was defined as serum creatinine >3 mg/dL or on dialysis or post-kidney transplant status or uremia status. The need for vasopressors, renal replacement therapy, and neuromuscular blockade was also recorded. We collected and calculated the daily cumulative dose and the number of days prescribed for the sedatives and analgesics administered to patients during their ICU stay. Patients were followed-up until hospital discharge, death, or day 30 in the ICU. Clinical outcomes, including ICU discharge, ventilator days, and survival status, were recorded.

Patient and public involvement

The patient and public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Sample size

The sample size was initially calculated for the study to evaluate the difference in ICU lengths of stay between patients with early deep sedation and with early light sedation.[21] Considering previous results reporting that the hazard ratio (HR) of ICU length between the sedation group (n = 70) and non-sedation group (n =70) was 1.86 (95% CI 1.05–3.23), the following values were required to calculate the number of subjects:$\widehat{S_{Deep\ Sedation}} = e^{-\lambda_{Deep} * t}$

$= e^{-0.03 * 28} = 0.43$, $S_{\widehat{Light\ Sedation}} = e^{-\lambda_{Light} * t} = e^{-0.02 * 28} = 0.57$, and HR = 1.5.[22] The importance of the two-sided test was set at 5%, the power was 80%, and the ratio between the light and deep sedation groups was set at 3:7. The sample size was inflated by approximately 30% to account for attrition. No interim efficacy analyses were planned. Finally, 660 patients were planned. Thereafter, this study to classify the pattern of sedation over time was conducted by using this sample.

Statistical analysis

The pattern of sedation over time was described using a group-based trajectory model that identified differential patterns of individual change in the population. The parameters of GBTM are generated by maximum likelihood estimation. The ultimate objective is to estimate a set of parameters, Ω, that maximize the probability of $Y_i = (y_{i1},...,y_{it})$. The equation describing the likelihood of an individual's observed repeated measures comprises two elements: (1) the probability of group membership and (2) the probability of the observed data given group membership. The finite mixture model is defined by

$$P(Y_i) = \sum_k \pi_k P^k(Y_i),$$

where k: trajectory group, i $(= 1,...,N)$: subject, and j $(= 1,...,T)$: measurement time. The group membership probabilities,

$$\pi_k = e^{\theta_k} / \sum_k e^{\theta_k}$$

$k = 1,...,K$, are not observed, so estimated by a multinomial logit function. For a given k, conditional independence is assumed for the sequential realizations of the elements of Y_i, y_{ij}, over the T periods of measurement. This assumption implies that for each individual within a given trajectory group k, the distribution of y_{ij} for period T is independent of the realized

level of the outcome in prior periods. The likelihood function is $L = \prod_{i=1}^{N} P(y_i|z_i, w_i)$ where $p(y_i|z_i, w_i) = \sum_{k=1}^{K} p(C_i = k \mid Z_i = z_i) p(Y_i = y_i \mid C_i = k, W_i = w_i)$; the first term is the probability of group membership and the second term is the probability of the observed data given group membership. $Y_i = (Y_{i1},...,Y_{iT}), Z_i = (Z_{i1},...,Z_{iR}), W_i = (W_{i1},...,W_{iT}), p = \frac{\exp(\theta_k + \lambda_k' z_i)}{\sum_{k=1}^{K} \exp(\theta_k + \lambda_k' z_i)}, and\ p(Y_i = y_i \mid C_i = k, W_i = w_i)$, which is specified by the distribution of Y_i. For count data, it is specified as the zero-inflated Poisson distribution, for censored data, the censored normal distribution and for binary data, it is specified as the binary logit distribution for binary data. In this study, we use a censored normal model. The final model was selected based on a combination of the Bayesian information criterion and the estimated trajectory group proportions that were sufficiently large.

Data are presented as numbers and proportions for categorical variables and as means ± standard deviations or medians (interquartile range) for continuous variables. Differences between groups were analyzed using the χ^2 test or Fisher's exact test and the independent two-sample t-test or Mann–Whitney *U* test with a normal or non-normal distribution, as appropriate. The normality of the data was assessed by inspecting histograms. For time-to-event analysis, the Kaplan–Meier method was used to estimate survival curves, whereas a log-rank test was used to test the importance of the differences. Univariable and multivariable Cox proportional hazards regression models were used to identify associations with clinical outcomes by adjusting known prognostic covariates, including age, gender, type of admission, type of ICU, vasopressor, and neuromuscular blockade. The results are presented as HR with 95% confidence interval (CI). Two-sided *p*-values <0.05 indicated significance. All analyses were performed using Statistical Analysis System (SAS) software version 9.4 (SAS Institute, Cary, NC).

RESULTS

In 20 participating centers, 676 patients were recruited from April 2020 to July 2021 (Figure S1). Of them, 45 patients were excluded because of missing data, an RASS date before mechanical ventilation, or were enrolled ≥48 h after mechanical ventilation. The final cohort included 631 patients. In this study, four-group solutions that best characterized the cohort were identified. A four-group model was chosen for the cohort based on specified selection criteria: trajectory 1 (persistent suboptimal; 13.2% of patients, RASS level ≤ −3 throughout the 30 days), trajectory 2 (delayed lightening; 13.9% of patients, RASS level ≥ −2 after the first 15 days), trajectory 3 (early lightening; 38.4% of patients, RASS level ≥ −2 after the first 7 days), and trajectory 4 (persistent optimal: 34.6%, RASS level ≥ −2 during the first 30 days) (Figure 1). The majority of patients in "persistent suboptimal" group were older, with 35.82% in the >80 age group (p-value = 0.002) (Table 1). Conversely, 39.24% and 40.46% of patients in the "early lightening" and "persistent optimal" groups, respectively, were aged between 50 and 69 years. Gender and body weight did not considerably differ between the trajectories. Considering the comorbidities, there was a significant difference in dementia between patients of different trajectories (p-value = 0.010). Although no significant difference was found, the "persistent suboptimal" group had the highest percentage of solid tumor and cerebrovascular disease (38.00%, p-value = 0.278; 28.00%, p-value = 0.101, respectively), whereas the "delayed lightening" group had the lowest percentage of moderate-to-severe chronic kidney disease (4.61%, p-value = 0.375). The "persistent suboptimal" and "delayed lightening" groups were more likely to be admitted to medical ICU (52.24% and 48.81% versus 34.72% and 31.63%, respectively) with a medical illness (61.19% and 58.33% versus 46.79% and 43.26%, respectively) and less likely

to be admitted to surgical ICU (44.78% and 50.00% versus 59.25% and 66.05%, respectively; *p*-value = 0.023) for a scheduled surgery (10.45% and 11.90% versus 23.77% and 23.72%, respectively; *p*-value = 0.001). The most common cause of ICU admission was respiratory (56.8%) in all groups, and the "delayed lightening" group had the highest proportion of respiratory-related admissions (67.86%), whereas the "early lightening" group had the lowest proportion (51.32%, *p*-value = 0.030). Cardiovascular-related ICU admissions were most common in the "early lightening" group (25.66%, *p*-value = 0.610), although there was no statistical significance. The APACHE Ⅱ score was significantly different among the four trajectories (27.82, 25.28, 21.39, and 24.07 for "persistent suboptimal," "delayed lightening," "early lightening," and "persistent optimal" groups, respectively; *p*-value < 0.001). As a part of ICU support within the first 48 h, the "delayed lightening" group received the largest number of vasopressor infusions (91.67%, *p*-value < 0.001), renal replacement therapy (26.19%, *p*-value = 0.078), and neuromuscular blockade use (46.43%, *p*-value < 0.001). In-hospital death occurred in 12.2% of patients in the entire cohort. By trajectory, in-hospital mortality was 49.52% in the "persistent suboptimal" group, 21.43% in the "delayed lightening" group, 6.79% in the "early lightening" group, and 3.72% in the "persistent optimal" group (*p*-value < 0.001). Similarly, differences according to the trajectories were observed for ICU discharge and extubation. The proportion of ICU discharge was 67.16%, 79.76%, 92.45%, and 92.09%, respectively (*p*-value < 0.001); rate of extubation was 68.16%, 78.57%, 95.47%, and 95.81%, respectively (*p*-value < 0.001). Moreover, differences in time to extubation (*p*-value < 0.001), ICU discharge (*p*-value < 0.001), and in-hospital mortality (*p*-value < 0.001) were observed among the four trajectories (Figure 2). Table 2 summarizes the representative phenotypes of each trajectory.

In adjusted Cox proportional hazard analyses, the "persistent suboptimal" (HR =

13.62, 95% CI 5.99–30.95, *p*-value < 0.001) and "delayed lightening" groups (HR = 5.62, 95% CI 2.36–13.38, *p*-value < 0.001) had a significantly higher risk of death than the "persistent optimal" group (Table 3). The "persistent suboptimal" (HR = 0.23, 95% CI 0.16–0.32, *p*-value < 0.001), "delayed lightening" (HR = 0.30, 95% CI 0.23–0.41, *p*-value < 0.001), and "early lightening" groups (HR = 0.72, 95% CI 0.59–0.87, *p*-value < 0.001) showed a reduced probability of extubation and were less likely to discharge from the ICU (HR = 0.36, 95% CI 0.26–0.51, *p*-value < 0.001; HR = 0.44, 95% CI 0.33–0.59, *p*-value < 0.001; HR = 0.80, 95% CI 0.65–0.97, *p*-value = 0.024, respectively) than the "persistent optimal" group. Patients undergoing scheduled surgery showed a higher probability of extubation (HR = 2.13, 95% CI 1.64–2.78, *p*-value < 0.001) and ICU discharge (HR = 2.10, 95% CI 1.59–2.78, *p*-value < 0.001) than outpatient admissions. Patients in the surgical ICU had a lower risk of death (HR = 0.45, 95% CI 0.23–0.89, *p*-value = 0.021) than medical ICU patients. No additional considerable differences were found with respect to age, gender, vasopressor infusions, or neuromuscular blockade.

DISCUSSION

To the best of our knowledge, this is the first study to characterize the longitudinal pattern of sedation level over time in patients who are mechanically ventilated. We identified four distinct trajectories of sedation depth in the first 30 days after mechanical ventilation in our patients. Only 34.6% patients were in an optimal depth of sedation during this period, whereas 13.2% were in the suboptimal range of RASS for most of this time, and the remaining patients achieved adequate depth of sedation 7 (early lightening: 38.4%) or 15 (delayed lightening: 13.9%) days after initiation. Patients who were at suboptimal levels of sedation throughout this period had a higher risk of mortality and lower probabilities of

extubation and ICU discharge than those who were at consistently optimal levels of sedation.

Group-based trajectory modeling is useful for characterizing longitudinal courses over time to identify distinct subgroups.[23 24] This trajectory model is used in different domains of clinical research, such as nonadherence spectrum in newly-diagnosed juvenile epilepsy, health status in outpatients with heart failure, neurologic postinjury recovery, and symptom burden nuances of patients with metastatic cancer.[20] Therefore, group-based trajectory modeling is a specialized method for sorting individuals into meaningful subgroups that show statistically similar trajectories.

There were several considerable differences in characteristics between the four trajectory groups. Patients in trajectory 1 (persistent suboptimal) experienced deep sedation throughout the study period, with RASS ranging from −3 to −5. This group was mainly characterized by elderly patients with cognitive impairment, admitted to a medical ICU for treating illnesses, such as respiratory problems, with the worst condition at admission. Conversely, patients in trajectory 2 (delayed lightening) experienced initial deep sedation, which improved to a light depth of RASS −2 after 15 days. This group was characterized by elderly patients with dementia with respiratory failure, receiving vasopressors, neuromuscular blockade, and renal replacement therapy. Interestingly, although the two trajectories had relatively similar characteristics and the “delayed lightening” group even required more ICU support within the first 48 h, the “persistent suboptimal” group had worse time to extubation, ICU discharge, and hospital mortality. These findings suggest that the longitudinal course of sedation depth in our subjects was not associated with the severity of illness; the difference in sedation practice between the two trajectories might have resulted into different outcomes.

A prospective multicenter study, conducted across 42 international ICUs, demonstrated that the time to extubation and mortality increased with sedation intensity.[18] In

observational and matched-pair analyses based on the APACHE II score and the type of admission, early deep sedation during the first 48 h of ICU stay was associated with worse outcomes, including long-term mortality.[7] We report similar findings in our study by comparing trajectories 3 and 4 with the earlier trajectories 1 and 2. Patients in trajectory 3 (early lightening) experienced early deep sedation, which became lighter after 7 days, whereas those in trajectory 4 (persistent optimal) experienced light sedation throughout. Patients in these groups (trajectories 3 and 4) were younger, had fewer medical conditions, and were mostly admitted to surgical ICUs than those in the other two groups (trajectories 1 and 2). They also had lower APACHE Ⅱ scores and needed less ICU support within the first 48 h. The patients in "early lightening" group, especially, had the lowest APACHE score, the lowest proportion of renal replacement therapy, and the fewest respiratory problems. Nevertheless, multivariable Cox proportional hazard analysis showed that patients in this group had a lower probability of extubation and ICU discharge than those in the "persistent optimal" group. The early practice of inadequate sedation in "early lightening" group might have induced this relatively worse prognosis in these patients. A recent meta-analysis assessing the literature on early sedation suggested that interventions targeting the depth of early sedation, starting with ICU admission, could improve patient outcomes.[25] Appropriate sedation is a critical aspect in the management of patients who are mechanically ventilated.

We observed that 65.9% patients in our study were deeply sedated for at least the first week after mechanical ventilation, whereas only 34.07% patients received consistent light sedation throughout the sedation period. This finding is consistent with previous data describing the sedation depth. A multinational survey among intensivists reported that 74% patients monitored using a validated sedation tool were deeply sedated.[26] A survey in Germany found that the actual depth of sedation was considerably deeper (39.5%–62.4%)

than the desired depth in all categories of sedation.[27] A Swedish study investigating the relationship between memory and sedation showed that only 39% of patients who were ventilated achieved their target sedation goal.[28] A previous systematic review estimated the incidence of oversedation in ICUs at 40%–60%, despite the poor quality of epidemiologic data.[2] In a recent study conducted in the emergency department, the incidence of deep sedation was 52.8%.[29] These data suggest that deep sedation remains a common real-world ICU practice. To improve the quality of patient care, further research is warranted focusing on the longitudinal profile in addition to the binary concept of sedation, light versus deep.

Our study has a few limitations. First, information bias may exist because only patients visiting tertiary or university-affiliated hospitals were included in our study. Second, unmeasured confounders could have affected the trajectories, despite many relevant variables in our study. Moreover, the nondifferential group of patients may have been misclassified. This restriction is inherent to group-based trajectory models with limited generalizability. Third, the causal relationship between trajectory and outcome could not be established in this study. For example, it is unclear whether a prolonged duration of extubation reflected the effects of sedative overdose or whether more sedation was needed because of longer mechanical ventilation. However, the strength, consistency, and temporal precedence of the association and agreement with existing evidence of this study suggested the possibility of a causal relationship.[30] Thus, prospective and randomized controlled studies are required to investigate the interaction of the two parameters (depth and duration) of sedation to better define the optimal practice. Fourth, there was a restriction on recruiting patients owing to the COVID-19 crisis. Although the number of patients with mechanical ventilation increased in the COVID-19 era, the lack of staff in the ICU led to a low rate of patient registration. Finally, we were unable to examine the long-term complications in the trajectory groups.

Furthermore, nationwide studies should evaluate long-term complications after sedation to comprehensively understand its socioeconomic and clinical burden.

In conclusion, this study captured the four trajectories of sedation level over time in patients who were mechanically ventilated. These patterns were considerably associated with time to extubation, ICU discharge, and hospital mortality. Our findings suggest that the sedation strategy in ICU patients should incorporate a longitudinal pattern of sedation level.

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Contributors

CML, HYG, and JHA have equally contributed to the study conception and design. Material preparation was performed by HYG. Data collection was performed DH, JHA, and CML. Statistical analysis were performed by CMN and CY. The first draft of the manuscript was written by DH and JHA, and all authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

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Competing interests

Ha-Yeong Gil is an employee of Pfizer Korea. The other authors declare that they have no competing interests. Pfizer Korea, sponsor of this study, made no influence on study design,

data collection and analysis, and writing.

Patient consent for publication

Not applicable.

Ethic approval

The study protocol was approved by the Institutional Review Boards of all participating medical centers (B-1911/577-405, AJIRB-MED-OBS-19-372, AJIRB-MED-OBS-19-373, 1908-156-1058, 1908-157-1058, 1910-003-083, 2019-1624, 2019-1039, 2019-10-0321, 2019-09-040, 2019-10-162, GCIRB2019-366, DSMC 2019-08-018, HALLYM 2019-08-021, HALLYM 2019-08-022, 2019-09-010, 2019-08-082, DAUHIRB-19-166, 4-2019-0821, 4-2019-0820, 2019-09-011-002, 2019-07-038-002, CR-19-117-L, 2019AN0376, 2019AN0478, 20-2019-92, 20-2019-91, 2019GR0461, 2020GR0103, 2020AS0054). All patients (or patient representatives) provided their written informed consent. Some participating centers' local review boards waived the need for informed consent considering the observational nature of this study. This study was conducted per the amended Declaration of Helsinki.

Data availability statement

Data are available on request.

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Figure legends

Figure 1 Trajectories of longitudinal Richmond Agitation-Sedation Scale in the first 30 days of sedation for mechanical ventilation. The percentage of patients included in each trajectory was presented in central illustration. Outcome of y-axis indicates the score of Richmond Agitation-Sedation Scale and T of x-axis represents day after the initiation of sedation.

Figure 2 Kaplan–Meier of clinical outcomes from admission according to the trajectory groups. (a) time to extubation in the intensive care unit, (b) length of stay in the intensive care unit, and (c) in-hospital mortality.

Table 1 Baseline Characteristics and Clinical Outcomes for the Total Cohort and for Each Trajectory of the Richmond Agitation–Sedation Scale

		Trajectory group				
Characteristic	All (N = 631)	1 (N = 67)	2 (N = 84)	3 (N = 265)	4 (N = 215)	*p*-value
Age						0.002
20–29	11 (1.74%)	0 (0.00%)	2 (2.38%)	6 (2.26%)	3 (1.40%)	
30–39	34 (5.39%)	0 (0.00%)	2 (2.38%)	12 (4.53%)	20 (9.30%)	
40–49	44 (6.97%)	3 (4.48%)	11 (13.10%)	13 (4.91%)	17 (7.91%)	
50–59	92 (14.58%)	6 (8.96%)	6 (7.14%)	44 (16.60%)	36 (16.74%)	
60–69	140 (22.19%)	12 (17.91%)	17 (20.24%)	60 (22.64%)	51 (23.72%)	
70–79	177 (28.05%)	22 (32.84%)	23 (27.38%)	80 (30.19%)	52 (24.19%)	
≥80	133 (21.08%)	24 (35.82%)	23 (27.38%)	50 (18.87%)	36 (16.74%)	
Male gender	404 (64.0)	44 (65.67)	57 (67.86)	165 (62.26)	138 (64.19)	0.807
Body weight, kg*	62.0 (53.0-71.0)	62.25 ± 10.69	62.81 ± 13.31	62.51 ± 13.01	63.79 ± 17.62	0.785
Comorbidity	448 (71.00)	50 (74.62)	65 (77.38)	183 (69.05)	150 (69.76)	0.434
Diabetes with end-organ damage	30 (4.31)	2 (4.00)	2 (3.07)	14 (7.65)	12 (8.00)	0.573
COPD	60 (8.6)	7 (14.00)	8 (12.30)	25 (13.66)	20 (13.33)	0.994
Congestive heart failure	49 (7.0)	3 (6.00)	7 (10.76)	19 (10.38)	20 (13.33)	0.596
Moderate-to-severe liver disease**	27 (3.8)	3 (6.00)	3 (4.61)	9 (4.91)	12 (8.00)	0.681
Moderate-to-severe CKD**	46 (6.6)	5 (10.00)	3 (4.61)	18 (9.83)	20 (13.33)	0.375
Solid tumor	127 (18.2)	19 (38.00)	15 (23.07)	48 (26.22)	45 (30.00)	0.278
Dementia	35 (5.0)	6 (12.00)	9 (13.84)	16 (8.74)	4 (3.00)	0.010
Cerebrovascular disease/TIA	82 (11.7)	14 (28.00)	14 (21.53)	28 (15.30)	26 (17.33)	0.101
Type of admission						0.023
Medical	307 (48.6)	41 (61.19)	49 (58.33)	124 (46.79)	93 (43.26)	
Emergency surgery	193 (30.5)	19 (28.36)	25 (29.76)	78 (29.43)	71 (33.02)	
Scheduled surgery	131 (20.7)	7 (10.45)	10 (11.90)	63 (23.77)	51 (23.72)	
Type of ICU						0.001
Medical ICU	236 (37.4)	35 (52.24)	41 (48.81)	92 (34.72)	68 (31.63)	
Surgical ICU	371 (58.8)	30 (44.78)	42 (50.00)	157 (59.25)	142 (66.05)	

Others	24 (3.8)	2 (2.99)	1 (1.19)	16 (6.04)	5 (2.33)	
Reason for ICU admission***						
Renal	16 (2.5)	1 (1.49)	0 (0.00)	7 (2.64)	8 (3.72)	0.294
Digestive	83 (13.1)	10 (14.93)	12 (14.29)	28 (10.57)	33 (15.35)	0.434
Cardiovascular	147 (23.3)	15 (22.39)	16 (19.05)	68 (25.66)	48 (22.33)	0.610
Hematologic	14 (2.2)	2 (2.99%)	3 (3.57%)	4 (1.51%)	5 (2.33%)	0.679
Respiratory	359 (56.8)	43 (64.18%)	57 (67.86%)	136 (51.32%)	123 (57.21%)	0.030
Miscellaneous	67 (10.6)	3 (4.48%)	11 (13.10%)	34 (12.83%)	19 (8.84%)	0.152
Neurologic	12 (1.9)	3 (4.48%)	1 (1.19%)	4 (1.51%)	4 (1.86%)	0.418
Others	105 (16.6)	11 (16.42%)	13 (15.48%)	42 (15.85%)	39 (18.14%)	0.907
APACHE Ⅱ, score*	23.4 ± 10.0	27.82 ± 9.73	25.28 ± 11.45	21.39 ± 9.59	24.07 ± 9.56	< 0.001
ICU support within first 48 hours						
Vasopressor infusions	486 (77.02)	57 (85.07)	77 (91.67)	199 (75.09)	153 (71.16)	< 0.001
Renal replacement	107 (16.9)	11 (16.42)	22 (26.19)	37 (13.96)	37 (17.21)	0.078
Neuromuscular blockade	171 (27.1)	27 (40.30)	39 (46.43)	69 (26.04)	36 (16.74)	< 0.001
Clinical outcomes						
In-hospital mortality	77 (12.2)	33 (49.52)	18 (21.43)	18 (6.79)	8 (3.72)	< 0.001
ICU discharge	555 (87.9)	45 (67.16)	67 (79.76)	245 (92.45)	198 (92.09)	< 0.001
Extubation	571 (90.4)	46 (68.66)	66 (78.57)	253 (95.47)	206 (95.81)	< 0.001
Length of ventilator support, days	5 (3–11)	11 (20–NE)	11.5 (7–23.5)	5 (3–8)	3 (2–5)	< 0.001
ICU length of stay, days	10 (5–18)	20 (12–NE)	18 (10–26)	9 (6–14)	4 (6–10)	< 0.001

Data are reported as mean ± standard deviation or median (interquartile range) for continuous variables and number (percentage) for categorical variables.
*Data on body weight are presented for all 605 patients, excluding 26 patients with missing data (4 in the light sedation group and 22 in the deep sedation group). Data on APACHE Ⅱ are presented for all 577 patients, excluding 54 patients with missing data (15 in the light sedation group and 39 in the deep sedation group).
** Moderate-to-severe liver disease is defined as cirrhosis and portal hypertension with or without variceal bleeding history. Moderate-to-severe CKD is defined as serum creatinine > 3 mg/dL or on dialysis or post-kidney transplant status or uremia status.
***172 patients had multiple reasons for ICU admission.
ICU = intensive care unit; SMD = standardized mean difference; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; TIA = transient ischemic attack; APACHE Ⅱ = acute physiology and chronic health evaluation Ⅱ; NE = not estimated

Table 2 Summary of the demographics of the trajectories and the trajectory ranks for characteristics

	Trajectory 1	**Trajectory 2**	**Trajectory 3**	**Trajectory 4**
Demographics				
Age	70–79 & ≥80	70–79 & ≥80	60–69 & 70–-79	60–69 & 70–-79
Gender	Male	Male	Male	Male
Comorbidity	Solid tumor, CVD/TIA, COPD	Solid tumor, CVD/TIA, Dementia	Solid tumor, CVD/TIA, COPD	Solid tumor, CVD/TIA, COPD
Type of ICU	Medical ICU	Surgical ICU	Surgical ICU	Surgical ICU
Reason for ICU admission	Respiratory & Cardiovascular	Respiratory & Cardiovascular	Respiratory & Cardiovascular	Respiratory & Cardiovascular
Ranks for characteristics				
Medical admission	1st	2nd	3rd	4th
Scheduled surgery	4th	3rd	2nd	1st
APACHE Ⅱ	1st	2nd	4th	3rd
Vasopressor infusions	2nd	1st	3rd	4th
Renal replacement therapy	3rd	1st	4th	2nd
Neuromuscular blockade	2nd	1st	3rd	4th

Representative demographics with more than half of the patients on each trajectory, except age on trajectory 4, are shown in the table. Rank-order of trajectories was determined by the comparison of proportion of variable within each trajectory. Trajectories are ordered from lowest (4th) to highest (1st) rank values.
ICU = intensive care unit; APACHE Ⅱ = acute physiology and chronic health evaluation Ⅱ; CVD = cardiovascular disease; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

Table 3 Multivariable Cox Proportional Hazard regression models of time to event

	Time to extubation			Time to ICU discharge			Time to in-hospital death	
	HR (95% CI)	***p*-value**		**HR (95% CI)**	***p*-value**		**HR (95% CI)**	***p*-value**
Trajectory group								
Group 1	0.23 (0.16–0.32)	< 0.001		0.36 (0.26–0.51)	< 0.001		13.62 (5.99–30.95)	< 0.001
Group 2	0.30 (0.23–0.41)	< 0.001		0.44 (0.33–0.59)	< 0.001		5.62 (2.36–13.38)	< 0.001
Group 3	0.72 (0.59–0.87)	< 0.001		0.80 (0.65–0.97)	0.024		1.76 (0.76–4.08)	0.185
Group 4	Reference			Reference			Reference	
Age								
20–29	Reference			Reference			Reference	
30–39	1.08 (0.53–2.21)	0.825		0.70 (0.35–1.42)	0.334		0.69 (0.06–7.72)	0.765
40–49	0.89 (0.43–1.81)	0.748		0.63 (0.31–1.25)	0.188		0.59 (0.06–5.28)	0.641
50–59	1.04 (0.53–2.03)	0.893		0.65 (0.34–1.23)	0.192		0.41 (0.04–3.46)	0.414
60–69	1.00 (0.52–1.93)	0.987		0.79 (0.42–1.48)	0.469		0.88 (0.11–6.75)	0.905
70–79	1.04 (0.54–1.99)	0.893		0.64 (0.34–1.20)	0.170		0.47 (0.06–3.65)	0.473
≥80	0.85 (0.44–1.64)	0.632		0.53 (0.28–1.00)	0.052		0.82 (0.10–6.26)	0.850
Female	0.85 (0.71–1.01)	0.075		0.98 (0.81–1.17)	0.848		1.17 (0.73–1.89)	0.50
Type of admission								
Medical	Reference			Reference			Reference	
Emergency surgery	1.02 (0.79–1.32)	0.839		1.17 (0.90–1.53)	0.234		1.35 (0.62–2.91)	0.444
Scheduled surgery	2.13 (1.64–2.78)	< 0.001		2.10 (1.59–2.78)	< 0.001		1.91 (0.87–4.16)	0.102
Type of ICU								
Medical ICU	Reference			Reference			Reference	
Surgical ICU	1.05 (0.83–1.33)	0.629		0.87 (0.68–1.12)	0.299		0.45 (0.23–0.89)	0.021
Others	1.53 (0.96–2.40)	0.068		1.28 (0.80–2.06)	0.289		0.55 (0.12–2.47)	0.441
Vasopressor infusions	0.85 (0.69–1.04)	0.116		0.85 (0.69–1.04)	0.122		1.25 (0.62–2.51)	0.529
Neuromuscular blockade	1.05 (0.86–1.28)	0.586		0.88 (0.72–1.07)	0.217		1.42 (0.88–2.29)	0.148

Hazard ratio > 1 indicates a higher probability of event than reference.
ICU = intensive care unit; HR hazard ratio = CI confidence interval.

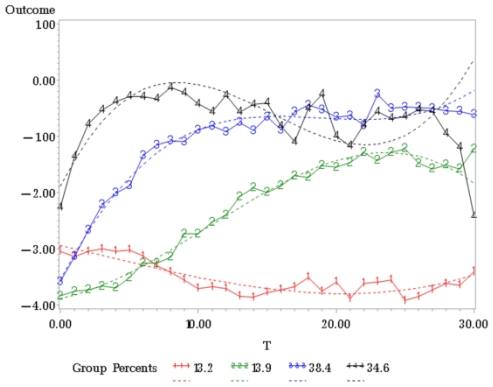

Figure 1 Trajectories of longitudinal Richmond Agitation Sedation Scale in the first 30 days of sedation for mechanical ventilation. The percentage of patients included in each trajectory were presented in central illustration. Outcome of y-axis indicates the score of richmond agitation sedation scale and T of x-axis represents day after the initiation of sedation.

338x190mm (200 x 200 DPI)

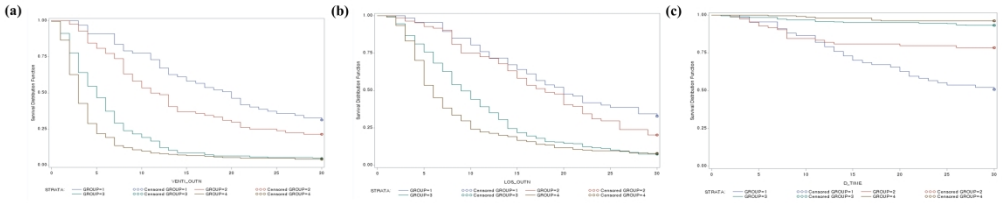

Figure 2. Kaplan–Meier of clinical outcomes from admission according to the trajectory groups. (a) time to extubation in the intensive care unit, (b) length of stay in the intensive care unit, and (c) in-hospital mortality.

199x112mm (600 x 600 DPI)

Longitudinal trajectories of sedation level and clinical outcomes in mechanically ventilated patients: a prospective, multicenter, longitudinal, observational study

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Table S1. Participating intensive care units

City	Participating hospitals	Investigators
Seoul	Asan Medical Center	Dong-gon Hyun, Jee Hwan Ahn, Suk-Kyung Hong, Chae-Man Lim
Seoul	Seoul National University Hospital	Sang-Min Lee, Ho-Geol Ryu
Seoul	Samsung Medical Center	Gee Young Suh, Chi Min Park
Seoul	Severance Hospital	Su Hwan Lee, Jeoung Min Kim
Seoul	Seoul St. Mary's Hospital	Seok Chan Kim
Seoul	Korea University Anam Hospital	Won Jai Jung, Jae-Myeong Lee
Seoul	Korea University Guro Hospital	Young-Seok Lee, Nak-Jun Choi
Seoul	Seoul National University Boramae Medical Center	Taeyun Park
Seongnam	Seoul National University Bundang Hospital	Dong Jung Kim
Suwon	Ajou University School of Medicine	Keu Sung Lee, Young-Gi Min
Busan	Pusan National University Hospital	Jae Hun Kim
Busan	Dong-A University Hospital	Dong-Hyun Lee
Busan	Inje University Haeundae Paik Hospital	Hang-Jea Jang, Ki Hoon Kim
Wonju	Yonsei University Wonju College of Medicine	Seok Jeong Lee
Incheon	Gachon University Gil Medical Center	Woo-Sung Choi
Daegu	Keimyung University School of Medicine	Jae-Bum Kim
Daegu	Yeungnam University Medical Center	Eun Young Choi, Jong-Hyun Baek
Daegu	Daegu Catholic University Medical Center	Eun Jin Kim
Anyang	Hallym University Sacred Heart Hospital	Sunghoon Park, Hyung Won Kim
Ansan	Korea University Ansan Hospital	Je Hyeong Kim

Table S2. Profile of analgesic and sedative within the first 48 hours

Type of Sedatives	N = 662
Diazepam	1 (0.2)
Cumulative dose (µg)	2000.0
Midazolam	127 (19.2)
Cumulative dose (µg)	64253.9 ± 133338.1
Lorazepam	14 (2.1)
Cumulative dose (µg)	2750 ± 1868.3
Other benzodiazepine	19 (2.9)
Cumulative dose (µg)	34294.7 ± 53960.7
Propofol	173 (26.1)
Cumulative dose (µg)	3444220.1 ± 2752320.0
Ketamine	53 (8.0)
Cumulative dose (µg)	1450147.2 ± 1830958.4
Haloperidol	1 (0.2)
Cumulative dose (µg)	5000.0
Dexmedetomidine	253 (38.2)
Cumulative dose (µg)	4080.2 ± 38325.4
Other non-benzodiazepine	21 (3.2)
Cumulative dose (µg)	75659.5 ± 133078.2
Type of analgesics	N = 528
Fentanyl	119 (22.5)
Cumulative dose (µg)	30861.1 ± 315168.1
Remifentanil	388 (73.5)
Cumulative dose (µg)	13227.8 ± 10971.7
Morphine	6 (1.1)
Cumulative dose (µg)	24000.0 ± 38740.2
Sufentanil	15 (2.8)
Cumulative dose (µg)	285.4 ± 280.6

Data are reported as means ± standard deviation for continuous variables and numbers (percentage) for categorical variables.
RASS = Richmond agitation-sedation scale

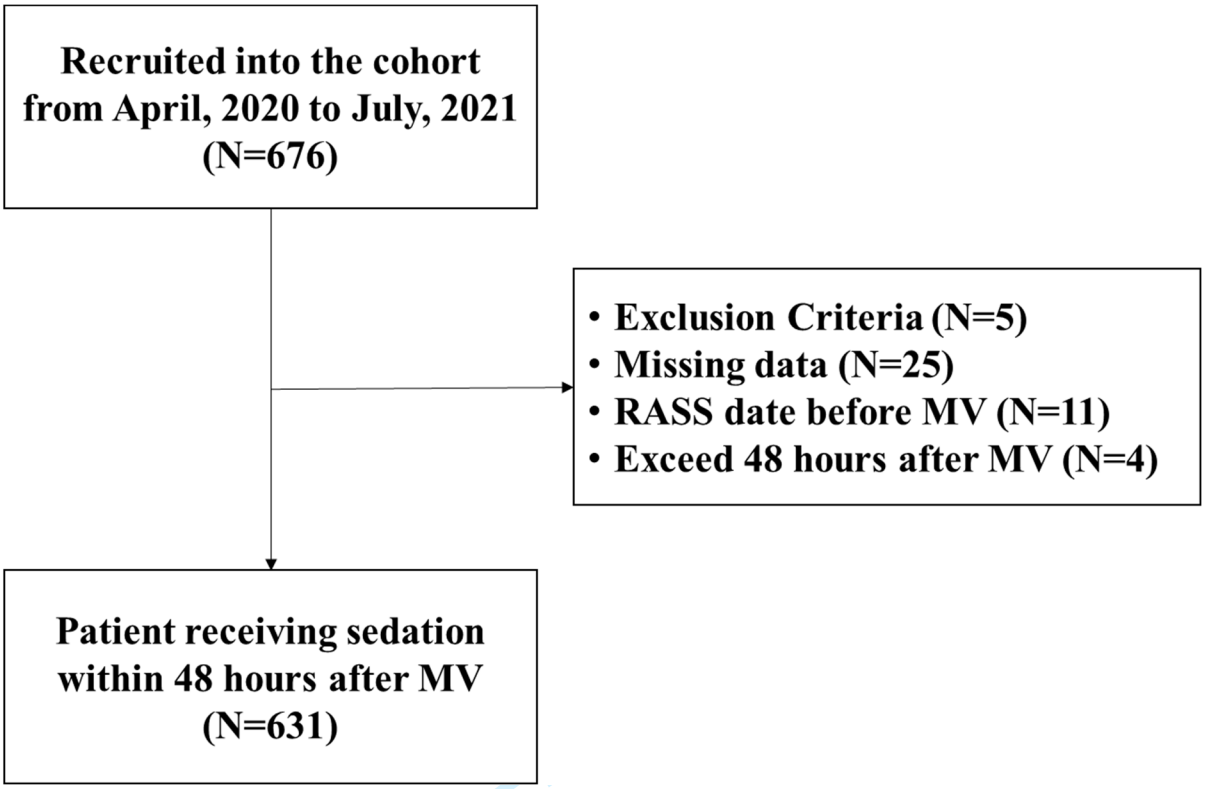

Figure S1. Flow diagram of patients in the present study.
MV = mechanical ventilation; RASS = Richmond agitation-sedation scale

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.