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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, multicentre, longitudinal and observational study in Korea

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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 multicentre, 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 hours 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 analysed 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 (HR: 0.23, 95% CI: 0.16 to 0.32, p<0.001), longer ICU stay (HR: 0.36, 95% CI: 0.26 to 0.51, p<0.001) and hospital mortality (HR: 13.62, 95% CI: 5.99 to 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 to 0.41, p<0.001; HR: 0.72, 95% CI: 0.59 to 0.87, p<0.001, respectively) and ICU discharge (HR: 0.44, 95% CI: 0.33 to 0.59, p<0.001 and HR: 0.80, 95% CI: 0.65 to 0.97, p=0.024) compared with 'persistently optimal'.

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large national data from 20 intensive care units 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 non-differential group as inherent restriction of group-based trajectory models with limited generalisability.
⇒ 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] Oversedation 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 favourable 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 multicentre, prospective, longitudinal and observational cohort study in 20 ICUs in Korea between April 2020 and July 2021, sponsored by Pfizer Korea Pharmaceuticals and involved 30 investigators (online supplemental table S1). We designed a harmonised 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 centre 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 hours and were expected to remain sedated and on mechanical ventilation for >48 hours. 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 non-effective therapy, and those who needed non-selective deep sedation owing to medical conditions, including brain damage and haemorrhage, 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 hours 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 analysing 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 analysing a scale form of RASS over the first 30 days after enrolment. To characterise 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 postkidney transplant status or uraemia 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 HR of ICU length between the sedation group (n=70) and non-sedation group (n=70) was 1.86 (95% CI: 1.05 to 3.23), the following values were required to calculate the number of subjects: $\widehat{S_{\text{Deep Sedation}}} = e^{-\lambda_{\text{Deep}}*t} = e^{-0.03*28} = 0.43$, $\widehat{S_{\text{Light Sedation}}} = e^{-\lambda_{\text{Light}*t}=e^{-0.02*28}=0.57}$, and HR=1.50.[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 maximise the probability of $Y_i = (y_{i1}, \ldots, y_{it})$. 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

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

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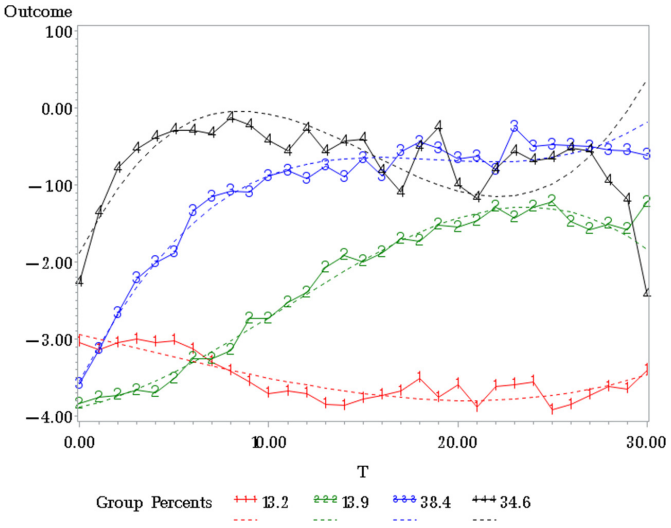

Figure 1 Trajectories of longitudinal Richmond Agitation–Sedation scale in the first 30 days of sedation for mechanical ventilation. The percentage of patients included in each trajectory was presented in central illustration. Outcome of y axis indicates the score of Richmond Agitation–Sedation scale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

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

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

$k=1,\ldots,K$, are not observed, so estimated by a multinomial logit function. For a given k, conditional independence is assumed for the sequential realisations 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 realised level of the outcome in prior periods. The likelihood function is $L = \prod_{i=1}^{N} P\left(y_i|z_i,\ w_i\right)$ where $p\left(y_i|z_i,\ w_i\right) = \sum_{k=1}^{K} p\left(C_i = k|Z_i = z_i\right) p\left(Y_i = y_i|C_i = k,\ W_i = w_i\right)$; the first term is the probability of group membership and the second term is the probability of the observed data given group membership. $Y_i = (Y_{i1},\ldots,Y_{iT})$, $Z_i = (Z_{i1},\ldots,Z_{iR})$, $W_i = (W_{i1},\ldots,W_{iT})$, $p = \frac{\exp\left(\theta_k+\lambda'_k z_i\right)}{\sum_{k=1}^{K}\exp\left(\theta_k+\lambda'_k z_i\right)}$, and $p\left(Y_i = y_i|C_i = k,\ W_i = w_i\right)$, 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±SD or medians (IQR) for continuous variables. Differences between groups were analysed 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% CI. Two-sided p values <0.05 indicated significance. All analyses were performed using Statistical Analysis System (SAS) software V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

In 20 participating centres, 676 patients were recruited from April 2020 to July 2021 (online supplemental figure S1). Of them, 45 patients were excluded because of missing data, an RASS date before mechanical ventilation, or were enrolled ≥48 hours after mechanical ventilation. The final cohort included 631 patients. In this study, four-group solutions that best characterised 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 tumour 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%

Table 1 Baseline characteristics and clinical outcomes for the total cohort and for each trajectory of the Richmond Agitation–Sedation Scale

Characteristics	All (n=631)	Trajectory group				P value
		1 (n=67)	2 (n=84)	3 (n=265)	4 (n=215)	
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 tumour	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
Haematologic	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

Continued

Table 1 Continued

Characteristics	All (n=631)	Trajectory group				P value
		1 (n=67)	2 (n=84)	3 (n=265)	4 (n=215)	
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±SD or median (IQR) 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 postkidney transplant status or uraemia status.
‡172 patients had multiple reasons for ICU admission.
APACHE II, Acute Physiology and Chronic Health Evaluation II; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NE, not estimated; SMD, standardised mean difference; TIA, transient ischemic attack.

and 48.81% vs 34.72% and 31.63%, respectively) with a medical illness (61.19% and 58.33% vs 46.79% and 43.26%, respectively) and less likely to be admitted to surgical ICU (44.78% and 50.00% vs 59.25% and 66.05%, respectively; p value=0.023) for a scheduled surgery (10.45% and 11.90% vs 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 hours, 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 summarises the representative phenotypes of each trajectory.

In adjusted Cox proportional hazard analyses, the 'persistent suboptimal' (HR=13.62, 95% CI: 5.99 to 30.95, p value <0.001) and 'delayed lightening' groups (HR=5.62, 95% CI: 2.36 to 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 to 0.32, p value <0.001), 'delayed lightening' (HR=0.30, 95% CI: 0.23 to 0.41, p value <0.001) and 'early lightening' groups (HR=0.72, 95% CI: 0.59 to 0.87, p value <0.001) showed a reduced probability of extubation and were less likely to discharge from the ICU (HR=0.36,

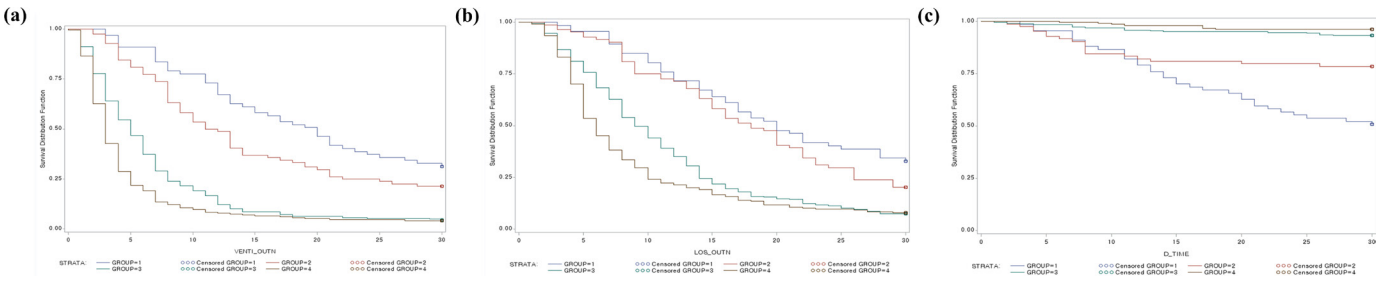

Figure 2 Kaplan-Meier of clinical outcomes from admission according to the trajectory groups. (A) Time to extubation in the intensive care unit, (B) length of stay in the intensive care unit and (C) in-hospital mortality.

Table 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 and ≥80	70–79 and ≥80	60–69 and 70–79	60–69 and 70–79
Gender	Male	Male	Male	Male
Comorbidity	Solid tumour, CVD/TIA, COPD	Solid tumour, CVD/TIA, dementia	Solid tumour, CVD/TIA, COPD	Solid tumour, CVD/TIA, COPD
Type of ICU	Medical ICU	Surgical ICU	Surgical ICU	Surgical ICU
Reason for ICU admission	Respiratory and cardiovascular	Respiratory and cardiovascular	Respiratory and cardiovascular	Respiratory and cardiovascular
Ranks for characteristics				
Medical admission	First	Second	Third	Fourth
Scheduled surgery	Fourth	Third	Second	First
APACHE II	First	Second	Fourth	Third
Vasopressor infusions	Second	First	Third	Fourth
Renal replacement therapy	Third	First	Fourth	Second
Neuromuscular blockade	Second	First	Third	Fourth

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 (fourth) to highest (first) rank values.
APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease ; CVD, cardiovascular disease; ICU, intensive care unit; TIA, transient ischemic attack.

95% CI: 0.26 to 0.51, p value <0.001; HR=0.44, 95% CI: 0.33 to 0.59, p value <0.001; HR=0.80, 95% CI: 0.65 to 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 to 2.78, p value <0.001) and ICU discharge (HR=2.10, 95% CI: 1.59 to 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 to 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 characterise 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 modelling is useful for characterising longitudinal courses over time to identify distinct subgroups.[23 24] This trajectory model is used in different domains of clinical research, such as non-adherence 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 modelling is a specialised 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 characterised 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 characterised 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 hours, 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 multicentre 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 hours 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 hours. 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.

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

Hazard ratio >1 indicates a higher probability of event than reference.
ICU, intensive care unit.

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 vers 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 non-differential group of patients may have been misclassified. This restriction is inherent to group-based trajectory models with limited generalisability. 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 randomised 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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