Supplemental Digital Content

Determinants of delayed recovery of consciousness after analgosedation discontinuation in the intensive care unit: insights from patients with COVID-19 hypoxemic respiratory failure

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Table of Contents:

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*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	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5–6
Methods			
Study design	4	Present key elements of study design early in the paper	6–7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6–8
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	6–8
Bias	9	Describe any efforts to address potential sources of bias	8–9
Study size	10	Explain how the study size was arrived at	N/A, all available data were included
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8–9
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	8–9
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	9
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10–11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9–10 7 N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10–11
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13–15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11–13
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
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	1

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

Supplemental Methods

Study approval

This study was approved by the Institutional Review Board (IRB) at each participating site: Columbia University Irving Medical Center (CUIMC)—IRB Protocol Number AAAT0120, "neurological intensive care unit observational COVID19 database with outcomes", approval date April 08, 2022; Massachusetts General Hospital (MGH)—IRB Protocol Number 2013P001024, "a database to support large-scale acute care research", approval date July 08, 2013; Weill Cornell Medicine (WCM)—IRB Protocol Number 20-080224920, "delayed recovery of consciousness after anesthetic coma in survivors of COVID-19 hypoxemic respiratory failure", approval date November 10, 2020. All study procedures were followed in accordance with the ethical standards of the institutional committees on human experimentation and with the Helsinki Declaration of 1975.

Outcome quantification

We used a Glasgow Coma Scale motor subscore (GCSm) of 6 from <6 to determine command following. The GCS is a validated tool to assess consciousness, (1) is easily applied in clinical settings, and was routinely implemented in our dataset. Clinical staff were trained on GCS administration as part of standard of care in the ICU, though there was no explicit institution-specific standardized protocol for GCS assessments. The frequency of GCS assessments was <4 hours in each ICU setting.

We defined RoC as the first GCSm subscore of 6 following GABA cessation. We chose the first GCSm subscore of 6 to capture the minimum time to RoC as GCS scores can fluctuate. Neuromuscular blockade (via rocuronium and/or cisatracurium in our cohort) was stopped a median of 10.3 days (IQR [4.1, 17.3]) before GABA cessation (time 0); the longest reported time to recovery of neuromuscular function for rocuronium is 20 hours, (2) and 90 minutes for cisatracurium in critically-ill patients. (3, 4) Thus our measured time to RoC (which begins at GABA cessation) was highly unlikely to be affected by residual weakness. Confusion Asssesment Method for the ICU (CAM-ICU) data for diagnosis and reporting of delirium were not reliably available in our dataset, and we chose not to build CAM-ICU scores from the clinical record based on its limited sensitivity for detecting delirium. (5, 6) While delirium could affect our GCSm 6 measurement, it is a disorder characterized by lucid intervals; because of the frequency of the GCS measurement in all patients, it is unlikely that delirium contributed to a significant miscalculation of time to RoC.

Exposure quantification

We obtained all analgosedative records for each patient, including opioid and sedative infusions, boluses, and oral agents. We calculated the total dose of each agent (propofol, benzodiazepines, opioids, dexmedetomidine, ketamine) by the hour from intubation until GABA cessation. Benzodiazepines are expressed as midazolam equivalents, and opioids are expressed as fentanyl equivalents. (7) Phenobarbital was only administered in 15 patients across our institutions (CUIMC n=0; MGH n=14; WCM n=1); zero patients received $GABA_B$ agonists or gabapentin.

We defined "tapering" of benzodiazepine and opioid infusions as 1) the initiation of standing oral or intermittent intravenous (IV) administration of benzodiazepine or opioid therapy within 48 hours of GABA cessation, and 2) a ≥20% reduction of oral or IV therapy every 48 hours.

Weighted cumulative exposures

The weighted cumulative exposure (WCE) for an analgosedative administered at a given time τ is defined as follows (**Supplemental Figure 1**):

$$WCE(\tau) = \sum_{t \leq \tau} w(\tau - t) \times dose(t)$$

where $w(\cdot)$ is the weight function, dose(t) is the dose received at time t, and the summation is over all time points t in which a dose was administered from intubation to time τ. We assign weights to each dose based on the time from administration, assuming first-order kinetics of dose clearance in a one-compartmental model. $w(\cdot)$ is defined as follows for a given time gap (Δt):

$$w(\Delta t) = \exp\left[-\frac{\Delta t}{t_{1/2}/\ln 2}\right]$$

WCE was then divided by body weight (actual body weight for patients whose actual body weight was <120% of ideal body weight (IBW), or adjusted body weight for those whose actual body weight was ≥120% of IBW. (8) In multinomial and time-to-event models, WCE variables were standardized by centering at the mean and dividing by the standard deviation (SD).

Determination of latest expected recovery of command following (LERoC)

To set a conservative bound on the latest time at which RoC is expected based on pharmacologic considerations alone ("LERoC"), we took the latest of the four time points below following GABA cessation (**Supplemental Figure 2**):

1. time of last benzodiazepine dose +5 half-lives (i.e., 120 hours in the standard model)
2. time of last propofol dose +5 half-lives (i.e., 35 hours in the standard model)
3. time that the patient's benzodiazepine WCE falls to an empirical population-defined threshold (defined below)
4. time that the patient's propofol WCE falls to an empirical population-defined propofol threshold (defined below)

Time points 3 and 4 were included to account for patients who received large sedative doses, and whom 5 standard half-lives may not allow for sufficient clearance. For example, in a patient who received high sedative doses, their WCE after 5 half-lives could be equivalent to another patient's baseline WCE who is on a lower overall sedative dose. Population-defined empirical thresholds were thus calculated to account for higher than usual doses that may delay ROC. Thresholds were defined as the median WCE 5 half-lives after cessation among patients who ever received the given GABAergic sedative between intubation and cessation (0.007 mg/kg for benzodiazepine and 0.412 mg/kg for propofol). We emphasize that LERoC is intended to be a conservative upper bound for the interval between GABA cessation and RoC, and not an estimate of the expected time to RoC.

Software

All analyses were performed in R (version 4.1.0). (9) Multinomial models were fit using the nnet package (version 7.3-16). (10) Time-to-event models were fit using the cmprsk package (version 2.2-10). (11)

Supplemental Results

Relationship of GABAergic sedative regimen to LERoC determination and outcome classification

Supplemental Table 1 summarizes the implementation of the algorithm for determining LERoC in the study population. Of patients who received propofol but no benzodiazepines (n=187), 31% had LERoC defined by 5 half-lives, meaning that the remainder (69%) had propofol WCE greater than the overall median propofol WCE, and thus LERoC was defined as

the time they reached the specified propofol threshold. (This is not 50% because the median calculation includes patients who received propofol alone as well as benzodiazepine with propofol.) Of patients who received benzodiazepine but no propofol (n=40), 100% had LERoC defined by reaching the benzodiazepine threshold, meaning that these patients all had benzodiazepine WCE greater than the specified benzodiazepine threshold at 5 half-lives following benzodiazepine cessation. Of patients who received both propofol and benzodiazepine, LERoC was mostly determined by 5 benzodiazepine half-lives (24%) or reaching the benzodiazepine threshold (55%). Generally, for patients receiving high GABAergic sedative doses, LERoC was largely determined by time points 3 and 4, which were longer than the corresponding time points 1 and 2.

Supplemental Table 2 summarizes the distribution of outcome categories after LERoC was calculated. All outcome categories were observed after stratifying by GABAergic sedative regimen (i.e., benzodiazepine infusion, propofol infusion, or both). For patients receiving both propofol and benzodiazepine sedation, the majority of patients had early events (i.e., events before LERoC).

Supplemental Table 3 describes demographics and sedative administration with respect to outcome category. Patients with early RoC were significantly younger and had less hypoxemia compared to other outcome categories, consistent with model results in **Table 2**. With regards to sedative administration, patients receiving low levels of a sedative agent will have lower WCE levels at GABA cessation, while patients with heavier sedation may have higher or lower WCE levels depending on the dynamics of sedative administration prior to GABA cessation. Notably, patients with early RoC had higher mean benzodiazepine and propofol WCE levels than patients with late RoC; thus, these patients were not simply receiving more mild sedation.

Determinants of early death/discharge

Compared to early RoC, the relative risk of early death/discharge was increased with increased age (one-year RRR 1.07 [1.05–1.09]), AKI (RRR 4.78 [2.92–7.82]), severe ARDS compared to mild/moderate ARDS (RRR 2.99 [1.57–5.70]), and higher opioid WCE at GABA cessation (one-SD difference RRR 2.00 [1.54–2.60]) (**Supplemental Table 4**). The relative risk of early death/discharge was decreased with higher dexmedetomidine WCE at GABA cessation (one-SD difference RRR 0.68 [0.47–0.97]), and opioid tapers following GABA cessation (RRR 0.18 [0.08–0.40]). Overall, adjustment for non-GABAergic sedatives did not substantially increase predictive value of the multinomial model (c=0.804 with versus 0.778 without).

Multinomial model estimates were robust to changes in half-lives and site adjustment (**Supplemental Figure 4**). When restricting analysis to patients without AKI, the effects of benzodiazepine and opioid tapers as well as opioid and dexmedetomidine WCE at GABA cessation on risk of early death/discharge were largely reduced.

Effects of sensitivity analyses on LERoC and outcome classification

To assess the robustness of our findings to variations in drug metabolism in critically-ill patients, we conducted sensitivity analyses using modified half-lives of midazolam and propofol of (1) 16 and 5 hours, (2) 36 and 7 hours, and (3) 24 and 24 hours, respectively. However, changing the assumed half-life of a GABAergic sedative changes both the WCE and LERoC, which may impact whether an event occurs before or after LERoC and thus affect a patient's outcome categorization. Further, changing assumed half-lives will affect the time between LERoC and an event. **Supplemental Table 6** shows the change (Δ) in the number of patients in each category compared to the primary analysis for each of our sensitivity analyses. Among 570 patients achieving RoC, our sensitivity analyses resulted in a reclassification of 6.1% (sensitivity 1), 7.4% (sensitivity 2), and 12.6% (sensitivity 3) of patients.

Supplemental References

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Supplemental Figure 1. Conversion of longitudinal sedative data to weighted cumulative exposure (WCE)

The WCE at a given time point is calculated by taking a recency-weighted sum of the weight-adjusted doses received up to that time point. Dexmedetomidine (half-life of 3 hours) is shown as an example. The data are summarized hourly; each dose represents the sum of the total doses received during a given hour. The WCE curve depicts how the WCE would be calculated at each time point, ending at GABA cessation

Supplemental Figure 2. Definition of latest expected recovery of consciousness (LERoC)

Supplemental Figure 3. Relative amounts of dexmedetomidine, opioids, and ketamine administered with respect to outcome category

Individual patients are displayed as in Figure 2b. For patients who received a given sedative agent, colored circles represent the percentile of the WCE (relative to the overall population who received that agent): dexmedetomidine (a), ketamine (b), and opioid (c). Percentiles range from 0^{th} percentile (dark purple), indicating the lowest non-zero dose, to 100^{th} percentile (yellow), indicating that highest dose. Patients who received none of the given sedative agent are indicated by a dark purple square. Abbreviations: LEROC, latest expected recovery of consciousness; RoC, recovery of consciousness

Supplemental Figure 4. Sensitivity analysis results for early death/discharge compared to early RoC

Point estimates and 95% confidence intervals are displayed for covariates in each of the different sensitivity analyses for the multinomial model. Relative risk ratios >1 indicate increased risk of early death/discharge. In the primary analysis, the midazolam half-life is 24 hours, and the propofol half-life is 7 hours. In sensitivity analyses 1, 2, and 3, midazolam and propofol half-lives are set as 16 and 5, 36 and 7, and 24 and 24 hours, respectively. No AKI refers to the sensitivity analysis where patients with acute kidney injury are excluded. Arrows indicate that the upper or lower limit of the 95% confidence interval exceeds the graphical area shown. Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; LI, liver injury; SD, standard deviation; WCE, weighted cumulative exposure

Supplemental Table 1. Application of LERoC determination algorithm, stratified by GABAergic sedative regimen

	Timepoint	Propofol Only (n=187)	Benzodiazepine Only (n=40)	Propofol and Benzodiazepine (n=557)
1	5 half-lives from last benzodiazepine dose	0 (0%)	0 (0%)	131 (24%)
2	5 half-lives from last propofol dose	58 (31%)	0 (0%)	62 (11%)
3	Reached the benzodiazepine threshold	0 (0%)	40 (100%)	306 (55%)
4	Reached the propofol threshold	129 (69%)	0 (0%)	58 (10%)

Abbreviations: LERoC, latest expected recovery of consciousness

Supplemental Table 2. Distribution of outcome categories after LERoC calculation, stratified by GABAergic sedative regimen

	Propofol Only	Benzodiazepine Only	Propofol and Benzodiazepine
n	**187**	**40**	**557**
LERoC defined by propofol (5 half-lives from last propofol dose or time to reach propofol threshold)			
Early RoC, n (%)	83 (44%)		49 (9%)
Early death/discharge, n (%)	26 (14%)		5 (1%)
Late RoC, n (%)	53 (28%)		56 (10%)
Late death/discharge, n (%)	25 (13%)		10 (2%)
LERoC defined by benzodiazepine (5 half-lives from last benzodiazepine dose or time to reach benzodiazepine threshold)			
Early RoC, n (%)		9 (23%)	238 (43%)
Early death/discharge, n (%)		25 (63%)	94 (17%)
Late RoC, n (%)		4 (10%)	80 (14%)
Late death/discharge, n (%)		2 (5%)	25 (4%)

Abbreviations: LERoC, latest expected recovery of consciousness; RoC, recovery of consciousness

Supplemental Table 3. Demographics and sedative use, stratified by outcome category

	Overall	Early RoC	Early death/discharge	Late RoC	Late death/discharge	p-value
n	784	379	150	191	64	
Site						
CUIMC	340 (43.4)	118 (31.1)	117 (78.0)	76 (39.8)	29 (45.3)	<0.001
MGH	185 (23.6)	136 (35.9)	6 (4.0)	38 (19.9)	5 (7.8)	
WCM	259 (33.0)	125 (33.0)	27 (18.0)	77 (40.3)	30 (46.9)	
Male Sex (%)	509 (64.9)	250 (66.0)	99 (66.0)	116 (60.7)	44 (68.8)	0.544
Race/Ethnicity						
White	159 (20.3)	73 (19.3)	19 (12.7)	50 (26.2)	17 (26.6)	0.139
Black or African American	92 (11.7)	40 (10.6)	21 (14.0)	24 (12.6)	7 (10.9)	
Hispanic or Latino	322 (41.1)	158 (41.7)	66 (44.0)	75 (39.3)	23 (35.9)	
Other/Missing	211 (26.9)	108 (28.5)	44 (29.3)	42 (22.0)	17 (26.6)	
Age, years (mean (SD))	61.4 (14.1)	55.8 (13.8)	67.0 (12.8)	66.0 (11.0)	67.8 (14.5)	<0.001
BMI, kg/m^2 (mean (SD))	29.9 (6.8)	30.3 (6.4)	30.1 (7.8)	29.8 (6.2)	27.9 (7.8)	0.077
BMI $\geq$35, kg/m^2 (%)	141 (18.0)	73 (19.3)	29 (19.3)	31 (16.2)	8 (12.5)	0.511
Benzodiazepine Taper (%)	110 (14.0)	64 (16.9)	4 (2.7)	36 (18.8)	6 (9.4)	<0.001
Opioid Taper (%)	234 (29.8)	126 (33.2)	8 (5.3)	88 (46.1)	12 (18.8)	<0.001
Hypoxemia (%)	398 (50.8)	164 (43.3)	75 (50.0)	120 (62.8)	39 (60.9)	<0.001
Acute Kidney Injury (%)	353 (45.0)	126 (33.2)	106 (70.7)	83 (43.5)	38 (59.4)	<0.001
ARDS Severity						
Mild (P:F 201-300)	14 (1.8)	11 (2.9)	1 (0.7)	2 (1.0)	0 (0.0)	<0.001
Moderate (P:F 101-200)	187 (23.9)	117 (30.9)	19 (12.7)	42 (22.0)	9 (14.1)	
Severe (P:F$\leq$100)	583 (74.4)	251 (66.2)	130 (86.7)	147 (77.0)	55 (85.9)	
Duration of GABAergic sedation, days (mean (SD))	17.0 (14.8)	17.5 (15.6)	14.9 (15.3)	19.1 (13.2)	12.7 (11.3)	0.005
Any benzodiazepine before cessation (%)	597 (76.1)	296 (78.1)	124 (82.7)	138 (72.3)	39 (60.9)	0.003
Any propofol before cessation (%)	744 (94.9)	370 (97.6)	125 (83.3)	189 (99.0)	60 (93.8)	<0.001

Any opioid before cessation (%)	780 (99.5)	379 (100)	149 (99.3)	190 (99.5)	62 (96.9)	0.014
Any ketamine before cessation (%)	120 (15.3)	81 (21.4)	8 (5.3)	26 (13.6)	5 (7.8)	<0.001
Any dexmedetomidine before cessation (%)	521 (66.5)	293 (77.3)	63 (42.0)	134 (70.2)	31 (48.4)	<0.001
Benzodiazepine WCE, mg/kg (mean (SD))	0.57 (1.36)	0.51 (1.59)	1.26 (1.43)	0.24 (0.61)	0.27 (0.53)	<0.001
Propofol WCE, mg/kg (mean (SD))	12.66 (10.85)	13.41 (10.95)	8.51 (11.92)	13.32 (8.45)	15.96 (11.66)	<0.001
Opioid WCE, mg/kg (mean (SD))	0.0214 (0.0227)	0.0187 (0.0217)	0.0342 (0.0274)	0.0164 (0.0167)	0.0225 (0.0213)	<0.001
Ketamine WCE, mg/kg (mean (SD))	0.0460 (0.3447)	0.0790 (0.4654)	0.0099 (0.1030)	0.0242 (0.2146)	0.0000 (0.0000)	0.071
Dexmedetomidine WCE, mg/kg (mean (SD))	0.0016 (0.0026)	0.0022 (0.0030)	0.0006 (0.0016)	0.0014 (0.0022)	0.0006 (0.0015)	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CUIMC, Columbia University Irving Medical Center; GABA, γ-Aminobutyric acid; MGH, Massachusetts General Hospital; P:F, ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2); RoC, recovery of consciousness; SD, standard deviation; WCE, weighted cumulative exposure; WCM, Weill Cornell Medicine

Supplemental Table 4. Multinomial model relative risks for early death/discharge (n=150) compared to early RoC (n=379).

Variable	RRR	p-value
Male Sex	1.23 [0.75, 2.02]	0.41
Race/Ethnicity (reference White)		
Black or African American	1.73 [0.74, 4.04]	0.2
Hispanic/Latino	1.84 [0.92, 3.65]	0.08
Other/Missing	1.53 [0.73, 3.18]	0.26
Age (years)	1.07 [1.05, 1.09]	<0.001
BMI ≥ 35 kg/m^2	1.83 [0.97, 3.43]	0.06
Benzodiazepine Taper	0.31 [0.09, 1.01]	0.05
Opioid Taper	0.18 [0.08, 0.40]	<0.001
Hypoxemia	0.84 [0.50, 1.41]	0.51
Acute Kidney Injury	4.78 [2.92, 7.82]	<0.001
Severe ARDS	2.99 [1.57, 5.70]	<0.001
Duration of GABAergic sedation (days)	1.00 [0.98, 1.01]	0.58
Opioid WCE (SD)	2.00 [1.54, 2.60]	<0.001
Ketamine WCE (SD)	0.49 [0.10, 2.43]	0.38
Dexmedetomidine WCE (SD)	0.68 [0.47, 0.97]	0.03
Interaction: Opioid*Ketamine	1.14 [0.65, 1.98]	0.64
Interaction: Opioid*Dexmedetomidine	0.93 [0.69, 1.25]	0.6
Interaction: Ketamine*Dexmedetomidine	1.39 [0.68, 2.84]	0.36

Estimated associations with p-values less than 0.05 are highlighted. Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; GABA, γ-Aminobutyric acid; RRR, relative risk ratio; SD, standard deviation; WCE, weighted cumulative exposure

Supplemental Table 5. Discharge dispositions among patient subcohorts

	Overall	Early RoC	Early death/discharge	Late RoC	Late death/discharge
n	784	379	150	191	64
Hospital LOS (median [IQR])	36.6 [22.1, 58.0]	33.8 [21.8, 53.2]	22.3 [13.1, 34.4]	56.8 [39.5, 75.4]	26.2 [19.5, 43.3]
Discharge Disposition (%)					
Home	164 (20.9)	121 (31.9)	0 (0.0)	40 (20.9)	3 (4.7)
Inpatient Rehabilitation	196 (25.0)	126 (33.2)	0 (0.0)	67 (35.1)	3 (4.7)
Skilled Nursing Facility	132 (16.8)	69 (18.2)	3 (2.0)	55 (28.8)	5 (7.8)
Long-term Care	74 (9.4)	46 (12.1)	4 (2.7)	20 (10.5)	4 (6.2)
Hospice	14 (1.8)	2 (0.5)	7 (4.7)	1 (0.5)	4 (6.2)
Death	196 (25.0)	11 (2.9)	134 (89.3)	6 (3.1)	45 (70.3)
Other†	8 (1.0)	4 (1.1)	2 (1.3)	2 (1.0)	0 (0.0)

†Other category includes intercampus transfer between NewYork-Presbyterian sites (Columbia University Irving Medical Center/Weill Cornell Medicine). Abbreviations: IQR, Interquartile range; LOS, length of stay; RoC, recovery of consciousness

Supplemental Table 6. Overall changes in patient outcome categories under different assumed half-lives for sensitivity analyses

	Half-lives (h)		RoC			Death/discharge		
	Benzodiazepine	**Propofol**	**Early**	**Late**	**Δ**	**Early**	**Late**	**Δ**
Primary analysis	24	7	379	191	0	150	64	0
Sensitivity analysis 1	16	5	344	226	+35	138	76	+12
Sensitivity analysis 2	36	7	421	149	-42	157	57	-7
Sensitivity analysis 3	24	24	451	119	-72	172	42	-22

When assumed half-lives are changed for benzodiazepine and propofol, LERoC can change, and patients may be categorized in a different group. The “Δ” column represents the number of patients who have shifted from early to late categories due to changes in LERoC: positive numbers represent more patients in late categories, and negative numbers represent more patients in early categories. Abbreviations: LERoC, latest expected recovery of consciousness; RoC, recovery of consciousness