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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Abstract

Objective: Prolonged disorders of consciousness are common in critically-ill patients receiving mechanical ventilation, and often attributed to prolonged sedative exposure in the setting of decreased drug clearance and/or reduced metabolism. Here in a large sample of critically-ill COVID patients obtained over a short period, we tested the assumption that prolonged unconsciousness following benzodiazepine and/or propofol sedation can be attributed to residual exposure. Further, we examine associations between clinical variables on time to recovery of consciousness (RoC) as a framework for the broader critically-ill population.

Design: Retrospective cohort study.

Setting: Massachusetts General Hospital, Weill Cornell Medicine, Columbia University Irving Medical Center.

Patients: Seven hundred eighty-four patients with COVID-19 critical illness in Spring–Summer 2020.

Interventions: None.

Measurements and Main Results: We estimated the latest expected recovery of consciousness (LERoC) using models of sedation exposure that account for sedative-specific pharmacokinetics and critical illness. Our primary exposure variable was a time-weighted dose of analgosedative agents at benzodiazepine and/or propofol cessation; our primary outcome was time to RoC. We estimated relative risks for late RoC (i.e., after LERoC) *via* multinomial logistic regression. Among individuals with late RoC, we fit a multivariate subdistribution hazard model for time to RoC. 73% of patients had RoC before hospital discharge, yet 34% of patients achieving RoC did not do so within pharmacologically plausible sedative elimination times. Patients with late RoC were older and exhibited hypoxemia and acute kidney injury. Patients with dexmedetomidine as an adjunct sedative had a disproportionately larger incidence of early

recovery. Patients with early versus late RoC did not have significantly different discharge dispositions.

Conclusions: In our cohort, the time to RoC was commonly prolonged beyond that expected from sedation exposures alone. These data may aid clinicians and families with expectations of RoC and warrant investigation of alternative determinants of delayed RoC in this population.

Key Points

Question: Can prolonged unconsciousness following benzodiazepine and/or propofol sedation be attributed to prolonged sedative washout in critically-ill patients?

Finding: In 784 patients with COVID-19 critical illness, 73% had recovery of consciousness (RoC) before hospital discharge, yet 34% of patients who achieved RoC did so outside of pharmacologically plausible elimination times. Discharge dispositions were not significantly different among patients with late versus early recovery, suggesting patients with delayed RoC can progress to favorable neurological outcomes.

Meaning: Delayed RoC following benzodiazepine and/or propofol sedation cannot be explained solely by drug washout, warranting investigation of alternative factors that may contribute to delayed RoC.

Introduction

Prolonged disorders of consciousness are common in critically-ill patients receiving mechanical ventilation. (1-4) While the underlying basis is unknown, delayed recovery is often attributed to prolonged sedative exposure, as critical illness may impair drug clearance and promote accumulation of active compounds and/or metabolites. (5) However, the natural course of recovery of consciousness (RoC) after analgosedation exposure has not been systematically described in critically-ill populations, and expectations regarding time to RoC after sedation cessation rely largely on clinical judgement.

Studies evaluating analgosedation in the intensive care unit (ICU) often group patient populations with different underlying etiologies, limiting interpretability and generalizability. Conversely, COVID-19-associated acute respiratory distress syndrome (ARDS) was the predominant etiology for ICU admission in metropolitan areas in the Northeastern United States in 2020. (6) Although sedative practices varied during the pandemic, and clinical endpoints were often difficult to achieve, (7) we reduced heterogeneity by studying ICU patients with unresponsiveness and ARDS from a single causative organism over a distinct time course.

Propofol and benzodiazepines have similar actions at the γ-aminobutyric acid type A ($GABA_A$) receptor and are the most commonly administered ICU sedatives, (8) including during the COVID-19 pandemic. (7) We previously demonstrated no association between total GABAergic sedative exposure and time to RoC in COVID-19 critical illness; (3) here, we explicitly test the hypothesis that prolonged unconsciousness following GABAergic sedative exposure can be attributed to sedation washout. In 784 patients across three institutions, we estimated the latest expected recovery of consciousness (LERoC) using a model that accounts for sedative-specific population pharmacokinetic elimination parameters and critical illness. Using LERoC as a threshold for “early” versus “late” RoC, we compared observed durations of unconsciousness to conservative predictions of sedative washout. Late RoC has also been

observed in post-cardiac arrest coma; though cerebral metabolic strain has been proposed as a mechanism, the contribution of individual variables to delayed RoC remains unknown. (9) Thus, using early RoC as a reference outcome, we examined associations between patient characteristics and late RoC, death, and discharge, with emphasis on disease-specific variables affecting neuronal downregulation (hypoxemia, impaired gas exchange, sedation duration). Lastly, among patients with late RoC, we examined the associations between clinical variables to time to RoC, which sometimes occurred weeks after GABAergic sedation cessation.

Methods

Patients

We included patients admitted to Massachusetts General Hospital (MGH), NewYork-Presbyterian Hospital/Columbia University Irving Medical Center (CUIMC), and NewYork-Presbyterian Hospital/Weill Cornell Medicine (WCM) with: (1) ICU admission following SARS-CoV-2 infection during Spring and Summer 2020, (2) invasive mechanical ventilation ≥24 hours, (3) intravenous infusion of GABAergic agent (propofol or benzodiazepine), (4) impairment of consciousness (Glasgow Coma Scale [GCS] motor subscore <6 from 6), (5) ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (P:F ratio) ≤300. We excluded patients who (1) died at cessation of GABAergic agent ("GABA cessation"), (2) were transferred from an outside facility >24 hours after intubation, (3) were transferred to an outside hospital, (4) underwent multiple intubations, or (5) had missing data (**Figure 1**). This study was approved by the Institutional Review Board of each participating site; see **Supplemental Methods** for more information.

Outcome

The primary outcome was time to recovery of consciousness (RoC), defined as the first GCS motor subscore of 6 following GABA cessation (**Supplemental Methods**). Patients were followed until RoC, in-hospital mortality, or hospital discharge.

Exposures

Primary exposures were recency-weighted cumulative exposures (WCEs) of GABAergic sedatives at GABA cessation: propofol and benzodiazepines (as intravenous midazolam equivalents (3)). Sedative exposures were weighted by time since administration using first-order kinetics (**Supplemental Methods**). (10) We additionally quantified WCEs of adjunct sedatives and analgesics at GABA cessation, including opioids (as intravenous fentanyl equivalents (11)), dexmedetomidine, and ketamine. Conservative elimination half-lives were used to reflect potential impaired clearance in critical illness: midazolam—24h, (5) propofol—7h, (12) opioids—10h, dexmedetomidine—3h, (5) ketamine—2.5h. (13)

Additional variables were defined as follows: Hypoxemia—PaO_2 <55 mmHg; acute kidney injury (AKI)—serum creatinine [SCr] ≥2x baseline on admission, SCr ≥4 mg/dL, or renal replacement therapy at any point between intubation and GABA cessation; (14) liver injury—serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level 5x upper limit of normal (using institution-specific laboratory thresholds). ARDS severity was categorized by the lowest P:F ratio during hospitalization: mild (201–300), moderate (101–200), severe (≤100). (15) Duration of GABAergic sedation was defined as days from intubation to GABA cessation. Opioid and benzodiazepine tapers were recorded given their routine use to prevent withdrawal (16, 17) and potential impact on RoC (**Supplemental Methods**).

Latest expected recovery of consciousness (LERoC)

The latest expected RoC (LERoC) is a conservative threshold of when a patient is expected to achieve RoC based solely on their GABAergic sedative exposure. It is defined as the latest of four time points following GABA cessation (time 0): five elimination half-lives after discontinuation of (1) propofol or (2) benzodiazepine (~97% elimination), or when propofol (3) or benzodiazepine (4) fell below a population median-derived threshold (**Supplemental Methods,** *weighted cumulative exposures* and *determination of LERoC* sections).

Outcome classification

Patients were classified into four mutually exclusive outcome categories relative to LERoC (**Figure 2a**). “Early events” occurred before LERoC, including patients who recovered consciousness (early RoC) and patients who either died or were discharged without RoC (early death/discharge). “Late events” occurred after LERoC and were also classified by outcome (late RoC, late death/discharge).

Statistical analyses

Multinomial model. We fit a multinomial regression model for outcomes of early RoC, early death/discharge, and late events. Early RoC was the reference category; relative risk ratios (RRR) were estimated for early death/discharge and late events. RRRs >1 indicate increased relative risk of death or prolonged unconsciousness. We adjusted for demographic and clinical covariates (hypoxemia, AKI, ARDS severity, intubation duration, benzodiazepine/opioid tapers), WCEs of opioids, dexmedetomidine, ketamine at GABA cessation, and their two-way interactions. Likelihood ratio tests were used to compare model fit with and without non-GABAergic sedative adjustment.

Time-to-event model. Among patients with late events, we fit a Fine-Gray subdistribution hazard model for time from LERoC (time 0) to RoC, accounting for the competing risk of death or discharge. (18, 19) Hazard ratios (HR) <1 indicate *delayed* events (RoC, death, or discharge). Covariate adjustment mirrored the multinomial model, excluding ketamine due to low exposure prevalence (n=13). Likelihood ratio tests were used to compare model fit with and without non-GABAergic sedative adjustment.

Sensitivity analyses

We assessed the sensitivity of our findings to pharmacokinetic variations in critically-ill patients by varying midazolam and propofol half-lives to (a) 16 and 5 hours, (b) 36 and 7 hours,

and (c) 24 and 24 hours, respectively. We also (d) excluded patients with AKI, (e) excluded patients with liver injury, and (f) adjusted for study site.

Results

784 patients were included: CUIMC (n=340), MGH (n=185), and WCM (n=259). Demographic and clinical characteristics by site are provided in **Table 1**. Mean age was 61.4 years (SD 14.1), and 509 (64.9%) patients were male. Patients predominantly had severe (74.4%, n=583) or moderate (23.9%, n=187) ARDS, and a mean mechanical ventilation duration of 17.0 days (SD 14.8). We identified 18 patients who received extracorporeal membrane oxygenation.

570 patients (72.7%) achieved RoC at a median of 1.25 days (IQR [0.21, 4.83]) following GABA cessation. The remaining 214 (27.3%) patients were followed for a median of 0.86 days (IQR [0.27, 4.12]). Among these, 195 (91.1%) died and 19 (8.9%) were discharged without RoC.

Among patients achieving RoC, 161 (28.2%) were discharged home, 124 (21.8%) to skilled nursing facilities, 66 (11.6%) to long-term care facilities, 193 (33.9%) to rehabilitation facilities, 3 (1.0%) to hospice, and 17 (3.0%) died.

Determinants of patient outcomes

Outcome categories included early RoC (48.3%), early death/discharge (19.1%), late RoC (24.4%), and late death/discharge (8.2%) (**Figure 2b)**. Sedative contributions to LERoC estimation are shown in **Supplemental Table 1** and **Supplemental Table 2**. Demographic, clinical, and analgosedative characteristics stratified by outcome are provided in **Supplemental Table 3** and **Supplemental Figure 3**.

Compared to early RoC, the relative risk of late events increased by 7% per year of age (RRR 1.07 [95% CI, 1.05–1.08]) (**Table 2**). The relative risk of late events was also increased with hypoxemia (RRR 2.01 [1.34–3.00]), AKI (RRR 2.07 [1.42–3.00]), and opioid tapers following GABA cessation (RRR 1.89 [1.25–2.86]). The relative risk of late events was decreased with higher dexmedetomidine WCE at GABA cessation (one-SD difference RRR

0.77 [0.62–0.95]). Relative risks of early death/discharge with respect to early RoC are described in **Supplemental Table 4.** Likelihood ratio testing demonstrated improved model fits with inclusion of non-GABAergic sedatives (12 degrees of freedom (df); p<0.001).

Discharge dispositions were not significantly different among patients with early versus late RoC when stratified by age, (**Table 3**). Dispositions stratified by outcome categories are provided in **Supplemental Table 5**.

Predicting time to RoC in patients with late events

HRs for time to late events are provided in **Table 2;** HRs <1 indicate delayed RoC. Among patients with late events, time to RoC was prolonged in patients with severe ARDS compared to mild/moderate ARDS (HR 0.44 [0.29–0.68]) and with higher opioid WCE at GABA cessation (one-SD difference HR 0.76 [0.62–0.94]). Higher dexmedetomidine WCE was associated with faster RoC (one-SD difference HR:1.21 [1.02–1.44]).

In patients with late events, death or discharge occurred later with longer duration of GABAergic sedation (one-day difference HR 0.97 [0.94–0.998]), and opioid tapers at GABA cessation (HR 0.38 [0.20–0.74]). Conversely, death or discharge occurred earlier in patients with AKI (HR 2.18 [1.18–4.05]) and higher opioid WCE at GABA cessation (one-SD difference HR 1.56 [1.11–2.19]). Likelihood ratio testing demonstrated improved model fits with inclusion of non-GABAergic sedatives for early death/discharge (3 df; p=0.022) and RoC (3 df; p=0.011).

Sensitivity analyses

Model estimates were robust to variation in half-lives and site adjustment (**Figure 3; Supplemental Figure 4; Supplemental Table 6**). When restricting analyses to patients without AKI, effect directions were largely preserved, however the association between hypoxia and late events was no longer significant. In time-to-event models, the HR for late RoC and late

death/discharge was no longer significant for opioid WCE and the HR for late death/discharge was no longer significant for opioid taper.

Discussion

We used a time-weighted model of analgosedative administration and pharmacokinetic elimination parameters to estimate LERoC, allowing a more rigorous assessment of sedative effects on time to RoC than previous reports of cumulative dose or sedation duration alone. (20-22) Consistent with prior work in critically-ill COVID patients, (3) total sedation exposure was not associated with time to RoC. In multinomial models, GABAergic sedation duration was significant but had a minimal (and negative) effect size. Model determinants were robust across a broad range of half-lives, suggesting that delayed RoC is not attributable to pharmacokinetic alterations alone.

Marked delays in RoC (12% ≥10 days) occurred well beyond expected drug elimination. Increased age was associated with late events. While the association of AKI with late events could reflect prolonged terminal elimination times exceeding our longest estimates, sensitivity analyses encompassed published terminal elimination times for active drug and metabolites of critically-ill patients. (23, 24) Alternatively, this association may reflect metabolic derangements from renal hypoperfusion independent of renal clearance. Hypoxemia remained associated with late events after accounting for sedative washout; although this association was lost when excluding patients with AKI, the effect direction remained in the reduced (~50%) sample size, possibly indicating type II error. Among patients with late events, graded ARDS severity was associated with prolonged time to RoC, supporting a graded effect of hypoxemia on neuronal function. Still, other unmeasured factors, including subclinical seizures, metabolic derangements, and encephalopathies (e.g., COVID-related vasculitides or neuroinflammation) may contribute to delayed RoC.

Delayed RoC *may reflect neuronal downregulation in the setting of limited metabolic reserve*

We hypothesize that late RoC reflects a “protective down-regulated state” (PDS), whereby a combination of hypoxemia, metabolic stress, and GABAergic sedation causes a global neuronal downregulation protecting neurons from further metabolic insults. (9) This phenomenon has been well characterized in anoxia-tolerant vertebrates experiencing hypothermia and limited oxygen supply in winter. (25, 26) The decreased cerebral metabolic rate of oxygen consumption from these conditions decreases ATP production and induces neuronal hyperpolarization *via* ATP-dependent potassium (K-ATP) channels. (25, 27) The process is maintained by marked (~80 fold) increases of endogenous GABA, which minimizes further ATP consumption and limits metabolic strain until conditions improve in the spring, with rapid recovery despite prolonged anoxia. (9)

A potential human PDS was first suggested in post-cardiac arrest patients with prolonged coma and eventual functional neurologic recovery after GABAergic sedation and therapeutic hypothermia, with RoC occurring 3–6 weeks after sedation cessation (28). We hypothesize that in patients with late RoC, the metabolic stress of COVID-19 infection, impaired gas exchange, and high sedation requirements could represent an analogous scenario. (9) Consistent with this hypothesis, hypoxemia was independently associated with late events, replicating our prior findings. (3) The association between older age and late RoC may reflect age-related limits on metabolic reserve, (29) such as those demonstrated with increased anesthetic sensitivity in aging. (30) Notably, discharge dispositions did not differ between early and late RoC when stratified by age, supporting preserved functional recovery despite delayed awakening. While this hypothesis is speculative, this unifying framework aligns with comparative biology and observed clinical courses, thus warranting further investigation, ideally substantiated with electroencephalography, functional neuroimaging, and/or biomarkers.

Choice of sedative regimen

Higher dexmedetomidine WCE at sedation cessation was associated with a *decreased* risk of late events and *hastened* time to RoC. This may reflect confounding by indication, as stable patients may better tolerate lighter sedation. However, dexmedetomidine has also been associated with shorter durations of delirium and coma compared to benzodiazepines, (31) potentially reducing ICU-related complications that may delay RoC (31-33). As a central α_2-adrenoceptor agonist, dexmedetomidine can reduce the release of neuronal inflammatory mediators and attenuate hypoxia-ischemia induced neuronal injury. (34, 35) Notably, in anoxia-tolerant vertebrates, the α_2 modulator adenosine plays an early role in initiating K-ATP channel activation in the setting of hypoxemia and increased GABA production. (36)

Opioid administration was associated with worse outcomes independent of sedative exposure. Higher opioid WCE was associated with increased early death/discharge, late events, and increased time to RoC. Opioid tapers were associated with an increased risk of late events, but also a decreased risk of early death/discharge. This association likely reflected confounding by indication, as patients with more severe illness, analgesic requirements, or agitation may have increased opioid requirements and/or opioid tapers. These findings may also reflect unmeasured clinical severity and underscore the need to identify strategies balancing analgesia with neurologic recovery in ARDS management.

Limitations

Our retrospective design limits causal inference. Key baseline variables that could influence RoC and disposition were unavailable, including prior functional status, chronic illness burden, and comorbidity measures. Additionally, potentially relevant in-hospital variables were missing, including standardized delirium assessments, sepsis, subclinical seizure, and measures of illness severity beyond ARDS classification. Model associations may have been attenuated due to adjustment of other variables (e.g., sedative exposure) on the causal pathway for the outcome. Long-term neurologic outcomes were unavailable, limiting assessment of the

impact of delayed RoC on functional recovery over time; however, discharge dispositions reflect a patient's clinical needs and abilities, and can provide partial insight into functional neurologic status.

Sedative choice was not randomized and reflected institutional practices, drug restrictions, drug availability, and clinician preference, making residual confounding by indication likely despite multivariable adjustment. Nevertheless, our findings were robust in sensitivity analyses adjusting for site. We could not assess less frequently administered agents, including barbiturates and ketamine. Prospective, randomized studies are needed to clarify relationships between sedative regimens and patient outcomes.

Due to the retrospective observational design, we were unable to determine patient-specific sedation pharmacokinetic profiles and sedative concentrations at time of GABAergic cessation. WCE calculations assumed simple first-order one-compartment pharmacokinetics, which can be influenced by individual susceptibility of GABA, μ-opioid, and glutamate receptors, (37) GABA receptor desensitization, (38) $GABA_A$ receptor subunit plasticity after exposure, (39) long-acting active metabolites (e.g., 1-hydroxymidazolam glucuronide), (40, 41) peripheral drug accumulation, (12) and heterogeneity in CYP450-mediated metabolism. (42) Propofol is best characterized using a three-compartment model, and benzodiazepines by two compartment models in critically-ill patients. (24, 43) In sensitivity analyses, we applied half-lives encompassing terminal elimination half-lives for active drug and metabolites reported for healthy volunteers and critically-ill patients from two- and three-compartment models (23) with robust results. Moreover, more complex models would remain vulnerable to patient variability and unmeasured illness effects.

The GCS motor subscore lacks the nuance of comprehensive behavioral assessments such as the Coma Recovery Scale-Revised. (44) GCS-based command following may be affected by delirium, sepsis, or neuromuscular weakness. Nonetheless, the GCS is the standard

ICU metric to assess level of consciousness, with good test-retest performance (45) and validated inter-rater reliability. (46, 47) In our critically-ill cohort, GCS assessments were performed at least every four hours, limiting RoC misclassification to hours and unlikely to meaningfully affect our results. Delirium is inherently fluctuating, making systematic failure to capture lucid intervals unlikely with this assessment frequency. Critical illness myopathy/polyneuropathy typically spares facial and ocular muscles, (48) allowing assessment of command following without limb movement. Residual neuromuscular blockade was unlikely as paralytics were discontinued a median of 10.3 days *before* GABA cessation.

The generalizability of our findings is limited. We focused our analysis to GABAergic sedatives and, in the absence of other sedatives and randomization of therapy, cannot comment on the clinical implications and/or utility of specific analgosedative regimens. Secondly, our findings reflect care delivered during the first wave of the COVID-19 pandemic, a period marked by a unique clinical population and clinical exigence. However, we previously showed consistent times to RoC in the first and second waves; (3) moreover, our observations are consistent with the clinical features and time course of patients with post-anoxic cardiac arrest coma. (28) Third, we excluded patients who died at GABA cessation and would not expect our findings to generalize to this sub-population. Further, our competing risks model only included patients who remained alive at LERoC; thus, patients in the time-to-event analysis may represent a more resilient subpopulation, and our findings cannot generalize to patients with early events. Latent frailty measures driving these processes may potentially be captured by joint modeling approaches which were not explored. Lastly, subgroup analyses, including time-to-event models (n=255) and analyses excluding patients with AKI (n=431), had limited sample size with wider confidence intervals, underscoring the need for cautious interpretation.

Summary

Among 784 critically-ill COVID patients, 73% achieved RoC before hospital discharge, however 34% of patients who achieved RoC did not do so within pharmacologically plausible elimination times. Late RoC was associated with older age, hypoxemia, and AKI. Discharge disposition did not significantly differ between early and late RoC when stratified by age, suggesting that time to RoC is uncoupled from functional status. Collectively, our results describe a phenomenon of late RoC that cannot be accounted for by sedation washout alone, may reflect profound neural downregulation, and does not by itself impair functional outcomes. Parallel observations in anoxia-tolerant vertebrates frame testable hypotheses for late RoC in critically-ill patients that go beyond sedation exposures alone. Ultimately, these data may inform clinical expectations and guide future studies to test determinants of neuronal downregulation and their functional implications for patient care.

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References

1. Bouchereau E, Sharshar T, Legouy C: Delayed awakening in neurocritical care. *Rev Neurol (Paris)* 2022; 178(1-2):21-33

2. Edlow BL, Claassen J, Victor JD, et al: Delayed reemergence of consciousness in survivors of severe COVID-19. *Neurocrit Care* 2020; 33(3):627-629

3. Waldrop G, Safavynia SA, Barra ME, et al: Prolonged Unconsciousness is Common in COVID-19 and Associated with Hypoxemia. *Ann Neurol* 2022; 91(6):740-755

4. Gurin L, Evangelist M, Laverty P, et al: Early Neurorehabilitation and Recovery from Disorders of Consciousness After Severe COVID-19. *Neurocrit Care* 2022; 36(2):357-371

5. Tse AHW, Ling L, Lee A, et al: Altered Pharmacokinetics in Prolonged Infusions of Sedatives and Analgesics Among Adult Critically Ill Patients: A Systematic Review. *Clin Ther* 2018; 40(9):1598-1615 e1592

6. Mathieu E, Ritchie H, Rodés-Guirao L, et al: Coronavirus Pandemic (COVID-19). ourworldindata.org, 2020,

7. Rucci JM, Law AC, Bolesta S, et al: Variation in Sedative and Analgesic Use During the COVID-19 Pandemic and Associated Outcomes. *CHEST Crit Care* 2024; 2(1)

8. Hughes CG, McGrane S, Pandharipande PP: Sedation in the intensive care setting. *Clin Pharmacol* 2012; 4:53-63

9. Schiff ND, Brown EN: Protective down-regulated states in the human brain: A possible lesson from COVID-19. *Proceedings of the National Academy of Sciences of the United States of America* 2022; 119(46):e2120221119

10. Abrahamowicz M, Bartlett G, Tamblyn R, et al: Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. *J Clin Epidemiol* 2006; 59(4):393-403

11. Patanwala AE, Duby J, Waters D, et al: Opioid conversions in acute care. *Ann Pharmacother* 2007; 41(2):255-266

12. Schuttler J, Ihmsen H: Population pharmacokinetics of propofol: a multicenter study. *Anesthesiology* 2000; 92(3):727-738

13. Hurth KP, Jaworski A, Thomas KB, et al: The Reemergence of Ketamine for Treatment in Critically Ill Adults. *Critical care medicine* 2020; 48(6):899-911

14. Machado MN, Nakazone MA, Maia LN: Acute kidney injury based on KDIGO (Kidney Disease Improving Global Outcomes) criteria in patients with elevated baseline serum creatinine undergoing cardiac surgery. *Rev Bras Cir Cardiovasc* 2014; 29(3):299-307

15. Force ADT, Ranieri VM, Rubenfeld GD, et al: Acute respiratory distress syndrome: the Berlin Definition. *JAMA : the journal of the American Medical Association* 2012; 307(23):2526-2533

16. Ego A, Halenarova K, Creteur J, et al: How to Manage Withdrawal of Sedation and Analgesia in Mechanically Ventilated COVID-19 Patients? *J Clin Med* 2021; 10(21)

17. Wang PP, Huang E, Feng X, et al: Opioid-associated iatrogenic withdrawal in critically ill adult patients: a multicenter prospective observational study. *Ann Intensive Care* 2017; 7(1):88

18. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999; 94(446):496-509

19. Wolkewitz M, Lambert J, von Cube M, et al: Statistical Analysis of Clinical COVID-19 Data: A Concise Overview of Lessons Learned, Common Errors and How to Avoid Them. *Clin Epidemiol* 2020; 12:925-928

20. Aragon RE, Proano A, Mongilardi N, et al: Sedation practices and clinical outcomes in mechanically ventilated patients in a prospective multicenter cohort. *Critical care* 2019; 23(1):130

21. Jakob SM, Ruokonen E, Grounds RM, et al: Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA : the journal of the American Medical Association* 2012; 307(11):1151-1160

22. Zaal IJ, Devlin JW, Hazelbag M, et al: Benzodiazepine-associated delirium in critically ill adults. *Intensive care medicine* 2015; 41(12):2130-2137

23. Gepts E, Camu F, Cockshott ID, et al: Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg* 1987; 66(12):1256-1263

24. Swart EL, Zuideveld KP, de Jongh J, et al: Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; 57(2):135-145

25. Lutz PL, Nilsson GE: Vertebrate brains at the pilot light. *Respir Physiol Neurobiol* 2004; 141(3):285-296

26. Fernandes JA, Lutz PL, Tannenbaum A, et al: Electroencephalogram activity in the anoxic turtle brain. *Am J Physiol* 1997; 273(3 Pt 2):R911-919

27. Hochachka PW: Defense strategies against hypoxia and hypothermia. *Science* 1986; 231(4735):234-241

28. Forgacs PB, Devinsky O, Schiff ND: Independent Functional Outcomes after Prolonged Coma following Cardiac Arrest: A Mechanistic Hypothesis. *Ann Neurol* 2020; 87(4):618-632

29. Demetrius LA, Magistretti PJ, Pellerin L: Alzheimer's disease: the amyloid hypothesis and the Inverse Warburg effect. *Frontiers in physiology* 2014; 5:522

30. Purdon PL, Pavone KJ, Akeju O, et al: The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. *British journal of anaesthesia* 2015; 115 Suppl 1:i46-i57

31. Pandharipande PP, Pun BT, Herr DL, et al: Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA : the journal of the American Medical Association* 2007; 298(22):2644-2653

32. Duprey MS, Devlin JW, van der Hoeven JG, et al: Association Between Incident Delirium Treatment With Haloperidol and Mortality in Critically Ill Adults. *Critical care medicine* 2021; 49(8):1303-1311

33. Ely EW, Shintani A, Truman B, et al: Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA : the journal of the American Medical Association* 2004; 291(14):1753-1762

34. Baserga M, DuPont TL, Ostrander B, et al: Dexmedetomidine Use in Infants Undergoing Cooling Due to Neonatal Encephalopathy (DICE Trial): A Randomized Controlled Trial: Background, Aims and Study Protocol. *Front Pain Res (Lausanne)* 2021; 2:770511

35. Ren X, Ma H, Zuo Z: Dexmedetomidine Postconditioning Reduces Brain Injury after Brain Hypoxia-Ischemia in Neonatal Rats. *J Neuroimmune Pharmacol* 2016; 11(2):238-247

36. Pek M, Lutz PL: Role for adenosine in channel arrest in the anoxic turtle brain. *J Exp Biol* 1997; 200(Pt 13):1913-1917

37. Schnider TW, Minto CF, Gambus PL, et al: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; 88(5):1170-1182

38. Mody I, Pearce RA: Diversity of inhibitory neurotransmission through GABA(A) receptors. *Trends Neurosci* 2004; 27(9):569-575

39. Liang J, Suryanarayanan A, Abriam A, et al: Mechanisms of reversible GABAA receptor plasticity after ethanol intoxication. *J Neurosci* 2007; 27(45):12367-12377

40. Boulieu R, Lehmann B, Salord F, et al: Pharmacokinetics of midazolam and its main metabolite 1-hydroxymidazolam in intensive care patients. *Eur J Drug Metab Pharmacokinet* 1998; 23(2):255-258

41. Meridian Medical Technologies: Seizalam (midazolam injection). Package insert. St. Louis, MO, Meridian Medical Technologies,, 2018,

42. Lin JH, Lu AY: Role of pharmacokinetics and metabolism in drug discovery and development. *Pharmacol Rev* 1997; 49(4):403-449

43. Sahinovic MM, Struys M, Absalom AR: Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clin Pharmacokinet* 2018; 57(12):1539-1558

44. Giacino JT, Kalmar K, Whyte J: The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004; 85(12):2020-2029

45. Reith FC, Van den Brande R, Synnot A, et al: The reliability of the Glasgow Coma Scale: a systematic review. *Intensive care medicine* 2016; 42(1):3-15

46. Fischer M, Ruegg S, Czaplinski A, et al: Inter-rater reliability of the Full Outline of UnResponsiveness score and the Glasgow Coma Scale in critically ill patients: a prospective observational study. *Critical care* 2010; 14(2):R64

47. Kebapci A, Dikec G, Topcu S: Interobserver Reliability of Glasgow Coma Scale Scores for Intensive Care Unit Patients. *Crit Care Nurse* 2020; 40(4):e18-e26

48. Hermans G, Van den Berghe G: Clinical review: intensive care unit acquired weakness. *Critical care* 2015; 19(1):274

Figure Captions

Figure 1. CONSORT diagram. Counts within each box for each exclusion criterion are not mutually exclusive, i.e., individuals can meet multiple exclusion criteria within each box. The overall count of patients excluded is provided above these counts and is summarized by site.

[a]Spring and Summer 2020 defined as 3/1/2020 – 6/30/2020 for MGH, 3/1/2020 – 5/16/2020 for WCMC, and 3/1/2020 – 9/1/2020 for CUIMC

[b]WCM excluded patients with documented P:F ratio ≤ 300 between intubation and the end of follow up

[c]Patients may be missing height and/or weight data

[d]Patients with multiple ICU stays but only one intubation and GABAergic sedative record were included

Figure 2. Outcome classification. **(a)** Categorization of patient outcomes with respect to Latest Expected Recovery of Consciousness (LERoC). Outcomes between GABA cessation and LERoC are referred to as “early events”, and outcomes following LERoC are referred to as “late events”. Early RoC (green) includes patients who experienced RoC before LERoC; early death/discharge (orange) includes patients who died or were discharged without RoC before LERoC; late RoC (red) includes patients who experienced RoC after LERoC; late death/discharge (blue) includes patients who died or were discharged without RoC after LERoC. **(b)** Observed outcomes relative to LERoC. Patients in the upper scatterplot experience RoC before death or discharge, and patients in the lower scatterplot experience death or discharge before RoC. Dashed diagonal lines are lines of identity and represent the time at which observed events would equal LERoC. Patients with time to RoC greater than 20.5 days are shown in dark red (n=27; maximum of 68 days) and patients with time to death without RoC

greater than 20.5 days are shown with dots in dark blue (n=10; maximum of 62 days). In our multinomial models, we compared patients with late events (both late RoC [red] and late death/discharge [blue]) and patients with early death/discharge (orange) to patients with early RoC (green) as our reference condition. In time-to-event models, only patients with late events (blue and red) were analyzed

Figure 3. Sensitivity analysis results for multinomial and time-to-event models. For the multinomial model, the reference category is early RoC. Relative risk ratios > 1 indicate increased risk of late RoC. For time-to-event models, a hazard ratio <1 indicates delayed events (RoC, death, or discharge). Point estimates and 95% confidence intervals are displayed for each covariate for each of the different sensitivity analyses. In the primary analysis, the midazolam half-life is assumed to be 24 hours and the propofol half-life is assumed to be 7 hours. Sensitivity 1, 2, and 3 refer to the three sensitivity analyses, where the 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. An arrow indicates that the upper 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

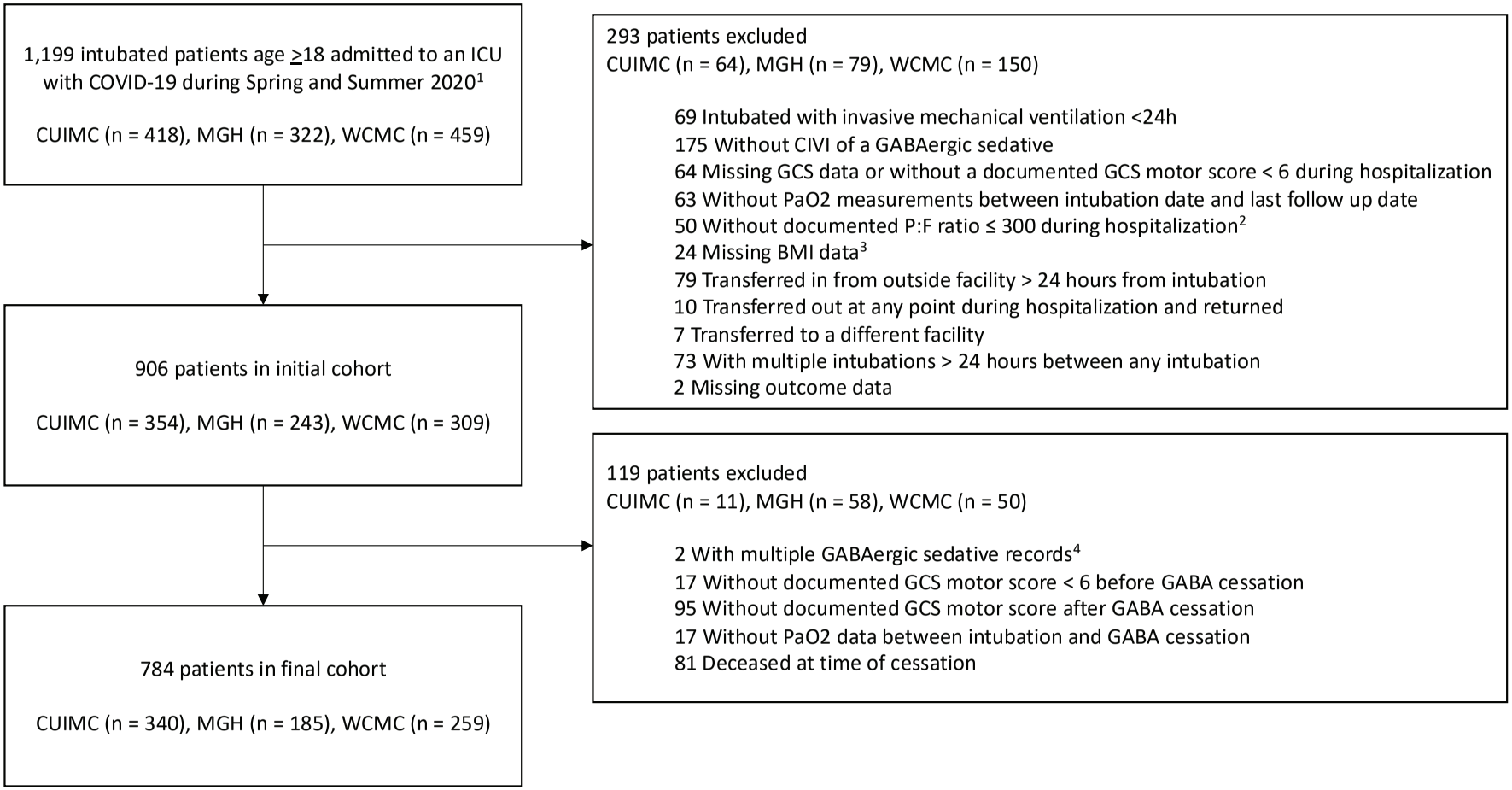
1,199 intubated patients age ≥18 admitted to an ICU with COVID-19 during Spring and Summer 2020[1]
CUIMC (n = 418), MGH (n = 322), WCMC (n = 459)
293 patients excluded
CUIMC (n = 64), MGH (n = 79), WCMC (n = 150)
69 Intubated with invasive mechanical ventilation <24h
175 Without CIVI of a GABAergic sedative
64 Missing GCS data or without a documented GCS motor score < 6 during hospitalization
63 Without PaO2 measurements between intubation date and last follow up date
50 Without documented P:F ratio ≤ 300 during hospitalization[2]
24 Missing BMI data[3]
79 Transferred in from outside facility > 24 hours from intubation
10 Transferred out at any point during hospitalization and returned
7 Transferred to a different facility
73 With multiple intubations > 24 hours between any intubation
2 Missing outcome data
906 patients in initial cohort
CUIMC (n = 354), MGH (n = 243), WCMC (n = 309)
119 patients excluded
CUIMC (n = 11), MGH (n = 58), WCMC (n = 50)
2 With multiple GABAergic sedative records[4]
17 Without documented GCS motor score < 6 before GABA cessation
95 Without documented GCS motor score after GABA cessation
17 Without PaO2 data between intubation and GABA cessation
81 Deceased at time of cessation
784 patients in final cohort
CUIMC (n = 340), MGH (n = 185), WCMC (n = 259)

Figure 1

Figure 2

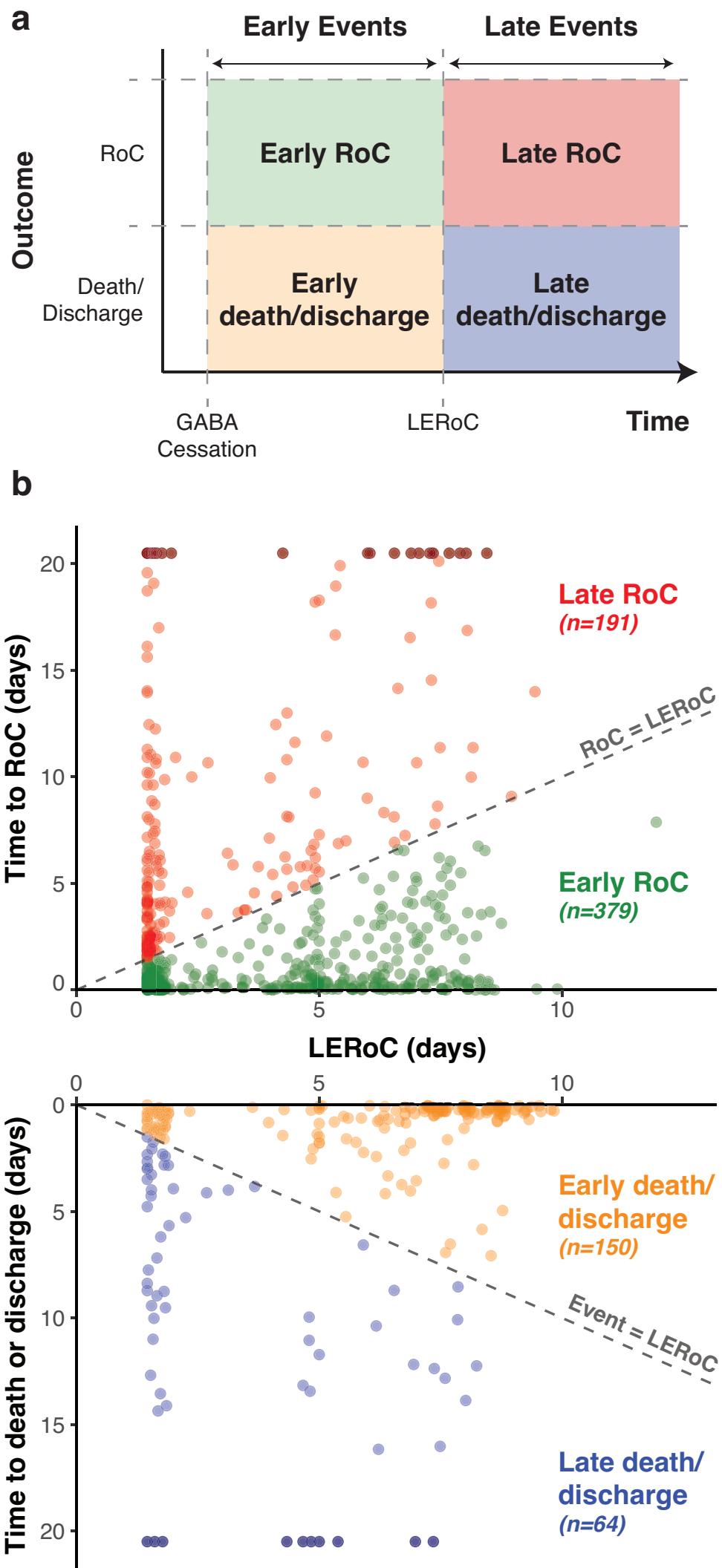
a
Early Events
Late Events
Outcome
RoC
Death/
Discharge
Early RoC
Late RoC
Early
death/discharge
Late
death/discharge
GABA
Cessation
LERoC
Time
b
Time to RoC (days)
LERoC (days)
Late RoC
(n=191)
RoC = LERoC
Early RoC
(n=379)
Time to death or discharge (days)
Early death/
discharge
(n=150)
Event = LERoC
Late death/
discharge
(n=64)

Figure 3

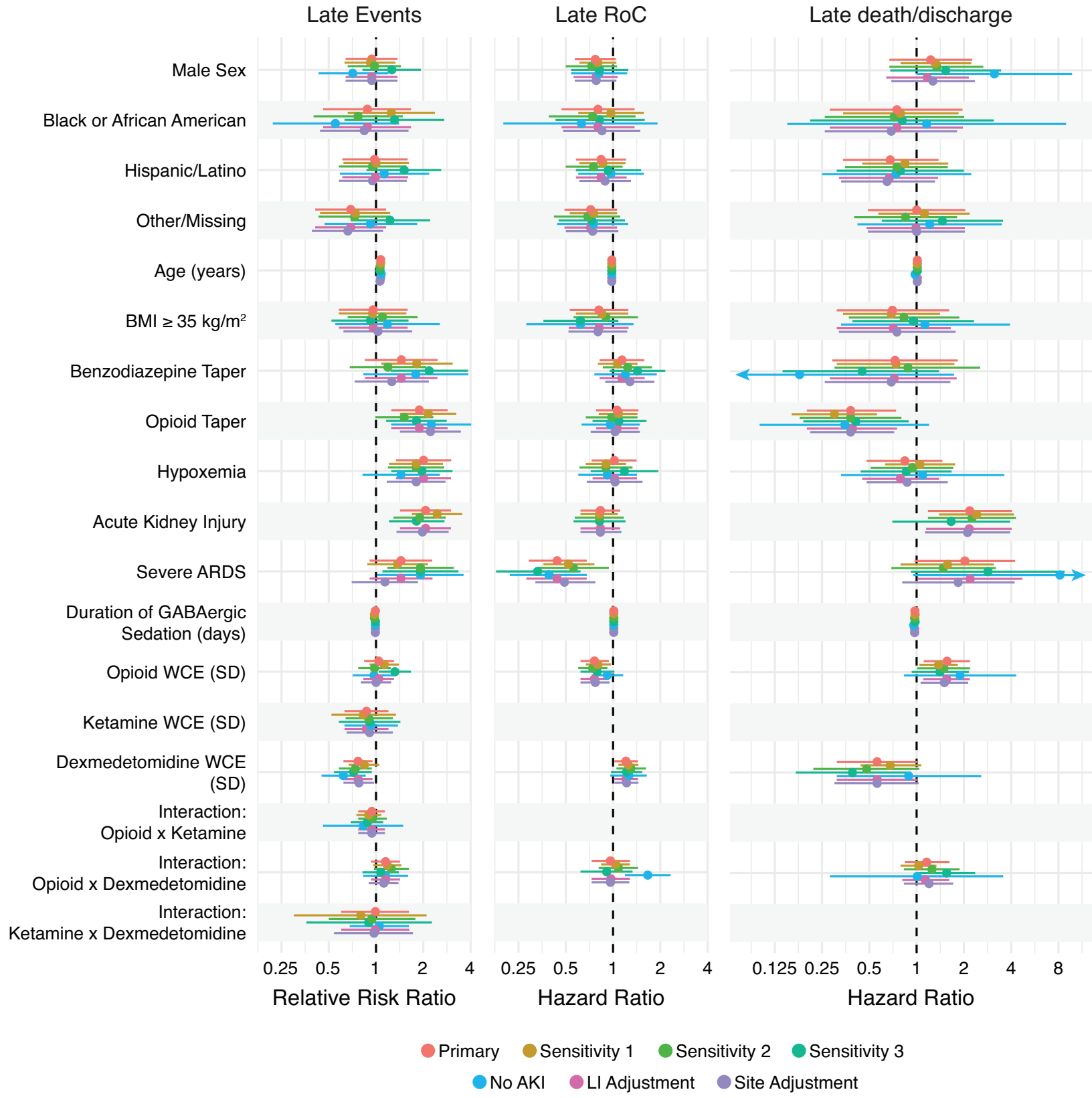
Late Events
Late RoC
Late death/discharge
Male Sex
Black or African American
Hispanic/Latino
Other/Missing
Age (years)
BMI ≥ 35 kg/m²
Benzodiazepine Taper
Opioid Taper
Hypoxemia
Acute Kidney Injury
Severe ARDS
Duration of GABAergic Sedation (days)
Opioid WCE (SD)
Ketamine WCE (SD)
Dexmedetomidine WCE (SD)
Interaction: Opioid x Ketamine
Interaction: Opioid x Dexmedetomidine
Interaction: Ketamine x Dexmedetomidine
0.25 0.5 1 2 4
0.25 0.5 1 2 4
0.125 0.25 0.5 1 2 4 8
Relative Risk Ratio
Hazard Ratio
Hazard Ratio
Primary
Sensitivity 1
Sensitivity 2
Sensitivity 3
No AKI
LI Adjustment
Site Adjustment

Table 1

Table 1 Demographics and sedative use, overall and stratified by site

	Overall	CUIMC	MGH	WCM
n	784	340	185	259
Male Sex (%)	509 (64.9)	216 (63.5)	119 (64.3)	174 (67.2)
Race/Ethnicity (%)				
White	159 (20.3)	43 (12.6)	45 (24.3)	71 (27.4)
Black	92 (11.7)	50 (14.7)	19 (10.3)	23 (8.9)
Hispanic or Latino	322 (41.1)	172 (50.6)	81 (43.8)	69 (26.6)
Other/Missing	211 (26.9)	75 (22.1)	40 (21.6)	96 (37.1)
Age, years (mean (SD))	61.4 (14.1)	61.9 (13.6)	57.7 (14.2)	63.3 (14.2)
BMI, kg/m^2 (mean (SD))	29.9 (6.8)	29.8 (7.3)	31.2 (6.2)	29.3 (6.3)
BMI ≥ 35 kg/m^2 (%)	141 (18.0)	55 (16.2)	45 (24.3)	41 (15.8)
Hypoxemia (%)	398 (50.8)	162 (47.6)	40 (21.6)	196 (75.7)
Acute Kidney Injury (%)	353 (45.0)	207 (60.9)	65 (35.1)	81 (31.3)
Liver Injury (%)	306 (39.0)	127 (37.4)	64 (34.6)	115 (44.4)
ARDS Severity				
Mild (P:F 201-300)	14 (1.8)	2 (0.6)	9 (4.9)	3 (1.2)
Moderate (P:F 101-200)	187 (23.9)	46 (13.5)	95 (51.4)	46 (17.8)
Severe (P:F ≤100)	583 (74.4)	292 (85.9)	81 (43.8)	210 (81.1)
Days of mechanical ventilation (mean (SD))	17.0 (14.8)	18.8 (16.7)	16.6 (11.1)	14.9 (14.2)
Days from hospital admission to GABA cessation (median [IQR])	16.3 [9.1, 25.3]	15.4 [6.6, 28.2]	15.8 [10.8, 23.0]	16.9 [10.8, 25.5]
Paralytic agent administration (%)	512 (65.3)	185 (54.4)	136 (73.5)	191 (73.7)
Days from last paralytic administration to GABA cessation (median [IQR])	10.3 [4.1, 17.3]	9.8 [2.1, 17.8]	14.7 [10.3, 20.5]	6.7 [3.1, 13.0]
Sedation Exposures				
Any benzodiazepine before cessation (%)	597 (76.1)	310 (91.1)	140 (75.7)	147 (56.8)
Any propofol before cessation (%)	744 (94.9)	300 (88.2)	185 (100)	259 (100)
Any barbiturate before cessation (%)	15 (1.9)	0 (0)	14 (7.6)	1 (0.4)
Any opioid before cessation (%)	780 (99.5)	339 (99.7)	185 (100)	256 (98.8)

Any ketamine before cessation (%)	120 (15.3)	27 (7.9)	79 (42.7)	14 (5.4)
Any dexmedetomidine before cessation (%)	521 (66.5)	231 (67.9)	159 (85.9)	131 (50.6)
Benzodiazepine WCE, mg/kg (mean (SD))	0.57 (1.36)	1.02 (1.84)	0.34 (0.72)	0.14 (0.55)
Propofol WCE, mg/kg (mean (SD))	12.66 (10.85)	7.14 (9.72)	14.18 (9.32)	21.73 (11.02)
Opioid WCE, mg/kg (mean (SD))	0.0214 (0.0227)	0.0286 (0.0249)	0.0145 (0.0190)	0.0170 (0.0191)
Ketamine WCE, mg/kg (mean (SD))	0.0460 (0.3447)	0.0135 (0.1250)	0.1589 (0.6712)	0.0080 (0.0826)
Dexmedetomidine WCE, mg/kg (mean (SD))	0.0016 (0.0026)	0.0014 (0.0023)	0.0026 (0.0035)	0.0010 (0.0020)
Benzodiazepine Taper (%)	110 (14.0)	64 (18.8)	17 (9.2)	29 (11.2)
Opioid Taper (%)	234 (29.8)	104 (30.6)	98 (53.0)	32 (12.4)

Data presented as number (percentage) or mean (standard deviation). WCEs are calculated at time of GABA cessation. Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CUIMC, Columbia University Irving Medical Center; IQR, interquartile range; MGH, Massachusetts General Hospital; SD, standard deviation; WCE, weighted cumulative exposure; WCM, Weill Cornell Medicine

Table 2 Multinomial and Time-to-Event model results

	Multinomial Model (n=784 overall)		Time-to-Event Model (n=255)			
Variable	**Late events (n=255) RRR**	**p-value**	**Late RoC HR**	**p-value**	**Late death/discharge HR**	**p-value**
Male Sex	0.94 [0.64, 1.37]	0.73	0.77 [0.57, 1.04]	0.09	1.23 [0.67, 2.26]	0.51
Race/Ethnicity (reference White)						
Black	0.88 [0.46, 1.67]	0.68	0.80 [0.47, 1.37]	0.42	0.75 [0.28, 1.96]	0.55
Hispanic/Latino	0.98 [0.61, 1.59]	0.93	0.84 [0.58, 1.21]	0.35	0.68 [0.34, 1.38]	0.29
Other/Missing	0.69 [0.41, 1.16]	0.16	0.72 [0.49, 1.06]	0.1	1.00 [0.49, 2.04]	0.99
Age (years)	1.07 [1.05, 1.08]	<0.001	0.98 [0.97, 1.00]	0.02	1.01 [0.98, 1.03]	0.53
BMI ≥ 35 kg/m^2	0.96 [0.58, 1.59]	0.87	0.81 [0.53, 1.25]	0.35	0.70 [0.31, 1.61]	0.41
Benzodiazepine Taper	1.45 [0.85, 2.47]	0.17	1.14 [0.82, 1.58]	0.44	0.73 [0.29, 1.83]	0.5
Opioid Taper	1.89 [1.25, 2.86]	0.002	1.06 [0.78, 1.45]	0.7	0.38 [0.20, 0.74]	0.004
Hypoxemia	2.01 [1.34, 3.01]	<0.001	1.02 [0.73, 1.41]	0.92	0.84 [0.48, 1.46]	0.54
Acute Kidney Injury	2.07 [1.42, 3.00]	<0.001	0.83 [0.62, 1.11]	0.21	2.18 [1.18, 4.05]	0.01
Severe ARDS	1.44 [0.91, 2.28]	0.12	0.44 [0.29, 0.68]	<0.001	2.03 [0.97, 4.24]	0.06
Duration of GABAergic sedation (days)	0.99 [0.97, 0.999]	0.03	1.01 [1.001, 1.02]	0.03	0.97 [0.94, 0.998]	0.04
Opioid WCE (SD)	1.04 [0.84, 1.30]	0.7	0.76 [0.62, 0.94]	0.01	1.56 [1.11, 2.19]	0.01
Ketamine WCE (SD)	0.87 [0.63, 1.20]	0.38	-	-	-	-
Dexmedetomidine WCE (SD)	0.77 [0.62, 0.95]	0.02	1.21 [1.02, 1.44]	0.03	0.56 [0.31, 1.01]	0.06
Interaction: Opioid*Ketamine	0.94 [0.77, 1.14]	0.52	-	-	-	-
Interaction: Opioid*Dexmedetomidine	1.15 [0.93, 1.42]	0.2	0.96 [0.73, 1.28]	0.8	1.16 [0.84, 1.62]	0.37
Interaction: Ketamine*Dexmedetomidine	0.99 [0.60, 1.62]	0.95	-	-	-	-

Multinomial model uses early RoC (n=379) as reference category; results for early death/discharge (n=150) are provided in **Supplementary Table 4**. 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; HR, hazard ratio; L-DD, late death/discharge; LE, late events; LEROC, latest expected recovery of command following; L-ROC, late recovery of command following; ROC, recovery of command following; RRR, relative risk ratio; SD, standard deviation; WCE, weighted cumulative exposure

Table 3. Discharge dispositions among patients with RoC, stratified by age

Age Group	**<50**		**50-59**	
Outcome	**Early RoC (n=123)**	**Late RoC (n=17)**	**Early RoC (n=95)**	**Late RoC (n=32)**
Hospital LOS (median [IQR])	29.9 [17.9, 52.9]	46.5 [37.6, 63.3]	31.1 [22.9, 42.4]	60.6 [39.9, 73.5]
Discharge Status (%)				
Home	56 (45.5)	9 (52.9)	30 (31.6)	8 (25.0)
Inpatient Rehabilitation	40 (32.5)	6 (35.3)	37 (38.9)	12 (37.5)
Skilled Nursing Facility	8 (6.5)	2 (11.8)	14 (14.7)	10 (31.2)
Long Term Care	16 (13.0)	0 (0)	12 (12.6)	1 (3.1)
Hospice	1 (0.8)	0 (0)	0 (0)	0 (0)
Death	0 (0.0)	0 (0)	1 (1.1)	0 (0)
Other†	2 (1.6)	0 (0)	1 (1.1)	1 (3.1)
p-value*	0.56		0.19	
Age Group	**60-69**		**≥70**	
Outcome	**Early RoC (n=104)**	**Late RoC (n=68)**	**Early RoC (n=57)**	**Late RoC (n=74)**
Hospital LOS (median [IQR])	38.1 [26.7, 58.3]	64.5 [40.2, 80.7]	34.3 [22.6, 60.2]	49.2 [39.4, 70.9]
Discharge Status (%)				
Home	22 (21.2)	10 (14.7)	13 (22.8)	13 (17.6)
Inpatient Rehabilitation	36 (34.6)	24 (35.3)	13 (22.8)	25 (33.8)
Skilled Nursing Facility	29 (27.9)	20 (29.4)	18 (31.6)	23 (31.1)
Long Term Care	13 (12.5)	11 (16.2)	5 (8.8)	8 (10.8)
Hospice	0 (0)	1 (1.5)	1 (1.8)	0 (0)
Death	4 (3.8)	1 (1.5)	6 (10.5)	5 (6.8)
Other†	0 (0)	1 (1.5)	1 (1.8)	0 (0)
p-value*	0.57		0.55	

*p-value estimations *via* Fisher exact test with Monte Carlo method (1×10^6 simulations).
†Other category includes intercampus transfer between NewYork-Presbyterian sites (Columbia University Irving Medical Center/Weill Cornell Medicine), leaving against medical advice, and short-term care facility. Abbreviations: IQR, interquartile range; LOS, length of stay; RoC, recovery of consciousness