

Prolonged Unconsciousness is Common in COVID-19 and Associated with Hypoxemia

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Objective: The purpose of this study was to estimate the time to recovery of command-following and associations between hypoxemia with time to recovery of command-following.

Methods: In this multicenter, retrospective, cohort study during the initial surge of the United States' pandemic (March–July 2020) we estimate the time from intubation to recovery of command-following, using Kaplan Meier cumulative-incidence curves and Cox proportional hazard models. Patients were included if they were admitted to 1 of

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3 hospitals because of severe coronavirus disease 2019 (COVID-19), required endotracheal intubation for at least 7 days, and experienced impairment of consciousness (Glasgow Coma Scale motor score <6).

Results: Five hundred seventy-one patients of the 795 patients recovered command-following. The median time to recovery of command-following was 30 days (95% confidence interval [CI] = 27–32 days). Median time to recovery of command-following increased by 16 days for patients with at least one episode of an arterial partial pressure of oxygen (PaO₂) value ≤55 mmHg ($p < 0.001$), and 25% recovered ≥10 days after cessation of mechanical ventilation. The time to recovery of command-following was associated with hypoxemia (PaO₂ ≤55 mmHg hazard ratio [HR] = 0.56, 95% CI = 0.46–0.68; PaO₂ ≤70 HR = 0.88, 95% CI = 0.85–0.91), and each additional day of hypoxemia decreased the likelihood of recovery, accounting for confounders including sedation. These findings were confirmed among patients without any imaging evidence of structural brain injury (n = 199), and in a non-overlapping second surge cohort (N = 427, October 2020 to April 2021).

Interpretation: Survivors of severe COVID-19 commonly recover consciousness weeks after cessation of mechanical ventilation. Long recovery periods are associated with more severe hypoxemia. This relationship is not explained by sedation or brain injury identified on clinical imaging and should inform decisions about life-sustaining therapies.

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Hundreds of thousands of people with coronavirus disease 2019 (COVID-19) have been or are currently being treated for acute respiratory distress syndrome (ARDS) in intensive care units (ICUs) worldwide.¹ However, for survivors of severe COVID-19,² the re-emergence of consciousness is often prolonged,³ leading to clinical and ethical uncertainty surrounding neurologic prognosis and goals of care.⁴ Given the uncertainty of recovery, clinicians and families often make management decisions, including withdrawal of life-sustaining therapy, without evidence-based guidance regarding the likelihood and time course of meaningful recovery.

Early in the pandemic, we and others observed a high incidence of prolonged disorders of consciousness (DoC) in patients with ARDS from severe COVID-19,^{2,5–7} often in those with prior hypoxemia.^{4,5,8,9} Emerging evidence suggests long-term cognitive deficits among ARDS cohorts, but neurocognitive outcomes have yet to be evaluated among these patients.¹⁰

Here, in a multicenter, retrospective study of 795 intubated patients with severe COVID-19 at three medical centers during the initial surge (March–July 2020), and a separate analysis during the second surge (n=427 October 2020 to April 2021), we determined the time to recovery of command-following and its association with hypoxemia. Our findings have immediate implications for the ongoing supportive care of critically ill patients with severe COVID-19.

Methods

Patients

This study includes data from New York Presbyterian Hospital/Columbia University Irving Medical Center (CUIMC), Massachusetts General Hospital (MGH), and New York Presbyterian Hospital/Weill Cornell Medical College (WCRC). Inclusion criteria were: (1) clinical presentation with severe COVID-19²; (2) admission to an ICU between March 1, 2020, and July 31, 2020; (3) endotracheal

intubation for at least 7 days; and (4) impairment of consciousness (defined as a Glasgow Coma Scale [GCS] motor score <6¹¹) on day 7 of intubation. Patients were excluded if they were transferred from an outside hospital more than 24 hours after intubation, had greater than one intubation with at least 24 hours between intubations, or if there was never a documented partial pressure of arterial oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) ratio (P:F ratio) <300. After data collection and analysis of the initial surge, an additional out-of-sample cohort was analyzed from the second surge (October 2020 to April 2021) using the same inclusion criteria. Data were retrospectively extracted from electronic medical records.

Variables

Our primary outcome was recovery of consciousness, specifically recovery of command-following, defined as a GCS⁹ motor score of 6 following a GCS motor score <6. The GCS assessments were performed and documented at least once daily as part of standard nursing clinical assessments, which includes the use of translators when needed. Many patients had multiple episodes of recovery of command-following by our definition, many of which were transient (eg, daily sedative interruptions); we thus based our analysis on the time of the last recovery of command-following during hospitalization.

Hypoxemia, the primary exposure, was defined as a PaO₂ value below a set threshold following intubation and before recovery of command-following or discharge. We considered two thresholds: 55 mmHg, the lower limit of ARDSNet protocols¹⁰; and 70 mmHg, the approximate median value of ARDSNet protocols. Days with hypoxemia were defined as the number of days with at least one PaO₂ value meeting criteria for hypoxemia during hospitalization. Days with hypoxemia need not be consecutive.

Potential confounders included other known mechanisms of disorders of consciousness through hypoxic neuronal injury,⁷ including anemic hypoxia (hemoglobin <7 mg/dl) and ischemic hypoxia (mean arterial pressure

<65 mmHg), as well as known confounders affecting level of consciousness (sedation, renal failure, hepatic insufficiency, and carbon dioxide narcosis). Cumulative doses of sedation and opioid analgesia from intubation to recovery of command-following or discharge were quantified in midazolam-equivalents and fentanyl-equivalents, respectively.¹² Unlike opioid equianalgesic conversions, benzodiazepine conversions are based on expert opinion and clinical practice. All sedatives except ketamine were converted to midazolam equivalents as follows: 1 mg midazolam = 0.5 mg lorazepam = 0.125 mg clonazepam = 0.25 mg alprazolam = 1.25 mg diazepam = 10 mg chlordiazepoxide = 40 mg propofol = 14.82 mcg dexmedetomidine. Cumulative ketamine doses were reported independently. Renal failure was defined as the use of any method of continuous renal replacement therapy (CRRT) during admission. Hepatic insufficiency was defined as aspartate aminotransferase (U/L) or alanine aminotransferase values (U/L) over 5 times the upper limit of normal for each hospital laboratory. Maximum partial pressure of arterial CO₂ (PaCO₂) was defined as the highest PaCO₂ (mmHg) at any time from intubation to death, discharge, or recovery of command-following.

Brain imaging reports, including computed tomography (CT) and magnetic resonance (MRI), were reviewed and categorized into acute injury, chronic findings, acute on chronic findings, or no pathology identified. Imaging was not included if it occurred after recovery of command-following and contained acute findings. Acute injury was defined as acute stroke, acute hemorrhage, new mass lesion, abscess, or evidence of hypoxic ischemic injury. Chronic injury was defined as stroke (large territory or lacunar), hemorrhage, mass lesion (without edema), or neurosurgical intervention (eg, ventriculoperitoneal shunt and surgical cavity). Imaging with isolated chronic white matter changes of any variety were categorized as no pathology identified.

Severity of ARDS was based on Berlin criteria¹³ and defined by P:F ratio, calculated using the nearest-time respective values. Duration of mechanical ventilation was defined as the time of intubation to the time that mechanical ventilation was no longer required (extubation or tracheostomy without mechanical ventilation), rounded to the nearest day. Pooled data are presented without weighted pooling methods, given the nearly equal sample size at each of the 3 sites.^{14–16}

Statistical Analysis

Demographics, clinical factors, laboratory tests, and medications were compared between cohorts and between hypoxemia thresholds (PaO₂ ≤55 mmHg, ≤70 mmHg) using

t tests for continuous data that were normally distributed, Wilcoxon rank-sum tests for non-normally distributed continuous variables, and chi-square or Fisher's exact test for categorical variables.

Our primary analyses, determined a priori, included patients from the initial surge (March–July 2020) who were alive and not following motor commands at day 7 of intubation, with hypoxemia occurring any time from intubation until the recovery of command-following or discharge. Unadjusted Kaplan–Meier cumulative incidence curves and median times to recovery of command-following were performed for both hypoxemia thresholds and days of hypoxemia, using log-rank tests for comparison. Cox proportional-hazards regression models estimated the hazard of hypoxemia on the time to recovery of command-following at each site and in a pooled analysis. The pooled analysis was performed using Cox proportional-hazard models with random effects for site, a shared frailty model. Patients entered the analysis on the day of intubation and were censored on the date of death if death occurred before recovery of command-following, or on the date of hospital discharge if the patient never recovered command-following. The adjusted models included the exposures of interest and a priori defined confounders of age, sex, race/ethnicity, lowest P:F ratio on the day of intubation, cumulative doses of midazolam-, fentanyl-, and ketamine-equivalents, days of continuous sedation, days of continuous neuromuscular blockade, and use of CRRT. Complete case analyses were used, as all variables included in the models contained <1% missing data.

Sensitivity analyses included multivariable Cox regressions, including a continuous covariate for maximum PaCO₂ per person, including minimum PaO₂ per person as primary exposure variable, including hypoxemia as a time-varying covariate and replacing time origin as time from GABA-ergic sedative cessation rather than intubation. Death before recovery of command-following was assessed as a competing risk of recovery of command-following using 2 different competing risk models: (1) a proportional subdistribution hazards model accounting for gamma frailty and (2) a semiparametric, Weibull proportional hazard model with cluster-specific random effects. AKaplan–Meier cumulative incidence curves were performed in patients from the second surge. Among patients in the initial surge additional Kaplan Meier cumulative incidence curves were performed 1) only among patients without structural brain injury identified on neuroimaging (performed before recovery of command-following) 2) stratified by quartiles of duration of continuous intravenous sedative infusions 3) stratified by quartiles of cumulative midazolam equivalents.

All statistical calculations and modeling were performed in STATA-16 (StataCorp, College Station, TX)

except for the Cox shared frailty models with competing risk using gamma distribution, which were performed using R statistical software, version 3.4.1 (R Project for Statistical Computing). Alpha values remained at 0.05 for all analyses. The protocol for this study received approval by the Institutional Review Board at Columbia University Medical Center, Mass General Brigham, and Weill Cornell Medical Center.

Results

Initial Surge

A total of 795 patients with severe COVID-19 (21,932 person-days) were included from the initial surge; CUIMC n = 333 (10,013 person-days), MGH n = 208 (4,857 person-days), and WCMC n = 254 (7,062 person-days; Fig 1). The overall median time to recovery of command-following was 30 days (interquartile range

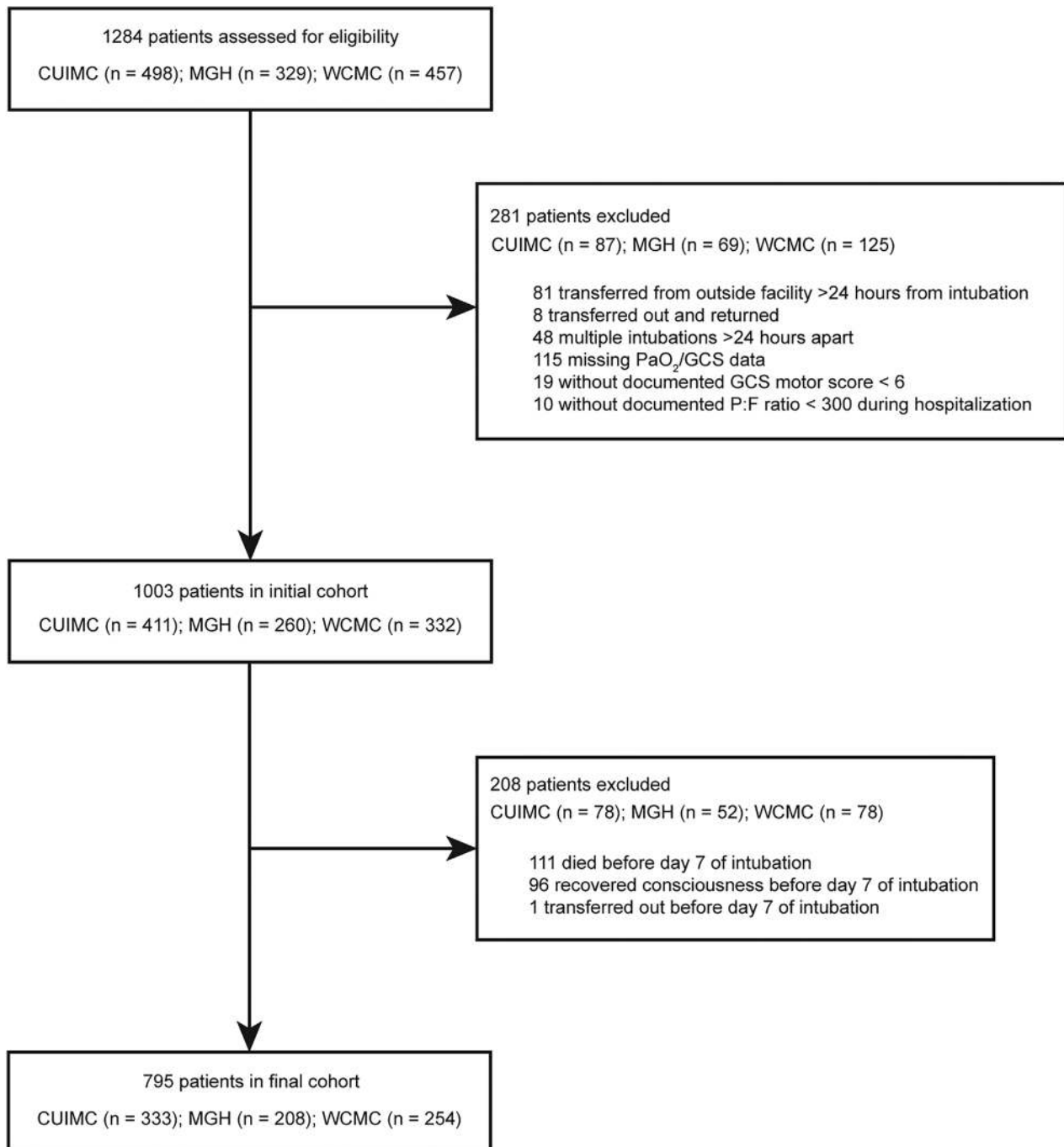


FIGURE 1: Participants, initial surge (March–July 2020). CUIMC = Columbia University Irving Medical Center; GCS = Glasgow Coma Scale; MGH = Massachusetts General Hospital; PaO₂ = arterial partial pressure of oxygen; WCMC = Weill Cornell Medical College.

[IQR] = 27–32 days). The mean age was 62 years (standard deviation [SD] = 14), 537 (68%) were men, and 388 (49%) were obese. Most patients were Hispanic or Latino ($n = 236$, 30%) or White ($n = 164$, 21%) with moderate ($n = 358$, 45%) to severe ARDS ($n = 316$, 40%) on the day of intubation.¹³

There were 422 (53%) patients with hypoxemia $\text{PaO}_2 \leq 55$ mmHg and 732 (92%) with hypoxemia $\text{PaO}_2 \leq 70$ mmHg, at least once (Tables 1 and 2). There were 310 (39%) patients with minimum PaO_2 values between 56 and 70 at least once. The median minimum PaO_2 value was 54 mmHg (IQR = 48–60). The median number of days with $\text{PaO}_2 \leq 55$ mmHg and $\text{PaO}_2 \leq 70$ mmHg was 1 (IQR = 0–2) and 6 (IQR = 3–12), respectively. A total of 571 patients (72%) recovered command-following before discharge, 190 (24%) died before recovery, and 34 (4%) did not recover command-following before discharge. Among the 571 patients who recovered, 336 (64%) recovered command-following after cessation of mechanical ventilation (days from cessation of mechanical ventilation to recovery of command-following IQR = 1–10). Furthermore, for 25% of patients, command-following emerged ≥ 10 days and 10% ≥ 23 days after cessation of mechanical ventilation. The mean number of ventilator free days within the first 28 days was 9 (SD = 9), and at day 28, 75% of all patients no longer required mechanical ventilation.

At hospital discharge, 140 (18%) patients were discharged home, 145 (18%) to a rehabilitation facility, 133 (17%) to a skilled nursing facility, 265 (33%) had died, and 5 (1%) to hospice. Differences between those with and without hypoxemia included race/ethnicity, lowest pulse oximetry value on day of intubation, severity of ARDS at intubation, CRRT use, cumulative analgesic and sedative exposure, and length of stay (Tables 1–4). Differences in patient characteristics among the 3 sites included demographics and severity of illness (Table S1).

$\text{PaO}_2 \leq 55$ mmHg

Unadjusted, pooled Kaplan–Meier cumulative incidence curves demonstrated an increase in median time to recovery of command-following of 16 days for those with $\text{PaO}_2 \leq 55$ mmHg compared to those without (Fig 2A). Further, compared to patients without $\text{PaO}_2 \leq 55$ mmHg we observed an increase in median time to recovery of command-following of 9 days for patients with 1 day of $\text{PaO}_2 \leq 55$ mmHg, and an increase of 21 days for patients with $\text{PaO}_2 \leq 55$ mmHg for 2 or more days (see Fig 2B). Individual sites also demonstrated increased median times to recovery of command-following for patients with $\text{PaO}_2 \leq 55$ mmHg compared to those without (CUIMC 13 days; MGH 11 days; and WCMC 18 days [log-rank $p < 0.001$]).

Pooled, univariate Cox regression demonstrated a 59% decreased likelihood of recovery of command-following before discharge for those with at least one $\text{PaO}_2 \leq 55$ mmHg compared to those without (hazard ratio [HR] = 0.41, 95% confidence interval [CI] = 0.34–0.49, $p < 0.001$). After adjusting for demographics, level of sedation, and severity of illness, there remained a 44% decreased likelihood of recovery of command-following before discharge among patients with $\text{PaO}_2 \leq 55$ mmHg compared to those without (HR = 0.56, 95% CI = 0.46–0.68, $p < 0.001$). Similarly, adjusted for the same variables, there was a 12% decreased likelihood of recovery of command-following before discharge for each additional day with at least one $\text{PaO}_2 \leq 55$ mmHg (HR = 0.88, 95% CI = 0.85–0.91, $p < 0.001$; Fig 3, Table S2).

In addition to hypoxemia, variables that were associated with later recovery in our multivariable models included days of continuous intravenous analgesedation, cumulative midazolam equivalents, cumulative fentanyl equivalents, days on continuous intravenous paralytics, use of CRRT, age, and male sex (Table S3).

$\text{PaO}_2 \leq 70$ mmHg

Unadjusted, pooled Kaplan–Meier cumulative incidence curves demonstrated an increase in median time to recovery of command-following of 18 days for those with $\text{PaO}_2 \leq 70$ mmHg compared to those without (Fig 4A). Compared to patients without $\text{PaO}_2 \leq 70$ mmHg, we observed an increase in median time to recovery of command-following of 1 day for patients with 1 day of $\text{PaO}_2 \leq 70$ mmHg, and of 20 days for patients with $\text{PaO}_2 \leq 70$ mmHg for 2 or more days (see Fig 4B).

Pooled, univariate analysis demonstrated a 75% decreased likelihood of recovery of command-following before discharge for those with at least one $\text{PaO}_2 \leq 70$ mmHg compared to those without (HR = 0.25, 95% CI = 0.18–0.35, $p < 0.001$). After adjusting for demographics, level of sedation, and severity of illness, the relationship lost significance (HR = 0.85, 95% CI = 0.85–1.19). Adjusting for the same variables, each additional day of $\text{PaO}_2 \leq 70$ mmHg incurred, on average, a 6% decreased likelihood of recovery of command-following before discharge (HR = 0.94, 95% CI = 0.93–0.95, $p < 0.001$; see Fig 3, Table S2).

Sensitivity Analyses

Sensitivities including treating death as a competing risk, including maximum PaCO_2 as covariate in multivariable regression models, modeling hypoxemia as a linear covariate, modeling hypoxemia as a time-varying covariate and including time origin as GABA-ergic sedation cessation (all

TABLE 1. Demographic, Behavioral, Clinical Variables by Hypoxemia (PaO₂ ≤55 mmHg)

	No hypoxemia (N = 373)	Hypoxemia (N = 422)	p value
Demographics			
Age, mean (SD)	62 (14)	63 (14)	0.08
Male sex	252 (68)	285 (68)	0.99
Race/ethnicity			0.02
White	89 (24)	75 (18)	
Black or African American	41 (11)	51 (12)	
Black, Hispanic, or Latino	11 (3)	8 (2)	
Hispanic or Latino	122 (33)	114(27)	
White, Hispanic, or Latino	22 (6)	41 (10)	
Asian	37 (10)	53 (13)	
Unknown or not described	51 (14)	80 (19)	
Obese (BMI ≥30, kg/m ²)	188 (50)	200 (47)	0.38
Clinical characteristics at intubation			
Lowest SpO ₂	84 (77–88)	78 (67–85)	<0.001
Lowest P:F ratio			<0.001
Not ARDS (P:F >300)	16 (4)	14 (3)	
Mild ARDS (P:F 201–300)	60 (16)	25 (6)	
Moderate ARDS (P:F 101–200)	183 (49)	175 (42)	
Severe ARDS (P:F < 100)	113 (30)	203 (48)	
MAP <65 (mmHg)	268 (72)	315 (74)	0.43
Lowest platelet count (10 ³ /μl)	232 (172–309)	235 (174–319)	0.56
Maximum creatinine (mg/dl)	1 (1–1)	1 (1–2)	0.89
Behavioral assessment			
Number of GCS assessments	55 (32–87)	76 (41–130)	<0.001
Number of days with GCS motor <6	14 (8–20)	20 (12–34)	<0.001
Number of days GCS total ≤8	18 (10–27)	24 (14–42)	<0.001
Number of days with RASS score –4 or –5	11 (7–17)	16 (9–24)	<0.001
Clinical characteristics throughout hospital course			
SARS-COV-2 positive	368 (99)	421 (100)	0.07
Number of PaO ₂ values	52 (32–85)	97 (59–150)	<0.001
Days of PaO ₂ ≤55 mmHg			<0.001

TABLE 1. Continued

	No hypoxemia (N = 373)	Hypoxemia (N = 422)	p value
None	373 (100)	0 (0)	
1 day	0 (0)	164 (39)	
≥2 days	0 (0)	258 (61)	
Days of PaO ₂ ≤70 mmHg			<0.001
None	63 (17)	0 (0)	
1 day	45 (12)	7 (2)	
≥2 days	262 (71)	418 (98)	
SpO ₂ < 84%	229 (61)	325 (77)	<0.001
Lowest SpO ₂	81 (68–86)	75 (58–83)	<0.001
Maximum PaCO ₂ (mmHg)	61 (52–72)	75 (62–90)	<0.001
Lowest P:F ratio			<0.001
Mild ARDS (P:F 201–300)	14 (4)	1 (0)	
Moderate ARDS (P:F 101–200)	160 (43)	53 (13)	
Severe ARDS (P:F < 100)	199 (53)	368 (87)	
Highest plateau pressure (mmHg)	29 (26–34)	33 (29–40)	<0.001
Highest PEEP (mmHg)	15 (12–18)	15 (12–18)	0.49
MAP <65 (mmHg)	365 (98)	421 (100)	0.01
Hemoglobin <7 (g/dl)	173 (46)	287 (68)	<0.001
Lowest platelet count (10 ³ /μl)	234 (161–361)	236 (147–396)	0.52
Maximum creatinine (mg/dl)	2 (1–6)	3(1–5)	0.92
Total bilirubin ≥2 (mg/dl)	101 (27)	141 (33)	0.06
Hepatic insufficiency	123 (33)	156 (37)	0.22
CRRT	104 (28)	140 (33)	0.1
ECMO	4 (1)	19 (5)	<0.001

hypoxemia occurring before entry) confirmed the above findings, although magnitudes of HRs differed (Table S2). The effect of hypoxemia, including dose -reponse was confirmed in Kaplan-Meier cumulative incidence curves stratified by quartiles of duration of intravenous sedation and cumulative midazolam equivalents. (Figures S1-S5). The relationship of delayed recovery for those with a PaO₂ ≤70 mmHg was not exclusively determined by patients with PaO₂ measurements ≤55 mmHg, as patients with lowest PaO₂ values between

TABLE 2. Sedation and Outcome Variables by Hypoxemia (PaO₂ ≤ 55 mmHg)

	No hypoxemia (N = 373)	Hypoxemia (N = 422)	p value
Sedation			
Days of continuous sedative infusion	14 (8–20)	19 (12–28)	<0.001
Cumulative midazolam equivalents (mg)	1,817 (891–3,710)	3,224 (1,560–6,224)	<0.001
Cumulative fentanyl equivalents (mg)	53 (21–98)	83 (39–196)	<0.001
Cumulative ketamine dose (mg) ^a	701(100–1,341)	2,481 (902–6,597)	0.03
Days of continuous paralytic infusion	0 (0–1)	1 (0–6)	<0.001
Outcome			
Days of mechanical ventilation	16 (10–23)	22 (15–35)	<0.001
Days from intubation to neuroimaging	16 (6–25)	25 (16–35)	<0.001
Ventilator free days (days 1–28)	12 (5–18)	6 (0–13)	<0.001
Breathing without assistance by day 28	327 (88)	270 (64)	<0.001
Recovered consciousness	276 (74)	295 (70)	0.20
Death before recovery of consciousness	79 (21)	111 (26)	0.09
Change of code status to comfort care	56 (15)	42 (10)	0.03
Length of stay (days)	28 (18–46)	43 (26–66)	<0.001
Discharge disposition			0.03
Home	71 (19)	69 (16)	
Inpatient rehabilitation	63 (17)	82 (19)	
Skilled nursing	78 (21)	55 (13)	
Hospice	3 (1)	2 (1)	
Death	116 (31)	149 (35)	
Other/not recorded	42 (11)	65 (15)	

Data are displayed as N (column %) or median (interquartile range) unless otherwise indicated. The *p* values calculated using 2-sided *t* test between means, Wilcoxon rank sum between medians, Fisher's exact or chi-square between proportions where indicated.

SI conversions: for platelet counts multiply by 1 for 10⁹/l, for serum creatinine multiply by 76.25 for mmol/l, for serum hemoglobin multiply by 10 for g/l, for serum bilirubin multiply by 17.104 μmol/l, for hepatic insufficiency defined as 5 times upper limit of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), multiply each by 0.0167 for μkat/l.

^aMedian (IQR) reported for those that received ketamine as only 4% of the cohort received ketamine infusion.

ARDS = acute respiratory distress syndrome; BMI = body mass index; CRRT = continuous renal replacement therapy; dl = deciliter; ECMO extracorporeal membrane oxygenation; g = gram; GCS = Glasgow Coma Scale; MAP = mean arterial pressure; mg = milligram; mmHg = millimeters of mercury; PaCO₂ = partial pressure of arterial carbon dioxide; PaO₂ = partial pressure of arterial oxygen; P:F = ratio of partial pressure of arterial oxygen over fraction of inspired oxygen; PEEP = positive end-expiratory pressure; RASS = Richmond Agitation Sedation Scale; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SpO₂ = pulse oximetry measure of oxygen saturation; μl = microliter.

56 and 70 mmHg also had prolonged time to recovery compared to those with PaO₂ values >70 mmHg (Fig 4C,F).

Structural Brain Injury

Head imaging was performed during admission for 322 (41%) of patients. Of these, 199 (62%) had no evidence of acute or chronic structural injury, 52 (16%) had evidence of acute structural brain injury before recovery of

command-following, 40 (12%) had evidence of chronic structural injury, and 31 (10%) had evidence of acute or chronic structural injury before recovery of command-following. Although there was a significantly greater proportion of patients with hypoxemia imaged, there were no significant differences in the proportion of patients with structural injury or type of structural injury across hypoxic thresholds, including days of hypoxemia (Table 5).

TABLE 3. Demographic, Behavioral, Clinical Variables by Hypoxemia (PaO₂ ≤70 mmHg)

	No hypoxemia (N = 63)	Hypoxemia (N = 732)	p value
Demographics			
Age, mean (SD)	64 (13)	62 (14)	0.26
Male sex	40 (61)	500 (68)	0.2
Race/ethnicity			0.64
White	14 (21)	151 (21)	
Black or African American	10 (15)	82 (11)	
Black, Hispanic, or Latino	2 (3)	17 (2)	
Hispanic or Latino	19 (29)	218 (30)	
White, Hispanic, or Latino	5 (8)	59 (8)	
Asian	10 (15)	80 (11)	
Unknown or not described	6 (9)	125 (17)	
Obese (BMI ≥ 30, kg/m ²)	30 (46)	359 (49)	0.57
Clinical characteristics at intubation			
Lowest SpO ₂	85 (79–90)	81 (71–87)	<0.001
Lowest P:F ratio			<0.001
Not ARDS (P:F >300)	8 (12)	25 (3)	
Mild ARDS (P:F 201–300)	18 (27)	67 (9)	
Moderate ARDS (P:F 101–200)	30 (46)	328 (45)	
Severe ARDS (P:F < 100)	10 (15)	306 (42)	
MAP <65 (mmHg)	267 (405)	315 (43)	0.42
Lowest platelet count (103/μl)	200 (158–275)	232 (169–307)	0.03
Maximum creatinine (mg/dl)	2 (1–3)	1 (1–2)	0.06
Behavioral assessment			
Number of GCS assessments	31 (14–60)	86 (41–184)	<0.001
Number of days with GCS motor <6	10 (5–15)	17 (10–28)	<0.001
Number of days with RASS score -4 or -5	8 (2–11)	14 (9–21)	<0.001
Clinical characteristics throughout hospital course			
SARS-COV-2 positive	59 (90)	640 (87)	0.64
Number of PaO ₂ values	26.5 (16–40)	79 (47–123)	<0.001
SpO ₂ < 84%	26 (39)	529 (72)	<0.001
Lowest SpO ₂	84 (77–88)	78 (62–84)	<0.001
Maximum PaCO ₂ (mmHg)	50 (46–62)	70 (57–83)	<0.001
Lowest P:F ratio	3 (5)	0 (0)	

TABLE 3. Continued

	No hypoxemia (N = 63)	Hypoxemia (N = 732)	p value
Mild ARDS (P:F 201–300)	13 (20)	2 (0)	
Moderate ARDS (P:F 101–200)	29 (44)	184 (25)	
Severe ARDS (P:F < 100)	21 (32)	546 (75)	
Highest plateau pressure (mmHg)	28 (24–33)	32 (27–38)	<0.001
Highest PEEP (mmHg)	11 (8–16)	14 (8–16)	0.03
MAP <65 (mmHg)	63 (96)	726 (99)	0.01
Hemoglobin <7 (g/dl)	28 (42)	433 (59)	0.01
Lowest platelet count (103/μl)	232 (148–357)	229 (152–362)	0.9
Maximum creatinine (mg/dl)	2 (1–7)	2 (1–5)	0.81
Total bilirubin ≥2 (mg/dl)	7 (11)	235 (32)	<0.001
Hepatic insufficiency	10 (16)	269 (37)	0.02
CRRT	22 (33)	223 (31)	0.63
ECMO	0 (0)	23 (3)	0.14

Unadjusted, pooled Kaplan–Meier cumulative incidence curves demonstrated an increase in median time to recovery of command-following of 18 days for those with PaO₂ ≤55 mmHg (41 days; 95% CI = 37–46) compared to those without (23 days; 95% CI = 20–26; Fig 5A). Compared to patients without PaO₂ ≤55 mmHg, there was an increase in median time to recovery of command-following of 13 days for patients with 1 day of PaO₂ ≤55 mmHg (36 days; 95% CI = 24–39), and of 23 days for patients with PaO₂ ≤55 mmHg for 2 or more days (46 days; 95% CI = 39–49; see Fig 5B). Unadjusted, pooled, Kaplan–Meier cumulative incidence curves also demonstrated an increase in median time to recovery of command-following of 15 days for those with PaO₂ ≤70 mmHg (35 days; 95% CI = 29–38) compared to those without (20 days; 95% CI = 1–25; see Fig 5C). Compared to patients without PaO₂ ≤70 mmHg, there was an increase in median time to recovery of command-following of 5 days for patients with 1 day of PaO₂ ≤70 mmHg (25 days; 95% CI = 21–27) and of 21 days for patients with PaO₂ ≤70 mmHg for two or more days (41 days; 95% CI = 37–46; see Fig 5D).

TABLE 4. Sedation and Outcome Variables by Hypoxemia (PaO₂ ≤ 70 mmHg)

Sedation			
Days of continuous sedative infusion	6 (2–11)	17 (11–26)	<0.001
Cumulative midazolam equivalents (mg)	525 (178–1,932)	2,615 (1,381–5,659)	<0.001
Cumulative fentanyl equivalents (mg)	18 (2–46)	69 (34–148)	<0.001
Cumulative ketamine dose (mg) ^a	7,723 (100–19,824)	6,040 (1,574–20,774)	0.55
Days of continuous paralytic infusion	1 (0–2)	3 (0–7)	<0.001
Outcome			
Days of mechanical ventilation	10 (7–15)	20 (13–29)	<0.001
Days from intubation to neuroimaging	3 (–5–10)	21 (12–32)	<0.001
Ventilator free days (days 1–28)	18 (13–21)	8 (0–15)	<0.001
Breathing without assistance by day 28	58 (92)	539 (74)	<0.01
Recovered consciousness	47 (71)	539 (74)	0.67
Death before recovery of consciousness	12 (18)	178 (24)	0.26
Change of code status to comfort care	9 (14)	89 (12)	0.73
Length of stay (days)	23 (14–37)	37 (22–60)	<0.001
Discharge disposition			0.14
Home	13 (20)	128 (18)	
Inpatient rehabilitation	6 (9)	139 (19)	
Skilled nursing	14 (21)	121 (17)	
Hospice	0 (0)	5 (0)	
Death	28 (42)	237 (32)	
Other/not recorded	5 (8)	102 (14)	

Data are displayed as N (column %) or median (interquartile range) unless otherwise indicated. The *p* values calculated using two-sided *t*-test between means, Wilcoxon rank sum between medians, Fisher's exact or Chi-square between proportions where indicated.

SI conversions: for platelet counts multiply by 1 for 10⁹/l, for serum creatinine multiply by 76.25 for mmol/l, for serum hemoglobin multiply by 10 for g/l, for serum bilirubin multiply by 17.104 μmol/l, for hepatic insufficiency defined as 5 times upper limit of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), multiply each by 0.0167 for μkat/l.

^aMedian (interquartile range) reported for those that received ketamine as only 4% of the cohort received ketamine infusion.

ARDS = acute respiratory distress syndrome; BMI = body mass index; CRRT = continuous renal replacement therapy; dl = deciliter; ECMO = extracorporeal membrane oxygenation; g = gram; GCS = Glasgow Coma Scale; MAP = mean arterial pressure; mg = milligram; mmHg = millimeters of mercury; PaCO₂ = partial pressure of arterial carbon dioxide; PaO₂ = partial pressure of arterial oxygen; PEEP = positive end-expiratory pressure; P/F = ratio of partial pressure of arterial oxygen over fraction of inspired oxygen; RASS = Richmond Agitation Sedation Scale; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SpO₂ = pulse oximetry measure of oxygen saturation; μl = microliter.

Second Surge

A total of 587 patients were assessed with 427 patients included in analysis of the second surge representing 11,169 person-days: CUMC *n* = 175 (4,973 person-days), MGH *n* = 89 (1,757 person-days), and WCMC *n* = 163 (4,440 person-days). There were 227 (53%) patients with at least one episode of hypoxemia PaO₂ ≤ 55 mmHg and 394 (92%) with hypoxemia

PaO₂ ≤ 70 mmHg. A total of 255 patients (60%) recovered command-following, 139 (33%) died before recovery of command-following, and 33 (8%) did not recover command-following before discharge. The median overall time to recovery of command-following was 32 days (IQR = 28–37 days). Unadjusted, pooled Kaplan–Meier cumulative incidence curves demonstrated an increase in median time to recovery of command-following of

TABLE 5. Patients with Head Imaging Among the Initial Surge (March–July 2020)

	Imaging available		Injury on imaging ^a			Acuity of injury				Total	
	No	Yes	<i>p</i> value	None	Present ^a	<i>p</i> value	Acute	Acute on Chronic	Chronic		<i>p</i> value
Total	473	322		199	123		52	17	54		795
PaO ₂ > 55	235 (63)	138 (37)	0.055	85 (62)	53 (38)	1.00	20 (38)	5 (9)	28 (53)	0.18	373
PaO ₂ ≤ 55	238 (56)	184 (44)		114 (62)	70 (38)		32 (46)	12 (17)	26 (37)		422
PaO ₂ > 70	47 (75)	16 (25)	0.009	11 (69)	5 (31)	0.61	2 (40)	1 (20)	2 (40)	0.77	63
PaO ₂ ≤ 70	426 (58)	306 (42)		188 (61)	118 (39)		50 (42)	16 (14)	52 (44)		732
PaO ₂ > 70	47 (75)	16 (25)		11 (69)	5 (31)		2 (40)	1 (20)	2 (20)		63
PaO ₂ 55–70	188 (61)	122 (39)	0.018	74 (61)	48 (39)	0.52	18 (38)	4 (8)	26 (54)	0.32	310
PaO ₂ ≤ 55	238 (56)	184 (44)		114 (62)	70 (38)		32 (46)	12 (17)	26 (37)		422
Days PaO ₂ ≤ 55											
0	235 (63)	138 (37)		85 (62)	53 (38)		20 (38)	5 (9)	28 (53)		373
1	96 (59)	68 (41)	0.13	45 (66)	23 (34)	0.85	10 (43)	5 (22)	8 (35)	0.40	164
2	142 (55)	116 (45)		69 (59)	47 (41)		22 (47)	7 (15)	18 (38)		258
Days PaO ₂ ≤ 70											
0	47 (75)	16 (25)		11 (69)	5 (31)		2 (40)	1 (20)	2 (40)		63
1	36 (69)	16 (31)	0.0087	6 (38)	10 (63)	0.11	5 (50)	0 (0)	5 (50)	0.74	52
2	390 (57)	290 (43)		182 (63)	108 (37)		45 (42)	16 (15)	47 (44)		680

Head imaging includes both computed tomography (CT) and magnetic resonance imaging (MRI). Data displayed as N (%) unless otherwise indicated. The *p* values calculated using 2-sided Fisher's exact test for proportions.

PaO₂ = partial pressure of arterial oxygen.

^aInjury on head imaging defined as any brain abnormality identified except for isolated chronic microvascular changes or non-specific findings (eg, artifact degradation).

24 days for those with PaO₂ ≤ 55 mmHg (45 days; 95% CI = 39–49) compared to those without (21 days; 95% CI = 18–24; see Fig 2C). Compared to patients without PaO₂ ≤ 55 mmHg, there was an increase in median time to recovery of command-following of 11 days for patients with 1 day of PaO₂ ≤ 55 mmHg (30 days; 95% CI = 24–39), and of 34 days for patients with PaO₂ ≤ 55 mmHg for 2 or more days (55 days; 95% CI = 47–67; see Fig 2D). Unadjusted, pooled, Kaplan–Meier cumulative incidence curves also demonstrated an increase in median time to recovery of command-following of 23 days for those with PaO₂ ≤ 70 mmHg (33 days; 95% CI = 29–41) compared to those without (10 days; 95% CI = 8–15; see Fig 4D). Compared to patients without PaO₂ ≤ 70 mmHg, there was an increase in median time to recovery of command-following of 6 days for patients with 1 day of PaO₂ ≤ 70 mmHg (16 days; 95% CI = 11–24) and

of 29 days for patients with PaO₂ ≤ 70 mmHg for 2 or more days (39 days; 95% CI = 31–43; see Fig 4E).

Discussion

The results of this multicenter, retrospective cohort study demonstrate that in patients with severe COVID-19 recovery of command-following 30 days after intubation is common if supportive care is provided. Prolonged unconsciousness is associated with hypoxemic events in a dose-dependent manner. Hypoxemia remains associated with time to recovery of command-following in severe COVID-19, adjusting for demographics, sedation exposures, and disease severity. This prolonged time to recovery, particularly exhibited in patients with hypoxemia, was observed in 3 large medical centers, and confirmed in patients without evidence of structural brain injury on

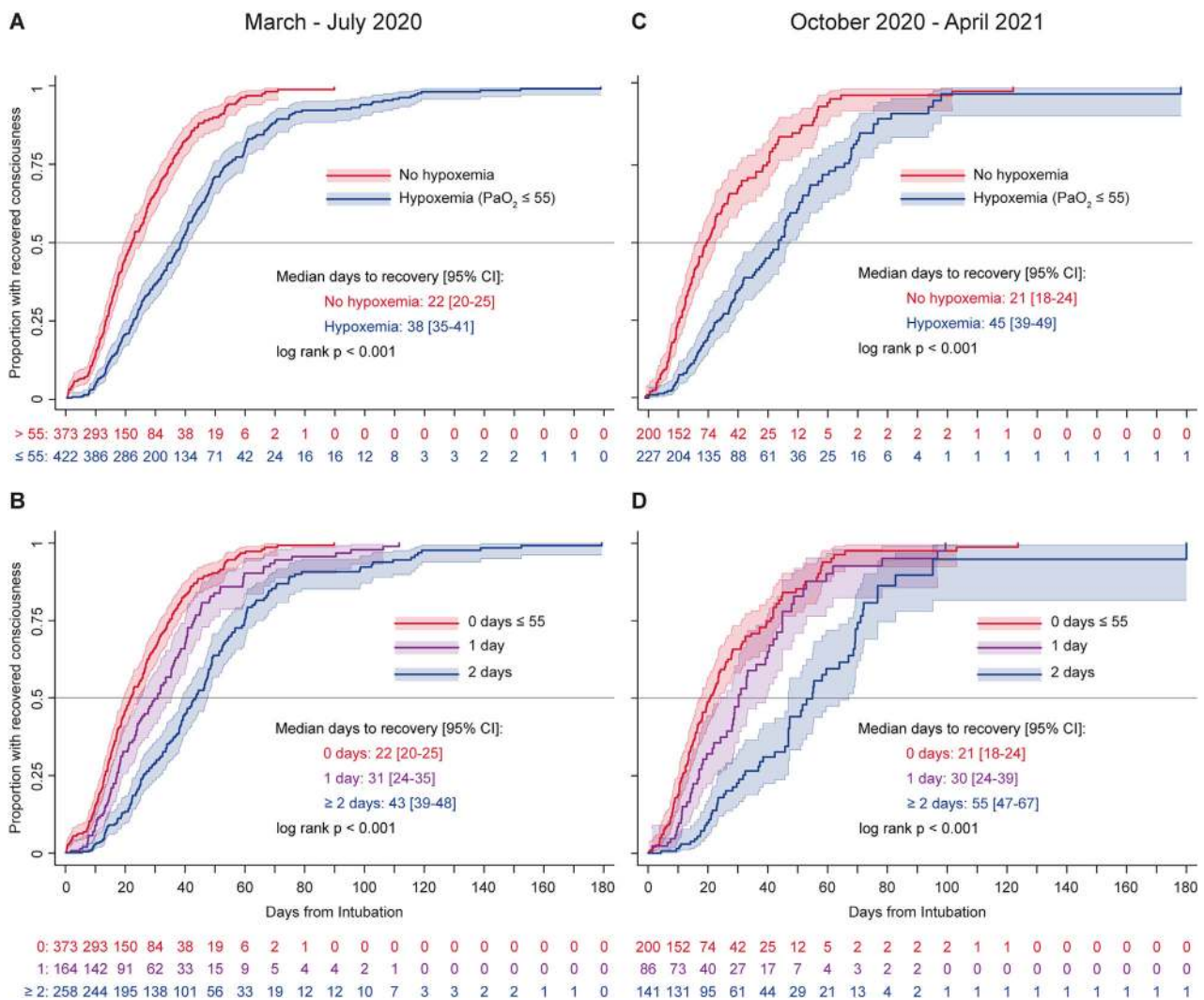


FIGURE 2: Kaplan–Meier cumulative incidence curves for recovery of command-following in patients with and without hypoxemia, for initial surge (March–July 2020) and second surge (October 2020 to April 2021). Kaplan–Meier curves for recovery of command-following in patients grouped by minimum $\text{PaO}_2 \leq 55$ mmHg versus >55 (A) initial surge, (C) second surge. Kaplan–Meier curves for patients grouped according to number of days of $\text{PaO}_2 \leq 55$ mmHg (B) initial surge, (D) second surge). CI = confidence interval; PaO_2 = partial pressure of arterial oxygen.

neuroimaging as well as in an out-of-sample cohort from the second surge.

Prolonged time to recovery of command-following, as observed in our study, should be considered in goals of care discussions between clinicians and surrogate decision makers. Our results indicate that most survivors of severe COVID-19 recover command-following, but that recovery may occur beyond 30 days and may be days or weeks after the patients no longer require mechanical ventilation. Our results highlight the need for a cautious approach to neuroprognostication in patients with severe COVID-19. Decisions to withdraw life-sustaining therapies should not be based solely on prolonged periods of unconsciousness, as patients may harbor prospects for recovery. Importantly, the degree of functional recovery remains unknown and warrants further investigation.

Although multiple factors besides hypoxemia may contribute to prolonged recovery of consciousness in severe COVID-19, including sedative exposure,¹⁷ disease severity (eg, critical illness,¹⁸ renal failure,¹⁹ and inflammation^{9,20}), hypercarbia, neurologic injury,²¹ and, in rare cases, possibly direct infection by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virus itself,²² the observed relationship between hypoxemia and prolonged recovery of consciousness in our study was independent of known clinical confounders. For example, after adjusting for cumulative exposure to analgesics and sedative medications, ARDS severity, and CRRT use, there remained a decreased likelihood of recovery of command-following for patients with hypoxemia ($\text{PaO}_2 < 55$ and < 70 mmHg) and with more days spent with a $\text{PaO}_2 < 55$. Thus, whereas hypoxemia is likely a surrogate marker for severity and natural history of

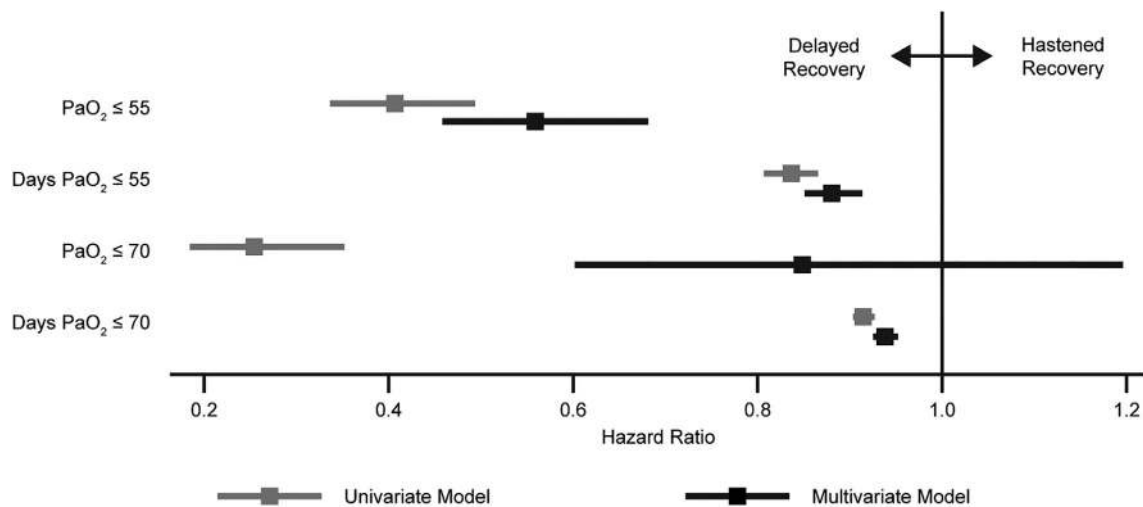


FIGURE 3: Pooled univariate and multivariable hazard ratios of primary hypoxemia exposure from Cox proportional hazard regressions clustered by site among initial surge. Each point estimate represents an independent regression model; 95% CIs are indicated with corresponding bars. Multivariable regressions included the exposure listed as well as covariates for demographics (age, sex, and race/ethnicity), level of sedation (cumulative analgesic and sedative dose, duration of continuous analgesic and sedative), and severity of illness (ARDS severity, neuromuscular blockade, CRRT). ARDS = acute respiratory distress syndrome; CI = confidence interval; CRRT = continuous renal replacement therapy.

disease, there remains an independent association of depth and duration of hypoxemia and delayed recovery of consciousness. Emerging evidence from clinical,^{8,9} radiologic,^{9,23} and pathologic^{24,25} studies further implicate cerebral microvascular injury in the pathogenesis of prolonged recovery of consciousness, due to microthrombosis,²⁶ microhemorrhage,²⁶ or endotheliitis.²⁷ In our study, we indeed observed a significantly greater proportion of patients with hypoxemia receiving brain imaging, possibly reflecting greater clinical suspicion of neurologic injury in patients with delayed recovery of consciousness. However, there was no difference in the proportion of radiologically identifiable structural brain injury across any hypoxemic thresholds tested. Moreover, the effects of hypoxemia on recovery of consciousness persisted when analyzing only patients without radiologic evidence of brain injury, suggesting that structural neurologic injury is not an independent explanation of our results.

There are several limitations in our study. Chiefly, the retrospective design, particularly given crisis standards of care during the initial surge, limits the generalizability of our primary results. The quantity of patients treated by unprepared health care systems in the initial surge forced changes in clinical practice²⁸: ICUs were erected in suboptimal settings, drug and medical supply shortages caused variability in sedation practices, and documentation requirements of health care professionals were adjusted to meet clinical demands.

However, these potential limitations to generalizability are mitigated by other aspects of the study. The

2 surges were separately analyzed, and the delayed recovery of command following as well as the hypoxemia effect was present during both time periods, despite the evolution of care and the disease. Additionally, our findings held across 3 centers, despite site-specific heterogeneity (ie, different demographics, different protocols for intubation triggers, and different levels of resource availability and treatments, etc.).

Second, our outcome measure, GCS motor score, is not a functional or long-term outcome. The outcome of GCS motor score was uniformly collected with validated inter-rater reliability,²⁹ yet was developed for trauma patients and lacks the complexities of a comprehensive behavioral examination, such as the Coma Recovery Scale-Revised.³⁰ However, a GCS motor score less than 6 reflects a patient's inability to follow commands, which is a clinically and functionally useful definition of impaired consciousness.

Third, in our population of intubated patients with severe COVID-19, assessing the relationship between hypoxemia and time to recovery of command-following is complicated by many potential confounders that cannot be completely excluded. A sensitivity analysis demonstrated a persistent association between hypoxemia and time to recovery of command-following independent of hypercapnia, the relationship between hypoxemia and hypercapnia remains challenging to fully model, especially given permissive hypercapnia strategies in ARDS management. Although we accounted for cumulative exposure to analgesics and sedative medications, complex interactions

although recent neuroimaging studies suggest that diffuse leukoencephalopathy,⁶ brainstem injury,^{30,32} and global changes in brain network connectivity^{30,32} may play contributing roles. Our results underscore the need for further investigation of the neuronal mechanisms of prolonged recovery of consciousness following severe hypoxemia and motivate studies to identify laboratory, imaging, and electrophysiological predictors of recovery. Independent of the underlying mechanisms yet to be uncovered, our findings provide key information that should be used to guide decisions of life-sustaining therapies.

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Author Contributions

G.W., S.S., M.B., J.V., E.B., J.F., B.E., N.S., and J.C. contributed to conceptualization, data curation, methodology, project administration and data visualization. A.B., J.C., C.D., K.D., and W.G. contributed data curation as well as verified the underlying data. G.W. and Q.S. contributed data analysis and validation for the manuscript.

Potential Conflict of Interest

David A. Berlin has been compensated for consulting and serving on safety monitoring board for a Bristol Myers Squibb study of a therapy for severe COVID-19. No other potential conflicts of interests by any authors.

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