

ORIGINAL WORK



Early Neurorehabilitation and Recovery from Disorders of Consciousness After Severe COVID-19

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Abstract

Background: Early neurorehabilitation improves outcomes in patients with disorders of consciousness (DoC) after brain injury, but its applicability in COVID-19 is unknown. We describe our experience implementing an early neurorehabilitation protocol for patients with COVID-19-associated DoC in the intensive care unit (ICU) and evaluate factors associated with recovery.

Methods: During the initial COVID-19 surge in New York City between March 10 and May 20, 2020, faced with a disproportionately high number of ICU patients with prolonged unresponsiveness, we developed and implemented an early neurorehabilitation protocol, applying standard practices from brain injury rehabilitation care to the ICU setting. Twenty-one patients with delayed recovery of consciousness after severe COVID-19 participated in a pilot early neurorehabilitation program that included serial Coma Recovery Scale-Revised (CRS-R) assessments, multimodal treatment, and access to clinicians specializing in brain injury medicine. We retrospectively compared clinical features of patients who did and did not recover to the minimally conscious state (MCS) or better, defined as a CRS-R total score (TS) ≥ 8 , before discharge. We additionally examined factors associated with best CRS-R TS, last CRS-R TS, hospital length of stay, and time on mechanical ventilation.

Results: Patients underwent CRS-R assessments a median of six (interquartile range [IQR] 3–10) times before discharge, beginning a median of 48 days (IQR 40–55) from admission. Twelve (57%) patients recovered to MCS after a median of 8 days (IQR 2–14) off continuous sedation; they had lower body mass index ($p = 0.009$), lower peak serum C-reactive protein levels ($p = 0.023$), higher minimum arterial partial pressure of oxygen ($p = 0.028$), and earlier fentanyl discontinuation ($p = 0.018$). CRS-R scores fluctuated over time, and the best CRS-R TS was significantly higher than the last CRS-R TS (median 8 [IQR 5–23] vs. 5 [IQR 3–18], $p = 0.002$). Earlier fentanyl ($p = 0.001$) and neuromuscular blockade ($p = 0.015$) discontinuation correlated with a higher last CRS-R TS.

Conclusions: More than half of our cohort of patients with prolonged unresponsiveness following severe COVID-19 recovered to MCS or better before hospital discharge, achieving a clinical benchmark known to have relatively favorable long-term prognostic implications in DoC of other etiologies. Hypoxia, systemic inflammation, sedation, and

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neuromuscular blockade may impact diagnostic assessment and prognosis, and fluctuations in level of consciousness make serial assessments essential. Early neurorehabilitation of these patients in the ICU can be accomplished but is associated with unique challenges. Further research should evaluate factors associated with longer-term neurologic recovery and benefits of early rehabilitation in patients with severe COVID-19.

Keywords: COVID-19, SARS-CoV-2, Coma, Unconsciousness, Early neurological rehabilitation

Introduction

Disorders of consciousness (DoC) occur following disruption of brainstem and/or cortical networks subserving arousal and awareness, respectively, or the connections between them and may manifest as coma, the vegetative state/unresponsive wakefulness state (VS/UWS), or the MCS [1]. Knowledge about DoC has advanced in the past decade [1, 2], and data increasingly suggest that early neurorehabilitation improves outcomes [3, 4]. Some patients with severe COVID-19 have impaired arousal and/or awareness after discontinuation of sedation [5, 6], consistent with DoC, which may contribute to the prolonged mechanical ventilation times [7] and ICU stays [8] that are characteristic of COVID-19 critical illness. There are calls for increased early neurorehabilitation efforts in this population [9]. Systematic data supporting the benefit of rehabilitation in COVID-19 are limited [10], although case reports suggest early rehabilitation can be safe and effective in COVID-19 critical illness [11]. Although encephalopathy is common in severe COVID-19 and depressed consciousness frequently prompts ancillary testing [12], little is known about recovery from COVID-19-associated DoC and the potential benefit of early neurorehabilitation for these patients. Prognostication in DoC is fraught with uncertainty, and prolonged DoC are associated with substantial psychological and moral distress for clinicians and caregivers [13, 14]. There is an urgent need to understand COVID-19-associated DoC to explore potential preventive and therapeutic opportunities.

New York City was an early COVID-19 epicenter. Between March 10, 2020, and May 20, 2020, New York University Langone Health (NYULH) Tisch/Kimmel Hospital admitted 261 patients with severe COVID-19 who required intubation. A subgroup of patients who remained unresponsive after discontinuation of sedation were enrolled in an early neurorehabilitation program guided by serial administration of the CRS-R that targeted recovery of consciousness [15, 16]. We demonstrate the feasibility of early neurorehabilitation guided by CRS-R in ICU patients with COVID-19-associated DoC and evaluate factors associated with recovery of consciousness prior to hospital discharge.

Methods

Study Design and Patient Cohort

In April 2020, in response to reports of persistent unresponsiveness and prolonged ICU stays in critically ill patients with COVID-19 at NYULH, we formed a quality improvement working group composed of representatives from critical care medicine, neurology, physical medicine and rehabilitation, occupational therapy (OT), physical therapy (PT), and speech–language pathology (SLP). Drawing on practice standards for neurorehabilitation of severe brain injury [17] and on our prior work demonstrating improved functional outcomes in ICU patients receiving early intensive rehabilitation [18], we developed and rapidly implemented an early neurorehabilitation protocol for patients with COVID-19-associated DoC.

We then conducted a retrospective observational study examining patients hospitalized with COVID-19 who participated in the first phase of this protocol. Patients were identified from the program clinical list in the electronic medical record (EMR) (Epic Systems Corporation, Madison, WI). Inclusion criteria were age ≥ 18 years; ICU admission before May 20, 2020; positive SARS-CoV-2 reverse transcriptase polymerase chain reaction result; presence of severely impaired arousal, awareness, or behavioral interaction despite discontinuation of continuous intravenous sedation/narcotics; completion of at least one CRS-R assessment; and absence of DoC prior to admission.

Standard Protocol Approvals, Registrations, and Consents

This study was approved with a waiver of authorization and informed consent by the NYULH Institutional Review Board.

Setting

NYULH is a quaternary care academic medical center. During the COVID-19 surge in New York City that occurred from March 2020 through May 2020, NYULH Tisch/Kimmel expanded its ICU capacity to 434 beds [19]. Level of care was determined according to prepandemic protocols.

Board-certified neurologists provided inpatient neurology consultation at the request of the primary medical

team. Brain magnetic resonance imaging (MRI) was obtained per neurologist recommendation or on the basis of decision-making by the primary medical team for patients with neurological deficits who could safely leave the ICU. Continuous 21-channel video electroencephalography (EEG) for ≥ 24 h was performed at the recommendation of a neurologist or on the basis of decision-making by the primary medical team with approval by an epileptologist [20]. Brain MRI images and EEGs were read in real-time in accordance with usual clinical protocols by board-certified radiologists and epileptologists, respectively.

CRS-R Assessment

The CRS-R, a 23-item instrument that detects neurobehavioral responsiveness, was chosen as the primary assessment tool to evaluate and track progress. Its six subscales evaluate auditory, visual, motor, oromotor, communication, and arousal processes [15]. Stimuli are presented in a standardized manner, and scoring is based on the presence or absence of behavioral responses. Low scores are consistent with reflexive behavior, whereas high scores reflect volitional activity [15]. TS range from 0 to 23; a TS ≥ 10 is considered to provide strong evidence of consciousness [21]. Although typically administered in the rehabilitation setting, the CRS-R has been used successfully in the ICU to guide early neurorehabilitation after severe brain injury [4, 22], and CRS-R TS is a strong predictor of outcome in the acute and postacute settings [23]. Although it has not been validated in patients with COVID-19, the CRS-R was used to assess recovery in two reports of patients with COVID-19 who had prolonged unresponsiveness [24, 25].

Under the guidance of NYULH therapists whose pre-pandemic clinical work included CRS-R administration for patients with severe brain injury in the acute care and rehabilitation settings, acute care OT, PT, and SLP therapists received structured CRS-R administration training, which included viewing a CRS-R training video and participating in two to three evaluations with a trained mentor. The CRS-R instrument and associated training video are available online [26] courtesy of Spaulding Rehabilitation Hospital. A total of 15 therapists, including mentors, were involved. CRS-R assessments were administered by one to two therapists at a time on a rotating schedule. Therapists used the CRS-R to develop an individualized structured plan of care for each patient and monitor for subtle neurobehavioral improvements over time. CRS-R scores were also used to communicate about improvement, or lack thereof, within the interdisciplinary team; this information was used by primary teams to guide prognostication and discharge planning discussions.

Therapists identified patients for the COVID-19 DoC program through chart reviews, during clinical rounds, and in discussions with providers and nursing staff. Although the intent of the program was to monitor and treat patients with DoC after severe COVID-19, patient identification was done informally, not systematically, so the program might not have included all patients with COVID-19-associated DoC, and the time from discontinuation of sedation to program enrollment varied. Following discontinuation of continuous intravenous sedation, CRS-R assessments were performed on a rotating schedule by PT, OT, and SLP therapists and embedded into standard therapy encounters at least 4 times per week or as clinically appropriate; this goal frequency was consistent with standard protocols for CRS-R administration in the acute rehabilitation setting at our institution and is based on data supporting increased diagnostic accuracy with serial, as compared to single, CRS-R assessments [27]. CRS-R was deferred if patients were restarted on continuous sedation or if there was a change in medical status that precluded rehabilitation therapy participation, as assessed by the primary team; rehabilitation assessment and therapies resumed after discontinuation of continuous sedation or confirmation of medical stability by the primary team. All patients involved in the COVID-19 DoC program were entered into a shared EMR list at the time of the first CRS-R assessment and observed until hospital discharge. Patients with CRS-R TS > 20 and/or who demonstrated consistent functional communication or functional object use on two consecutive evaluations were transitioned from the DoC program to a standard rehabilitation therapy protocol at a frequency based on their skilled rehabilitation needs at the time.

Therapeutic Interventions

In addition to serial evaluations, the COVID-19 DoC program included a variety of treatment modalities. Rehabilitation therapists provided multimodal sensory stimulation therapy. For patients with CRS-R TS < 8 , consistent with VS/UWS, this included upright positioning, gentle stretching, range of motion exercises, oral care, music, and exposure to familiar visual stimuli; as patients improved, additional interventions included use of situational commands and personally relevant questions, early mobilization, functional object use, use of speaking valves and alternative/adaptive communication systems, swallowing trials, and involvement of family via video platforms. Pharmacologic interventions to promote consciousness (“neurostimulants”) were used by primary teams as clinically appropriate on a case-by-case basis. Primary teams could additionally choose to consult the medically complex rehabilitation service, staffed by board-certified psychiatrists, or the neurophysiatry

service, staffed by a physiatrist board certified in brain injury medicine (BIM) in collaboration with a neuropsychiatrist board certified in brain injury medicine; when involved, neurophysiatry provided guidance on neurostimulant use.

Data Collection

Patients were identified, and CRS-R assessments were performed and documented prospectively. For the subsequent analysis, prehospitalization and hospitalization data were obtained retrospectively from the EMR via manual chart review.

Brain MRI and EEG data were abstracted from radiologist and epileptologist reports, respectively, with attention to findings that have been associated previously with severe COVID-19 [28–31]. Reading radiologists and epileptologists were not associated with this study and were not aware of patients' CRS-R findings, and findings were included only if described in the formal EMR report. Edlow and colleagues [32] have recently proposed common data elements (CDEs) for COVID-19 neuroimaging, divided into descriptive "feature-based" CDEs and interpretive "syndromic" CDEs. Because radiologic interpretation of COVID-19-associated findings changed rapidly during the first few months of the pandemic as more familiarity was gained with the virus, we extracted only feature-based CDEs from radiologist reports: these included decreased global brain parenchymal volume, susceptibility-weighted imaging hypointensities, T2 hyperintensities, diffusion-weighted imaging hyperintensities, and contrast enhancement.

For EEG, abstracted findings included generalized and focal slowing, epileptiform discharges, seizures, frontal intermittent rhythmic delta activity, lateralized rhythmic delta activity, generalized rhythmic delta activity, generalized periodic epileptiform discharges, and triphasic waves [20, 33]. The presence or absence of a posterior dominant rhythm was also recorded.

For patients who underwent multiple brain MRI scans and EEGs, a finding was considered to be present if it occurred on at least one study.

Study Outcomes

The primary outcome was recovery of consciousness to MCS or better, defined as CRS-R TS ≥ 8 on at least one assessment. The current standard for diagnosis of DoC relies on integrated clinical assessment of multiple behavioral features captured by the CRS-R subscales; specifically, high scores on any single subscale other than arousal can indicate MCS, with presence or absence of evidence of intact language function further subdividing patients into MCS-plus or MCS-minus, respectively. Several factors specific to this early period

in COVID-19 critical care were identified contemporaneously as potentially selectively limiting patients' ability to score maximally on certain CRS-R subscales. The most important of these was limited access to speaking valves for patients with tracheostomies: because of infection control protocols and the importance of maintaining closed-system ventilation during an airborne virus pandemic, the use of speaking valves was commonly not feasible, potentially limiting patients' performance on CRS-R oromotor/verbal function and communication subscales. Beyond this, significant weakness due to residual neuromuscular blockade and/or critical illness neuropathy/myopathy was common and identified as a potential confound for the motor function subscale as well as for the auditory function subscale, for which maximal points are awarded for movement to command. Finally, ongoing intermittent use of sedatives and analgesics was a potential confound for the arousal subscale.

Because the CRS-R assesses consciousness only indirectly, by way of eliciting behavioral responses to perceived stimuli, it is intrinsically vulnerable to confounders interfering with sensory perception and volitional behavioral control, even under the best of circumstances [34]. For our cohort, given the nearly universal presence of obvious confounders to select CRS-R subscales, we opted to use the CRS-R TS as a global measure of performance, with a score cutoff of 8 serving as a proxy for diagnosis of MCS. Previous work suggests that the CRS-R TS may have diagnostic value. In a cohort of 252 patients with DoC, Bodien et al. [21] found that a CRS-R TS cutoff of ≥ 8 offered the best balance between diagnostic sensitivity and specificity, correctly identifying MCS or better in 93% of cases and correctly excluding 96% of patients who did not meet these criteria. Although a TS cutoff of ≥ 10 yielded a specificity of 100%, sensitivity was only 78% (i.e., conscious patients were misdiagnosed as unconscious 22% of the time). We selected a TS cutoff of ≥ 8 to capture as many recoveries as possible while minimizing false-positive diagnoses.

Although CRS-R scores were impacted by confounding factors in some cases, we assigned subscale scores reflecting best performance across all participants (i.e., there were no missing scores). This provided a standardized method for obtaining a flat TS cutoff for consciousness. With a flat score cutoff, we sought to minimize reliance on any one subscale and provide all patients with a standardized way to demonstrate MCS that could be accomplished even with artificially reduced scores in one or multiple areas. We acknowledge that this is an imperfect solution to the problem of pervasive CRS-R confounders, and use of subscale data might have identified more patients in MCS.

Secondary study outcomes included best CRS-R TS, last CRS-R TS, hospital length of stay (LOS), and ventilator days.

Statistical Methods

Descriptive statistics (proportions for categorical variables and median IQR for continuous variables) were used to summarize clinical, imaging, and EEG features. We performed the Mann–Whitney *U*-test for nonnormally distributed continuous variables and Fisher's exact test for categorical variables to compare clinical features of patients who did and did not achieve at least one CRS-R TS ≥ 8 . Spearman rank-order correlation for nonparametric continuous variables was performed to examine the relationship of secondary outcomes to age; body mass index (BMI); minimum oxygen saturation; number of days of sedative/narcotic, steroid, and vasopressor exposure; and timing of key events during hospitalization (intubation, initiation of therapies/medications, and specialty consultation). We did not perform correction for multiple comparisons given the exploratory nature of the analyses. Statistical analysis was performed by using IBM SPSS Statistics for Windows version 25 (IBM Corporation, Armonk, NY).

Data Availability

Data collected for this study will be made available via email request to the corresponding author.

Results

Patient Characteristics on Admission

Twenty-one patients were included in this program. Baseline patient characteristics are summarized in Table 1. Seventy-one percent ($n=15$) of patients were white, 68% ($n=18$) were male, and the median age was 68 (IQR 63–72). Most patients had never smoked ($n=18$; 86%) but had hypertension ($n=17$; 81%). Eight (38%) patients had neuropsychiatric comorbidities, including Parkinson disease ($n=2$; 10%), dementia ($n=1$; 5%), prior stroke ($n=1$; 5%), major depressive disorder ($n=3$; 14%), bipolar disorder ($n=1$; 5%), and substance use disorder ($n=1$; 5%). The median BMI was 32 (IQR 27–36).

Hospital Admission

Hospital admission characteristics are summarized in Table 2. The median LOS was 73 days (IQR 61–90). Nine (43%) patients died; three (33%) died following withdrawal of life-sustaining therapy. Six (29%) were discharged to long-term acute care hospitals, five (24%) to acute rehabilitation, and one (5%) to home. All had hypoxic respiratory failure requiring intubation a median of 3 days after admission (IQR 2–6), tracheostomy placement a median of 22 (IQR 15–36) days after

admission, and ventilator support for a median of 58 (IQR 49–81) days. Of the 12 patients discharged alive, nine (75%) were weaned from the ventilator before discharge.

Median values for maximum temperature, heart rate, and systolic blood pressure were 103.3°F (IQR 102.7–104.2), 157 beats per minute (IQR 145–172), and 218 mm Hg (IQR 183–234), respectively. Oxygen saturation and partial arterial pressure of oxygen reached median lows of 55% (IQR 37–79) and 48 mm Hg (IQR 40–55), respectively. Peak serum inflammatory marker levels were elevated, with median levels as follows: C-reactive protein level, 368 mg/L (IQR 269–402); D-dimer, 7387 ng/mL (IQR 2476–10,000); and ferritin, 6,231 ug/L (IQR 2800–14,730).

Nearly all patients experienced renal failure ($n=19$; 90%); 11 (52%) required renal replacement therapy. Nine patients (43%) had at least one cardiac arrest. Three patients (14%) had clinical or electrographic seizures, and one patient developed Guillain–Barré syndrome.

All patients received multiple parenteral and enteral sedatives/narcotics (Table 3). Opioids and benzodiazepines were administered for a median of 37 days (IQR 27–56) and 25 days (IQR 11–32), respectively. All patients received fentanyl for a median of 23 days (IQR 14–32); 17 (81%) received oxycodone for a median of 10 days (IQR 1–17). Seventeen patients (81%) received antipsychotics for a median of 6 (IQR 1–20) days; quetiapine was most common (16 of 17; 94%).

All patients underwent brain MRI a median of 36 days from admission (IQR 28–50). MRI findings are summarized in Fig. 1. Ten patients (48%) had multiple MRI scans; for these patients, the last MRI scan occurred a median of 54 days from admission (IQR 44–71). The most common finding was T2 hyperintensities ($n=18$; 86%), and a majority had susceptibility-weighted imaging hypointensities ($n=15$; 71%). Eight patients (38%) received contrast; of these, three (38%) had contrast enhancement. In eight patients (38%), MRI findings demonstrated no acute abnormality.

Eighteen patients (86%) underwent EEG a median of 39 days from admission (IQR 29–49); seven (39%) were receiving continuous intravenous sedatives/narcotics during EEG. For the six patients who underwent multiple EEGs, the last EEG occurred a median of 51 days from admission (IQR 44–66). EEG findings are summarized in Fig. 2. A posterior dominant rhythm was present for half the patients who had an EEG ($n=9$; 50%). Every patient who underwent EEG had generalized slowing; two (11%) had focal slowing. Six patients (33%) had epileptiform discharges, and three (17%) had electrographic seizures.

Table 1 Baseline clinical characteristics of patients enrolled in early neurorehabilitation

Characteristic	All patients (N = 21)	VS/UWS (n = 9)	MCS (n = 12)	p value
Median age (IQR) (yr)	68 (63–72)	66 (53–72)	71 (64–75)	0.19
Male sex, no. (%)	18 (86)	7 (78)	11 (92)	0.55
Race and ethnicity, no. (%)				
Hispanic or Latino	3 (14)	1 (11)	2 (17)	1
White	15 (71)	6 (67)	9 (75)	1
Asian American	1 (5)	1 (11)	0	0.43
Black	1 (5)	1 (11)	0	0.43
Unknown	1 (5)	0	1 (8)	1
Body mass index, median (IQR)	32 (27–36)	35 (32–41)	26 (23–32)	0.009*
Smoking status, no. (%)				
Current smoker	0	0	0	–
Former smoker	2 (10)	1 (11)	1 (8)	1
Never smoker	18 (86)	7 (78)	11 (92)	0.55
Unknown smoking status	1 (5)	1 (11)	0	0.43
Coexisting disorder, no. (%)				
Atrial fibrillation	1 (5)	3 (33)	2 (17)	0.61
Congestive heart failure	2 (10)	1 (11)	1 (8)	1
Coronary artery disease	11 (52)	6 (67)	5 (42)	0.39
Chronic kidney disease	6 (29)	3 (33)	3 (25)	1
COPD	1 (5)	0	1 (8)	1
Dementia	1 (5)	1 (11)	0	0.43
Diabetes mellitus	11 (52)	6 (67)	5 (42)	0.39
Hypertension	17 (81)	8 (89)	9 (75)	0.6
Obstructive sleep apnea	4 (19)	2 (22)	2 (17)	1
Parkinson disease	2 (10)	1 (11)	1 (8)	1
Psychiatric disorder	5 (24)	2 (22)	3 (25)	1
Stroke	1 (5)	1 (11)	0	0.43
ED vital signs, median (IQR)				
Heart rate (beats per min)	105 (84–118)	115 (104–122)	87 (80–106)	0.08
Oxygen saturation (%)	90 (84–96)	95 (87–97)	87 (84–95)	0.1
Systolic blood pressure (mm Hg)	145 (128–169)	148 (127–160)	141 (119–169)	0.81
Temperature (°F)	100 (98.9–100.8)	100.1 (99.0–102.5)	99.9 (98.3–100.5)	0.25
Initial inflammatory markers, median (IQR)				
C-reactive protein (mg/L)	180 (116–279)	133 (68–328)	209 (143–270)	0.6
D-dimer (ng/mL)	378 (232–1017)	325 (217–2289)	390 (236–997)	0.75
Ferritin (µg/L)	751 (425–1322)	505 (260–1061)	1001 (702–2659)	0.08

COPD, chronic obstructive pulmonary disease; ED, emergency department; IQR, interquartile range; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness state

*Statistically significant ($p < 0.05$)

Evaluation and Management of DoC

CRS-R assessment began in the ICU for all patients a median of 48 days from admission (IQR 40–55) and occurred a median of six times (IQR 3–12) before hospital discharge. Median initial, best, and last CRS-R TS were three (IQR 1–6), eight (IQR 5–23), and five (IQR 3–19), respectively. Twelve patients (57%) recovered to MCS or better (“MCS group”), as defined by achievement of at least one CRS-R TS \geq 8. Figure 3

demonstrates initial, best, and last CRS-R TS for each patient.

All patients had consultations by PT (first encounter median of 31 days from admission, IQR 24–43) and OT (first encounter median of 39 days from admission, IQR 27–56); all but one had SLP consultation (first encounter median of 50 days from admission, IQR 32–65). All patients were seen by neurology; the initial consultation occurred a median of 33 days after admission (IQR

Table 2 Hospital admission characteristics of patients enrolled in early neurorehabilitation

Characteristic	All patients (N=21)	VS/UWS (n=9)	MCS (n=12)	p value
Length of stay, median days (IQR)	73 (61–90)	79 (62–90)	68 (54–89)	0.38
Day of intubation, median (IQR)	3 (2–6)	4 (2–8)	3 (2–4)	0.6
Day of tracheostomy, median (IQR)	22 (15–36)	27 (15–44)	20 (15–30)	0.35
Ventilator days, median (IQR)	58 (49–81)	74 (56–87)	52 (48–74)	0.13
Discharge location, no. (%)				
Home	1 (5)	0	1 (8)	1
Acute rehabilitation	5 (24)	0	5 (42)	0.045*
Long-term acute care hospital	6 (29)	3 (33)	3 (25)	1
Died	9 (43)	6 (67)	3 (25)	0.09
After cardiopulmonary arrest	5 (24)	3 (33)	2 (17)	0.61
By neurologic criteria	1 (5)	1 (11)	0	0.43
Withdrawal of life-sustaining therapies	3 (14)	2 (22)	1 (8)	0.55
Vital signs, median (IQR)				
Heart rate maximum (beats per min)	157 (145–172)	161 (150–179)	153 (143–162)	0.19
Heart rate minimum (beats per min)	45 (38–55)	46 (42–57)	43 (31–56)	0.42
Oxygen saturation minimum (%)	55 (37–79)	46 (44–55)	66 (49–79)	0.19
Pao ₂ minimum (mm Hg)	48 (40–55)	41 (33–50)	52 (43–58)	0.028*
Systolic blood pressure maximum (mm Hg)	218 (183–234)	199 (183–238)	220 (185–232)	0.7
Systolic blood pressure minimum (mm Hg)	55 (50–61)	55 (50–57)	54 (47–66)	1
Temperature maximum (°F)	103.3 (102.7–104)	103.6 (102.8–104.8)	103 (102.4–103.8)	0.19
Peak inflammatory markers, median (IQR)				
C-reactive protein (mg/L)	368 (269–402)	396 (381–407)	299 (249–362)	0.023*
D-dimer (ng/mL)	7387 (2476–10,000)	8305 (3697–10,000)	7217 (2449–10,000)	0.75
Ferritin (ug/L)	6231 (2800–14,730)	6,413 (2,825–27,406)	6039 (2749–13,184)	0.082
Complication, no. (%)				
Atrial fibrillation with rapid ventricular rate	15 (71)	7 (78)	8 (67)	0.66
Cardiac arrest	9 (43)	5 (56)	4 (33)	0.4
Dysautonomia	10 (48)	5 (56)	5 (42)	0.67
Extracorporeal membrane oxygenation	1 (5)	0	1 (8)	1
Guillain-Barré syndrome	1 (5)	0	1 (8)	1
Hypoxic respiratory failure	21 (100)	9 (100)	12 (100)	–
Renal failure	19 (90)	9 (100)	10 (83)	0.49
Renal replacement therapy	11 (52)	6 (67)	5 (42)	0.39
Seizure	3 (14)	2 (22)	1 (8)	0.55
COVID-19 treatments, no. (%)				
Azithromycin	19 (90)	9 (100)	10 (83)	0.49
Clazakizumab	4 (19)	0	4 (33)	0.1
Convalescent plasma	4 (19)	2 (22)	2 (17)	1
Hydroxychloroquine	20 (95)	9 (100)	11 (92)	1
Lopinavir–ritonavir	4 (19)	3 (33)	1 (8)	0.27
Remdesivir	6 (29)	3 (33)	3 (25)	1
Steroids	18 (86)	9 (100)	9 (75)	0.23
Therapeutic anticoagulation	19 (90)	9 (100)	10 (83)	0.49
Tocilizumab	8 (38)	5 (56)	3 (25)	0.2
Zinc	16 (76)	8 (89)	8 (67)	0.34

IQR, interquartile range; MCS, minimally conscious state; Pao₂, partial arterial pressure of oxygen; VS/UWS, vegetative state/unresponsive wakefulness state

*Statistically significant ($p < 0.05$)

Table 3 Use of sedatives, narcotics, and supportive medications in patients receiving early neurorehabilitation

Medications	All patients (N=21)	VS/UWS (n=9)	MCS (n=12)	p value
Amantadine, no. (%)	11 (52)	6 (67)	5 (42)	0.39
Day of initiation, median (IQR)	51 (40–66)	63 (43–71)	41 (36–59)	0.13
Day of discontinuation, median (IQR)	78 (62–88)	78 (72–81)	64 (57–93)	0.93
Total days, median (IQR)	1 (0–13)	3 (0–11)	0 (0–14)	0.81
Antipsychotics, no. (%)	17 (81)	7 (78)	10 (83)	1
Day of initiation, median (IQR)	16 (9–23)	18 (11–23)	15 (7–23)	0.81
Day of discontinuation, median (IQR)	46 (18–64)	24 (14–46)	50 (22–74)	0.16
Total days, median (IQR)	6 (1–20)	2 (1–13)	10 (1–27)	0.28
Benzodiazepines, no. (%)	21 (100)	9 (100)	12 (100)	–
Day of initiation, median (IQR)	6 (4–9)	5 (2–13)	7 (4–8)	0.92
Day of discontinuation, median (IQR)	56 (37–71)	59 (52–78)	51 (28–67)	0.35
Total days, median (IQR)	25 (11–32)	25 (7–45)	23 (12–28)	0.42
Dexmedetomidine, no. (%)	20 (95)	8 (89)	12 (100)	0.43
Day of initiation, median (IQR)	8 (4–11)	10 (7–11)	6 (3–12)	0.27
Day of discontinuation, median (IQR)	39 (29–58)	35 (23–61)	41 (30–51)	0.62
Total days, median (IQR)	19 (9–27)	21 (7–28)	19 (9–25)	1
Fentanyl, no. (%)	21 (100)	9 (100)	12 (100)	–
Day of initiation, median (IQR)	4 (3–8)	5 (2–8)	4 (3–8)	0.7
Day of discontinuation, median (IQR)	55 (46–68)	56 (62–81)	48 (42–62)	0.018*
Total days, median (IQR)	23 (14–32)	24 (12–33)	23 (15–32)	0.75
Ketamine, no. (%)	17 (81)	6 (67)	11 (92)	0.27
Day of initiation, median (IQR)	7 (4–13)	7 (3–19)	7 (4–11)	0.96
Day of discontinuation, median (IQR)	19 (10–26)	21 (14–28)	17 (8–30)	0.56
Total days, median (IQR)	4 (1–8)	3 (3–8)	4 (2–10)	0.51
Modafinil, no. (%)	12 (57)	5 (56)	7 (58)	1
Day of initiation, median (IQR)	45 (36–57)	47 (40–69)	42 (36–47)	0.29
Day of discontinuation, median (IQR)	55 (43–70)	66 (53–80)	47 (37–66)	0.11
Total days, median (IQR)	1 (0–6)	1 (0–10)	2 (0–5)	1
Neuromuscular blockade, no. (%)	20 (95)	9 (100)	11 (92)	1
Day of initiation, median (IQR)	5 (3–8)	5 (4–13)	5 (3–7)	0.66
Day of discontinuation, median (IQR)	26 (20–50)	34 (20–61)	23 (20–30)	0.23
Total days, median (IQR)	8 (4–13)	6 (4–18)	8 (2–10)	0.97
Oxycodone, no. (%)	17 (81)	6 (67)	11 (92)	0.27
Day of initiation, median (IQR)	26 (12–40)	35 (16–68)	25 (9–34)	0.26
Day of discontinuation, median (IQR)	59 (46–86)	63 (36–85)	59 (47–89)	0.88
Total days, median (IQR)	10 (1–17)	1 (0–13)	13 (9–22)	0.03*
Propofol, no. (%)	20 (95)	9 (100)	11 (92)	1
Day of initiation, median (IQR)	4 (2–8)	4 (2–8)	4 (3–8)	0.66
Day of discontinuation, median (IQR)	27 (13–51)	41 (12–64)	19 (14–30)	0.3
Total days, median (IQR)	7 (4–14)	7 (5–18)	7 (2–11)	0.42
Vasopressors, no. (%)	21 (100)	9 (100)	12 (100)	–
Day of initiation, median (IQR)	4 (2–7)	4 (4–7)	3 (1–7)	0.38
Day of discontinuation, median (IQR)	53 (36–77)	50 (24–64)	57 (39–86)	0.22
Total days, median (IQR)	27 (15–35)	38 (21–52)	24 (16–46)	0.51

IQR, interquartile range, MCS, minimally conscious state, VS/UWS, vegetative state/unresponsive wakefulness state

*Statistically significant ($p < 0.05$)

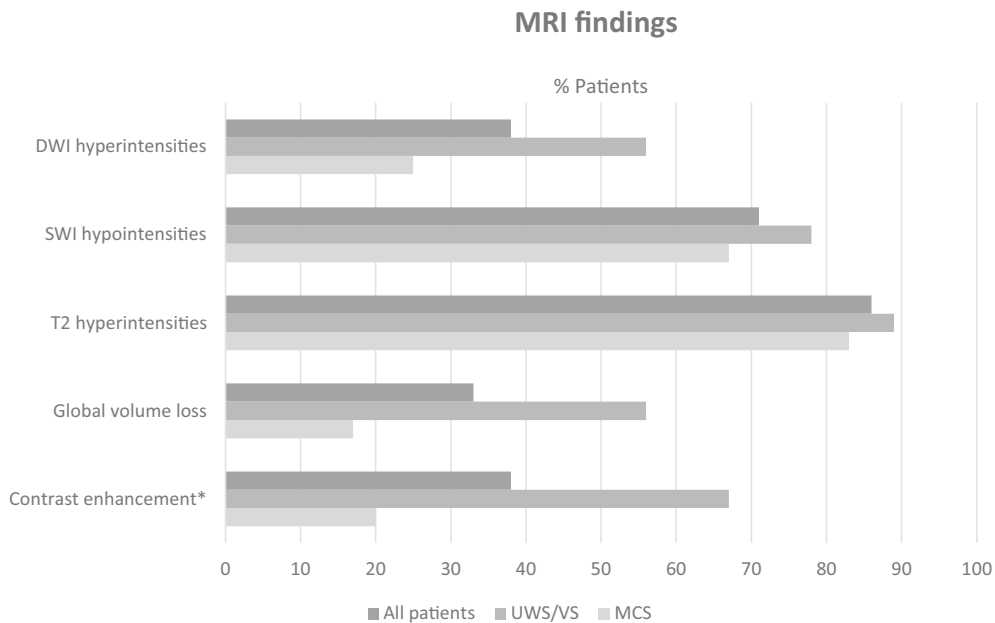


Fig. 1 Feature-based common data element findings on brain MRI [32], by percentage of patients ($N = 21$). The asterisk denotes the percentage of patients who received contrast ($n = 8$). DWI diffusion-weighted imaging, MCS minimally conscious state, MRI magnetic resonance imaging, SWI susceptibility-weighted imaging, UWS/VS unresponsive wakefulness state/vegetative state

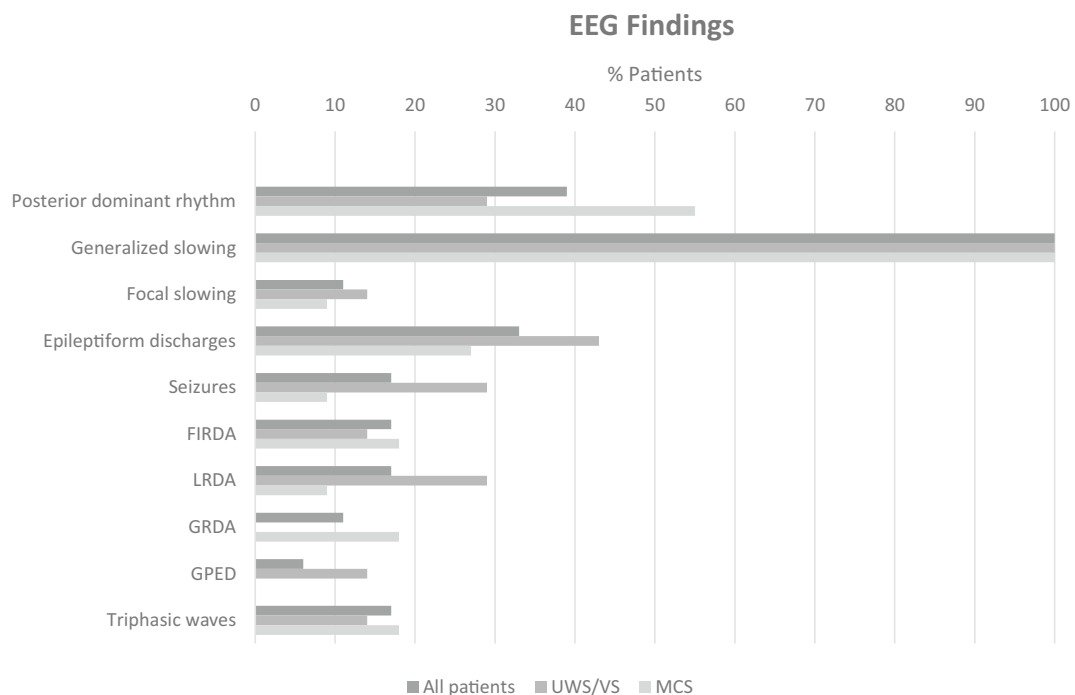
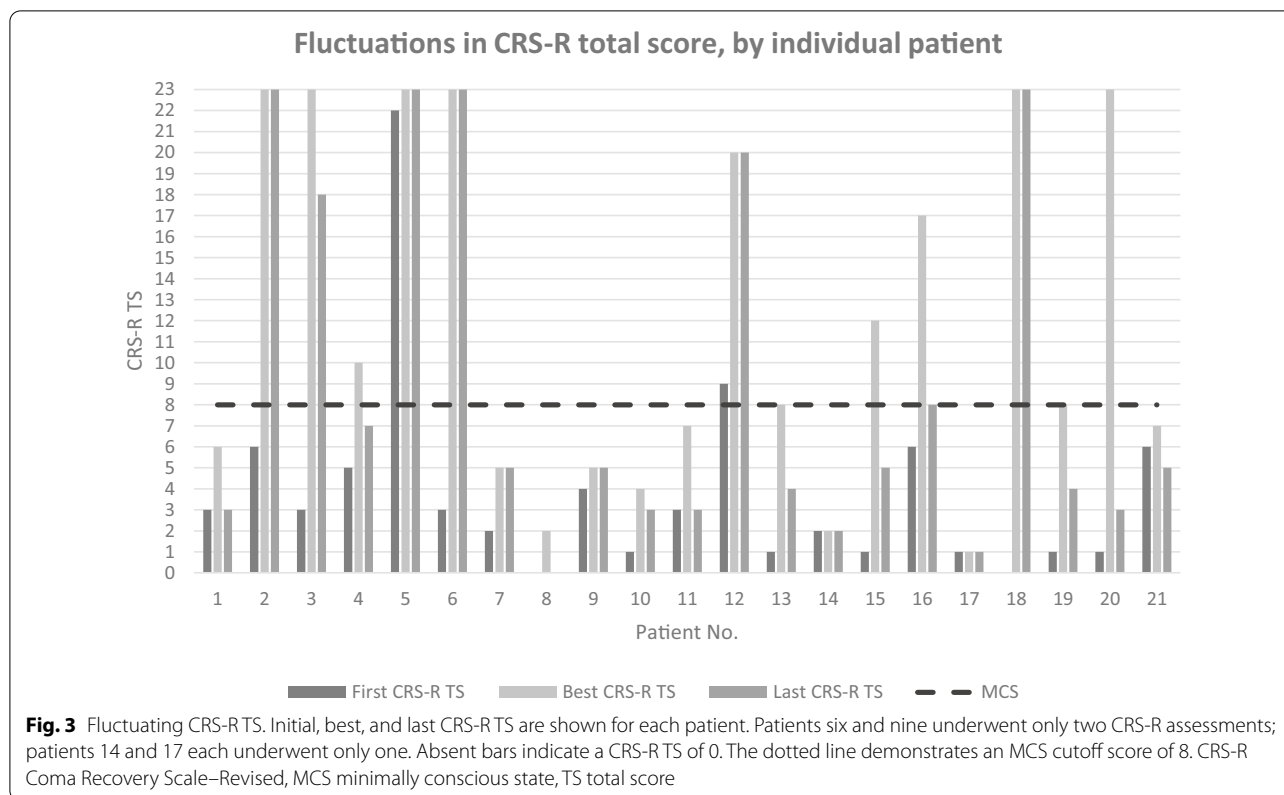


Fig. 2 EEG findings, by percentage of patients ($n = 18$). EEG, FIRDA frontal intermittent rhythmic delta activity, GPED generalized periodic epileptiform discharges, GRDA generalized rhythmic delta activity, LRDA lateralized rhythmic delta activity, MCS minimally conscious state, UWS/VS unresponsive wakefulness state/vegetative state



23–48). Sixteen (76%) patients had psychiatry consultation a median of 60 days from admission (IQR 46–64); of these, 12 (75%) were seen by neurophysiatry.

Most patients ($n=15$; 71%) received at least one neurostimulant, initiated a median of 44 days from admission (IQR 35–59). Amantadine ($n=11$; 52%) and modafinil ($n=12$; 57%) were most common. The median number of treatment days was 12 (IQR 6–25) for patients receiving amantadine and 4 (IQR 1–13) for those receiving modafinil. Three patients (19%) received levodopa, two of whom had premorbid Parkinson disease. Zolpidem and methylphenidate were each administered to one patient (5%).

Relationship of Clinical Features to Recovery of Consciousness

Although the two groups did not differ regarding initiation/discontinuation dates or total days of antipsychotics, benzodiazepines, dexmedetomidine, ketamine, propofol, neurostimulants, or total opioids, the MCS group had fentanyl discontinued earlier (median hospital day 48 [IQR 42–62] vs. 56 [IQR 62–81], $p=0.018$) and received oxycodone for more days (median 13 [IQR 9–22] vs. 1 [IQR 0–3], $p=0.03$). Patients who recovered to MCS first did so a median of 8 days (IQR 2–14) after discontinuation of continuous sedation. Table 4

summarizes the timing and nature of clinical consultations and CRS-R assessments for the full cohort and both subgroups.

The initial CRS-R TS was not significantly different across the two groups, but the MCS group scored significantly higher on their best CRS-R TS (median 22 [IQR 12–23] vs. 5 [IQR 2–6], $p<0.001$) and last CRS-R TS (median 13 [IQR 5–23] vs. 3 [IQR 2–5], $p=0.002$). Although the total number of CRS-R assessments varied from patient to patient, the median number of CRS-R assessments did not differ significantly between the MCS and VS/UWS groups.

Patients who recovered to MCS had significantly lower BMI (median 26 [IQR 23–32] vs. 35 [IQR 32–41], $p=0.009$), higher minimum partial arterial pressure of oxygen (median 52 mm Hg [IQR 43–58] vs. 41 mm Hg [IQR 33–50], $p=0.028$), and lower peak C-reactive protein levels (median 299 mg/L [IQR 249–362] vs. 396 mg/L [IQR 381–407], $p=0.023$) than those who did not. The groups did not differ regarding other baseline or admission characteristics, including MRI/EEG findings. The MCS group was significantly more likely to be discharged to acute rehabilitation ($n=5$ [42%] vs. 0, $p=0.045$) and less likely to have do not resuscitate code status ($n=2$ [17%] vs. $n=6$ [67%], $p=0.032$). Withdrawal of life-sustaining therapy did not differ between groups.

Table 4 Evaluation and management of disorders of consciousness in patients receiving early neurorehabilitation

Characteristics	All patients (N = 21)	VS/UWS (n = 9)	MCS (n = 12)	p value
Consultations				
Neurology consultation, no. (%)	21 (100)	9 (100)	12 (100)	–
Day of neurology consultation, median (IQR)	33 (25–46)	32 (23–58)	34 (23–42)	0.86
Physiatry consultation, no. (%)	16 (76)	6 (67)	10 (83)	0.61
Neurophysiatry consultation, no. (%)	11 (52)	6 (67)	5 (42)	0.39
Day of physiatry consultation, median (IQR)	60 (49–64)	53 (44–72)	62 (49–64)	0.71
Physical therapy consultation, no. (%)	21 (100)	9 (100)	12 (100)	–
Day of first encounter, median (IQR)	31 (24–43)	40 (23–60)	31 (25–36)	0.42
Occupational therapy consultation, no. (%)	21 (100)	9 (100)	12 (100)	–
Day of first encounter, median (IQR)	39 (27–56)	43 (32–62)	34 (26–55)	0.35
Speech therapy consultation, no. (%)	20 (95)	8 (89)	12 (100)	0.43
Day of first encounter, median (IQR)	50 (32–65)	51 (25–71)	49 (33–65)	0.62
CRS-R				
Hospital day of first CRS-R assessment, median (IQR)	48 (40–55)	51 (43–61)	47 (34–52)	0.22
Days from discontinuation of intravenous sedation to first CRS-R assessment, median (IQR)	4 (2–9)	6 (3–15)	3 (2–7)	0.13
Days from discontinuation of intravenous sedation to last CRS-R assessment, median (IQR)	9 (2–21)	6 (2–16)	18 (3–23)	0.22
Days from discontinuation of intravenous sedation to CRS-R TS \geq 8, median (IQR)	–	–	8 (2–14)	–
Days from first CRS-R assessment to score \geq 8, median (IQR)	–	–	10 (4–15)	–
Total no. of CRS-R assessments, median (IQR)	6 (3–10)	9 (2–10)	6 (5–9)	0.92

CRS-R, Coma Recovery Scale–Revised; IQR, interquartile range; MCS, minimally conscious state; TS, total score; VS/UWS, vegetative state/unresponsive wakefulness state

Secondary Outcomes

First and last CRS-R TS correlated significantly ($p = 0.01$), as did best and last CRS-R TS ($p < 0.001$). The best CRS-R TS was significantly higher than the last CRS-R TS for all patients (median 8 [IQR 5–23] vs. 5 [IQR 3–18], $p = 0.002$) and within each of the subgroups (MCS group: median 22 [IQR 12–23] vs. 13 [IQR 5–23], $p = 0.018$; VS/UWS group: median 5 [IQR 2–6] vs. 3 [IQR 2–5], $p = 0.042$).

Best and last CRS-R TS both correlated with earlier discontinuation of fentanyl ($p = 0.02$ and $p = 0.001$, respectively), more days of oxycodone ($p = 0.007$ and $p = 0.011$, respectively), and more days of antipsychotics ($p = 0.036$ and $p = 0.003$, respectively). Last CRS-R TS also correlated with earlier discontinuation of neuromuscular blockade ($p = 0.015$) and earlier initiation of amantadine ($p = 0.022$) and modafinil ($p = 0.046$). There was no significant relationship between best or last CRS-R TS and any other demographic or clinical variables.

The total number of CRS-R assessments correlated significantly with longer hospital LOS ($p = 0.005$) and more days of mechanical ventilation ($p = 0.001$). There was no relationship between number of CRS-R assessments and either best or last CRS-R TS.

Hospital LOS correlated significantly with peak C-reactive protein level ($p = 0.003$); peak ferritin level

($p = 0.003$); number of ventilator days ($p < 0.001$); dates of first SLP and OT evaluations ($p = 0.002$); date of first physiatry consultation ($p = 0.013$); number of days of fentanyl ($p = 0.042$), lorazepam ($p = 0.033$), and ketamine ($p = 0.018$); and discontinuation dates of fentanyl ($p < 0.001$), oxycodone ($p = 0.003$), hydromorphone ($p < 0.001$), lorazepam ($p = 0.013$), and neuromuscular blockade ($p = 0.004$). Number of ventilator days similarly correlated with peak ferritin level ($p = 0.022$), dates of first SLP and OT evaluations ($p = 0.031$), and discontinuation dates of fentanyl ($p = 0.004$), hydromorphone ($p = 0.007$), lorazepam ($p = 0.013$), and propofol ($p = 0.011$).

Discussion

Our group previously demonstrated that patients with neurological complications of COVID-19 are more likely to require ICU care, spend more days hospitalized and on ventilators, and have increased in-hospital mortality and are less likely to be discharged home compared with patients without neurological complications [35]. In this study, we enrolled some of our most severely neurologically impaired patients with COVID-19 in an ICU-based early neurorehabilitation protocol and describe the recovery trajectories of these patients as measured by serial CRS-R assessment. Although patient selection for

inclusion in our early neurorehabilitation program and subsequent study was done informally rather than systematically, findings from this cohort can improve our understanding of recovery of consciousness in patients with severe COVID-19.

Diagnosis can be challenging in DoC, with estimated misdiagnosis rates of 40% [36], but early differentiation of MCS from VS/UWS has important prognostic implications: in a landmark study of 36 patients with mixed-etiology DoC, 80% of patients admitted to rehabilitation in MCS became fully conscious, as compared to only 45% of those admitted in VS/UWS, and all patients admitted in VS/UWS who became fully conscious transitioned to MCS within 8 weeks of injury [37]. Of 23 patients with long-term follow-up, ten (43%) achieved household independence and five (22%) returned to work or school, demonstrating that good recovery from DoC is possible. The CRS-R, administered by trained examiners, is an important bedside tool to increase diagnostic accuracy in patients with DoC [17, 21].

Of the 21 patients included in our study, 12 (57%) recovered to MCS or better, as defined by at least one CRS-R TS ≥ 8 . As the CRS-R recovery trajectories demonstrate, recovery from DoC takes time and is marked by fluctuations. These findings reinforce the importance of serial evaluations and of avoiding the therapeutic nihilism, which often pervades care of patients with severe brain injuries [13]. Although higher initial CRS-R TS correlated with higher best and last CRS-R TS, suggesting that a higher initial score may be a positive prognostic indicator, low initial TS did not preclude recovery. Additionally, although patients who recovered to MCS did not consistently sustain a CRS-R TS consistent with MCS, these patients were less often converted to do not resuscitate code status and were ultimately more frequently discharged to acute rehabilitation, facilitating a continuous chain of intensive rehabilitation that may improve outcomes in DoC [38].

Consistent with reports of high pharmacological requirements in patients with severe COVID-19 [39], our patients received sedatives, narcotics, antipsychotics, and neuromuscular blockade, all of which can adversely impact recovery from critical illness and DoC [40–42]. Patients who achieved the MCS score cutoff did not do so until a median of 8 days (IQR 2–14) after discontinuation of continuous intravenous sedatives/narcotics. Although only fentanyl showed an association between earlier discontinuation and recovery to MCS, this does not exclude the impact of other sedatives/narcotics on consciousness in this population, and it is important to recognize (1) that we did not measure cumulative doses of each medication, (2) that BMI and renal and hepatic function affect drug metabolism, and (3) that medication

half-lives differ. Additionally, later discontinuation of neuromuscular blockade was associated with lower last CRS-R TS, suggesting that iatrogenic neuromuscular weakness could have confounded some patients' CRS-R performance.

The MCS group received more days of oxycodone, and greater number of oxycodone days correlated with higher best and last CRS-R TS; additionally, increased days of antipsychotic administration correlated with higher best and last CRS-R TS. Although these findings could indicate that parenteral drugs were being weaned earlier in this patient population or that these enteral medications were more likely to be given to patients who were less sick, we do not have data to confirm this. It is worth noting that some data suggest that oxycodone and antipsychotics may be neuroprotective. In a mouse model of cerebral ischemia/reperfusion injury, oxycodone reduced hippocampal neuronal death [43]. In contrast to fentanyl, which interacts primarily with μ -opioid receptors, oxycodone acts at multiple opioid receptors including κ -opioid receptors [44]; κ -opioid receptor agonists may offer some neuroprotection in brain ischemia [45]. Although typical antipsychotics can impede neurorecovery [46], atypical antipsychotics (such as quetiapine) may confer antiinflammatory and neuroprotective benefits [47, 48]. A recent retrospective matched cohort study demonstrated decreased mortality and improved neurologic outcomes in critically ill patients with traumatic brain injury who received low-dose quetiapine [49]. Antipsychotics are additionally being explored for possible antiviral activity against SARS-CoV-2 [50, 51]. More work is needed to evaluate potential neuroprotective agents in patients with severe COVID-19.

Limited data support neurostimulant use in DoC, although these data were not derived from patients with COVID-19. The strongest evidence exists for amantadine, which was shown in a large ($n=184$) placebo-controlled trial to hasten functional recovery in patients with traumatic DoC [52] and has demonstrated benefit for non-traumatic DoC in case reports [2]. Modafinil improved fatigue and facilitated admission to acute rehabilitation in patients hospitalized with stroke in a retrospective study [53], but only one small ($n=24$) retrospective study demonstrated its benefit in DoC [54]. Although there was no difference in neurostimulant use between the CRS-R TS <8 and ≥ 8 groups, we observed a trend between earlier initiation of amantadine and modafinil and higher last CRS-R TS. Neurostimulant dosing in this cohort was limited and nonstandardized, making it difficult to draw conclusions. We also found that earlier OT and SLP initiation was associated with shorter LOS and fewer ventilator days; although these therapies could have been initiated earlier for patients who were already

recovering better, these findings are consistent with prior work at our institution demonstrating shorter ICU LOS for patients receiving intensive early rehabilitation [18]. Further research on the role of neurostimulants and early therapy initiation in this population is needed.

The mechanisms by which neurological injury occurs in COVID-19 are not fully understood. Patients may develop temporary or permanent brain damage due to hypoxia, coagulopathy and cerebral microvascular pathology, para-infectious neuroinflammation, secondary effects of the systemic hyperinflammatory “cytokine storm,” or direct invasion of the central nervous system by SARS-CoV-2 [55]. Advanced age and higher BMI are associated with prolonged mechanical ventilation in COVID-19 [56]. We found that patients who recovered to MCS were less obese, had less severe hypoxia, and had lower elevations of C-reactive protein levels compared with patients who did not. Patients did not differ regarding medical complications, including cardiac arrest, or MRI or EEG findings. Our findings suggest that severity of hypoxia, independent of cardiopulmonary arrest, may play a key role in the brain injury seen in some patients with COVID-19 and that systemic inflammation is associated with poorer neurologic outcomes.

This study has a number of limitations. Importantly, because of the unique clinical and logistical challenges associated with the initial COVID-19 surge in New York City, patient inclusion was not systematic, and there was marked variability in the type and dose of pharmacologic and nonpharmacologic therapeutic interventions. Specifically, CRS-R assessment intervals and frequency were not standardized, although the median total number of CRS-R assessments did not differ between the two groups, and there was no relationship between number of CRS-R assessments and either best or last CRS-R TS. In fact, longer hospital LOS and greater number of days on mechanical ventilation both correlated with greater number of CRS-R assessments, suggesting that sicker patients received more assessments; nonetheless, it is still possible that some patients could have demonstrated behavioral evidence of MCS if additional assessments were performed. Because all patients received early neurorehabilitation, our findings may not be generalizable to patients who did not receive this intervention; comparison with a control group of patients with COVID-19-associated DoC receiving usual care could help clarify the impact of nuanced diagnostic assessment and multimodal neurorehabilitation on outcomes.

The CRS-R has good interrater reliability when administered by trained examiners [16]; despite this, there could have been interrater variability in CRS-R assessments. We attempted to avoid this by providing standardized training to each therapist. Even when administered

properly, however, the CRS-R is known to be intrinsically vulnerable to a variety of potential pitfalls related to factors beyond level of consciousness that might interfere with the ability to perceive external stimuli and/or deliver an appropriate behavioral response; these include polyneuropathy/myopathy (motor subscale), aphasia (oromotor and communication), and cortical blindness (visual), among others [34]. Additional potential confounders specific to the ICU setting include patients’ fluctuating medical needs and sedation requirements (arousal), use of neuromuscular blockade (motor), and reliance on mechanical ventilation (oromotor and communication). Although we attempted to account for these potential confounders via use of CRS-R TS as a global outcome measure, it is possible that some patients who were classified as being in a VS/UWS could have been classified as being in an MCS by using a different methodology. Examination of subscale data in a future investigation could highlight specific patterns in this population and inform more precise approaches to assessment, management, and prognostication in COVID-19-related DoC.

Although serial CRS-R assessments are known to increase diagnostic accuracy in non-COVID-19 patients with DoC by accounting for expected behavioral fluctuations [27], we recognize that not all institutions have the necessary staffing to attempt four or more CRS-R assessments per week. This burden may be mitigated to some extent by embedding the CRS-R into standard therapy encounters, in which it can serve as both a diagnostic measure and a framework for a session’s therapeutic interventions, but less frequent administration with an awareness of fluctuating performance as a potential confound may still yield useful diagnostic and prognostic information.

Our cohort was small and, with the exception of CRS-R scores, data were collected retrospectively via chart review. Additional characteristics may correlate with recovery in a larger cohort. Because we performed multiple independent statistical analyses, some of our findings could have achieved statistical significance due to chance. Because of limited research in the acute setting using serial CRS-R assessment, we cannot differentiate whether our results are specific to patients with severe COVID-19 or relevant to critically ill patients in general.

Further research is needed to examine recovery from DoC in patients with COVID-19 beyond acute care using standardized serial neurobehavioral assessments, such as the CRS-R. Advanced functional imaging techniques could also be useful diagnostically and prognostically: in a case report by Fischer et al. [24], resting-state functional MRI findings demonstrated intact default mode network connectivity in a patient with prolonged unresponsiveness after severe COVID-19 who subsequently recovered

consciousness. Although resting-state functional imaging cannot be used to diagnose level of consciousness and is not included in routine clinical assessment of DoC currently, it may prove useful in the future for prognostication of patients with DoC of mixed etiologies, including COVID-19.

Conclusions

Some patients with persistent unresponsiveness after severe COVID-19 can recover at least minimal consciousness after a delay; although this finding is of uncertain long-term significance in patients with COVID-19, recovery to MCS is an important favorable prognostic indicator in DoC of other etiologies. Avoidance of premature nihilism is crucial in these patients. Early neurorehabilitation of COVID-19-associated DoC in the ICU is associated with unique challenges, but use of the CRS-R may support nuanced diagnosis of level of consciousness, provide important prognostic data, and serve as a framework for therapeutic intervention. Hypoxia, systemic inflammation, and sedation may be related to persistently low CRS-R performance, and neuromuscular blockade may confound scores. CRS-R scores may fluctuate, so serial evaluations are needed to guide therapy and prognosticate. Additional research is needed to evaluate longer-term neurologic recovery and the benefits of early neurorehabilitation in patients with severe COVID-19 in the ICU and beyond.

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Author contributions

LG: conception and design, data collection, analysis and interpretation of data, drafting the manuscript, and final approval of the manuscript. ME: conception and design, data collection, drafting the manuscript, and final approval of the manuscript. PL: conception and design, data collection, drafting the manuscript, and final approval of the manuscript. KH: conception and design, drafting the manuscript, and final approval of the manuscript. JC: conception and design, drafting the manuscript, and final approval of the manuscript. JH: conception and design, drafting the manuscript, and final approval of the manuscript. BI: conception and design, drafting the manuscript, and final approval of the manuscript. JF: critical revision of the manuscript and final approval of the manuscript. SF: critical revision of the manuscript and final approval of the manuscript. SG: critical revision of the manuscript and final approval of the manuscript. AL: conception and design, supervision, critical revision of the manuscript, and final approval of the manuscript. LG takes full responsibility for the data, its analysis and interpretation, and the conduct of this research. Dr. Gurin has full access to all of the data and has the right to publish any and all data independent of any sponsor.

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Conflict of interest

John Corcoran serves as an international medical rehabilitation surveyor for the Commission on Accreditation of Rehabilitation Facilities and receives financial compensation for this role. Lindsey Gurin, Megan Evangelist, Patricia Laverty, Kaitlin Hanley, Jodi Herbsman, Brian Im, Jennifer Frontera, Steven Flanagan, Steven Galetta, and Ariane Lewis declare they have no conflicts of interest.

Ethical approval/informed consent

This study was approved by the NYULH Institutional Review Board with a waiver of informed consent.

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