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Delirium and Neuropsychological Outcomes in Critically Ill Patients with COVID-19: an Institutional Case Series

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Abstract

Objective: To characterise the clinical course of delirium for patients with Coronavirus Disease 2019 (COVID-19) in the intensive care unit, including post-discharge neuropsychological outcomes.

Design: Retrospective chart review and prospective survey study.

Setting: Intensive care units, large academic tertiary-care centre (USA).

Participants: Patients (n=148) with COVID-19 admitted to an intensive care unit at Michigan Medicine between 1 March 2020 and 31 May 2020 were eligible for inclusion.

Primary and secondary outcome measures: Delirium was the primary outcome, assessed via validated chart review method. Secondary outcomes included measures related to delirium, such as delirium duration, antipsychotic use, length of hospital and intensive care unit stay, inflammatory markers, and final disposition. Neuroimaging data were also collected. Lastly, a telephone survey was conducted between 1-2 months after discharge to determine neuropsychological function via the following tests: Family Confusion Assessment Method, Short Blessed Test, Patient-Reported Outcomes Measurement Information System Cognitive Abilities 4a, and Patient-Health Questionnaire-9.

Results: Delirium was identified in 108/148 (73%) patients, with median (interquartile range) duration lasting 10 (4 – 17) days. In the delirium cohort, 50% (54/108) of patients were African American, and delirious patients were more likely to be female (76/108, 70%) (absolute standardized differences >.30). Sedation regimens, inflammation, delirium prevention protocol deviations, and hypoxic-ischemic injury were likely contributing factors, and the most common disposition for delirious patients was a skilled care facility (41/108, 38%). Among patients who were delirious during hospitalization, 4/17 (24%) later screened positive for delirium at home based on caretaker assessment, 5/22 (23%) demonstrated signs of questionable cognitive impairment or cognitive impairment consistent with dementia, and 3/25 (12%) screened positive for depression within two months after discharge.

Conclusion: Patients with COVID-19 commonly experience a prolonged course of delirium in the intensive care unit, likely with multiple contributing factors. Furthermore, neuropsychological impairment may persist after discharge.

Strengths and limitations of this study

- The validated chart review method increases confidence in the delirium findings reported.
- Granular details included (i.e., inflammatory profiles, neuroimaging findings, post-discharge neuropsychological function) provide a comprehensive assessment of delirium phenotype in this patient population along with related complications.
- As a single-centre study, findings are restricted to the institution included.
- Many patients were lost to follow-up after hospital discharge.

Introduction:

The outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes Coronavirus Disease (COVID-19), emerged as a public health threat in December 2019 and was declared a pandemic by World Health Organization in March 2020. Major neurological complications, such as encephalopathy, delirium, strokes, seizures, and ataxia, have all been observed.[1-5] Delirium appears to be a common complication, with previous investigations demonstrating an incidence of approximately 65-80% in the intensive care unit (ICU).[1 4] Delirium may occur due to direct coronavirus invasion of the central nervous system, [6] and systemic inflammatory responses may further exacerbate neurocognitive impairment. In the ICU, synergistic factors such as sedation regimen, social isolation, and deviation from standard care protocols may further increase risk. Delirium is also associated with prolonged hospitalization, long-term cognitive and functional impairment, and increased mortality.[7-9] As such, there is a critical need to improve understanding of this syndrome in patients with COVID-19.

While a high incidence of delirium has been reported in COVID-19 patients, fundamental questions persist. The clinical course of delirium, including average duration and post-discharge cognitive trajectory, remains unknown. Pathophysiologic drivers of delirium are incompletely understood, and the extent to which standard prevention protocols are implemented is unclear. Such detailed understanding will contribute to delirium phenotyping of COVID-19 patients and provide insight into the clinical and neurocognitive burden associated with COVID-19. In this context, the

objective of this study was to determine granular details associated with delirium in ICU patients with COVID-19. Specifically, the clinical course of delirium, presence of exacerbating factors, nature of prevention strategy implementation, and post-discharge cognitive outcomes were all characterized.

Methods:

Study design and overview

This was a single-centre case series from Michigan Medicine. Detailed chart review data were collected from critically ill patients with COVID-19 (3/1/2020 – 5/31/2020), and post-discharge telephone surveys were conducted to test neuropsychological function after discharge. All study operations were conducted at Michigan Medicine, Ann Arbor MI USA, and approval was obtained from the University of Michigan Medical School Institutional Review Board (HUM00182646). A Health Insurance Portability and Accountability Act waiver was granted in order to retrospectively review patient medical records, and informed consent was not required for retrospective chart review. Patients who agreed to complete telephone surveys after discharge were consented over the telephone prior to survey administration using a comprehensive consent document. A waiver of documentation of consent was approved in conjunction with Institutional Review Board approval and as required by U.S. Department of Health and Human Services regulations and policy. Lastly, the CAse REport guidelines checklist is included in the supplemental online material (Supplemental Table 1). These guidelines provide reporting standards for case reports of one or more patients.[10]

Eligibility criteria

All patients with a COVID-19 diagnosis admitted to a Michigan Medicine ICU between 03/01/2020 – 05/31/2020 were eligible for study inclusion. ICU patients admitted during this time, without a diagnosis of COVID-19, were not eligible for study inclusion.

Outcomes

The primary outcome was delirium presence (yes/no, %) at any point during admission. Delirium was evaluated via chart review method (described below). Several secondary outcomes were also collected in relation to delirium and overall clinical trajectory. These outcomes included the following: duration of delirium (days), antipsychotic administration, length of hospital stay, length of ICU stay, number of days requiring ventilator support, inflammatory laboratory values (white blood cell count, c-reactive protein, ferritin, lactate dehydrogenase, d-dimer, and interleukin-6), new psychiatry consults, new antidepressant use, and final disposition (e.g., home, long-term care facility, death). Delirium prevention strategies, based on the ABCDEF ICU liberation bundle,[11 12] were also recorded. These included the following: structured mobility exercises, placing familiar objects from home at the bedside, promoting use of visual and hearing aids, and spontaneous awakening/breathing trials. The total number of times a prevention strategy was charted was recorded for each patient, and this number was divided by the *expected* number of times that intervention should have occurred based on length of ICU stay and protocolised schedule. This provided the estimated compliance rate for each intervention. Neuroimaging data were also collected and reviewed.

Lastly, a telephone survey was conducted between 30-60 days post-discharge to determine whether subjective or objective signs of cognitive impairment were present. During telephone interviews, the following tests were conducted: the Patient-Reported Outcomes Measurement Information System (PROMIS)[13] Cognitive Function Abilities

4a, Short Blessed Test (score 0-4 = normal cognition, score 5-9 = questionable impairment, score ≥10 = impairment consistent with dementia),[14] Family Confusion Assessment Method (FAM-CAM) for delirium,[15] and the Patient Health Questionnaire-9 (scores ≥10 were considered positive screens for depression).[16 17]

Data collection

Screening for eligible patients was first performed for via DataDirect, a software tool from the University of Michigan Office of Research that enables research teams to retrospectively search for patient cohorts. Charts that screened positive were then manually reviewed by study team members to confirm study eligibility.

Charts were then reviewed in further detail for outcome abstraction. Delirium was assessed via validated, publicly available chart review method.[18] Briefly, any instance of an acute confusional state was recorded in the instrument and counted as an episode of delirium. The methodology is drawn from the Confusion Assessment Method,[19] which assesses for acute changes in cognition, fluctuating course, inattention, altered levels of consciousness, and disorganized thinking. This was the core set of delirium symptoms in this cohort, and hyperactive states (e.g., agitation) were reported as well. The source of information was recorded, along with the date and time. The total number of days with acute confusion was also included in the instrument, along with any evidence of reversibility or improvement of the confusion state. Other clinical outcomes, along with laboratory values, were collected directly from the charts. Neuroimaging studies were

manually reviewed by a board certified radiologist with a Certificate of Added Qualification in neuroradiology (R.L.).

Patient and Public Involvement

Neither patients nor the public were involved in this research.

Statistical Analysis

Analyses were performed using IBM SPSS version 27 (Armonk, NY USA) and SAS version 9.4 (SAS Institute, Cary, NC USA). Exploratory data analysis techniques were used to assess the distribution of dependent measures for determining the appropriate analytical strategy. The Shapiro-Wilk test was used to assess the distribution of continuous outcomes, and Independent t-tests or Mann-Whitney U tests were used as appropriate. Mean (standard deviation) or median (interquartile range) was reported for parametric and non-parametric data, respectively. For binary outcomes and proportions, The Chi-Square Test or Fisher's Exact Test were used, as appropriate. Absolute standardized differences were calculated for determining differences in baseline characteristics between groups, with differences >.20 considered to be imbalanced. The threshold for significance was set to $p<0.05$ across all tests otherwise. For post-discharge cognitive outcomes, descriptive statistics were reported.

Results

Baseline characteristics are presented in Table 1. The majority of patients were African-American and non-Hispanic, and the most common comorbidities were hypertension, Diabetes mellitus, and obesity. Absolute standardized differences between delirium and non-delirium groups were largest (>.30) for sex, race, and weight. The highest proportion of patients in the delirium group were African-American (n=54, 50%), and weight was significantly higher in the delirium group (105 [87 – 127] kg vs. 93 [97 – 113] kg, *P*<.05).

Delirium and Neuropsychological Outcomes

Delirium incidence was high in the cohort (108/148, 73%), and median (interquartile range) duration was 10 (4 – 17) days (Table 2). Delirium prevention activities occurred relatively infrequently, with estimated unit protocol compliance rates less than 50% for each intervention reported (see Table 2 legend for description of protocol activity schedule). The mobility exercise activity compliance rate (%) was significantly lower in the delirium group (37% [26 – 55]) compared to the non-delirium group (62% [31 – 152]; *P*=.009). Likewise, daily promotion of visual and hearing aids occurred less frequently in the delirium group (27% [13 – 63]) compared to the non-delirium group (77% [14 – 213]; *P*=.005). New antidepressant use was more common for those with delirium (27/108, 25%) compared to those without delirium (3/40, 7.5%; *P*=.01). Similarly, a psychiatry consult was obtained for 21/108 (19%) delirious patients compared to 0/40 (0%) in the non-delirium group (*P*=.003). Lastly, no evidence of reversal or improvement was reported for more than 30% of patients during index hospitalization.

Hospitalization and Post-Discharge Outcomes

Median length of hospitalization was 25 (13 – 48) days, and median length of ICU stay was 15 (7 – 31) days across the cohort (Table 3). Length of hospitalization, ICU length of stay, and duration of mechanical ventilation were all significantly prolonged in patients experiencing delirium (Table 3). Correspondingly, sedative-hypnotic use was higher in patients with delirium. Delirious patients demonstrated higher white blood cell counts, c-reactive protein levels, and d-dimer levels compared to non-delirious patients. Less than half of patients were ultimately discharged home, and the most common disposition for those with delirium was a skilled care facility (41/108, 38%) after discharge (Table 3).

Neuropsychological outcomes after discharge are reported in Table 4. Among patients who were still alive and available to complete survey materials, nearly 25% of patients (4/17) scored positive for delirium based on family assessment (FAM-CAM), and all of these patients were delirious during hospitalization. Similarly, approximately 23% of patients (5/22) demonstrated either questionable impairment or impairment consistent with dementia based on the Short Blessed Test, and all five of these patients were also delirious during hospitalization. Of note, three of these five patients also screened positive for delirium based on the FAM-CAM. Lastly, 12% of patients (3/25) screened positive for depression after discharge. The three patients who screened positive also experienced delirium during ICU admission.

Neuroradiological Findings

In total, 47 patients underwent neuroimaging during hospitalization. The majority of imaging results were unremarkable or demonstrated incidental findings unrelated to COVID-19. However, some notable findings were present. A brain MRI was ordered for a patient with COVID-19 pneumonia and worsening encephalopathy (i.e., no response to commands or noxious stimulus). Imaging revealed abnormal fluid attenuated inversion recovery (FLAIR) hyperintensity affecting the occipital and temporal lobes (Figures 1A, 1B), microhemorrhage in the splenium of the corpus callosum (Figures 1B, 1C) and posterior leptomeningeal enhancement Figures 1C, 1D), suggestive of encephalitis. A brain MRI was ordered for another patient presenting with seizures and recent COVID-19 diagnosis. Results revealed diffuse dural thickening and enhancement (Supplemental Figure 1A) one day prior to positive COVID testing. The differential diagnosis included intracranial hypotension, inflammation, infection, and neoplastic processes. No definitive diagnosis was reached, though this enhancement resolved approximately one month later (Supplemental Figure 1B). Lastly, one patient demonstrated diffuse parenchymal abnormalities on MRI suggestive of bilateral hypoxic-ischemic injury after multiple cardiopulmonary arrests (Supplemental Figure 2). A non-contrast head CT two weeks later demonstrated poor sulcation bilaterally, suggesting global hypoxic-ischemic injury (Supplemental Figure 3).

Discussion

In a cohort of ICU patients with COVID-19, delirium was a common complication, affecting more than 70% of patients. Furthermore, delirium was associated with prolonged hospitalization, increased length of ICU stay, discharge to skilled care facilities, and positive screens for neuropsychological impairment up to two months after discharge. Delirium occurred in the setting of multiple sedative-hypnotic agents, acute inflammatory responses, deviation from delirium prevention protocols, and cerebrovascular events, which are all factors that could have further catalysed delirium precipitation. ICU liberation activities were infrequently implemented compared to the protocolised frequency expected. Overall, the burden of cognitive impairment was high in patients with COVID-19, as was the risk of related complications.

These results align with previous data demonstrating a high incidence of delirium in critically ill patients with COVID-19.[1-4] Our findings also highlight the multifactorial nature of delirium risk factors. In terms of demographics, 50% of patients in the delirium group were African American. COVID-19 has adversely, and disproportionately, impacted racial and ethnic minority communities,[20 21] and our results further suggest an increased risk of attendant complications (e.g., delirium) during hospitalization. Efforts to reduce racial healthcare disparities may thus, by extension, mitigate risk of delirium and related consequences of COVID-19. Patients experiencing delirium also demonstrated significantly increased weight, and obesity may drive organ dysfunction via immune system dysregulation.[22] Additionally, there was a disproportionate number of female patients in the delirium group (absolute standardized difference >.30). These results are

discrepant from a prior case series of critically ill patients with COVID-19 demonstrating an increased risk of delirium with male patients.[4] Male sex has also been identified as an independent risk factor for delirium in other patient populations, possibly due to underlying comorbidity severity.[23 24] Whether the findings in this study are spurious or reflect an underlying biological phenomenon is unclear. Further investigation is warranted to improve understanding of the impact that such demographic factors on delirium risk in patients with COVID-19.

Cognitive dysfunction may also occur as a result of direct coronavirus invasion of the central nervous system[6] or other indirect mechanisms, such as polypharmacy, systemic inflammatory responses, and cerebrovascular events. Indeed, benzodiazepine sedation was common in this patient cohort, with nearly 60% of patients receiving midazolam at one point during ICU admission. Lorazepam was a common sedation agent as well, and benzodiazepine use is associated with delirium in critically ill patients.[25-27] Whether benzodiazepine administration served as a driver of delirium, or reflected worsening agitation (prompting additional sedative agents), remains unclear. Inflammation may have also contributed to delirium risk. Inflammatory markers (e.g., c-reactive protein, ferritin, interleukin-6, lactate dehydrogenase) were considerably elevated in this patient cohort. In fact, serum levels observed in this study aligned with – or exceeded – previously reported values in patients with severe COVID-19,[2 5] and there was MRI evidence of neuroinflammation for at least two patients in this series. C-reactive protein was elevated in delirious patients, and c-reactive protein increases blood-brain barrier permeability in basic science models.[28] However, this was an unadjusted, bivariable

analysis, and confounding remains possible. Cerebral ischemia may also contribute to delirium in patients with COVID-19. Severe hypoxic-ischemic injury occurred in a patient who experienced multiple cardiopulmonary arrests during the course of illness. Stroke has previously been reported in patients with COVID-19,[29] as thromboembolic phenomena and cerebral malperfusion may both occur during the clinical course of COVID-19. Lastly, overall illness severity may increase delirium risk. Indeed, patients with delirium had prolonged hospital and ICU lengths of stay, longer duration of mechanical ventilation, and were more likely to require haemodialysis. Overall, multiple processes likely contribute to delirium in patients with COVID-19. Targeted case-control studies can be conducted to determine independent risk factors for delirium in this patient population.

Delirium prevention and management are inherently challenging for COVID-19 patients. While delirium prevention bundles have been demonstrated to reduce risk,[30 31] unique challenges posed by COVID-19 hinder the implementation of standard prevention practices. Spontaneous awakening and breathing trials, for example, may not have been possible due to illness severity and associated ventilator requirements. Clinicians may have also been limited in terms of sedation regimen. Agitation was commonly observed, and nearly 30% of patients required antipsychotics in this cohort. Agitation and hyperactive delirium likely prompted additional sedation and prolonged use of physical restraints. Early mobility was limited given illness severity, and family engagement was not possible due to visitor policy restrictions. In-person interactions with clinicians were also limited given the intent of reducing virus transmission. As such,

the culmination of disease severity, limited face-to-face time spent with patients, and visitor restriction policies likely hindered ICU liberation bundle implementation. Novel strategies for implementing delirium prevention bundles in this patient population may help to further mitigate risk and should be tested in prospective trials.

Neuropsychological impairment after discharge was also present for some patients based on subjective reporting, caretaker assessment, and objective testing for depression and cognitive impairment. Furthermore, all patients that screened positive for possible impairment also experienced delirium in the hospital. These estimates may have been even higher, given that many patients called for post-discharge assessments were unable to be reached, refused participant, or were still admitted to skilled care facilities. Whether post-discharge cognitive impairment was related specifically to COVID-19 or critical illness more broadly is unclear. Indeed, cognitive impairment is common at discharge for patients who experienced delirium while in the ICU, and delirium is present for nearly 20% of patients newly admitted to acute care facilities.[7 32] Moreover, cognitive impairment can be present for months-to-years after acute respiratory distress syndrome and sepsis,[33-35] and symptoms of depression and post-traumatic stress disorder are commonly reported among ICU survivors.[36] Neuropsychological impairment after discharge may thus, in part, reflect critical illness, rather than pathophysiologic insults specific to COVID-19. Nonetheless, ICU patients with COVID-19 experience considerable neuropsychological burden both during and after hospitalization. Identifying such vulnerable patients will be important for providing appropriate longitudinal care and resources.

The strengths of this study include granular data with respect to delirium, identification of potential risk factors, characterization of delirium prevention strategies, and post-discharge outcomes. Data were representative of an academic tertiary care centre with nearly 150 patients. A validated, standardized chart review method was used to identify delirium,[18] and the study measures used to characterize cognitive function, such as the FAM-CAM, Short Blessed Test, and PROMIS assessments, are standard measures that increase confidence in the results. In terms of limitations, this is a this was a single-centre analysis, and the results are restricted to the institution studied. The study was not conducted with a matched control cohort, as this was a descriptive study. The post-discharge telephone-based assessments served as screening tools rather than thorough neuropsychological testing batteries. As such, these post-discharge results are preliminary and warrant rigorous, follow-up analysis. Additionally, neuropsychological impairment may have been present at baseline for some patients, particularly for those with previous neurological disorders. Baseline neuropsychological testing was not possible for this study. Lastly, data were limited for post-discharge cognitive outcomes, as more than half of patients called were unavailable to complete assessments.

In summary, delirium is common complication of COVID-19 with multiple contributing factors. Furthermore, neuropsychological impairment may persist in some patients after discharge. Further research should aim to identify independent risk factors in this population and novel, effective prevention strategies.

Author contributions:

The study was originally conceived by J.R., A.M., M.Z., and P.E.V. Data acquisition was conducted by J.R., A.M., M.Z., J.B., M.H.C., Y.A., and P.E.V. Data analysis was conducted by J.R., A.M., M.Z., J.B., M.H.C., M.I., Y.A., G.M., and P.E.V. Final statistical analysis was conducted by G.M. and P.E.V. Neuroimaging studies were acquired and analyzed by R.L., and the final neuroimaging figures were generated by R.L. and P.E.V. All authors contributed to the manuscript writing, critically reviewed the manuscript for intellectual content, and approved the final manuscript.

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Figure 1. Axial fluid-attenuated inversion recovery (FLAIR) (A, B) images at the level of the basal ganglia show abnormal FLAIR hyperintense signal (arrows) affecting the bilateral occipital, temporal lobes. This appears almost sulcal suggesting a higher protein component within the cerebrospinal fluid. Note the elevated FLAIR signal in the splenium of the corpus callosum (arrow) suggesting parenchymal insult. Axial susceptibility weighted imaging (SWI) (C) at the level of the splenium of the corpus callosum shows small areas of susceptibility (arrow) in the splenium, likely related to microhemorrhage. Axial T1 (D) post-contrast with fat suppression at the level of the basal ganglia shows subtle, though true, enhancement (arrows) in the posterior sulci, arachnoid pial (leptomeningeal) pattern suggesting a degree of encephalitis.

Table 1. Baseline Characteristics

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**	**Absolute Standardized Difference**
Age (IQR)	59 (49 – 71)	58 (47 – 71)	62 (54 – 71)	.26
Male sex, n (%)	98 (66)	32 (30)	18 (45)	.32
Race, n (%)				.32
Caucasian	66 (45)	47 (44)	19 (48)	
African-American	70 (47)	54 (50)	16 (40)	
Other	1 (0.7)	1 (0.9)	0 (0)	
Not reported	11 (7.4)	6 (5.6)	5 (13)	
Ethnicity, n (%)				.31
Non-Hispanic	137 (93)	100 (93)	38 (93)	
Hispanic	5 (3.4)	5 (4.7)	0 (0)	
Unknown/not reported	6 (4.1)	3 (2.8)	3 (7.5)	
Weight, kg (IQR)	103 (83 – 127)	105 (87 – 127)	93 (79 – 113)	.36
BMI (IQR)	34 (28 – 40)	34 (29 – 41)	31 (28 – 39)	.16
Comorbidities, n (%)				
Asthma	24 (16)	17 (16)	7 (18)	.05
Atrial fibrillation	22 (15)	14 (13)	8 (20)	.19
Cancer	25 (17)	20 (19)	5 (13)	.17
Chronic kidney disease	40 (27)	30 (28)	10 (25)	.06
Congestive heart failure	19 (13)	13 (12)	6 (15)	.09

COPD	14 (9.5)	8 (7.4)	6 (15)	.24
Coronary artery disease	27 (18)	18 (17)	9 (23)	.15
Depression	17 (11)	11 (10)	6 (15)	.15
Diabetes mellitus	75 (51)	58 (54)	18 (43)	.23
Hypertension	102 (69)	74 (66)	29 (70)	.03
Obstructive sleep apnoea	31 (21)	22 (20)	9 (23)	.05
Seizures	8 (5.4)	5 (4.6)	3 (7.5)	.12
Stroke	9 (6.1)	5 (4.6)	4 (10)	.21
Substance abuse	9 (6.1)	6 (5.6)	3 (7.5)	.21
TIA	5 (3.4)	3 (2.8)	2 (5)	.12

Median (interquartile range, IQR) data presented. *Kg* kilograms, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *TIA* transient ischemic attack.

Table 2. Delirium and Neuropsychological Outcomes

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**	***P* Values**
Delirium measures				
Delirium, n (%)	108 (73)	108 (100)	---	---
Duration of delirium, days (IQR)	10 (4 – 17)	10 (4 – 17)	---	---
Agitation (n, %)	--	54 (50)	--	--
Antipsychotic use, n (%)	43 (29%)	42 (39)	1 (2.5)	<.001
Evidence of reversal, n (%)	---	71 (66)	---	---
ICU liberation bundle activity compliance rate, % (IQR)				
Mobility exercises	40 (28 – 67)	37 (26 – 55)	62 (31 – 152)	.009
Familiar objects at bedside	14 (4.4 – 31)	14 (5.9 – 25)	18 (0 – 62)	.38
Daily visual and hearing aids	33 (13 – 76)	27 (13 – 63)	77 (14 – 213)	.005
Daily spontaneous awakening/breathing trials	14 (2.3 – 25)	14 (7.9 – 25)	6.7 (0 – 23)	.07
Psychiatric outcomes				
New antidepressant use, n (%)	30 (20)	27 (25)	3 (7.5)	.01
New psychiatry consults, n (%)	21 (14)	21 (19)	0 (0)	.003

Delirium prevention measures are based on the standard ICU liberation bundle protocols (see text for details). Per institutional protocol, clinicians conduct mobility exercises three times daily, place familiar objects at the bedside once daily, promote visual and hearing aid use daily, and conduct daily spontaneous awakening/breathing trials daily (if eligible). Given this schedule, compliance/occurrence

rates (%) were calculated for each patient by calculating the total number of activities charted divided by the total number expected based on length of ICU stay (day of ICU discharge was not counted). *IQR,* interquartile range.

Table 3. Hospitalization

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**	***P Value***
Length of hospitalization, days (IQR)	25 (13 – 48)	31 (18 – 52)	11 (7 – 25)	<.001
Length of ICU stay, days (IQR)	15 (7 – 31)	19 (12 – 38)	4 (2 – 8)	<.001
Ventilator time, days, (IQR)	12 (3 – 28)	18 (10 – 29)	0 (0 – 7)	<.001
Required haemodialysis, n (%)	45 (30)	40 (37)	5 (13)	.004
Sedative-hypnotics, n (%)				
Propofol	113 (76)	98 (91)	15 (38)	<.001
Midazolam	87 (59)	75 (69)	12 (30)	<.001
Dexmedetomidine	97 (66)	89 (82)	8 (20)	<.001
Lorazepam	58 (39)	52 (49)	6 (15)	<.001
Laboratories				
WBC (n=148) 4.0 – 10.0 (K/μL)	10.1 (7.8 – 13.9)	11.3 (8.4 – 15.1)	8.7 (6.3 – 10.9)	.002
C-reactive protein (n=145) 1.0 – 3.0 (mg/L)	10.2 (5.1 – 18.0)	11.7 (5.3 – 20.7)	8.9 (4.3 – 13.9)	.03
Ferritin (n=147)	1,208 (591 – 1,786)	1276 (714 – 1990)	994 (478 – 1406)	.09

18.0 – 320.0 (ng/mL)				
Lactate dehydrogenase (n=135) 120 – 240 (IU/L)	455 (328 – 572)	458 (343 – 633)	398 (276 – 515)	.05
IL-6 (n=52) < 17.4 pg/mL	69.4 (27.5 – 201.3)	69.4 (32.6 – 186.7)	62.7 (19.9 – 361)	.77
D-dimer (n=142) < 0.59 mg/L	3.1 (1.5 – 6.8)	3.67 (1.84 – 7.75)	1.65 (1.27 – 4.41)	.002
Disposition, n (%)				.03
Home (unassisted)	62 (42)	40 (37)	22 (55)	
Skilled care facility	47 (32)	41 (38)	6 (15)	
Death	39 (26)	27 (25)	12 (30)	

Institutional reference ranges are reported for laboratory values. *ICU* intensive care unit, *IQR* interquartile range, *WBC* white blood cell count, *IL-6* interleukin-6.

Table 4. Post-Discharge Neuropsychological Outcomes†

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**
Positive FAM-CAM, n (%) (n=17)	4 (24)	4 (31)	0 (0)
PROMIS 4A Cognitive Abilities Score, median (IQR) (n=25)	16 (10 – 20)	17 (9 – 20)	14 (6)
Short Blessed Test – Normal, n (%) (n=22)	17 (74)	10 (67)	7 (100)
Short Blessed Test – questionable cognitive impairment, n (%) (n=22)	2 (8.7)	2 (13)	0 (0)
Short Blessed Test – cognitive impairment, n (%) (n=22)	3 (13)	3 (20)	0 (0)
PHQ-9 screen positive, n, (%) (n=25)	3 (12)	3 (17)	0 (0)

FAM-CAM Family-based Confusion Assessment Method for delirium, *PROMIS* Patient-Reported Outcomes Measurement Information System, *PHQ* Patient Health Questionnaire. †For each post-discharge survey, proportions are calculated based on the total numbers of surveys completed. In total, 25 surveys were completed for the PROMIS 4A test, 25 surveys were completed for the PHQ-9, 17 surveys were completed for the FAM-CAM, and 22 surveys were completed for the Short Blessed Test.

Reasons for not completing a test included the following: unable to contact (n=54), patient deceased (n=43), refusal (n=18), unable to provide consent (n=5), and admission to skilled care facility (n=3).

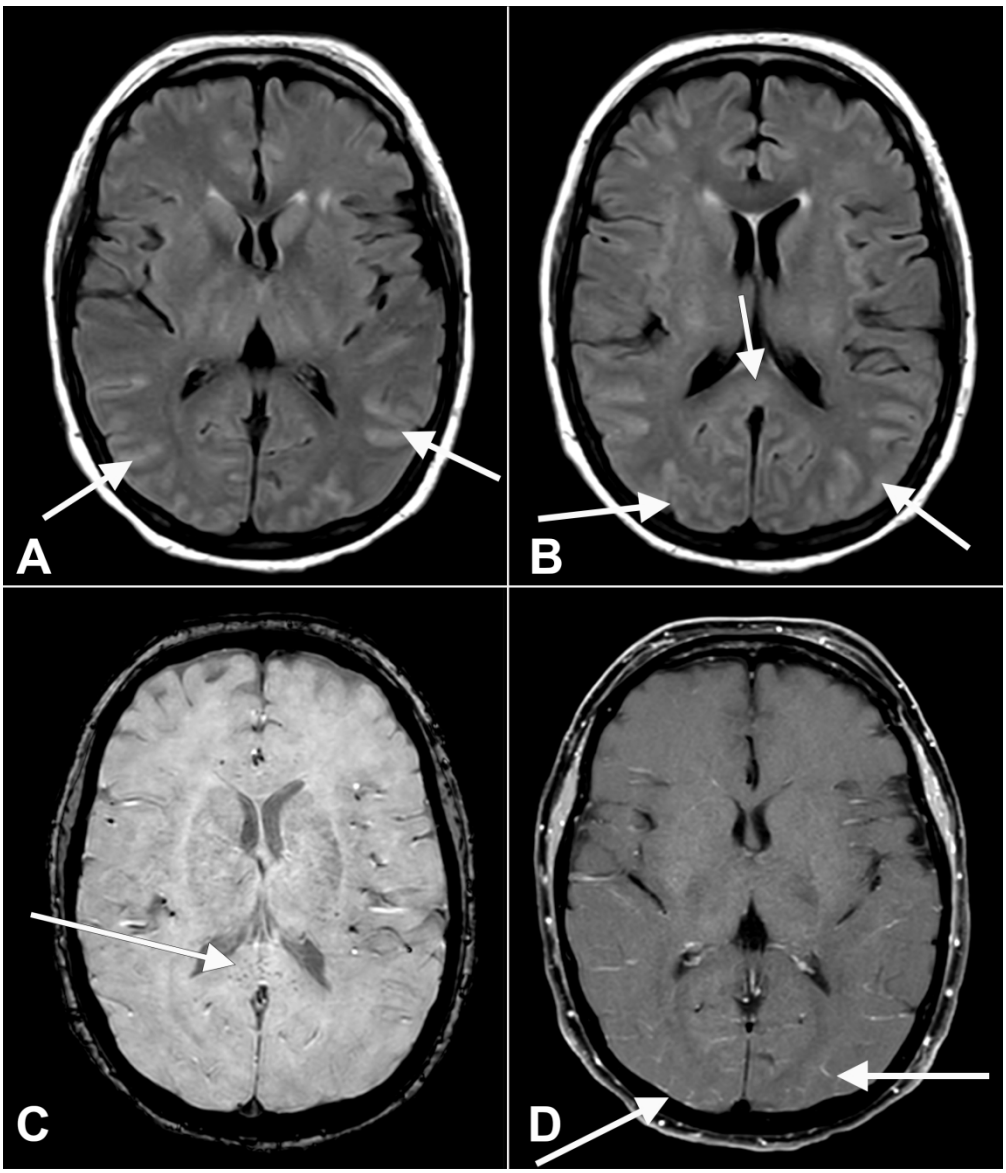

Figure 1 - Axial fluid-attenuated inversion recovery (FLAIR) (A, B) images at the level of the basal ganglia show abnormal FLAIR hyperintense signal (arrows) affecting the bilateral occipital, temporal lobes. This appears almost sulcal suggesting a higher protein component within the cerebrospinal fluid. Note the elevated FLAIR signal in the splenium of the corpus callosum (arrow) suggesting parenchymal insult. Axial susceptibility weighted imaging (SWI) (C) at the level of the splenium of the corpus callosum shows small areas of susceptibility (arrow) in the splenium, likely related to microhemorrhage. Axial T1 (D) post-contrast with fat suppression at the level of the basal ganglia shows subtle, though true, enhancement (arrows) in the posterior sulci, arachnoid pial (leptomeningeal) pattern suggesting a degree of encephalitis.

202x235mm (300 x 300 DPI)

The Natural History of Delirium in COVID-19 Intensive Care Unit patients: an Institutional Case Series

Background:

The outbreak of CoV-2, the virus that causes COVID-19, emerged as a public health threat in December 2019 and declared a pandemic by World Health Organization in March 2020. Several case reports and studies have described the serious nature of complications associated with this disease. Neurological complications, affecting both the central and peripheral nervous systems, have also been reported. Central nervous system (CNS) complications have been particularly harrowing. Seizures, ataxia, and encephalopathy have all been observed with this disease (1,2).

Critically ill patients with COVID-19 have an accelerated risk of delirium due to multiple factors. This can be directly due to invasion of COVID to Central nervous system, or indirectly related to the severity of inflammatory response and induction of CNS inflammatory mediators (3,4). Other accelerating factors unique to patients who are admitted to ICU include effect of sedative strategies, prolonged mechanical ventilation, secondary effect of other organ failure, and social isolation and quarantine from family and care givers. In addition, delirium in the ICU worsen overall prognosis. If left unmitigated, delirium can exacerbate related complications such as ICU acquired weakness, dementia, depression, and PTSD (5,9).

In this context we propose to conduct a case series analysis to better characterize the natural history of delirium in COVID patients. The objective of this study is to better understand the natural history of delirium in in ICU COVID patients. We hypothesize that delirium is a common

complication associated with COVID-19, and it is associated with substantial morbidity and mortality.

Methods:

Study design and overview

This is a single center, observational case series analysis to analyze the incidence of delirium in ICU patients with COVID-19 infection. Post-discharge screening surveys using psychometric screening tools will also be performed. All study operations will be conducted at Michigan Medicine, Ann Arbor MI USA. Institutional Review Board exemption will be sought from University of Michigan Medical School (IRBMED).

Eligibility criteria

All adult patients (age 18 and older) with a COVID–19 diagnosis admitted to an ICU within Michigan Medicine between the dates of 03/01/2020 –05/31/2020 (N=154).

Data collection

Analysis will be conducted via retrospective chart reviews of patients who were diagnosed with COVID-19 and who were admitted to a Michigan Medicine ICU between 03/01/2020 – 05/31/2020. The charts will be reviewed for delirium presence using validated chart review method (6). Review of the entire medical record, including progress notes, nursing notes, consult notes, will be conducted. Delirium will be coded as "yes" if any key terms or descriptors were present based on chart review methodology. Other extracted data will include:

- Presence of other organ failures
- Presence of Inflammatory markers including CRP, Ferritin and Interlukin-6
- Neuro-radiological findings

- Delirium prevention measures in ICU
- Approach to use of sedation medications and anticholinergic agents in ICU admission
- Use of antidepressants
- Psychiatry consult
- Length of hospital stay
- Disposition of patients to home, nursing or care facility.

Qualitative analysis will be conducted via prospective post discharge screening of COVID-19 patients who were admitted to Intensive care units or patients' families. A phone call will be placed within 30-60 days post discharge, and a one-time phone interview will be conducted to probe cognitive function abilities of all surviving patients and their family members (see Exploratory Outcomes below).

Outcomes

Primary Outcome

Delirium presence (yes/no) at any point during ICU stay. Delirium incidence will then be the formal outcome.

Secondary Outcomes

- Number of delirium days (n)
- Intensive care unit length of stay (days)
- Hospital length of stay (days)
- Ventilator (or ventilator free days)

- Laboratory values:
    - WBC
    - Inflammatory markers
        - CRP
        - Ferritin
        - IL-6
- Neuroradiologic findings
    - Stroke (via MRI)
    - Perfusion abnormalities (via MRI)
    - White matter hyperintensities (MRI)
    - Leptomeningeal enhancement
- Psychiatry consults, n (%)
- Antipsychotic use
- Antidepressant use
- Delayed discharge (%) due to cognitive impairment
- Disposition (to home or Long-term acute care facility)

Exploratory Outcomes

- Post-discharge PROMIS cognitive function score (via phone; Cognitive Function Abilities 4a)
- Post-discharge Blessed Test score (via phone)
- PHQ-9 – depression screen
- Post-discharge FAM CAM results (via phone) when families are available

Statistical Analysis

Descriptive statistics will be reported for all outcomes. Exploratory data analysis techniques, such as histograms, QQ-Plots, box-plots, scatterplots and basic descriptive (means, medians, IQR) will be used to assess the distribution of dependent measures.

Discussion

Delirium has been consistently identified as an independent risk factor for mortality and substantial morbidity in critically ill patients. Data regarding delirium in the COVID-19 patients are very limited. Critically ill patients who are infected with SARS-CoV-2 appear to have high risk of cognitive dysfunction. This can be as a result of direct invasion of CNS or indirect mechanisms due to other organ failure.

ICU delirium prevention bundles consistently reduce risk when implemented (7,8). However, unique challenges related to COVID-19 (e.g., propofol avoidance, social distancing, prolonged ventilation) have hindered standard prevention bundle implementation. As a result, COVID-19 ICU patients may have particularly high risk for delirium and related encephalopathies. The quantitative aspects of this study will provide an estimate of delirium incidence in COVID ICU patients, and the qualitative aspects may help elicit the impact of COVID-19 on the quality of survival after hospital discharge.

Strengths

This study will help to determine the natural history of delirium in hospitalized critically ill patients with COVID-19.

Limitations

This is a single center analysis; the results will be restricted to the institution studied. This is also retrospective chart review with limited – and descriptive – reporting.

Quantitative results will only reflect descriptive reporting. The reason as to why ICU team may or may not have followed certain treatment or sedation protocols will not be available. In terms of the qualitative arm of the study, results are predicated upon successfully obtaining phone survey data from patients and families. These data maybe limited given patient and family availability.

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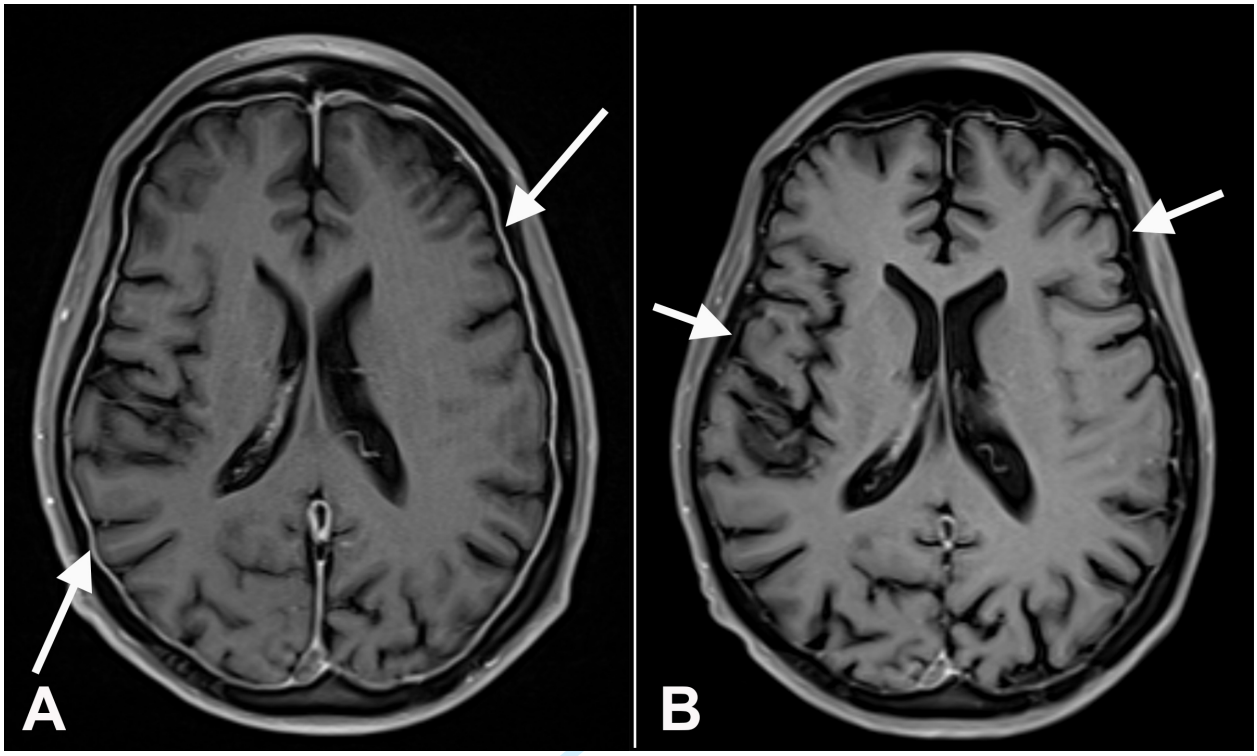
CARE case report guidelines

CARE Checklist of information to include when writing a case report

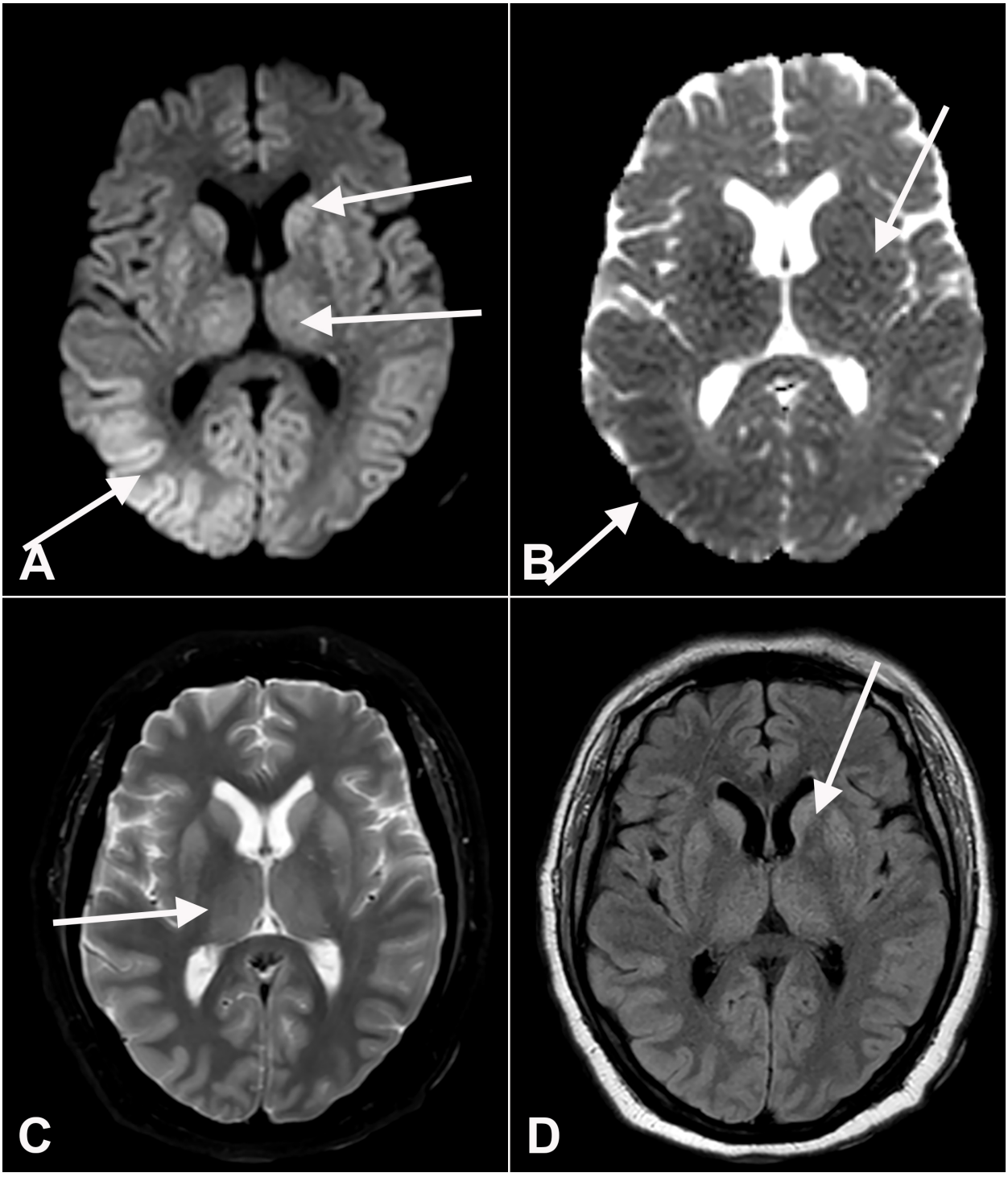
Topic	Item	Checklist item description	Reported on Line
Title	**1**	The diagnosis or intervention of primary focus followed by the words "case report"	
Key Words	**2**	2 to 5 key words that identify diagnoses or interventions in this case report, including "case report"	
Abstract (no references)	**3a**	Introduction: What is unique about this case and what does it add to the scientific literature?	
	3b	Main symptoms and/or important clinical findings	
	3c	The main diagnoses, therapeutic interventions, and outcomes	
	3d	Conclusion—What is the main "take-away" lesson(s) from this case?	
Introduction	**4**	One or two paragraphs summarizing why this case is unique (**may include references**)	
Patient Information	**5a**	De-identified patient specific information.	
	5b	Primary concerns and symptoms of the patient.	
	5c	Medical, family, and psycho-social history including relevant genetic information	
	5d	Relevant past interventions with outcomes	
Clinical Findings	**6**	Describe significant physical examination (PE) and important clinical findings.	
Timeline	**7**	Historical and current information from this episode of care organized as a timeline	
Diagnostic Assessment	**8a**	Diagnostic testing (such as PE, laboratory testing, imaging, surveys).	
	8b	Diagnostic challenges (such as access to testing, financial, or cultural)	
	8c	Diagnosis (including other diagnoses considered)	
	8d	Prognosis (such as staging in oncology) where applicable	
Therapeutic Intervention	**9a**	Types of therapeutic intervention (such as pharmacologic, surgical, preventive, self-care)	
	9b	Administration of therapeutic intervention (such as dosage, strength, duration)	
	9c	Changes in therapeutic intervention (with rationale)	
Follow-up and Outcomes	**10a**	Clinician and patient-assessed outcomes (if available)	
	10b	Important follow-up diagnostic and other test results	
	10c	Intervention adherence and tolerability (How was this assessed?)	
	10d	Adverse and unanticipated events	
Discussion	**11a**	A scientific discussion of the strengths AND limitations associated with this case report	
	11b	Discussion of the relevant medical literature **with references**.	
	11c	The scientific rationale for any conclusions (including assessment of possible causes)	
	11d	The primary "take-away" lessons of this case report (without references) in a one paragraph conclusion	
Patient Perspective	**12**	The patient should share their perspective in one to two paragraphs on the treatment(s) they received	
Informed Consent	**13**	Did the patient give informed consent? Please provide if requested	**Yes** ☐ **No** ☐

Supplemental Figure 1



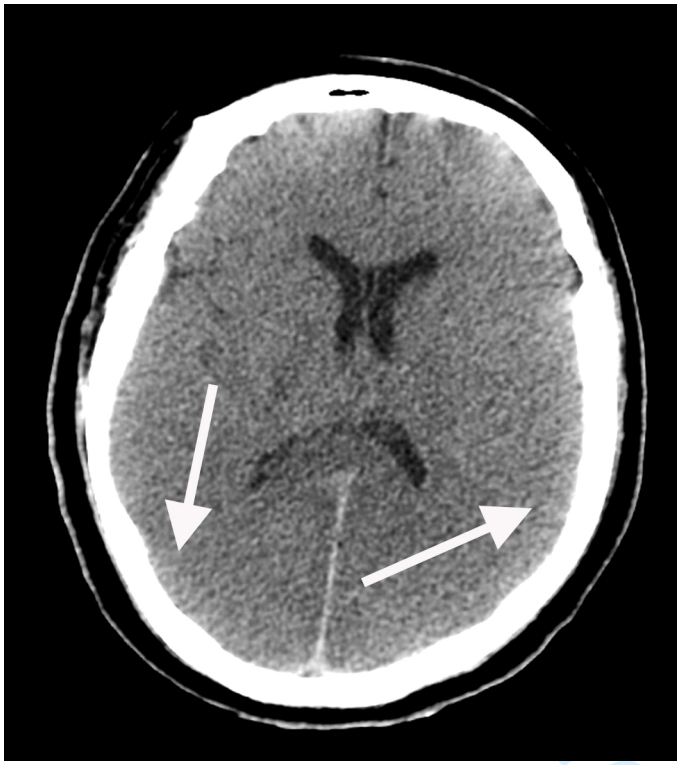
A, Axial T1 post-contrast with fat suppression images at the level of the mid lateral ventricles demonstrate smooth dural enhancement (arrows) along the bilateral cerebral convexities. B, This feature resolves one month later (arrows). The overall pattern of dura-arachnoid/ pachymeningeal enhancement is non-specific, can be seen with intracranial hypotension, in the procedural setting (e.g., lumbar puncture), and other scenarios (e.g., infection, inflammation).

Supplemental Figure 2



After initial non-contrast head CT (which was unremarkable), the patient had diffuse parenchymal abnormalities on MRI examination. A, Axial diffusion-weighted imaging shows hyperintense signal (arrows) at the bilateral basal ganglia, thalami, and posterior cortices, regions are hypointense (arrows) on corresponding apparent diffusion coefficient map (B). These same locations are hyperintense on T2 (C) and FLAIR (D), especially at the basal ganglia and thalami.

Supplemental Figure 3



Non-contrast head CT performed approximately two weeks after cardiopulmonary arrest shows poor sulcation (arrows) bilaterally, suggesting global insult, most likely hypoxic-ischemic in etiology

CARE case report guidelines

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BMJ Open

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Delirium and Neuropsychological Outcomes in Critically Ill Patients with COVID-19: a Cohort Study

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Abstract

Objective: To characterise the clinical course of delirium for patients with Coronavirus Disease 2019 (COVID-19) in the intensive care unit, including post-discharge neuropsychological outcomes.

Design: Retrospective chart review and prospective survey study.

Setting: Intensive care units, large academic tertiary-care centre (USA).

Participants: Patients (n=148) with COVID-19 admitted to an intensive care unit at Michigan Medicine between 1 March 2020 and 31 May 2020 were eligible for inclusion.

Primary and secondary outcome measures: Delirium was the primary outcome, assessed via validated chart review method. Secondary outcomes included measures related to delirium, such as delirium duration, antipsychotic use, length of hospital and intensive care unit stay, inflammatory markers, and final disposition. Neuroimaging data were also collected. Lastly, a telephone survey was conducted between 1-2 months after discharge to determine neuropsychological function via the following tests: Family Confusion Assessment Method, Short Blessed Test, Patient-Reported Outcomes Measurement Information System Cognitive Abilities 4a, and Patient-Health Questionnaire-9.

Results: Delirium was identified in 108/148 (73%) patients, with median (interquartile range) duration lasting 10 (4 – 17) days. In the delirium cohort, 50% (54/108) of patients were African American, and delirious patients were more likely to be female (76/108, 70%) (absolute standardized differences >.30). Sedation regimens, inflammation, delirium prevention protocol deviations, and hypoxic-ischemic injury were likely contributing factors, and the most common disposition for delirious patients was a skilled care facility (41/108, 38%). Among patients who were delirious during hospitalization, 4/17 (24%) later screened positive for delirium at home based on caretaker assessment, 5/22 (23%) demonstrated signs of questionable cognitive impairment or cognitive impairment consistent with dementia, and 3/25 (12%) screened positive for depression within two months after discharge.

Conclusion: Patients with COVID-19 commonly experience a prolonged course of delirium in the intensive care unit, likely with multiple contributing factors. Furthermore, neuropsychological impairment may persist after discharge.

Strengths and limitations of this study

- The validated chart review method increases confidence in the delirium findings reported.
- Granular details included (i.e., inflammatory profiles, neuroimaging findings, post-discharge neuropsychological function) provide a comprehensive assessment of delirium phenotype in this patient population along with related complications.
- As a single-centre study, findings are restricted to the institution included.
- Many patients were lost to follow-up after hospital discharge.

Introduction

The outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes Coronavirus Disease (COVID-19), emerged as a public health threat in December 2019 and was declared a pandemic by World Health Organization in March 2020. Major neurological complications, such as encephalopathy, strokes, seizures, and ataxia, have all been observed.[1-5] Delirium appears to be a common complication, with previous investigations demonstrating an incidence of approximately 65-80% in the intensive care unit (ICU).[1 4] Delirium may occur due to direct coronavirus invasion of the central nervous system, [6] and systemic inflammatory responses may further exacerbate neurocognitive impairment. In the ICU, multiple delirium risk factors are often present and can increase risk in an additive manner.[7] Delirium is also associated with prolonged hospitalization, long-term cognitive and functional impairment, and increased mortality.[8-10] As such, there is a critical need to improve understanding of this syndrome in patients with COVID-19.

While a high incidence of delirium has been reported in COVID-19 patients, fundamental questions persist. The clinical course of delirium, including average duration and post-discharge cognitive trajectory, remains incompletely understood. Pathophysiologic drivers of delirium require advanced understanding, and the extent to which standard prevention protocols are implemented is unclear. Such detailed understanding will contribute to delirium phenotyping of COVID-19 patients and provide insight into the clinical and neurocognitive burden associated with COVID-19. In this context, the objective of this study was to determine granular details associated with

delirium in ICU patients with COVID-19. Specifically, the clinical course of delirium, presence of exacerbating factors, nature of prevention strategy implementation, and post-discharge cognitive outcomes were all characterized.

Methods

Study design and overview

This was a single-centre cohort study from Michigan Medicine. Detailed chart review data were collected from critically ill patients with COVID-19 (3/1/2020 – 5/31/2020), and post-discharge telephone surveys were conducted to test neuropsychological function after discharge. All study operations were conducted at Michigan Medicine, Ann Arbor MI USA, and approval was obtained from the University of Michigan Medical School Institutional Review Board (HUM00182646). A Health Insurance Portability and Accountability Act waiver was granted to retrospectively review patient medical records, and informed consent was not required for retrospective chart review. Patients who agreed to complete telephone surveys after discharge were consented over the telephone prior to survey administration using a comprehensive consent document. A waiver of documentation of consent was approved in conjunction with Institutional Review Board approval and as required by U.S. Department of Health and Human Services regulations and policy. Lastly, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist is included in the supplemental online material (Supplemental Table 1). These guidelines provide reporting standards for observational studies.[11]

Eligibility criteria

All patients with a COVID-19 diagnosis admitted to a Michigan Medicine ICU between 03/01/2020 – 05/31/2020 were eligible for study inclusion. ICU patients admitted during this time, without a diagnosis of COVID-19, were not eligible for study inclusion.

Outcomes

The primary outcome was delirium presence (yes/no, %) at any point during admission (see "Data collection" section for delirium assessment details). Several secondary outcomes were also collected in relation to delirium and overall clinical trajectory. These outcomes included the following: duration of delirium (days), antipsychotic administration (which may serve as a surrogate marker for hyperactive delirium and/or agitation), length of hospital stay, length of ICU stay, number of days requiring ventilator support, haemodialysis (given the association between renal injury an delirium),[12] inflammatory laboratory values that have been implicated with COVID-19 and cognitive dysfunction (white blood cell count, c-reactive protein, ferritin, lactate dehydrogenase, d-dimer, and interleukin-6),[2 4 5] new psychiatry consults, new antidepressant use (given the possibility of major depressive disorder with critical illness),[13] and final disposition (e.g., home, long-term care facility, death). Delirium prevention strategies, based on the ABCDEF ICU liberation bundle,[14 15] were also recorded. These included the following: structured mobility exercises, placing familiar objects from home at the bedside, promoting use of visual and hearing aids, and spontaneous awakening/breathing trials. The total number of times a prevention strategy was charted was recorded for each patient, and this number was divided by the *expected* number of times that intervention should have occurred based on length of ICU stay and protocolised schedule. This provided the estimated compliance rate for each intervention. Neuroimaging data were also collected and reviewed. There was no neuroimaging protocol in place for patients

with COVID-19. Rather, neuroimaging was ordered at the discretion of clinical care teams as indicated.

Lastly, a telephone survey was conducted after hospital discharge to determine whether subjective or objective signs of cognitive impairment were present. The initial phone call was placed between 30-60 days post-discharge. Twenty patients did not return phone calls until after 60 days, and the average length of time between discharge and survey administration was 83 days. Telephone surveys were conducted by a member of the research team (A.M.) with formal training in the Confusion Assessment Method for delirium.[16] Phone calls were placed between the hours of 9:00 AM and 4:00 PM, Monday through Saturday, and a total of three telephone contact attempts were made before considering loss to follow-up. Voicemail messages were left after each phone call. During telephone interviews, the following tests were conducted: the Patient-Reported Outcomes Measurement Information System (PROMIS)[17] Cognitive Function Abilities 4a, Short Blessed Test (score 0-4 = normal cognition, score 5-9 = questionable impairment, score ≥10 = impairment consistent with dementia),[18] Family Confusion Assessment Method (FAM-CAM) for delirium,[19] and the Patient Health Questionnaire-9 (scores ≥10 were considered positive screens for depression).[20 21]

Data collection

Screening for eligible patients was first performed for via DataDirect, a software tool from the University of Michigan Office of Research that enables research teams to

retrospectively search for patient cohorts. Charts that screened positive were then manually reviewed by study team members to confirm study eligibility.

Charts were then reviewed in further detail for outcome abstraction. Delirium was defined by the presence of either of the following criteria: (1) a positive Confusion Assessment Method screen,[22] as conducted by the bedside nurse, or (2) the presence of an acute confusional state, as documented in the medical record and elucidated via validated, standardized, chart review method.[23] In terms of Confusion Assessment Method screening, this is conducted every 12 hours by the bedside intensive care unit nurse per hospital protocol. Nurses at our institution receive formal training in the Confusion Assessment Method for delirium during their clinical training. For the chart review method, members of the research team reviewed patient charts with the aim of identifying any instance of an acute confusional state, which would count as an episode of delirium. The methodology for defining an acute confusion state is also drawn from the Confusion Assessment Method,[22] which assesses for acute changes in cognition, fluctuating course, inattention, altered levels of consciousness, and disorganized thinking. This was the core set of delirium symptoms in this cohort, and hyperactive states (e.g., agitation) were reported as well. If these symptoms were present for a given patient, the patient was considered as having delirium, and the source of information was recorded along with the date and time. The total number of days with acute confusion was also included in the instrument, along with any evidence of reversibility or improvement of the confusion state. Thus, overall, a case of delirium was counted either for (1) a positive Confusion Assessment Method screen or (2) an acute

confusional state documented in the medical record as abstracted by the chart review method described. Other clinical outcomes, along with laboratory values, were collected directly from the charts. Neuroimaging studies were manually reviewed by a board-certified radiologist with a Certificate of Added Qualification in neuroradiology (R.L.).

Patient and Public Involvement

Neither patients nor the public were involved in this research.

Statistical Analysis

Analyses were performed using IBM SPSS version 27 (Armonk, NY USA) and SAS version 9.4 (SAS Institute, Cary, NC USA). Exploratory data analysis techniques were used to assess the distribution of dependent measures for determining the appropriate analytical strategy. The Shapiro-Wilk test was used to assess the distribution of continuous outcomes, and Independent t-tests or Mann-Whitney U tests were used as appropriate. Mean (standard deviation) or median (interquartile range) was reported for parametric and non-parametric data, respectively. For binary outcomes and proportions, The Chi-Square Test or Fisher's Exact Test were used, as appropriate. Absolute standardized differences were calculated for determining differences in baseline characteristics between groups, with differences >.20 considered to be imbalanced. The threshold for significance was set to $p<0.05$ across all tests otherwise. For post-discharge cognitive outcomes, descriptive statistics were reported with no missing data plan for loss to follow-up. As a descriptive study, with chart data available for all patients, there was no missing data analysis.

Results

In total, 148 patients were included in the final cohort analysis (Supplemental Figure 1). Baseline characteristics are presented in Table 1. The majority of patients were African American and non-Hispanic, and the most common comorbidities were hypertension, Diabetes mellitus, and obesity. Absolute standardized differences between delirium and non-delirium groups were largest (>.30) for sex, race, and weight. The highest proportion of patients in the delirium group was African American (n=54, 50%).

Delirium and Neuropsychological Outcomes

Delirium incidence was high in the cohort (108/148, 73%), and median (interquartile range) duration was 10 (4 – 17) days (Table 2). Delirium prevention activities occurred relatively infrequently, with estimated unit protocol compliance rates less than 50% for each intervention reported (see Table 2 legend for description of protocol activity schedule). The mobility exercise activity compliance rate (%) was significantly lower in the delirium group (37% [26 – 55]) compared to the non-delirium group (62% [31 – 152]; p=.009). Likewise, daily promotion of visual and hearing aids occurred less frequently in the delirium group (27% [13 – 63]) compared to the non-delirium group (77% [14 – 213]; p=.005). New antidepressant use was more common for those with delirium (27/108, 25%) compared to those without delirium (3/40, 7.5%; p=.01). Similarly, a psychiatry consult was obtained for 21/108 (19%) delirious patients compared to 0/40 (0%) in the non-delirium group (p=.003). Lastly, no evidence of delirium reversal or improvement was reported for more than 30% of patients during index hospitalization.

Hospitalization and Post-Discharge Outcomes

Median length of hospitalization was 25 (13 – 48) days, and median length of ICU stay was 15 (7 – 31) days across the cohort (Table 3). Length of hospitalization, ICU length of stay, and duration of mechanical ventilation were all significantly prolonged in patients experiencing delirium (Table 3). Correspondingly, sedative-hypnotic use was higher in patients with delirium. Delirious patients demonstrated higher white blood cell counts, c-reactive protein levels, and d-dimer levels compared to non-delirious patients. Less than half of patients were ultimately discharged home, and the most common disposition for those with delirium was a skilled care facility (41/108, 38%) after discharge (Table 3).

Neuropsychological outcomes after discharge are reported in Table 4. Among patients who were still alive and available to complete survey materials, nearly 25% of patients (4/17) scored positive for delirium based on family assessment (FAM-CAM), and all of these patients were delirious during hospitalization. Similarly, approximately 23% of patients (5/22) demonstrated either questionable impairment or impairment consistent with dementia based on the Short Blessed Test, and all five of these patients were also delirious during hospitalization. Of note, three of these five patients also screened positive for delirium based on the FAM-CAM. Lastly, 12% of patients (3/25) screened positive for depression after discharge. The three patients who screened positive also experienced delirium during ICU admission.

Neuroradiological Findings

In total, 47 patients underwent neuroimaging during hospitalization. Neuroimaging studies were ordered at the discretion of clinical care teams based on clinical assessment. No standardized neuroimaging protocols were in place for patients with COVID-19. The majority of imaging results were unremarkable or demonstrated incidental findings unrelated to COVID-19. However, some notable findings were present. A brain MRI was ordered for a patient with COVID-19 pneumonia and worsening encephalopathy (i.e., no response to commands or noxious stimulus). Imaging revealed abnormal fluid attenuated inversion recovery (FLAIR) hyperintensity affecting the occipital and temporal lobes (Figures 1A, 1B), microhaemorrhage in the splenium of the corpus callosum (Figures 1B, 1C) and posterior leptomeningeal enhancement Figures 1C, 1D), suggestive of encephalitis. A brain MRI was ordered for another patient presenting with seizures and recent COVID-19 diagnosis. Results revealed diffuse dural thickening and enhancement (Supplemental Figure 2A) one day prior to positive COVID testing. The differential diagnosis included intracranial hypotension, inflammation, infection, and neoplastic processes. No definitive diagnosis was reached, though this enhancement resolved approximately one month later (Supplemental Figure 2B). Lastly, one patient demonstrated diffuse parenchymal abnormalities on MRI suggestive of bilateral hypoxic-ischemic injury after multiple cardiopulmonary arrests (Supplemental Figure 3). A non-contrast head CT two weeks later demonstrated poor sulcation bilaterally, suggesting global hypoxic-ischemic injury (Supplemental Figure 4).

Discussion

In a cohort of ICU patients with COVID-19, delirium was a common complication, affecting more than 70% of patients. Furthermore, delirium was associated with prolonged hospitalization, increased length of ICU stay, discharge to skilled care facilities, and positive screens for neuropsychological impairment during the months after discharge. Delirium occurred in the setting of multiple sedative-hypnotic agents, acute inflammatory responses, deviation from delirium prevention protocols, and cerebrovascular events, which are all factors that could have further catalysed delirium precipitation. ICU liberation activities were infrequently implemented compared to the protocolised frequency expected. Overall, the burden of cognitive impairment was high in patients with COVID-19, as was the risk of related complications.

These results align with previous data demonstrating a high incidence of delirium in critically ill patients with COVID-19.[1-4] Moreover, the median duration of delirium (10 days) is relatively long compared to other critically ill populations.[24-27] Our findings also highlight the multifactorial nature of delirium risk factors. In terms of demographics, 50% of patients in the delirium group were African American. The proportion of African American patients admitted to the intensive care unit and experiencing delirium was disproportionately high compared to our expected hospital demographic profile. COVID-19 has adversely, and disproportionately, impacted racial and ethnic minority communities,[28 29] and our results further suggest an increased risk of attendant complications (e.g., delirium) during hospitalization. Efforts to reduce racial healthcare disparities may thus, by extension, mitigate risk of delirium and related consequences of

COVID-19. Patients experiencing delirium also demonstrated significantly increased weight, and obesity may drive organ dysfunction via immune system dysregulation.[30] Additionally, there was a disproportionate number of female patients in the delirium group (absolute standardized difference >.30). These results are discrepant from a prior case series of critically ill patients with COVID-19 demonstrating an increased risk of delirium with male patients.[4] Male sex has also been identified as an independent risk factor for delirium in other patient populations, possibly due to underlying comorbidity severity.[31 32] Whether the findings in this study are spurious or reflect an underlying biological phenomenon is unclear. Further investigation is warranted to improve understanding of the impact that such demographic factors on delirium risk in patients with COVID-19.

Cognitive dysfunction may also occur as a result of direct coronavirus invasion of the central nervous system[6] or other indirect mechanisms, such as polypharmacy, systemic inflammatory responses, and cerebrovascular events. Indeed, benzodiazepine sedation was common in this patient cohort, with nearly 60% of patients receiving midazolam at one point during ICU admission. Lorazepam was a common sedation agent as well, and benzodiazepine use is associated with delirium in critically ill patients.[33-35] Whether benzodiazepine administration served as a driver of delirium or reflected worsening agitation (prompting additional sedative agents) remains unclear. Inflammation may have also contributed to delirium risk. Inflammatory markers (e.g., c-reactive protein, ferritin, interleukin-6, lactate dehydrogenase) were considerably elevated in this patient cohort. In fact, serum levels observed in this study aligned with – or exceeded –

previously reported values in patients with severe COVID-19,[2 5] and there was MRI evidence of neuroinflammation for at least two patients in this cohort. C-reactive protein was elevated in delirious patients, and c-reactive protein increases blood-brain barrier permeability in basic science models.[36] However, this was an unadjusted, bivariable analysis, and confounding remains possible. Cerebral ischemia may also contribute to delirium in patients with COVID-19. Severe hypoxic-ischemic injury occurred in a patient who experienced multiple cardiopulmonary arrests during the course of illness. Stroke has previously been reported in patients with COVID-19,[37] as thromboembolic phenomena and cerebral malperfusion may both occur during the clinical course of COVID-19. Lastly, overall illness severity may increase delirium risk. Indeed, patients with delirium had prolonged hospital and ICU lengths of stay, longer duration of mechanical ventilation, and were more likely to require haemodialysis. Overall, multiple processes likely contribute to delirium in patients with COVID-19. Targeted case-control studies with appropriate statistical modelling strategies can be conducted to determine independent risk factors for delirium in this patient population.

Delirium prevention and management are inherently challenging for COVID-19 patients. While delirium prevention bundles have been demonstrated to reduce risk,[38 39] unique challenges posed by COVID-19 hinder the implementation of standard prevention practices. Spontaneous awakening and breathing trials, for example, may not have been possible due to illness severity and associated ventilator requirements. Clinicians may have also been limited in terms of sedation regimen. Agitation was commonly observed, and nearly 30% of patients required antipsychotics in this cohort. Agitation

and hyperactive delirium likely prompted additional sedation and prolonged use of physical restraints. Early mobility was limited given illness severity, and family engagement was not possible due to visitor policy restrictions. In-person interactions with clinicians were also limited given the intent of reducing virus transmission. As such, the culmination of disease severity, limited face-to-face time spent with patients, and visitor restriction policies likely hindered ICU liberation bundle implementation. Novel strategies for implementing delirium prevention bundles in this patient population may help to further mitigate risk and should be tested in prospective trials.

Neuropsychological impairment after discharge was also present for some patients based on subjective reporting, caretaker assessment, and objective testing for depression and cognitive impairment. Furthermore, all patients that screened positive for possible impairment also experienced delirium in the hospital. These estimates may have been even higher, given that many patients called for post-discharge assessments were unable to be reached, refused participant, or were still admitted to skilled care facilities. In fact, a large-scale, retrospective cohort study recently demonstrated an association between COVID-19 and subsequent neurologic and psychiatric impairment in the following six months, particularly for patients with severe illness.[40] Whether post-discharge cognitive impairment is related specifically to COVID-19 or critical illness more broadly is unclear. Indeed, cognitive impairment is common at discharge for patients who experienced delirium while in the ICU, and delirium is present for nearly 20% of patients newly admitted to acute care facilities.[8 41] Moreover, cognitive impairment can be present for months-to-years after acute respiratory distress

syndrome and sepsis,[42-44] and symptoms of depression and post-traumatic stress disorder are commonly reported among ICU survivors.[45] Neuropsychological impairment after discharge may thus, in part, reflect critical illness, rather than pathophysiologic insults specific to COVID-19. Additional research is needed to disambiguate these possibilities. Nonetheless, ICU patients with COVID-19 experience considerable neuropsychological burden both during and after hospitalization. Ongoing longitudinal COVID-19 registry studies[37 46] will thus be important for (1) identifying such vulnerable patients who may require long-term care and resources and (2) understanding the underlying aetiology of cognitive decline in this patient population

The strengths of this study include identification of potential delirium risk factors, characterization of delirium prevention strategies, and post-discharge outcomes. Data were also representative of an academic tertiary care centre with nearly 150 patients. A validated, standardized chart review method was used to identify delirium,[23] and the study measures used to characterize cognitive function, such as the FAM-CAM, Short Blessed Test, and PROMIS assessments, are standard measures that increase confidence in the results.

In terms of limitations, this was a single-centre analysis, and the results are restricted to the institution studied and intensive care units only. The study was not conducted with a matched control cohort, as this was a descriptive analysis. Results from this study can be used to inform future study designs focused on identifying risk factors for delirium in this population. Delirium was assessed retrospectively for this study, and such

retrospective techniques are not equivalent to prospective evaluation by an expert using gold-standard, Diagnostic and Statistical Manual of Mental Disorders criteria.[47] Evidence for delirium reversal was also predicated on chart review and may have been underestimated. Delirium was also not differentiated from other encephalopathic states, which is neurobiologically challenging and outside of the scope of the current study. One patient was heavily sedated prior to death, and no formal delirium analysis was conducted. The post-discharge telephone-based assessments served as screening tools rather than thorough neuropsychological testing batteries. As such, these post-discharge results are preliminary and warrant rigorous, follow-up analysis. Additionally, neuropsychological impairment may have been present at baseline for some patients, particularly for those with previous neurological disorders. Baseline neuropsychological testing was not possible for this study. Lastly, data were limited for post-discharge cognitive outcomes, as more than half of patients called were unavailable to complete assessments.

In summary, delirium is common complication of COVID-19 with multiple contributing factors. Furthermore, neuropsychological impairment may persist in some patients after discharge. Further research should aim to identify independent risk factors in this population and novel, effective prevention strategies.

Data Availability Statement

Data will be made available upon request via Data Use Agreement. No additional unpublished data are available.

Ethics Approval

Approval for this study was obtained from the University of Michigan Medical School Institutional Review Board (HUM00182646). A Health Insurance Portability and Accountability Act waiver was granted to retrospectively review patient medical records, and informed consent was not required for retrospective chart review. Patients who agreed to complete telephone surveys after discharge were consented over the telephone prior to survey administration using a comprehensive consent document. A waiver of documentation of consent was approved in conjunction with Institutional Review Board approval and as required by U.S. Department of Health and Human Services regulations and policy

Author contributions:

The study was originally conceived by J.R., A.M., M.Z., and P.E.V. Data acquisition was conducted by J.R., A.M., M.Z., J.B., M.H.C., Y.A., and P.E.V. Data analysis was conducted by J.R., A.M., M.Z., J.B., M.H.C., M.I., Y.A., G.M., and P.E.V. Final statistical analysis was conducted by G.M. and P.E.V. Neuroimaging studies were acquired and analyzed by R.L., and the final neuroimaging figures were generated by R.L. and P.E.V. All authors contributed to the manuscript writing, critically reviewed the manuscript for intellectual content, and approved the final manuscript.

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Figure 1. Axial fluid-attenuated inversion recovery (FLAIR) (A, B) images at the level of the basal ganglia show abnormal FLAIR hyperintense signal (arrows) affecting the bilateral occipital, temporal lobes. This appears almost sulcal suggesting a higher protein component within the cerebrospinal fluid. Note the elevated FLAIR signal in the splenium of the corpus callosum (arrow) suggesting parenchymal insult. Axial susceptibility weighted imaging (SWI) (C) at the level of the splenium of the corpus callosum shows small areas of susceptibility (arrow) in the splenium, likely related to microhaemorrhage. Axial T1 (D) post-contrast with fat suppression at the level of the basal ganglia shows subtle, though true, enhancement (arrows) in the posterior sulci, arachnoid pial (leptomeningeal) pattern suggesting a degree of encephalitis.

Table 1. Baseline Characteristics

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**	**Absolute Standardized Difference**
Age (IQR)	59 (49 – 71)	58 (47 – 71)	62 (54 – 71)	.26
Male sex, n (%)	98 (66)	32 (30)	18 (45)	.32
Race, n (%)				.32
Caucasian	66 (45)	47 (44)	19 (48)	
African American	70 (47)	54 (50)	16 (40)	
Other	1 (0.7)	1 (0.9)	0 (0)	
Not reported	11 (7.4)	6 (5.6)	5 (13)	
Ethnicity, n (%)				.31
Non-Hispanic	137 (93)	100 (93)	38 (93)	
Hispanic	5 (3.4)	5 (4.7)	0 (0)	
Unknown/not reported	6 (4.1)	3 (2.8)	3 (7.5)	
Weight, kg (IQR)	103 (83 – 127)	105 (87 – 127)	93 (79 – 113)	.36
BMI (IQR)	34 (28 – 40)	34 (29 – 41)	31 (28 – 39)	.16
Comorbidities, n (%)				
Asthma	24 (16)	17 (16)	7 (18)	.05
Atrial fibrillation	22 (15)	14 (13)	8 (20)	.19
Cancer	25 (17)	20 (19)	5 (13)	.17
Chronic kidney disease	40 (27)	30 (28)	10 (25)	.06
Congestive heart failure	19 (13)	13 (12)	6 (15)	.09

COPD	14 (9.5)	8 (7.4)	6 (15)	.24
Coronary artery disease	27 (18)	18 (17)	9 (23)	.15
Depression	17 (11)	11 (10)	6 (15)	.15
Diabetes mellitus	75 (51)	58 (54)	18 (43)	.23
Hypertension	102 (69)	74 (66)	29 (70)	.03
Obstructive sleep apnoea	31 (21)	22 (20)	9 (23)	.05
Seizures	8 (5.4)	5 (4.6)	3 (7.5)	.12
Stroke	9 (6.1)	5 (4.6)	4 (10)	.21
Substance use disorders	9 (6.1)	6 (5.6)	3 (7.5)	.21
TIA	5 (3.4)	3 (2.8)	2 (5)	.12

Median (interquartile range, IQR) data presented. *Kg* kilograms, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *TIA* transient ischemic attack.

Table 2. Delirium and Neuropsychological Outcomes

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**	***P* Values**
Delirium measures				
Delirium, n (%)	108 (73)	108 (100)	---	---
Duration of delirium, days (IQR)	10 (4 – 17)	10 (4 – 17)	---	---
Agitation (n, %)	--	54 (50)	--	--
Antipsychotic use, n (%)	43 (29%)	42 (39)	1 (2.5)	<.001
Evidence of delirium reversal, n (%)	---	71 (66)	---	---
ICU liberation bundle activity compliance rate, % (IQR)				
Mobility exercises	40 (28 – 67)	37 (26 – 55)	62 (31 – 152)	.009
Familiar objects at bedside	14 (4.4 – 31)	14 (5.9 – 25)	18 (0 – 62)	.38
Daily visual and hearing aids	33 (13 – 76)	27 (13 – 63)	77 (14 – 213)	.005
Daily spontaneous awakening/breathing trials	14 (2.3 – 25)	14 (7.9 – 25)	6.7 (0 – 23)	.07
Psychiatric outcomes				
New antidepressant use, n (%)	30 (20)	27 (25)	3 (7.5)	.01
New psychiatry consults, n (%)	21 (14)	21 (19)	0 (0)	.003

Delirium prevention measures are based on the standard ICU liberation bundle protocols (see text for details). Per institutional protocol, clinicians conduct mobility exercises three times daily, place familiar objects at the bedside once daily, promote visual and hearing aid use daily, and conduct daily

spontaneous awakening/breathing trials daily (if eligible). Given this schedule, compliance/occurrence rates (%) were calculated for each patient by calculating the total number of activities charted divided by the total number expected based on length of ICU stay (day of ICU discharge was not counted). *IQR,* interquartile range.

Table 3. Hospitalization

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**	***P Value***
Length of hospitalization, days (IQR)	25 (13 – 48)	31 (18 – 52)	11 (7 – 25)	<.001
Length of ICU stay, days (IQR)	15 (7 – 31)	19 (12 – 38)	4 (2 – 8)	<.001
Ventilator time, days, (IQR)	12 (3 – 28)	18 (10 – 29)	0 (0 – 7)	<.001
Required haemodialysis, n (%)	45 (30)	40 (37)	5 (13)	.004
Sedative-hypnotics, n (%)				
Propofol	113 (76)	98 (91)	15 (38)	<.001
Midazolam	87 (59)	75 (69)	12 (30)	<.001
Dexmedetomidine	97 (66)	89 (82)	8 (20)	<.001
Lorazepam	58 (39)	52 (49)	6 (15)	<.001
Laboratories				
WBC (n=148) 4.0 – 10.0 (K/μL)	10.1 (7.8 – 13.9)	11.3 (8.4 – 15.1)	8.7 (6.3 – 10.9)	.002
C-reactive protein (n=145) 1.0 – 3.0 (mg/L)	10.2 (5.1 – 18.0)	11.7 (5.3 – 20.7)	8.9 (4.3 – 13.9)	.03
Ferritin (n=147)	1,208 (591 – 1,786)	1276 (714 – 1990)	994 (478 – 1406)	.09

18.0 – 320.0 (ng/mL)				
Lactate dehydrogenase (n=135) 120 – 240 (IU/L)	455 (328 – 572)	458 (343 – 633)	398 (276 – 515)	.05
IL-6 (n=52) < 17.4 pg/mL	69.4 (27.5 – 201.3)	69.4 (32.6 – 186.7)	62.7 (19.9 – 361)	.77
D-dimer (n=142) < 0.59 mg/L	3.1 (1.5 – 6.8)	3.67 (1.84 – 7.75)	1.65 (1.27 – 4.41)	.002
Disposition, n (%)				.03
Home (unassisted)	62 (42)	40 (37)	22 (55)	
Skilled care facility	47 (32)	41 (38)	6 (15)	
Death	39 (26)	27 (25)	12 (30)	

Institutional reference ranges are reported for laboratory values. *ICU* intensive care unit, *IQR* interquartile range, *WBC* white blood cell count, *IL-6* interleukin-6.

Table 4. Post-Discharge Neuropsychological Outcomes†

	All Patients (n=148)	**Delirium (n=108)**	**No Delirium (n=40)**
Positive FAM-CAM, n (%) (n=17)	4 (24)	4 (31)	0 (0)
PROMIS 4A Cognitive Abilities Score, median (IQR) (n=25)	16 (10 – 20)	17 (9 – 20)	14 (6)
Short Blessed Test – Normal, n (%) (n=22)	17 (74)	10 (67)	7 (100)
Short Blessed Test – questionable cognitive impairment, n (%) (n=22)	2 (8.7)	2 (13)	0 (0)
Short Blessed Test – cognitive impairment, n (%) (n=22)	3 (13)	3 (20)	0 (0)
PHQ-9 screen positive, n, (%) (n=25)	3 (12)	3 (17)	0 (0)

FAM-CAM Family-based Confusion Assessment Method for delirium, *PROMIS* Patient-Reported Outcomes Measurement Information System, *PHQ* Patient Health Questionnaire. Initial phone calls were placed between 30 and 60 days after hospital discharge, and the average time to survey completion was 83 days post-discharge. †For each post-discharge survey, proportions are calculated based on the total numbers of surveys completed. In total, 25 surveys were completed for the PROMIS 4A test, 25 surveys

were completed for the PHQ-9, 17 surveys were completed for the FAM-CAM, and 22 surveys were completed for the Short Blessed Test. Reasons for not completing a test included the following: unable to contact (n=54), patient deceased (n=43), refusal (n=18), unable to provide consent (n=5), and admission to skilled care facility (n=3).

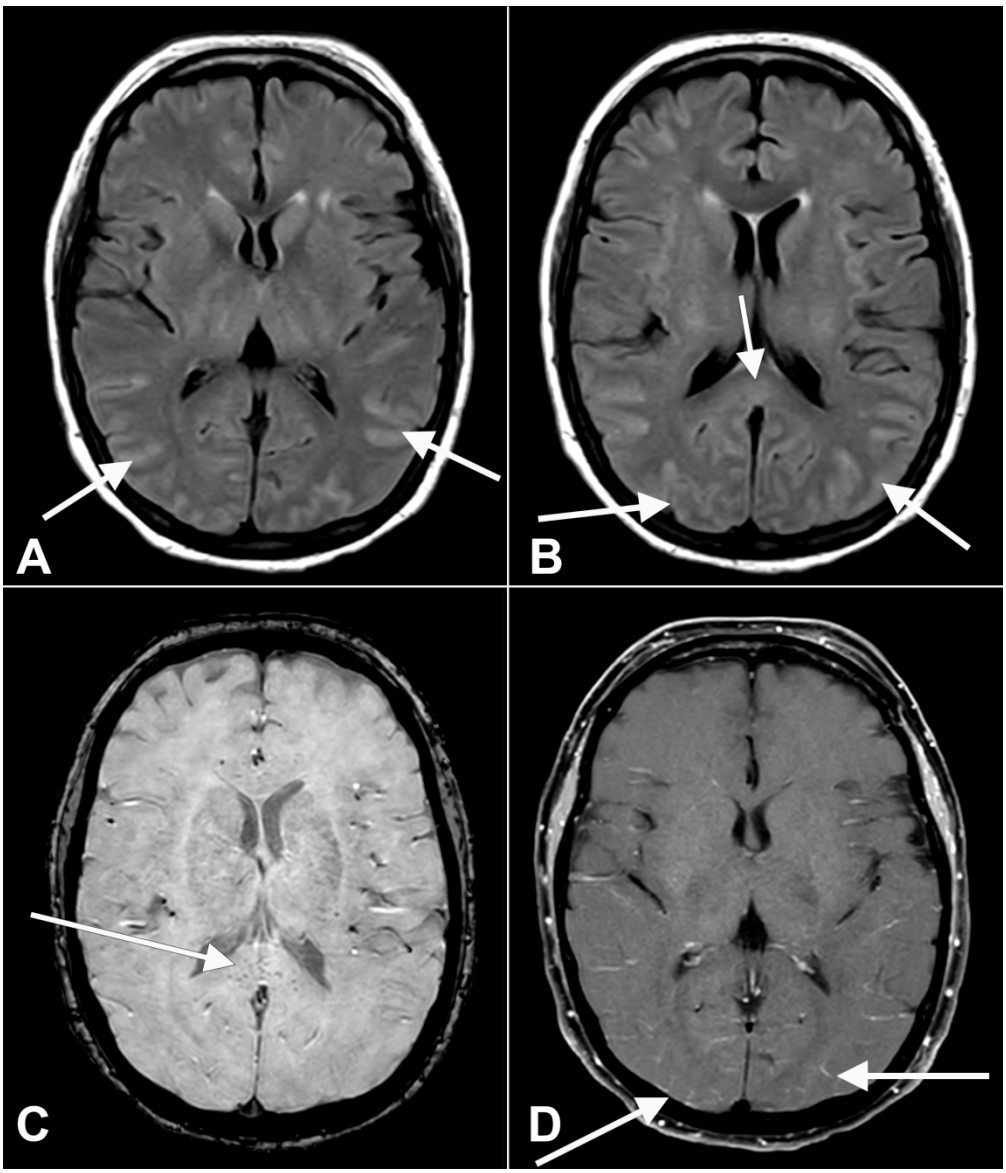


Figure 1 - Axial fluid-attenuated inversion recovery (FLAIR) (A, B) images at the level of the basal ganglia show abnormal FLAIR hyperintense signal (arrows) affecting the bilateral occipital, temporal lobes. This appears almost sulcal suggesting a higher protein component within the cerebrospinal fluid. Note the elevated FLAIR signal in the splenium of the corpus callosum (arrow) suggesting parenchymal insult. Axial susceptibility weighted imaging (SWI) (C) at the level of the splenium of the corpus callosum shows small areas of susceptibility (arrow) in the splenium, likely related to microhemorrhage. Axial T1 (D) post-contrast with fat suppression at the level of the basal ganglia shows subtle, though true, enhancement (arrows) in the posterior sulci, arachnoid pial (leptomeningeal) pattern suggesting a degree of encephalitis.

202x235mm (300 x 300 DPI)

Supplemental Table 1 – STROBE Checklist

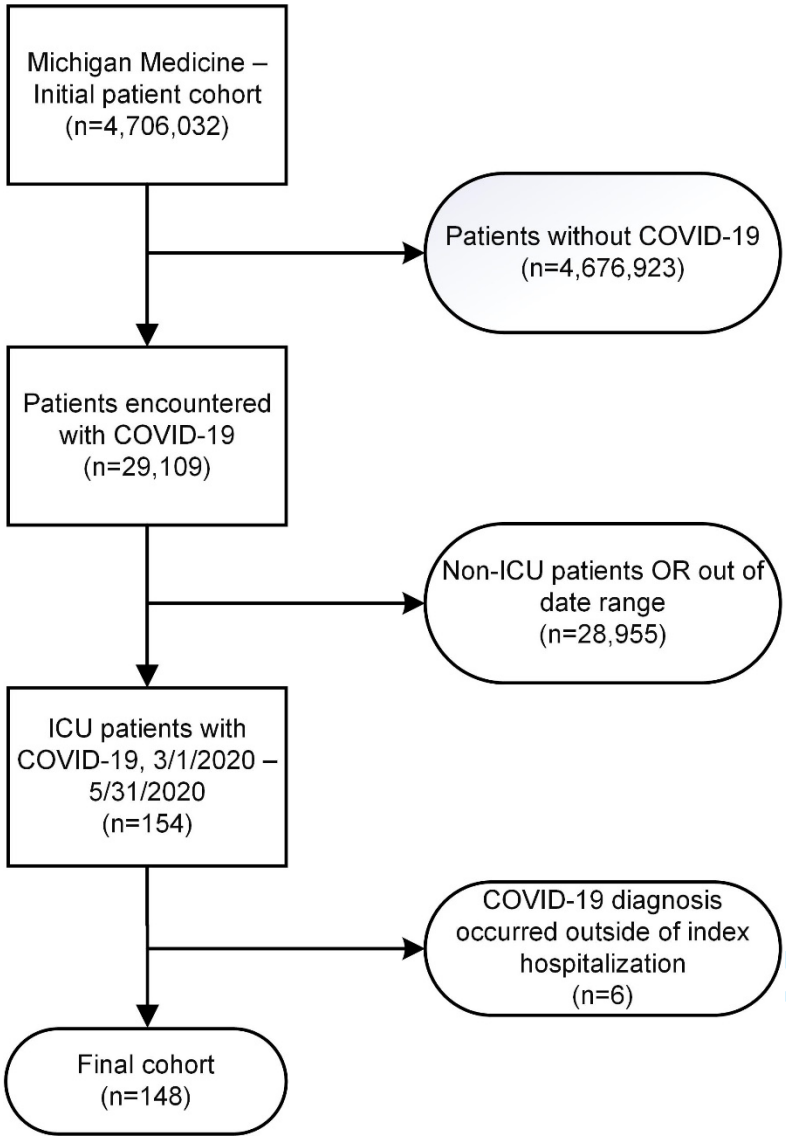
	Item No	Recommendation	Page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1; Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6,7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8-11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-12
Bias	9	Describe any efforts to address potential sources of bias	N/A; descriptive study
Study size	10	Explain how the study size was arrived at	8; Supplemental Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	12 (N/A)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	12

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplemental Figure 1
		(b) Give reasons for non-participation at each stage	Supplemental Figure 1
		(c) Consider use of a flow diagram	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10 (for post-discharge timeline)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	13 – 15 (Tables 1-4)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13 – 15 (Tables 1-4; summary statistics and descriptive analyses).
		(*b*) Report category boundaries when continuous variables were categorized	10 and Table 4 (post-discharge outcomes)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21
Other information			

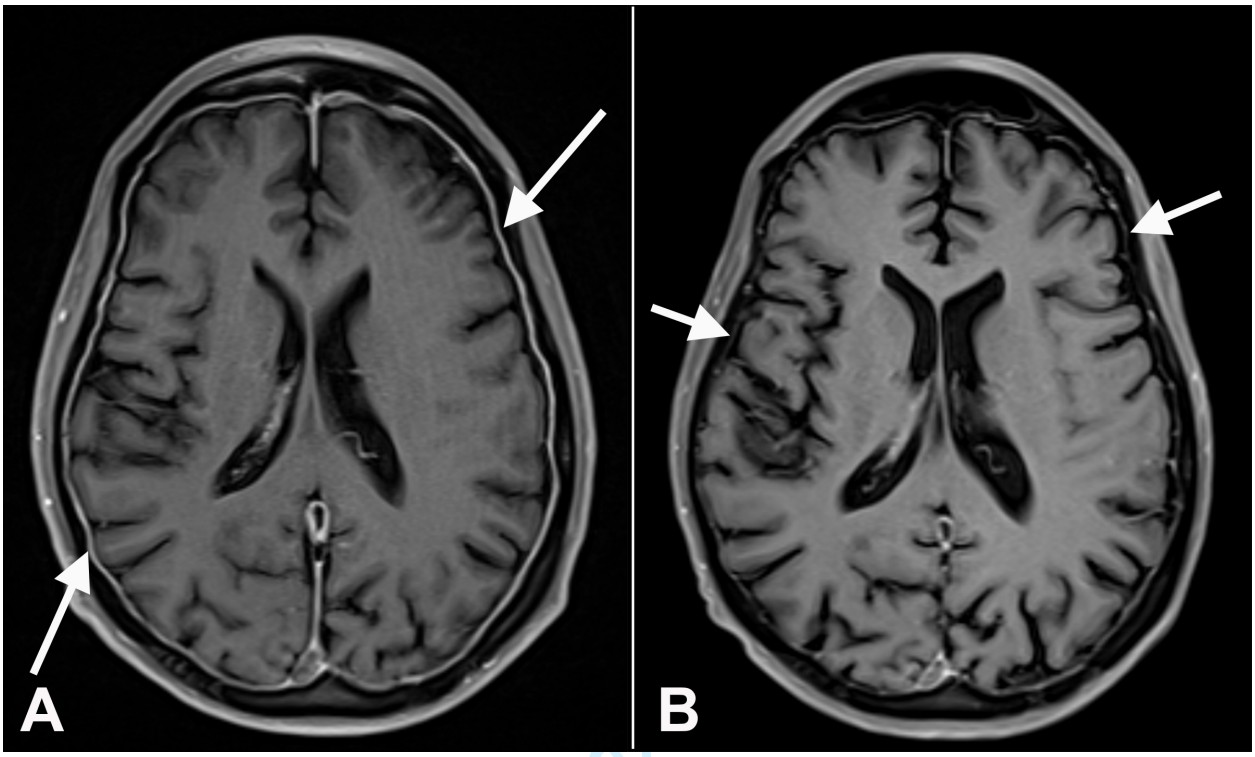
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

Supplemental Figure 1



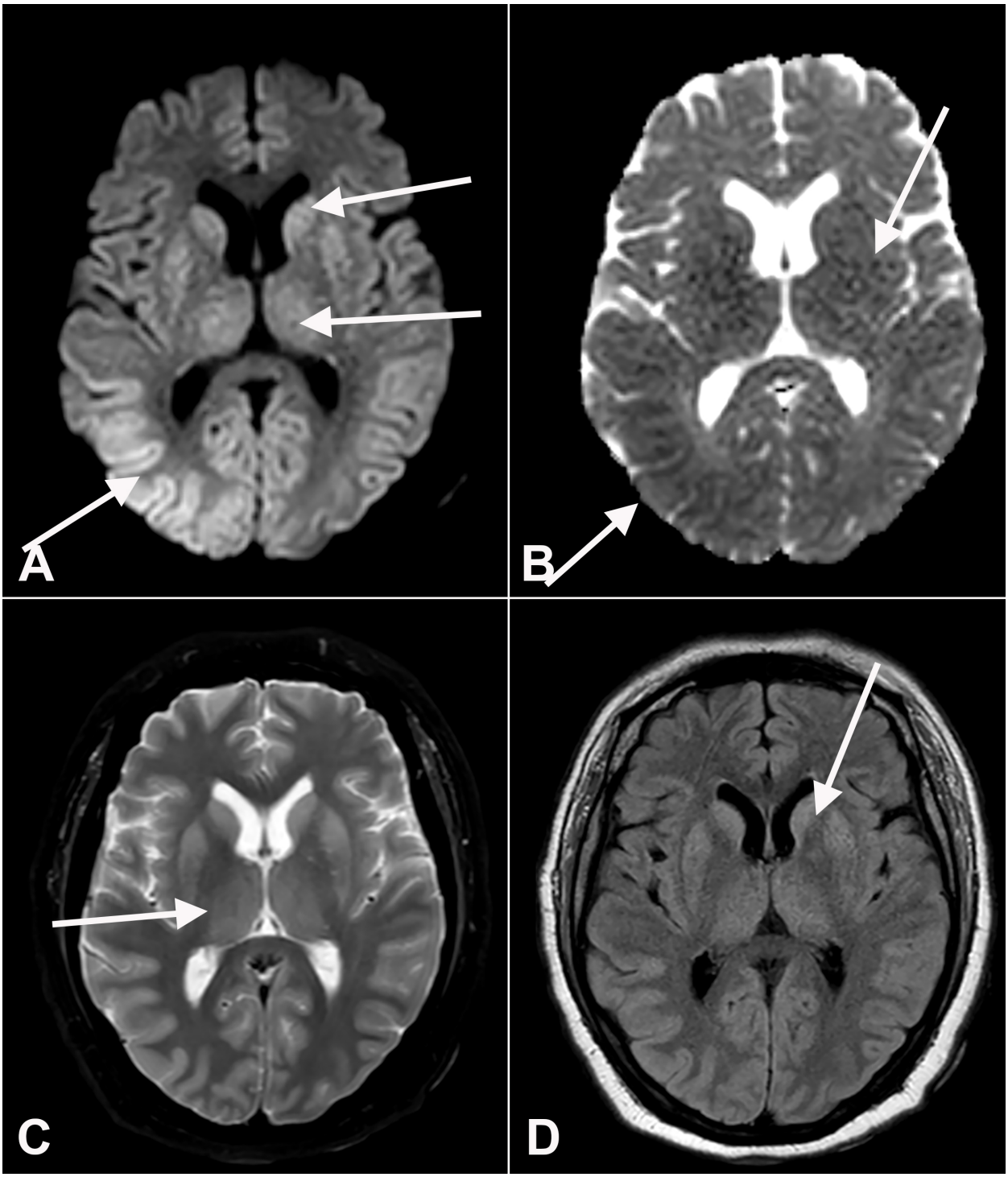
Study flow illustrated. In total, 148 patients were included for the final analysis.

Supplemental Figure 2



A, Axial T1 post-contrast with fat suppression images at the level of the mid lateral ventricles demonstrate smooth dural enhancement (arrows) along the bilateral cerebral convexities. B, This feature resolves one month later (arrows). The overall pattern of dura-arachnoid/pachymeningeal enhancement is non-specific, can be seen with intracranial hypotension, in the procedural setting (e.g., lumbar puncture), and other scenarios (e.g., infection, inflammation).

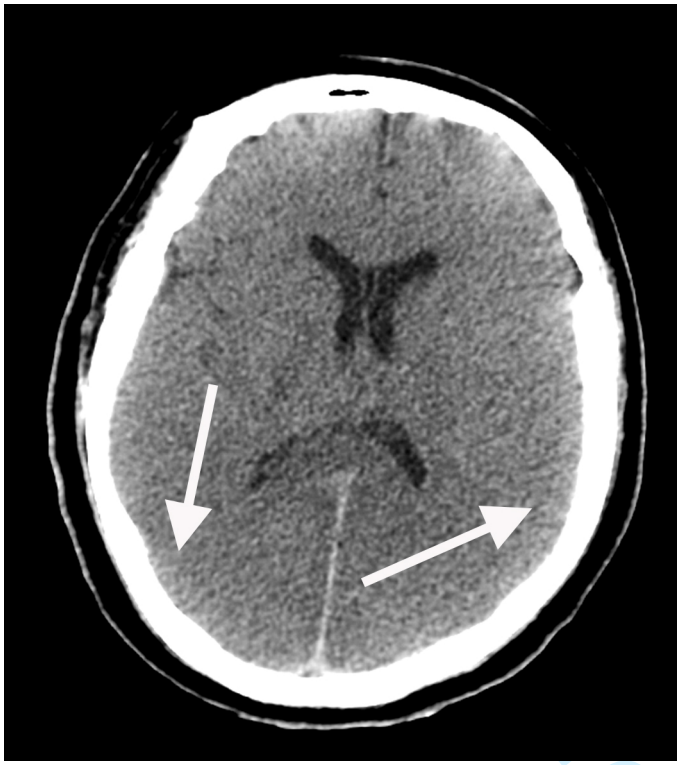
Supplemental Figure 3



After initial non-contrast head CT (which was unremarkable), the patient had diffuse parenchymal abnormalities on MRI examination. A, Axial diffusion-weighted imaging shows hyperintense signal (arrows) at the bilateral basal ganglia, thalami, and posterior cortices, regions are hypointense (arrows)

on corresponding apparent diffusion coefficient map (B). These same locations are hyperintense on T2 (C) and FLAIR (D), especially at the basal ganglia and thalami.

Supplemental Figure 4



Non-contrast head CT performed approximately two weeks after cardiopulmonary arrest shows poor sulcation (arrows) bilaterally, suggesting global insult, most likely hypoxic-ischemic in etiology