PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Delirium and Neuropsychological Outcomes in Critically Ill Patients with COVID-19: a Cohort Study
AUTHORS	Ragheb, Jacqueline; McKinney, Amy; Zierau, Mackenzie; Brooks, Joseph; Hill-Caruthers, Maria; Iskander, Mina; Ahmed, Yusuf; Lobo, Remy; Mentz, Graciela; Vlisides, Phillip E.

VERSION 1 – REVIEW

REVIEWER	Alkeridy , Walid King Saud University, Medicine
REVIEW RETURNED	07-Apr-2021

GENERAL COMMENTS	Well done study and answers an important question in a timely fashion

REVIEWER	Medeiros , Gregory Hospital Moinhos de Vento, Intensive Care Unit
REVIEW RETURNED	31-May-2021

GENERAL COMMENTS	This study addresses a relevant research issue in an interesting way, including a follow-up after hospital discharge. Here are some aspects to be clarified and contributions after reading the paper: - In the eligibility criteria section, I ask if no groups other than non-COVID patients have been excluded. - The follow-up needs to be better described. Who performed the follow-up calls? Was there any type of training or standardization? How many contact attempts before considering loss to follow-up? How they were considered, if any, patients unable to respond to the phone call. I also didn't find this information in the supplementary material. - About neuroimaging exams. What type of neuroimaging were the patients submitted to? Did some type of institutional protocol demand imaging exams in patients with COVID19 and Delirium? What are the criteria for requesting an image exam? Is there a standardization? - We need to clarify some aspects related to the evaluation of Delirium in the study ICU. Who performs the Delirium scales in the ICU (doctor, nurse, another professional)? How often (Once a day, all shifts, weekends)? What kind of training? - About the follow-up phone calls. What is the average contact time after discharge? All calls took place between 30 and 60 days? Was there any deviation in this follow-up? - I suggest including a flowchart that allows to better understand the inclusions - A multivariate analysis of risk factors for delirium would be feasible

	and interesting in this paper. - It would be important to understand if there was any change in the ICU organization in view of the measures to COVID19 pandemic, such as restrictions on family visits, for example.

REVIEWER	Hollinger, Alexa University Hospital Basel, Anaesthesiology, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy
REVIEW RETURNED	01-Jun-2021

GENERAL COMMENTS	Thank you for giving me the opportunity to review the manuscript "Delirium and Neuropsychological Outcomes in Critically Ill Patients with COVID-19: an Institutional Case Series. There are some important points to be described in detail before the manuscript can be reviewed completely: 1) The topic is interesting and important. However, there is lack of clarification of how delirium was diagnosed and differentiated from critical illness encephalopathy. Since all COVID-19 patients were eligible for inclusion how was delirium diagnosed in patients sedated for days to weeks that underwent prone positioning, for example. Please explain in detail since delirium was identified in 73% of patients. How were the different types of delirium (hypoactive, hyperactive, mixed) diagnosed? 2) Please describe the "validated chart review" within the manuscript. Strengths and limitations: The first bullet point could be deleted since delirium is assessed retrospectively by chart review. Data collection: "..., any instance of acute confusional state was recorded... and counted as an episode of delirium" - as indicated in the discussion, patients stayed in the ICU for up to 31 days and therefore encephalopathy due to critical illness might be responsible for these confessionals states. Moreover, roughly one third of patients did not improve (as stated in Results) and image findings such as hypoxic-ischemic injury was reported. Please explain. - Unspecific laboratory values such as CRP (which is considered a biomarker of delirium) might as well reflect severity of critical illness and may again undermine the point above (differentiation of delirium from critical illness encephalopathy).

REVIEWER	van Reekum, Emma McMaster University Faculty of Health Sciences, Department of Psychiatry and Behavioural Neurosciences
REVIEW RETURNED	08-Jun-2021

GENERAL COMMENTS	Overall: Dear authors and editors, thank you for the opportunity to review this interesting and topical contribution. The manuscript primarily examines the rate of delirium in COVID-19 patients admitted to the ICU, as well as characterizes relevant factors related to delirium including comorbidities, COVID-19 severity, pharmacotherapy, and use of delirium prevention strategies in the ICU. I have made several minor comments in the form of questions that I hope will inspire reflection and ultimately improve the quality of the manuscript. In particular, the paper could be strengthened by enhancing the definition of important terms (including delirium) and

	with a greater discussion of the rationale to look at COVID-19-delirium as a different entity than delirium occurring in the context of other infectious and non-infectious etiologies. Overall, I was impressed with the comprehensive and multifactorial analysis of delirium, the clear writing style, and appropriate description of strengths and limitations. I do believe that this paper will substantially contribute to the existing literature. I am happy to be contacted by the authors directly to discuss any of my recommendations in more detail, or to discuss any potential concern about these recommendations. Abstract: • Is there enough data to suggest that patients with COVID-19 are likely to experience prolonged delirium? What is the average duration of non-COVID-related delirium in the ICU setting? Introduction: • Is there a definable and supported difference between encephalopathy and delirium? Are these interchangeable phenomena? • Would it strengthen the sentence “In the ICU, synergistic factors such as sedation…” by citing prior literature? • In terms of the rationale for the paper, is there any evidence or potential biological reason that delirium in the context of COVID-19 would be different than other etiological contexts? Methods: • Would it strengthen the paper to compare to non-COVID ICU patients as well? If not, why? • What is the rationale for assessing antipsychotic administration? (e.g., is this meant to convey severity of delirium? A marker for agitation? Can use exacerbate delirium?) • Similarly, what is the rationale for assessing new antidepressant use? • What is meant by “new antidepressant use”? Were the medications started prior to hospitalization / onset of delirium? Or were they started during the delirium? • Would it help to expand on or clarify the definition of delirium employed for chart review? Why were standardized DSM-5 criteria not used? If only one criterion of CAM were met (e.g., agitation), was the assumption that the patient satisfied criteria for delirium? At what score was the delirium considered resolved? • Is there literature that supports assessing specific inflammatory markers like IL-6 and D-dimer in delirium? Or was the inflammatory panel collected somewhat exploratorily? • What is meant by “evidence of reversal”? Results: • Is it meaningful to state that 50% of delirious patients identified as African American when this population encompassed 47% of the participants overall? • What does the finding that 19% of delirious patients received a psychiatric consult compared to 0% of those without delirium add to the overall paper? Was it expected or hoped that this number would be greater for delirious patients? • What is the rationale for assessing hemodialysis? Was hemodialysis requirement meant to serve as a marker for COVID-19 severity or meant to capture that worsening kidney function, uremia, etc. can exacerbate or cause delirium? Both perhaps? • Is there baseline dementia and depression data available for the

	cohort? For instance, the finding that 5 patients screened positive for dementia post discharge – is this a new finding or did the impairment predate admission? If the cognitive impairment was pre-existing, would this not have increased risk for delirium? • What benefit did obtaining neuroimaging (and discussing some of the results) provide to this study? • What was the process for collecting post-discharge outcomes? Was the process standardized? For instance, how many times were patients called if they were not reached on the first try, were patients or SDMs called if they had recently transitioned to long-term care facilities, was the phone call standardized to a certain time of day? Discussion: • An excellent description of potential exacerbating factors for delirium in the cohort was summarized. Is it possible that SARS-CoV-2 infection was not the predominant etiology of delirium but rather a contributing factor for some of these patients? Would it be possible to construct a timeline for patients to help tease out the etiology further (for instance, when antidepressants and benzodiazepines were initiated, were patients delirious prior to ventilation, etc.)? • The authors allude to a greater risk of COVID-19 delirium in African American patients. Does the data suggest this? Might the data instead suggest a greater likelihood of contracting COVID-19 in this population? Or perhaps the authors' hospital services a greater proportion of African American patients which partially explains the finding? • Why is it unclear whether the benzodiazepines were drivers of delirium or reflected worsening delirium? Would a further chart review help to elucidate this somewhat (e.g., by assessing whether the lorazepam was a longstanding medication or started during ICU admission)? • Is delirium a common complication of COVID-19 or is it common in COVID-19 patients admitted to the ICU? Is there any reason to expect the prevalence of delirium in the ICU to be different for patients with COVID-19 compared to patients with other reasons for ICU admission? • Similarly, prolonged delirium is common, and delirium is a known to increase risk of neuropsychiatric outcomes like dementia. Why would this be different in the context of COVID-19? Why would delioriogenic risk factors be different? Perhaps this should be assessed in future research? • Might results be further situated in the current COVID-19 landscape? Especially as pertains to larger sampled, recent papers e.g., https://pubmed.ncbi.nlm.nih.gov/33836148/ Grammatical Notes: • Page 19 line 20 has a grammatical error "this is a this was" • Table 1: suggest rephrasing "substance abuse" with less stigmatizing terminology – e.g., "substance use" or "substance use disorders"

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Well done study and answers an important question in a timely fashion

RESPONSE: We would like to thank the reviewer for the kind words and time spent reviewing the manuscript.

Reviewer 2:

This study addresses a relevant research issue in an interesting way, including a follow-up after hospital discharge. Here are some aspects to be clarified and contributions after reading the paper:

- In the eligibility criteria section, I ask if no groups other than non-COVID patients have been excluded.

RESPONSE: For the purposes of this study, we categorized all screened critically ill patients as those with COVID-19 and those without COVID-19. All critically ill patients without COVID-19 were excluded from the study (see "Eligibility Criteria," pg. 8, second sentence), regardless of reason for admission. We do point out that, during this time, our ICUs were mainly dedicated to the care of patients with COVID-19, as all elective surgeries were postponed.

- The follow-up needs to be better described. Who performed the follow-up calls? Was there any type of training or standardization? How many contact attempts before considering loss to follow-up? How they were considered, if any, patients unable to respond to the phone call. I also didn't find this information in the supplementary material.

RESPONSE: The follow-up phone calls were conducted by the Clinical Research Project Manager (author A.M.) of our research division, and she has been formally trained in Confusion Assessment Method administration (Maybrier HR et al. BMJ Open 2018). A total of three telephone contact attempts were made before considering loss to follow-up. Voicemail messages were left following each phone call attempt. This information has been added to the Methods (second paragraph of the "Outcomes" section).

- About neuroimaging exams. What type of neuroimaging were the patients submitted to? Did some type of institutional protocol demand imaging exams in patients with COVID19 and Delirium? What are the criteria for requesting an image exam? Is there a standardization?

RESPONSE: Neuroimaging studies were obtained during the course of clinical care at the discretion of care team. Specific imaging studies were determined based on clinical indication, and neuroimaging details are provided in the "Neuroradiological Findings" section and figure legends.

These studies were generally ordered for acute changes in neurological exam with concern for pathological intracranial processes (e.g., stroke) based on intensive care unit team assessment. No standardized protocols were in place for neuroimaging studies of patients with COVID-19. These points have been clarified ("Outcomes" paragraph of the Methods section and "Neuroradiological Findings" paragraph of the Results section).

- We need to clarify some aspects related to the evaluation of Delirium in the study ICU. Who performs the Delirium scales in the ICU (doctor, nurse, another professional)? How often (Once a day, all shifts, weekends)? What kind of training?

RESPONSE: Trained ICU nurses conduct delirium assessments every 12 hours, which coincides with the beginning of each nursing shift, as per our hospital's intensive care unit

protocol. All nurses are trained in the Confusion Assessment Method for delirium as part of their ICU clinical training. Results from the CAM screens, as well as additional details in the nursing notes, are available in the electronic medical record, and our chart reviews were conducted with these nursing-derived Confusion Assessment Method screens *and* notes. We have added this additional detail to the Methods section ("Data collection") and have updated the language to include this additional information.

- About the follow-up phone calls. What is the average contact time after discharge? All calls took place between 30 and 60 days? Was there any deviation in this follow-up?

RESPONSE: The initial phone call was placed between 30-60 days after discharge. There were indeed deviations, as 20 patients did not return phone calls until >60 days after hospital discharge. With these deviations, the average time to survey completion was 83 days. This information has been added to the Methods section and the Table 4 legend.

- I suggest including a flowchart that allows to better understand the inclusions

RESPONSE: A flowchart figure has been added to the supplemental appendix (as the journal only allows for 5 figures/tables in the primary manuscript). This figure is included as Supplemental Figure 1.

- A multivariate analysis of risk factors for delirium would be feasible and interesting in this paper.

RESPONSE: This is an excellent suggestion to advance understanding of risk factors for delirium in this patient population. Unfortunately, as a limited cohort study without a matched control group, we do not have the ability to perform multivariable regression modeling for delirium in this dataset. We have mentioned this limitation in the second-to-last paragraph of the Discussion section.

- It would be important to understand if there was any change in the ICU organization in view of the measures to COVID19 pandemic, such as restrictions on family visits, for example.

RESPONSE: The major organizational changes on a hospital level were the following: visitor/family restrictions and major deviations from standard ICU liberation protocols (including reduced time clinicians spent at the bedside to minimize risk of virus transmission). These changes likely affected delirium risk, as described on pgs. 18-19 (Discussion section).

Reviewer 3:

To whom it may concern

Thank you for giving me the opportunity to review the manuscript "Delirium and Neuropsychological Outcomes in Critically Ill Patients with COVID-19: an Institutional Case Series. There are some important points to be described in detail before the manuscript can be reviewed completely:

1) The topic is interesting and important. However, there is lack of clarification of how delirium was diagnosed and differentiated from critical illness encephalopathy. Since all COVID-19 patients were eligible for inclusion how was delirium diagnosed in patients sedated for days to weeks that underwent prone positioning, for example. Please explain in detail since delirium was identified in 73% of patients. How were the different types of delirium (hypoactive, hyperactive, mixed) diagnosed?

RESPONSE: We have added additional detail regarding how delirium events were identified (i.e., via [1] positive CAM screens or [2] identification of acute confusional states as elucidated by the chart review method). An expanded description is now described on pages 11-12 – "Data collection" of the Methods section. While many patients were indeed prone and paralyzed for a portion of their ICU course, many still had windows available for assessment (i.e., supine and not paralyzed) during which acute confusion states were charted.Only one patient was heavily sedated, proned, and paralyzed (prior to passing away) to such an extent that formal delirium analysis was not possible. This is included in the limitations section.

No formal diagnostic workup was undertaken for delirium subtypes (e.g., hypoactive, hyperactive, mixed). Rather, any descriptive instance of agitation, based on the chart review tool, was recorded and reported. We acknowledge that this was a descriptive study, based on screening tools (e.g., CAM) and retrospective chart review. These strategies are not equivalent to a prospective evaluation by a clinician expert (e.g., geriatrician, psychiatrist) using DSM-based criteria for delirium assessment. These limitations have been highlighted in the discussion section.

Lastly, we did not differentiate delirium from critical illness encephalopathy. We acknowledge the difficulty with drawing this distinction, as the pathophysiology of delirium – and related encephalopathic status – is incompletely understood. We have added this as a limitation in the Discussion section.

2) Please describe the "validated chart review" within the manuscript.

RESPONSE: An expanded description has been added (pgs. 11-12, "Data collection" section of the Methods).

3) Strengths and limitations: The first bullet point could be deleted since delirium is assessed retrospectively by chart review.

RESPONSE: The first item listed, "granular data with respect to delirium," has been deleted.

4) Data collection: "..., any instance of acute confusional state was recorded... and counted as an episode of delirium" - as indicated in the discussion, patients stayed in the ICU for up to 31 days and therefore encephalopathy due to critical illness might be responsible for these confessionals states. Moreover, roughly one third of patients did not improve (as stated in Results) and image findings such as hypoxic-ischemic injury was reported. Please explain.

RESPONSE: Yes, these are each important points. Point-by-point responses below:

-- We have provided additional detail/explanation for the chart review method and acute confusion states on pgs. 11-12 ("Data collection" paragraph).

-- We were aiming to make the point that encephalopathy – and long-term cognitive impairment – could conceivably be due to (1) COVID-19 itself and/or (2) critical illness more broadly (Reviewer #4 raised this point as well). We address this in the 5th paragraph (beginning with "Neuropsychological impairment") of the Discussion section. We have added that registry work and long-term follow-up studies will be important for advancing etiologic understanding of such cognitive impairment. For example, hypoxic-ischemic injury, such as stroke, recurrent stroke, etc., may be a driver of cognitive impairment in this population.

-- Hypoxic-ischemic injury was observed in this cohort, likely due to either (1) thromboembolic complications that have been identified with the COVID-19 syndrome or (2) cardiopulmonary arrest and anoxic brain injury with severe illness. This is the rationale for including neuroimaging evidence of hypoxic-ischemic injury in this study.

-- In terms of patients not improving: this is in reference to the chart review method and probing notes for evidence of delirium reversal/resorption. Evidence of delirium reversal (i.e., description in the notes that patients were back to being alert and oriented), this was only noted for n=71 (66%) patients in the cohort. True delirium reversal may have been higher, but we were unable to determine this from available chart data. This has also been added to the Limitations paragraph of the Discussion section.

5) Unspecific laboratory values such as CRP (which is considered a biomarker of delirium) might as well reflect severity of critical illness and may again undermine the point above (differentiation of delirium from critical illness encephalopathy).

RESPONSE: We agree – c-reactive protein, and related biomarkers, may very well reflect critical illness more broadly rather than serve as a specific biomarker for delirium. The rationale for including c-reactive protein, and other serum biomarkers, is that they have been implicated with COVID-19 related cognitive impairment and neuroinflammation. This rationale and associated references have been added to the Methods section ("Outcomes" paragraph).

Reviewer 4:

Overall: Dear authors and editors, thank you for the opportunity to review this interesting and topical contribution. The manuscript primarily examines the rate of delirium in COVID-19 patients admitted to the ICU, as well as characterizes relevant factors related to delirium including comorbidities, COVID-19 severity, pharmacotherapy, and use of delirium prevention strategies in the ICU. I have made several minor comments in the form of questions that I hope will inspire reflection and ultimately improve the quality of the manuscript. In particular, the paper could be strengthened by enhancing the definition of important terms (including delirium) and with a greater discussion of the rationale to look at COVID-19- delirium as a different entity than delirium occurring in the context of other infectious and non-infectious etiologies. Overall, I was impressed with the comprehensive and multifactorial analysis of delirium, the clear writing style, and appropriate description of strengths and limitations. I do believe that this paper will substantially contribute to the existing literature. I am happy to be contacted by the authors directly to discuss any of my recommendations in more detail, or to discuss any potential concern about these recommendations.

RESPONSE: We thank the reviewer for the kind words of encouragement, and we do aim to incorporate this feedback to strengthen the manuscript.

Abstract
Is there enough data to suggest that patients with COVID-19 are likely to experience prolonged delirium? What is the average duration of non-COVID-related delirium in the ICU setting?

RESPONSE: This is a good question. We have performed a literature review to compare the median length of delirium in this study (10 [4 – 17)] days) to other representative ICU populations, including those with ARDS (Hsieh SH et al., Am J Respir Crit Care med 2015), sepsis (Bruck E et al., J Intensive Care 2018), cardiac impairment (Gamberini M et al., Crit Care Med 2009), and medical ICU patients (Ely EW et al., Crit Care Med 2007). Although there is overlap, a median of 10 days still appears relatively prolonged comparatively. We have added a sentence discussing this consideration, along with the references, in the Discussion section (second paragraph).

Introduction
Is there a definable and supported difference between encephalopathy and delirium? Are these interchangeable phenomena?

RESPONSE: Delirium is certainly a form of encephalopathy, but we do not draw a distinction between the two in this study. In fact, the neurobiology of altered states of consciousness remains an active, multidisciplinary area of research, and there remain many unanswered

questions. We have referenced these considerations in the limitations paragraph of the Discussion section.

Would it strengthen the sentence “In the ICU, synergistic factors such as sedation…” by citing prior literature?

RESPONSE: Yes, thank you. We have modified the sentence and incorporated a supporting reference.

In terms of the rationale for the paper, is there any evidence or potential biological reason that delirium in the context of COVID-19 would be different than other etiological contexts?

RESPONSE: In the first paragraph, we highlight the rationale for why delirium may be unique in this population – from the possibility of coronavirus invasion of the central nervous system to associated synergistic factors, such as social isolation and impediments to implementing standard prevention bundles.

Methods
Would it strengthen the paper to compare to non-COVID ICU patients as well? If not, why?

RESPONSE: Such a study is certainly warranted, particularly for identifying independent risk factors for delirium in this patient population. Our goal with this study, however, was to first fundamentally report detailed characteristics of delirium and related clinical considerations in the critically ill population. When we first began this study in the summer of 2020, very few case series had been published, and ouroal was to generate a detailed case series/cohort study that could inform such a subsequent study aimed at identifying risk factors for delirium in patients with COVID-19. We have expanded this explanation in the Discussion section (in the paragraph describing limitations).

What is the rationale for assessing antipsychotic administration? (e.g., is this meant to convey severity of delirium? A marker for agitation? Can use exacerbate delirium?)

RESPONSE: Yes – this is meant to serve as a surrogate marker for agitation and/or hyperactive delirium. This has been clarified in the Methods section.

Similarly, what is the rationale for assessing new antidepressant use?

RESPONSE: Given the association between critical illness and depression/depressive symptoms (Wintermann GB et al., Crit Care Res Practice, 2018), this served as a surrogate marker for possible depression (or depressive symptoms) during hospitalization.

What is meant by “new antidepressant use”? Were the medications started prior to hospitalization / onset of delirium? Or were they started during the delirium?

RESPONSE: We apologize for the confusion. This reflects presence of antidepressant administration that was not being taken at home prior to admission (i.e., an antidepressant was given during hospitalization, and the patient was not previously on antidepressant medication).

Would it help to expand on or clarify the definition of delirium employed for chart review? Why were standardized DSM-5 criteria not used? If only one criterion of CAM were met (e.g., agitation), was the assumption that the patient satisfied criteria for delirium? At what score was the delirium considered resolved?

RESPONSE: This is an excellent – and very fair – question. We have added expanded detail on the chart review method, and rationale for this method (e.g., standardized approach, validation, etc.) in the Methods section. In brief, the chart review tool prompts a detailed probe of any possible acute confusional state. Beyond scanning for any single term, such as agitation, the tool compels a thorough review of the documentation surrounding such an acute confusional state. The event is recorded verbatim, in detail, and the source documentation

(e.g., nursing notes, physician notes, resulting orders/actions) are also recorded. There is no quantitative score, per se, that triggers a positive delirium screen; rather, the screening tool is binary. The presence of such a confusional state is viewed as binary (yes/no).

This approach offers a reasonable sensitivity (74%) and specificity (83%) when prospective, in-person assessment is not available (Inouye SK et al. 2005).

Is there literature that supports assessing specific inflammatory markers like IL-6 and D-dimer in delirium? Or was the inflammatory panel collected somewhat exploratorily?

RESPONSE: These markers were included as part of routine clinical care at the time based on ICU and COVID-19 protocols. However, we included them in this analysis given that there is a body of literature implicating IL-6 with cognitive dysfunction (reviewed by Bradburn S et al., Frontiers Aging Neuroscience 2017). D-dimer was included given the possibility of thromboembolic events (and possible stroke) in this population.

What is meant by "evidence of reversal"?

RESPONSE: Evidence for reversal/resorption of delirium (i.e., the patient is no longer delirious). This has been clarified in the Results section and associated table.

Results

Is it meaningful to state that 50% of delirious patients identified as African American when this population encompassed 47% of the participants overall?

RESPONSE: We do think these findings are still relevant, particularly given the reasons outlined in the second paragraph of the Discussion section.

What does the finding that 19% of delirious patients received a psychiatric consult compared to 0% of those without delirium add to the overall paper? Was it expected or hoped that this number would be greater for delirious patients?

RESPONSE: This is meant to convey that these patients required more resources for managing relevant psychiatric conditions (e.g., delirium, depression). Additionally, this also adds an extra dimension of convergent validity, to so speak, in addition to chart reviews for delirium. In other words, the increased proportion of psychiatric consults and antipsychotic use in patients we identified as delirious lends additional evidence (supplementary to our chart review strategy) that (1) delirious patients were identified and (2) additional clinical resources were required in these patients.

What is the rationale for assessing hemodialysis? Was hemodialysis requirement meant to serve as a marker for COVID-19 severity or meant to capture that worsening kidney function, uremia, etc. can exacerbate or cause delirium? Both perhaps?

RESPONSE: Both to serve as a marker for disease severity and the association between worsening kidney function (e.g., uremia) and delirium (Siew ED et al., Am J Respir Crit Care Med 2017). This sentence and reference have been added to the Methods section ("Outcomes" paragraph).

Is there baseline dementia and depression data available for the cohort? For instance, the finding that 5 patients screened positive for dementia post discharge – is this a new finding or did the impairment predate admission? If the cognitive impairment was pre-existing, would this not have increased risk for delirium?

RESPONSE: Unfortunately, as this was a retrospective chart review, baseline dementia/depression screens were not obtained (nor were any clinically available).

What benefit did obtaining neuroimaging (and discussing some of the results) provide to this study?

RESPONSE: The neuroimaging results, in our view, helped to identify a diverse array of etiologies that could contribute to delirium (e.g., neuroinflammation, stroke/hypoxic-ischemic injury, encephalitis, etc.).

What was the process for collecting post-discharge outcomes? Was the process standardized? For instance, how many times were patients called if they were not reached on the first try, were patients or SDMs called if they had recently transitioned to long-term care facilities, was the phone call standardized to a certain time of day?

RESPONSE: An expanded discussion of these telephone surveys has been added to the Methods section. In brief, phone calls were conducted by a member of the research team (A.M.) with formal training in the Confusion Assessment Method for delirium. Calls were placed between the hours of 9a – 4p (Mon-Sat), and three telephone contact attempts were made before considering loss to follow-up. Voicemail messages were left after each phone call.

DISCUSSION

An excellent description of potential exacerbating factors for delirium in the cohort was summarized. Is it possible that SARS-CoV-2 infection was not the predominant etiology of delirium but rather a contributing factor for some of these patients? Would it be possible to construct a timeline for patients to help tease out the etiology further (for instance, when antidepressants and benzodiazepines were initiated, were patients delirious prior to ventilation, etc.)?

RESPONSE: It is certainly possible that SARS-CoV-2 may not have been the primary driver of delirium in certain patients. Other factors, such as sedation regimen/benzodiazepine use may have certainly played a primary role. Highlighting these additional potential causes (e.g., polypharmacy) was one of our main goals in the third paragraph of the Discussion section.

The idea of a timeline is appealing, and we have performed a cursory review of our records pertaining to delirium and temporal relationships with candidate risk factors. Unfortunately, these relationships are incredibly difficult to establish. In many instances, patient would experience several of episodes of delirium over the course of a few days concurrent with simultaneous risk factors (e.g., changing sedation regimens, thromboembolic events, etc.). An improved approach, that we propose, would be to conduct a targeted case-control study with appropriate statistical modeling strategies to identify independent risk factors (pg. 18, Discussion section, last sentence of the first paragraph).

The authors allude to a greater risk of COVID-19 delirium in African American patients. Does the data suggest this? Might the data instead suggest a greater likelihood of contracting COVID-19 in this population? Or perhaps the authors' hospital services a greater proportion of African American patients which partially explains the finding?

RESPONSE: We have attempted to clarify – and simplify – our interpretation. Our main point is that the proportion of African American patients admitted to the ICU during this timeframe was disproportionately high compared to expected hospital demographic profiles.

We cannot determine the underlying causes of this observation, though we do acknowledge that COVID-19 has disproportionately and deleteriously impacted racial and ethnic minority communities, as cited, and associated hospital complications (such as delirium) also warrant acknowledgement.

Why is it unclear whether the benzodiazepines were drivers of delirium or reflected worsening delirium? Would a further chart review help to elucidate this somewhat (e.g., by assessing whether the lorazepam was a longstanding medication or started during ICU admission)?

RESPONSE: As mentioned above, many events were concurrently happening in these patients along with benzodiazepine administration. A dedicated case-control study, focused on independent risk factor identification with appropriate statistical modeling strategies, would be better suited to address the individual contributions of each candidate risk factor.

Is delirium a common complication of COVID-19 or is it common in COVID-19 patients admitted to the ICU? Is there any reason to expect the prevalence of delirium in the ICU to be different for patients with COVID-19 compared to patients with other reasons for ICU admission?

RESPONSE: This is a great question and a key distinction to address. First, we do have to cite a primary limitation of our study – we did not analyze delirium in non-ICU patients with COVID-19 (as such, we cannot make any definitive comparisons in this study). It is likely that severe illness requiring intensive care unit admission also inherently increased delirium risk. However, ICU-specific factors, such as polypharmacy, sedation regimen, deviation from standard liberation bundles, etc., also likely contributed to risk. These considerations have been added to the Discussion section.

In terms of comparisons to other disease settings (e.g., ARDS, sepsis) – this remains a relatively new syndrome, and we are all still learning. It is striking that the length of delirium in this study (median 10 days) was relatively long compared to other disease processes (as described above). The reasons for this remain incompletely understood.

Similarly, prolonged delirium is common, and delirium is a known to increase risk of neuropsychiatric outcomes like dementia. Why would this be different in the context of COVID-19? Why would delioriogenic risk factors be different? Perhaps this should be assessed in future research?

RESPONSE: These are excellent questions. We certainly agree that this association has been established (between delirium and subsequent dementia/neurocognitive disorders). What remains unknown, in this population, is whether the ICU neurologic injury that increases dementia risk is due directly to COVID-19 (e.g., the virus itself, complications, etc.) or from critical illness more generally. In this context, we do call for additional research and support ongoing registry studies to advance etiologic understanding of long-term cognitive impairment/decline in this patient population. We have added some additional language to support these concepts in the Discussion section (pararaph beginning with "Neuropsychological impairment").

Risk factors may be different for a few key reasons. First, there is the possibility of direct coronavirus invasion (distinct from "toxic-metabolic" etiologies commonly ascribed to delirium in the ICU). Second, cerebral ischemia (and attendant complications, such as cognitive impairment) appears to be a distinct risk in critically ill patients with COVID-19. Third, the care surrounding these patients, in our view, has been fundamentally different compared to other disease setting (e.g., ARDS, sepsis). As described in the manuscript, clinicians often limited the time spent at the bedside with the intent of minimizing virus spread (particularly early in the pandemic when personal-protective equipment was limited). Elements of ICU liberation bundles, such as daily awakening trials, mobility exercises, etc., were also infrequently implemented. As such, deviation from standard practices and protocols may have increased risk.

Might results be further situated in the current COVID-19 landscape? Especially as pertains to larger sampled, recent papers e.g., https://pubmed.ncbi.nlm.nih.gov/33836148/

RESPONSE: Indeed, results from this study align with our findings. We have incorporated this study into the Discussion section accordingly in the context of discussing post-discharge neuropsychological impairment.

Grammatical Notes:
Page 19 line 20 has a grammatical error "this is a this was"

RESPONSE: This has been corrected.

Table 1: suggest rephrasing "substance abuse" with less stigmatizing terminology – e.g., "substance use" or "substance use disorders"

RESPONSE: Thank you – this has been changed.

VERSION 2 – REVIEW

REVIEWER	Medeiros , Gregory Hospital Moinhos de Vento, Intensive Care Unit
REVIEW RETURNED	10-Aug-2021

GENERAL COMMENTS	This is a relevant study that addresses a clinical issue of fundamental importance in view of the global epidemic of COVID19. The changes in form and content made by the authors respond to the suggestions of the review and clarify aspects of the methodology that ensure adequate conciseness and reproducibility. The design is adequate to answer the research question and the conclusions are supported by the results.

REVIEWER	van Reekum, Emma McMaster University Faculty of Health Sciences, Department of Psychiatry and Behavioural Neurosciences
REVIEW RETURNED	25-Jul-2021

GENERAL COMMENTS	Excellent clarifications and revisions. Thank you for involving me in this interesting paper! Take care.