COVID-19 Delirium and Motoric Subtypes:

Opportunities to Improve Outcomes

Randall T. Espinoza, MD, MPH, and Aaron Kaufman, MD

Managing delirium is difficult business under any scenario and has been especially challenging during the coronavirus disease 2019 (COVID-19) global pandemic. The plethora of manifestations and complications of COVID-19 were quickly evident.[1–3] The contagious nature of this illness fomented fear and forced isolation.[4] Early waves of infection were met with lockdowns, and for those hospitalized, the pandemic resulted in the near absence of family or caregiver bedside support or visitation, with attendant consequences for both patient and family members.[5,6] Death ravaged intensive care units and nursing homes. The unique circumstances of COVID-19 imposed significant barriers early on due to unforeseen logistical problems and ethical issues. Disrupted care pathways, debates over resource allocation, strains on health care resources in general but particularly in underserved communities, and staffing shortages, among other challenges, emerged.[7] Conditions slowly improved with the advent of viable treatments and vaccinations. New coronavirus variants, while more contagious, may cause less severe illness, at least in those who are vaccinated and boosted. Now, as the world enters the fourth year since the start of the pandemic, a new landscape surfaces, and after a collective sigh, we can reflect on lessons learned and new questions to answer.

In this issue of JCP, in a multicenter longitudinal study undertaken in Italy early in the pandemic, Trevisan et al[8] investigated the association between delirium subtypes (hypoactive, hyperactive, or mixed) present on admission in patients with confirmed SARS-CoV-2 infection and in-hospital and post–hospital discharge mortality risk. Previous studies had shown that motoric subtypes of delirium may relate to short- and long-term morbidity, mortality, and functional and mental health outcomes.[9–12] In this study, the median observation period was relatively long, at just over 8 months. Unsurprisingly, the population was older (median age: 68 years), with patients over age 60 comprising 67% of the sample. Less than 5% of patients were younger than 40 years. Interestingly, males constituted the majority of hospitalized patients, at about 64%. Overall, nearly 17% presented with delirium within 24 to 48 hours of admission, and in those with available information, all delirium subtypes were represented: hyperactive (30%), hypoactive (43%), and mixed (27%). However, in the mixed category, around 70% (43/61) could not be sufficiently characterized. Compared to other subtypes in this cohort, those with hyperactive delirium tended to be younger and healthier (as measured by mobility, dementia prevalence, and number of chronic diseases). Regardless of subtype, delirium was lethal. Compared to those without delirium, there was a nearly 2-fold in-hospital (hazard ratio [HR] = 1.94) and postdischarge (HR = 2.01) mortality risk. Further, the hypoactive delirium subtype conferred the strongest associations with both in-hospital and postdischarge mortality. Strengths of the study include, among others, the relatively long follow-up period, efforts to identify and assess for delirium early during hospitalization clinically and systematically with validated scales, and characterization of delirium subtypes and associations with in-hospital and postdischarge mortality risk, which is rarely done.

Clearly, for those involved in direct clinical care and patient management of hospitalized patients, identification of delirium is critical, but so is early detection. Importantly, as seen in this study, early detection, including in an illness like SARS-CoV-2 infection, is possible. Clinically useful and systemic approaches to diagnosis are available[13,14] and likely aid in early detection and accurate diagnosis.[15,16] This matters because either a delay in diagnosis or misdiagnosis likely contribute, if not directly lead, to higher morbidity and mortality.[17] Trevisan et al[8] admirably show that early in the pandemic amid scarce resources, limited staffing, and few treatments, clinical care principles could be followed. Both delays in diagnosis and misdiagnosis may result in deferred intervention, inappropriate treatments, or polypharmacy. For the latter problem, recent studies show a much more limited role for or benefit from psychopharmacologic agents such as antipsychotics or anxiolytics, which themselves may

confer independent risks when used in delirious patients.[18,19] Further, delirium subtype may be a moderator of outcomes. For example, the hyperactive or mixed subtype may lead to overprescribing or inappropriate prescribing of medication with an inability to distinguish among ongoing distress, medication side effects, or a new problem. Conversely, the hypoactive subtype may lead to overlooking of clinical deterioration or a different complication. Hypoactive delirious patients may not "cause" problems and tend to be neglected. Although this study cannot inform how delirium subtype in SARS-CoV-2 infection influenced treatment intervention, Trevisan et al do show that characterization of subtype is possible, and subtyping provides important prognostic information over the acute hospital course and postdischarge period for up to several months. Another finding was that patients with the hyperactive subtype were healthier and younger at baseline, suggesting that those with hypoactive or mixed subtypes had lower functional or cognitive reserve, higher rates of frailty, or more medical comorbidity, all factors known to associate with poorer short- and long-term outcomes. However, given that delirium etiology is often multifactorial, associations among pathoetiology, subtype, and treatment intervention remain to be fully elucidated.[20] Understanding of pathomechanisms of SARS-CoV-2 illness may inform management strategies in delirium, such as the use of melatonin or orexin antagonists to address sleep-wake cycle disruption.[20]

That acute delirium in SARS-CoV-2 illness is associated with higher in-hospital (short-term) mortality is not a new finding and has been previously shown.[3,10,17,19] Aside from characterizing motoric subtypes in SARS-CoV-2–related delirium, what this study adds is the association with the hypoactive subtype and shorter postdischarge survival and suggests that new efforts are needed to understand what antecedent risk factors influence hospital course and post-hospital management. Indeed, most of the recent literature in delirium care has focused on prevention and in-hospital management. General recommendations include identifying at risk populations, screening for vision and hearing impairment, (re)assessing medication lists, maintaining sleep-wake cycle, avoiding polypharmacy, and focusing on the environment for safety and comfort.[15,18,21,22] Thus, delirium is best avoided if at all possible. Similarly, development of delirium while in hospital appears to confer a worse prognosis across populations and diagnoses and may be related to lower functional or cognitive reserve, fragility, severity of underlying illness(es), development of complications, exposure to polypharmacy, or injudicious use of psychotropics. Several of these factors were used as covariates in this study. For SARS-CoV-2 delirious patients, at least early in the pandemic when little was known about illness course, treatments were few, staffing shortages were rampant, and patients were isolated, there was not much to offer. If multisystem failure occurred and more complications developed, delirium understandably became more difficult to address. Most poignantly, the isolation of patients from family and caregivers exacted the worst toll. Without caregiver advocates nearby to help or alert staff, it is not surprising that morbidity and mortality in SARS-CoV-2 illness were as high as reported, though causality remains speculative.[5,6,16,17]

Lastly, although surviving acute hospitalization with SARS-CoV-2 illness early on was no small feat, Trevisan et al show that our work may not be done and ongoing vigilance is necessary. If their finding of association between hypoactive delirium and shorter postdischarge survival is replicated, important prognostic information will be available. Further, understanding what type of care management is needed in the 6-month postdischarge period remains to be fully elucidated. Remaining questions include whether this higher mortality risk is the result of long COVID, is related to new causes of death or ongoing disturbances in affected systems, or reflects new treatment needs and opportunities for surveillance.

Article Information

Published Online: August 21, 2023. https://doi.org/10.4088/JCP.23com14814

J Clin Psychiatry 2023;84(5):23com14814

To Cite: Espinoza RT, Kaufman A. COVID-19 delirium and motoric subtypes: opportunities to improve outcomes. *J Clin Psychiatry.* 2023;84(5):23com14814.

Author Affiliations: Resnick Neuropsychiatric Hospital at UCLA and Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, University of California, Los Angeles.

Corresponding Author: Randall T. Espinoza, MD, MPH, 300 UCLA Medical Plaza, Ste 2235, Los Angeles, CA 90095 (REspinoza@mednet.ucla.edu).

Relevant Financial Relationships: None.

Funding/Support: Funded by the Muriel Harris Endowed Chair of Geriatric Psychiatry, Geffen School of Medicine at UCLA (Dr Espinoza), and R01MH128690 (Dr Espinoza).

References

1. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry.* 2020;7(7):611–627.
2. Misra S, Kolappa K, Prasad M, et al. Frequency of neurologic manifestations in COVID-19: a systematic review and meta-analysis. *Neurology.* 2021;97(23):e2269–e2281.
3. Taquet M, Geddes JR, Husain M, et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry.* 2021;8(5):416–427.
4. Holden D. What has lockdown done to us? *New York Times*. December 8, 2020. https://www.nytimes.com/2020/12/08/opinion/covid-lockdown-isolation.html
5. Azoulay E, Resche-Rigon M, Megarbane B, et al. Association of COVID-19 acute respiratory distress syndrome with symptoms of posttraumatic stress disorder in family members after ICU discharge. *JAMA*. 2022;327(11):1042–1050.
6. McPeake J, Kentish-Barnes N, Banse E, et al. Clinician perceptions of the impact of ICU family visiting restrictions during the COVID-19 pandemic: an international investigation. *Crit Care*. 2023;27(1):33.
7. Pfefferbaum B, North CS. Mental health and the COVID-19 pandemic. *N Engl J Med.* 2020;383(6):510–512.
8. Trevisan C, Grande G, Rebora P, et al. Early onset delirium during hospitalization increases in-hospital and postdischarge mortality in COVID-19 patients: a multicenter prospective study. *J Clin*

Psychiatry. 2023;84(5):22m14565.
9. Hayhurst CJ, Marra A, Han JH, et al. Association of hypoactive and hyperactive delirium with cognitive function after critical illness. *Crit Care Med*. 2020;48(6):e480–e488.
10. Fialho Silva IT, Assis Lopes P, Timotio Almeida T, et al. Impact of delirium and its motor subtypes on stroke outcomes. *Stroke*. 2021;52(4):1322–1329.
11. Rengel KF, Hayhurst CJ, Jackson JC, et al. Motoric subtypes of delirium and long-term functional and mental health outcomes in adults after critical illness. *Crit Care Med*. 2021;49(5):e521–e532.
12. la Cour KN, Andersen-Ranberg NC, Weihe S, et al. Distribution of delirium motor subtypes in the intensive care unit: a systematic scoping review. *Crit Care*. 2022;26(1):53.
13. Chester JG, Beth Harrington M, Rudolph JL; VA Delirium Working Group. Serial administration of a modified Richmond Agitation and Sedation Scale for delirium screening. *J Hosp Med*. 2012;7(5):450–453.
14. Bellelli G, Morandi A, Davis DH, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing*. 2014;43(4):496–502.
15. Kotfis K, Williams Roberson S, Wilson JE, et al. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care*. 2020;24(1):176.
16. Duggan MC, Van J, Ely EW. Delirium assessment in critically ill older adults: considerations during the COVID-19 pandemic. *Crit Care Clin*. 2021;37(1):175–190.
17. Wilke V, Sulyok M, Stefanou MI, et al. Delirium in hospitalized COVID-19 patients: predictors and implications for patient outcome. *PLoS One*. 2022;17(12):e0278214.
18. Baller EB, Hogan CS, Fusunyan MA, et al. Neurocovid: pharmacological recommendations for delirium associated with COVID-19. *Psychosomatics*. 2020;61(6):585–596.
19. Garcez FB, Aliberti MJR, Poco PCE, et al. Delirium and adverse outcomes in hospitalized patients with COVID-19. *J Am Geriatr Soc*. 2020;68(11):2440–2446.
20. Sher Y, Rabkin B, Maldonado JR, et al. COVID-19-associated hyperactive intensive care unit delirium with proposed pathophysiology and treatment: a case report. *Psychosomatics*. 2020;61(5):544–550.
21. Inouye SK. The importance of delirium and delirium prevention in older adults during lockdowns. *JAMA*. 2021;325(17):1779–1780.
22. Radhakrishnan NS, Mufti M, Ortiz D, et al. Implementing delirium prevention in the era of COVID-19. *J Alzheimers Dis*. 2021;79(1):31–36.