FULL-LENGTH ARTICLE NPub.org/nmqj1d

Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19

Emad Nader Eskandar, MD, MBA, David J. Altschul, MD, Rafael de la Garza Ramos, MD, et al.

Cite as: *Neurology*® 2021;96:e1527-e1538. doi:10.1212/WNL.0000000000011356

Correspondence
Dr. Altschul
daltschu@montefiore.org

Study Question

Are certain neurologic syndromes associated with increased risk of inpatient mortality in patients with COVID-19?

What Is Known and What This Paper Adds

It remains unclear whether acute neurologic manifestations impact mortality of SARS-CoV-2 illness and whether this risk is present in the absence of imaging findings. This investigation's results suggest that the incidence of altered mentation or stroke on admission predicts a modest but significantly higher risk of in-hospital mortality independent of disease severity.

Methods

For this retrospective matched cohort study, the investigators analyzed data from 4,711 patients admitted with COVID-19 between March 1st and April 16th, 2020 to a hospital system in New York City. Of these, 581 patients had neurologic symptoms and underwent neuroimaging studies. Each of these 581 patients was matched by age and COVID severity with 3 patients without neurologic issues (n = 1,743 controls). Primary outcome measure was in-hospital mortality and a Cox proportional-hazards regression model to detect associations with specific neurologic syndromes.

Results and Study Limitations

The specific neurologic manifestations observed included altered mentation (n = 258), normal mentation with other neurologic signs and symptoms compatible with COVID-19 (i.e., neuro–COVID-19 complex; n = 216), stroke (n = 55), seizures (n = 26), and incidentally discovered brain lesions (n = 26). In-hospital mortality was higher among patients with neurologic manifestations (34% vs 29%; odds ratio [OR], 1.27; 95% CI, 1.04–1.56). Patients with altered mentation (n = 258, OR 1.39, CI 1.04–1.86) or radiologically confirmed stroke (n = 55, OR 3.1, CI 1.65–5.92) had the higher risk of mortality than age and severity-matched controls. A limitation of the present study is that it relies on data from a disease surge that placed considerable strain on hospital resources, and this might have increased mortality rates.

Table Associations Between Specific Neurologic Manifestations and In-Hospital Mortality

Neurologic manifestation	OR (95% CI) for in-hospital mortality
Altered mentation	1.39 (1.04–1.86)
Stroke	3.1 (1.65–5.92)
Neuro–COVID-19	1.0 (0.7–1.42)
Seizures	1.26 (0.4–3.98)
Incidental brain lesions	0.54 (0.2–1.6)

Study Funding and Competing Interests

This study received no funding. The authors report no competing interests. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editor's Note: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Dr. Frontera et al. examined the prevalence and associated mortality of well-defined neurologic diagnoses in a prospective, multicenter, observational study of 4,491 consecutive hospitalized adults in the New York City (NYC) metropolitan area with laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Neurologic disorders were diagnosed in 13.5% of these patients with coronavirus disease-2019 (COVID-19) and were associated with higher in-hospital mortality and lower likelihood of discharge home. In response, Dr. Kumar et al. contrast the most common neurologic clinical diagnoses in this study (toxic/metabolic encephalopathy, stroke, seizure, and hypoxic/ischemic brain injury) with the most common imaging diagnoses in another study by Dr. Kremer et al. of patients with COVID-19 who underwent brain MRI (ischemic strokes, leptomeningeal enhancement, and encephalitis). They note that the study by Dr. Frontera et al. reported raised protein in the CSF in several of the patients, suggestive of intrathecal inflammation as may be seen with meningitis/encephalitis, although white cell counts were low. They wonder whether the low frequency of brain MRI in the study may have led to underdetection of meningitis/encephalitis. In another response, Dr. Liotta et al. note that they reported similar rates of stroke, seizure, Guillain-Barre Syndrome, encephalitis, and meningitis in their recent Chicago-based study but had higher rates of encephalopathy. They note that in their own study, they adjudicated all charts, not just those for patients receiving neurologic consultations, and used protocolized delirium assessments to identify encephalopathy. They contend that Dr. Frontera et al. may have missed several cases of encephalopathy with their methodology and suggest that excluding headache as a neurologic symptom may have limited the scope of SARS-CoV-2 neuropathogenesis. They also note the lower in-hospital mortality in their cohort, potentially related to the absence of an overwhelming case surge in Chicago compared with NYC, and emphasize the importance of public health measures against COVID-19 to help sustain health care infrastructure. Responding to these comments, the authors question whether patients in the imaging study by Dr. Kremer et al. actually met accepted diagnostic criteria for encephalitis, noting that CSF SARS-CoV-2 RT-PCR (reverse transcription PCR) was negative in 20 patients and positing that some of the imaging findings could have represented postinfectious encephalitis. They also caution that many of the reported MRI findings are nonspecific and can be seen with nonencephalitic conditions, in particular hypoxic/ischemic injury, given the high frequency of acute respiratory distress syndrome and supplemental oxygen requirement among these patients. They also note that the elevated CSF protein in their own study is a nonspecific finding and highlight the need to follow rigorous standards when ascribing meningitis/encephalitis to SARS-CoV-2 infection. Regarding their lower rates of encephalopathy compared with the Chicago study, the authors argue that they coded toxic-metabolic encephalopathy only in patients off sedation or after a sedation washout, whereas the Chicago study may have included patients with sedation-related delirium, which may have different outcomes than other etiologies of encephalopathy. However, they acknowledge that they may have underestimated the overall prevalence of neurologic injury in the most critically ill patients who could not be assessed off sedation, or who were unable to express other neurologic symptoms. Notwithstanding the older age of their cohort, they agree that the critical surge and strain on health care resources in NYC likely affected mortality and echo the importance of public health measures to stem such surges. This exchange demonstrates important differences that can arise in incidence or frequency estimates of different neurologic manifestations in COVID-19 based on the methodology that is followed.

Aravind Ganesh, MD, DPhil, FRCPC

Neurology® 2021;96:548. doi:10.1212/WNL.0000000000011604

Author disclosures are available upon request (journal@neurology.org).

Reader Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Anand Kumar (Varanasi, India), Neha Lall (Varanasi, India), and Varun Kumar Singh (Varanasi, India)
Neurology® 2021;96:549. doi:10.1212/WNL.0000000000011614

We read with interest the article by Frontera et al.[1] studying neurologic disorders in hospitalized COVID-19 patients in New York City. The overall prevalence of neurologic disorders among hospitalized COVID-19 patients was 13.5%. The most common neurologic symptoms were toxic/metabolic encephalopathy (309/606, 51%), stroke (84/606, 14%), seizure (74/606, 12%), and hypoxic/ischemic brain injury (65/606, 11%). In a recent study by Kremer et al.,[2] correlated neurologic and neuroimaging findings of COVID-19 patients concluded that among 64 patients with neurologic symptoms who underwent brain MRI, ischemic strokes (27%) were the most common finding, followed by leptomeningeal enhancement (17%) and encephalitis (13%). Even in present study, the CSF findings (table 2) show raised protein [median 61, IQR (42–106) mg/dL], favoring intrathecal inflammation and possibility of meningitis and/or encephalitis. Although there were few cells in the CSF [2 (1–4)], in COVID-19 patients, atypical inflammatory response without CSF pleocytosis is not uncommon.[3] Another possible explanation of not picking up any encephalitis or meningitis in the present study is the lesser number of brain MRI (15%) being performed. We are unable to understand the difference between stroke and hypoxic/ischemic brain injury because they were categorized separately in the current study!

1. Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 2021;96:e575–e586.
2. Kremer S, Lersy F, Anheim M, et al. Neurologic and neuroimaging findings in patients with COVID-19. Neurology 2020;95:e1868–e1882.
3. Edén A, Kanberg N, Gostner J, et al. CSF biomarkers in patients with COVID-19 and neurological symptoms. Neurology 2020;96:e294–e300.

Author Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Jennifer A. Frontera (New York), Laura Balcer (New York), and Steven Galetta (New York)
Neurology® 2021;96:549–550. doi:10.1212/WNL.0000000000011609

We appreciate the comments by Kumar et al. on our article.[1] The referenced Kremer study[2] was a retrospective case series and included patients with positive MRI findings only. It is unclear whether the patients with the diagnosis of "encephalitis" met diagnostic or causal criteria outlined by the International Encephalitis Consortium[3] and others.[4] Indeed, CSF SARS-CoV-2 RT-PCR was negative in 20 patients. In 2 of 3 with CSF pleocytosis (>5 cell/mm^3), imaging was performed >2 weeks from symptom onset, possibly representing postinfectious autoimmune encephalitis and not infectious encephalitis. Many of the MRI findings described are nonspecific and can be seen in hypoxic/ischemic brain injury, metabolic encephalopathy, or postseizure. Notably, 100% of "encephalitis" patients required oxygen and 75% had ARDS, suggesting that a proportion of the MRI changes may represent hypoxic/ischemic injury (defined as a global insult due to hypoxemia, hypotension, or cardiac arrest). Although we detected elevated CSF protein in some patients,[1] this is nonspecific and can be found in stroke, hemorrhage (or traumatic tap), hypoxic/ischemic injury, diabetes, uremia, tumor, neuropathy, and many other conditions. Because the implications of SARS-CoV-2 neurotropism are far reaching, we believe that it is critical to follow the most rigorous standards and criteria when ascribing encephalitis/meningitis/myelitis to SARS-CoV-2 infection.

Author disclosures are available upon request (journal@neurology.org).

1. Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 2021;96:e575–e586.
2. Kremer S, Lersy F, Anheim M, et al. Neurologic and neuroimaging findings in patients with COVID-19. Neurology 2020;95: e1868–e1882.
3. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013;57:1114–1128.
4. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol 2020;19:767–783.

Reader Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Eric M. Liotta (Chicago), Ayush Batra (Chicago), and Igor J. Koralnik (Chicago)
Neurology® 2021;96:550. doi:10.1212/WNL.0000000000011613

Frontera et al.[1] should be commended on the breadth of their report on neurologic diagnoses in COVID-19. Although stroke, seizure, GBS, encephalitis, and meningitis rates are similar to our recent study,[2] and others,[3,4] their rates of encephalopathy were markedly lower (6.9% vs 31.8%).[1,2] This likely reflects their methodology of adjudicating diagnoses only from chart review of patients with neurologic consultation. Our study similarly included patients with confirmed SARs-CoV-2 RT PCR and ascribed diagnoses by neurologist adjudication. We recognized that delirium—an entity within the encephalopathy spectrum—is the purview of multiple specialties.[5] As such, encephalopathy would not reliably result in neurologic consultation; we adjudicated all charts and leveraged protocolized delirium assessments. The methodology of Frontera et al. likely failed to identify many encephalopathic patients, limiting their estimation of neurologic morbidity. Nevertheless, encephalopathy remained the most frequent neurologic diagnosis. In addition, prematurely excluding headache as a "neurologic symptom" limits the scope and understanding of SARS-CoV-2 neuropathogenesis. As we determine optimal management and decipher the long-term consequences of COVID-19 and encephalopathy, study methodologies should consider that not all neurologic complications result in in-hospital neurologic consultation. Consistently, neurologic manifestations of COVID-19 are common and encephalopathy impacts morbidity. Interestingly, despite similar ventilation rates (26.3% vs 22.0%), our cohort's hospital mortality was considerably lower (8.4% vs 21.4%).[1,2] Although New York experienced a critical strain on hospital infrastructure early in the pandemic, our Chicago area hospital system never experienced the same overwhelming case surge. Taken together, Frontera et al. and our study may reflect the magnitude of public health benefit that could be realized by avoiding case volumes that overwhelm health care infrastructure. This should further emphasize the benefit of universal masking, social distancing, and building redundancy into health care infrastructure.

1. Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 2021;96:e575–e586.
2. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020;7:2221–2230.
3. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683–690.
4. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology 2020;95:e1060–e1070.
5. Slooter AJC, Otte WM, Devlin JW, et al. Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies. Intensive Care Med 2020;46:1020–1022.

Author disclosures are available upon request (journal@neurology.org).

Author Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Jennifer A. Frontera (New York), Ariane Lewis (New York), Laura Balcer (New York), and Steven Galetta (New York)

Neurology® 2021;96:551. doi:10.1212/WNL.0000000000011611

We appreciate these comments on our article.[1] We coded toxic-metabolic encephalopathy only in patients off sedation or after an adequate sedation washout, in contrast to the Chicago study,[2] which included patients who may have been receiving sedation or had a positive Confusion Assessment Method (CAM). Although sedation-related delirium has been associated with worse outcomes, the implications for long-term neurologic recovery differ based on the underlying etiologies of encephalopathy, which can best be ascertained when eliminating the confounding effect of sedative medications. Because a proportion of patients were too hypoxic for assessment off sedation, we recognize that we may be underestimating the overall prevalence of neurologic injury in the most critically ill patients. Similarly, hospitalized patients are often unable to express neurologic symptoms because of the severity of illness; hence, findings such as headache, anosmia, or dysgeusia are typically underrepresented and their prevalence is better studied in the outpatient setting. Although our cohort was somewhat older than the Chicago group—median age 65 vs 58 years—we agree that the critical surge and strain on resources in NYC likely impacted mortality rates, which were similarly high in other area hospitals during this time frame.[3,4] Preventative efforts to stem such surges in hospitalizations—including masking and social distancing—are essential.

1. Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 2021;96:e575–e586.
2. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020;7:2221–2230.
3. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763–1770.
4. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 2020;323:2052–2059.

CORRECTION

Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19

Neurology® 2021;96:551. doi:10.1212/WNL.0000000000011607

In the post-acceptance published version of the article "Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19," by Nader Eskandar et al.,[1] an author was accidently omitted. The author byline and appendix should have included Jonathan Gursky, MD, from the Department of Neurology at Montefiore Medical Center, for his major role in acquisition of data. The omission is corrected in the final published version of the article. The authors regret the omission.

Reference

1. Nader Eskandar E, Altschul DJ, de La Garza Ramos R, et al. Neurologic syndromes predict higher in-hospital mortality in COVID-19. Neurology Epub 2020 Dec 18.

Author disclosures are available upon request (journal@neurology.org).