Radiology

Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection

Sedat G. Kandemirli, MD • Lerzan Dogan, MD • Zeynep T. Sarikaya, MD • Simay Kara, MD • Canan Akinci, MD • Dilaver Kaya, MD • Yildiz Kaya, MD • Duzgun Yildirim, MD • Filiz Tuzuner, MD • Mustafa S. Yildirim, MD • Enes Ozluk, MD • Bulent Gucyetmez, MD • Ercan Karaarslan, MD • Isil Koyluoglu, MD • Hande S. Demirel Kaya, MD • Orkhan Mammadov, MD • Ilkay Kisa Ozdemir, MD • Nazire Afsar, MD • Beyza Citci Yalcinkaya, MD • Sevdinaz Rasimoglu, MD • Duygu E. Guduk, MD • Ararso Kedir Jima, MD • Aylin Ilksoz, MD • Vildan Ersoz, MD • Meltem Yonca Eren, MD • Nilufer Celtik, MD • Serdar Arslan, MD • Bora Korkmazer, MD • Saban S. Dincer, MD • Elif Gulek, MD • Ibrahim Dikmen, MD • Murathan Yazici, MD • Serkan Unsal, MD • Taner Ljama, MD • Ismail Demirel, MD • Aykut Ayyildiz, MD • Isil Kesimci, MD • Sahika Bolsoy Deveci, MD • Melih Tutuncu, MD • Osman Kizilkilic, MD • Lutfi Telci, MD • Rehile Zengin, MD • Alp Dincer, MD • Ibrahim O. Akinci, MD* • Naci Kocer, MD*

From the Department of Radiology, University of Iowa Hospital and Clinics, Iowa City, Iowa (S.G.K.); Departments of Anesthesiology and Reanimation (L.D., Z.T.S., H.S.D.K., O.M., I.K.O., S.R., D.E.G., A.K.J., A.I., I.O.A.), Neurology (N.A.), and Infectious Diseases and Clinical Microbiology (R.Z.), Acibadem Altunizade Hospital, Istanbul, Turkey; Departments of Radiology (S.K.) and Neurology (D.K.), Acibadem University School of Medicine, Istanbul, Turkey; Departments of Anesthesiology and Reanimation (C.A., V.E., M.Y.E., N.C., I.O.A.) and Neurology (Y.K., B.C.Y.), Acibadem Fulya Hospital, Istanbul, Turkey; Departments of Radiology (D.Y.) and Anesthesiology and Reanimation (F.T., M.Y., S.U., T.L., I.O.A.), Acibadem Taksim Hospital, Istanbul, Turkey; Department of Anesthesiology and Reanimation, Acibadem Kozyatagi Hospital, Istanbul, Turkey (M.S.Y., S.S.D., E.G., I. Dikmen, I.O.A.); Departments of Radiology (E.O.) and Anesthesiology and Reanimation (B.G., L.T.), Acibadem University Atakent International Hospital, Istanbul, Turkey; Departments of Radiology (E.K.) and Anesthesiology and Reanimation (I. Koyluoglu, I. Demirel, A.A., I. Kesimci, S.B.D., I.O.A.), Acibadem Maslak Hospital, Istanbul, Turkey; Division of Neuroradiology, Departments of Radiology (S.A., B.K., O.K., N.K.) and Neurology (M.T.), Cerrahapasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey; Department of Radiology, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey (A.D.); and Center for Neuroradiological Applications and Research, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey (A.D.). Received April 19; revision requested April 22; revision received May 5; accepted May 5. **Address correspondence to** N.K. Istanbul University, Cerrahpasa Medical Faculty, Department of Neuroradiology, Kocamustafapasa, Istanbul, Turkey (e-mail: *nkocer@istanbul.edu.tr*).

* A.D. and I.O.A. contributed equally to this work.

Conflicts of interest are listed at the end of this article.

Online supplemental material is available for this article.

Radiology 2020; 297:E232–E235 • https://doi.org/10.1148/radiol.2020201697 • Content codes: NR MR •

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused an outbreak of severe pneumonia (coronavirus disease 2019 [COVID-19]) in China that rapidly spread throughout the globe. Recent evidence highlights a relatively high percentage (36%) of central nervous system symptoms, including headache, altered mental status, acute cerebrovascular disease, and epilepsy, in patients with COVID-19 (1). The rate of neurologic symptoms is higher in patients with a more severe respiratory disease status (1). The relatively high percentage of neurologic symptoms is concordant with studies showing neurotropism of coronavirus (2).

The current literature is limited regarding neuroimaging findings in patients with COVID-19, including acute hemorrhagic necrotizing encephalopathy and meningoencephalitis (3–5). The purpose of this study was to describe brain MRI findings in the evaluation of patients in the intensive care unit (ICU) with COVID-19 pneumonia.

Materials and Methods

Local institutional review board approval was obtained for this retrospective study for patients evaluated between March 1 and April 18, 2020. The requirement for informed consent was waived. The clinical course, neurologic findings, laboratory data (including cerebrospinal fluid analysis), and neuroimaging findings were retrospectively reviewed using a structured research form.

Indications and timing for brain MRI in patients on mechanical ventilation were determined using a protocol established by ICU teams. Full details are in Appendix E1 (online). MRI scans were initially analyzed by neuroradiologists at the institution. Subsequently, all images were reviewed by two neuroradiologists (A.D., with 29 years of experience in neuroradiology and N.K., with 29 years of experience in neuroradiology) in consensus.

Results

Of 749 inpatients with COVID-19 infection at eight hospitals (two university hospitals and six university-affiliated hospitals), 235 patients (31%) required ICU admission during hospitalization. Fifty of the 235 ICU patients (21%; 95% confidence interval [CI]: 16%, 27%) developed neurologic symptoms.

Brain MRI was performed in 27 of 50 patients (54%) with neurologic symptoms (Fig 1, Table). The median age of patients who underwent MRI was 63 years (range, 34–87 years; 21 men). Twelve of 27 patients (44%, 95% CI: 25%, 65%) who underwent MRI had acute findings. In 10 of 27 patients (37%), cortical fluid-attenuated inversion recovery MRI scans showed signal intensity abnormality (Fig 2; Figures E1–E4 [online]). Accompanying subcortical and deep white matter signal intensity abnormality on fluid-attenuated inversion recovery images was seen in three patients. Abnormalities involved the frontal lobe in four patients, the parietal lobe in three patients, the occipital lobe in four patients, the temporal lobe in one patient, the insular cortex in three patients, and the cingulate gyrus in three patients.

Cerebrospinal fluid was obtained in five of 10 patients with cortical signal intensity abnormalities. The total

protein level was elevated (mean, 79.9 mg/dL; range, 59.9–109.7 mg/dL) in four of these patients. The cell count, glucose levels, immunoglobulin G index, and albumin level were within normal limits, and reverse-transcription polymerase chain reaction tests for herpes simplex virus DNA and SARS-CoV-2 yielded negative results in all five specimens. Oligoclonal bands were tested in three specimens and had negative results.

Other acute intracranial findings in the absence of cortical signal abnormality included one patient with acute transverse sinus thrombosis and one patient with acute infarction in the right middle cerebral artery territory.

In 15 of 27 patients (56%), MRI did not reveal any COVID-19–related or acute intracranial findings. Cerebrospinal fluid was obtained in two of these patients and showed elevated cerebrospinal fluid protein level (mean, 98 mg/dL) despite negative MRI findings. A full description of MRI findings is in Appendix E1 (online).

Discussion

Current evidence suggests an association of neurologic manifestations with COVID-19 infection, including acute stroke (6%) and altered mental status (15%) (1). Neurotropism of coronavirus may account for the relatively high percentage of neurologic involvement (6,7). In addition to neurotropism, another potential mechanism for neurologic manifestations might be related to cytokine storm syndrome (8). In addition to findings of encephalitis, increased thrombosis rates in coronavirus infection have been reported. In patients with severe acute respiratory syndrome coronavirus, an increased incidence of deep venous thrombosis and pulmonary embolism was observed despite optimal anticoagulant therapy (9). Additionally, intracranial arterial stroke has been reported in patients with severe acute respiratory syndrome who receive intravenous immunoglobulin treatment (9).

A recent series from France (5) reported that neurologic signs were present in 84% of patients with COVID-19 admitted to the ICU (49 of 58 patients). Brain MRI was performed in 13 patients, and leptomeningeal enhancement was noted in eight (5). In our series, the most common imaging finding was cortical signal intensity abnormalities on fluid-attenuated inversion recovery images (10 of 27 patients [37%]), accompanied by cortical diffusion restriction, leptomeningeal enhancement, or cortical blooming artifact in some of these patients. The main differential diagnosis for these findings is infectious or autoimmune encephalitis, seizure, hypoglycemia, and hypoxia (10–16). The cases with bilateral frontal involvement may have hypoxia as underlying pathogenesis given the underlying respiratory distress and frontotemporal hypoperfusion, as demonstrated by Helms et al (5), in patients with COVID-19 admitted to the ICU. Cortical microhemorrhages and breakdown of the blood-brain barrier can accompany hypoxia, which can result in such an imaging pattern. Postictal state is also a plausible cause for our imaging findings; however, the relative symmetry and deep white matter involvement in our patients do not support postictal changes. Hypoglycemia can act as a potential mimicker; however, no episode of hypoglycemia occurred during the ICU course of patients. COVID-19, with its neurotropic potential, may result in infectious or autoimmune encephalitis (3,4). Certain viral and autoimmune encephalitis can have a specific pattern of involvement that can help establish a differential list. However, the nonspecific imaging pattern in our series can make it difficult to achieve a specific diagnosis on the basis of MRI results (10). In addition, the complex clinical course, including comorbid conditions such as diabetes mellitus, a long ICU stay with multidrug regimens, and respiratory distress with hypoxia episodes, can all act as confounding factors. A clear cause-and-effect relationship between COVID-19 infection and MRI findings is hard to establish in the absence of more specific cerebrospinal fluid findings. More data are needed to determine which imaging findings are related to neurotropism of COVID-19 and which are related to other causes such as cytokine storm syndrome, hypoxia, subclinical seizures, and critical illness–related encephalopathy.

Limitations of the current study are its retrospective and multicenter nature and the lack of standardization of indications across hospitals.

This report may help increase awareness of possible neurologic involvement of SARS-CoV-2 in patients in the ICU and especially in patients who do not tolerate extubation despite improvement of respiratory findings.

Author contributions: Guarantors of integrity of entire study, S.K., F.T., S.U., L.T., R.Z., A.D., N.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, S.G.K., L.D., S.K., E.K., H.S.D.K., N.A., A.I., S.A., B.K., I. Dikmen, S.U., I. Demirel, A.A., I. Kesimci, S.B.D., O.K., R.Z., A.D., I.O.A., N.K.; clinical studies, L.D., S.K., C.A., D.K., Y.K., D.Y., F.T., M.S.Y., E.O., B.G., E.K., I. Koyluoglu, H.S.D.K., I.K.O., N.A., B.C.Y., S.R., D.E.G., A.I., V.E., M.Y.E., N.C., S.S.D., E.G., I. Dikmen, M.Y., S.U., T.L., I. Demirel, I. Kesimci, M.T., O.K., L.T., R.Z., A.D., I.O.A., N.K.; experimental studies, H.S.D.K., A.I., S.U., R.Z.; statistical analysis, L.D., E.O., H.S.D.K., A.I., S.U., R.Z., I.O.A., N.K.; and manuscript editing, S.G.K., S.K., D.K., E.K., H.S.D.K., N.A., A.I., S.A., B.K., S.U., R.Z., A.D., I.O.A., N.K.

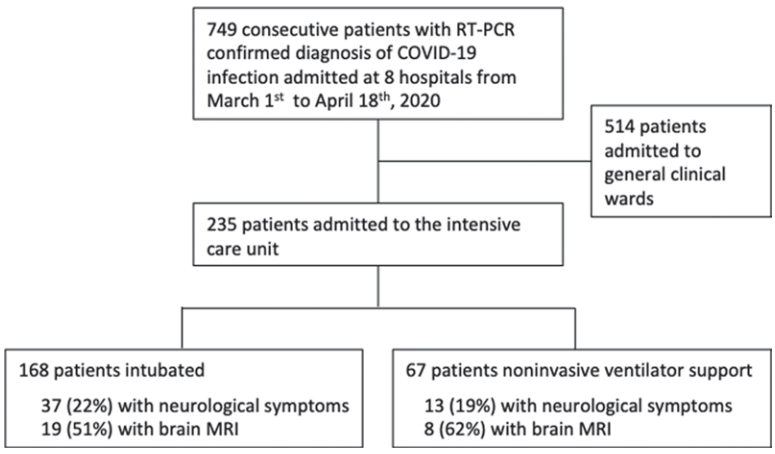

Figure 1: Flowchart of patient inclusion. COVID-19 = coronavirus disease 2019, RT-PCR = reverse-transcription polymerase chain reaction.

Demographic and Clinical Features of Patients with COVID-19 Infection in the ICU with Cranial MRI

Characteristic	All Patients with Brain MRI (*n* = 27)	Patients with Abnormal Brain MRI (*n* = 12)	Patients with Normal Brain MRI (*n* = 15)
Median age (y)*	63 (34–87)	62 (34–87)	63 (51–77)
Men†	21 (78)	11 (92)	10 (67)
Comorbidities	HT (*n* = 16); DM (*n* = 11); CVA (*n* = 2); CAD (*n* = 3); AF (*n* = 1); CHF (*n* = 2); CKD (*n* = 4); lung cancer (*n* = 1); Addison disease (*n* = 1)	HT (*n* = 6); DM (*n* = 5); CAD (*n* = 1); AF (*n* = 1); CKD (*n* = 1); Addison disease (*n* = 1)	HT (*n* = 10); DM (*n* = 6); CVA (*n* = 2); CAD (*n* = 2); CHF (*n* = 2); CKD (*n* = 3); lung cancer (*n* = 1)
Time from symptom onset to ICU admission (d)*	3 (0–20)	3 (0–20)	4 (0–14)
Intubation	19	9	10
Noninvasive ventilator support	8	3	5
Cerebrospinal fluid analysis†	7 (26)	5 (42)‡	2 (13)§
Median time from ICU admission to MRI examination (d)*	7 (0–24)	8 (0–16)	4 (0–24)

Note.—AF = atrial fibrillation, CAD = coronary artery disease, CKD = chronic kidney disease, COVID-19 = coronavirus disease 2019, CVA = cerebrovascular accident, DM = diabetes mellitus, HT = hypertension, ICU = intensive care unit.

* Numbers in parentheses are the minimum and maximum range.

† Numbers in parentheses are percentages.

‡ Four patients had increased protein without pleocystosis.

§ Two patients had increased protein without pleocystosis.

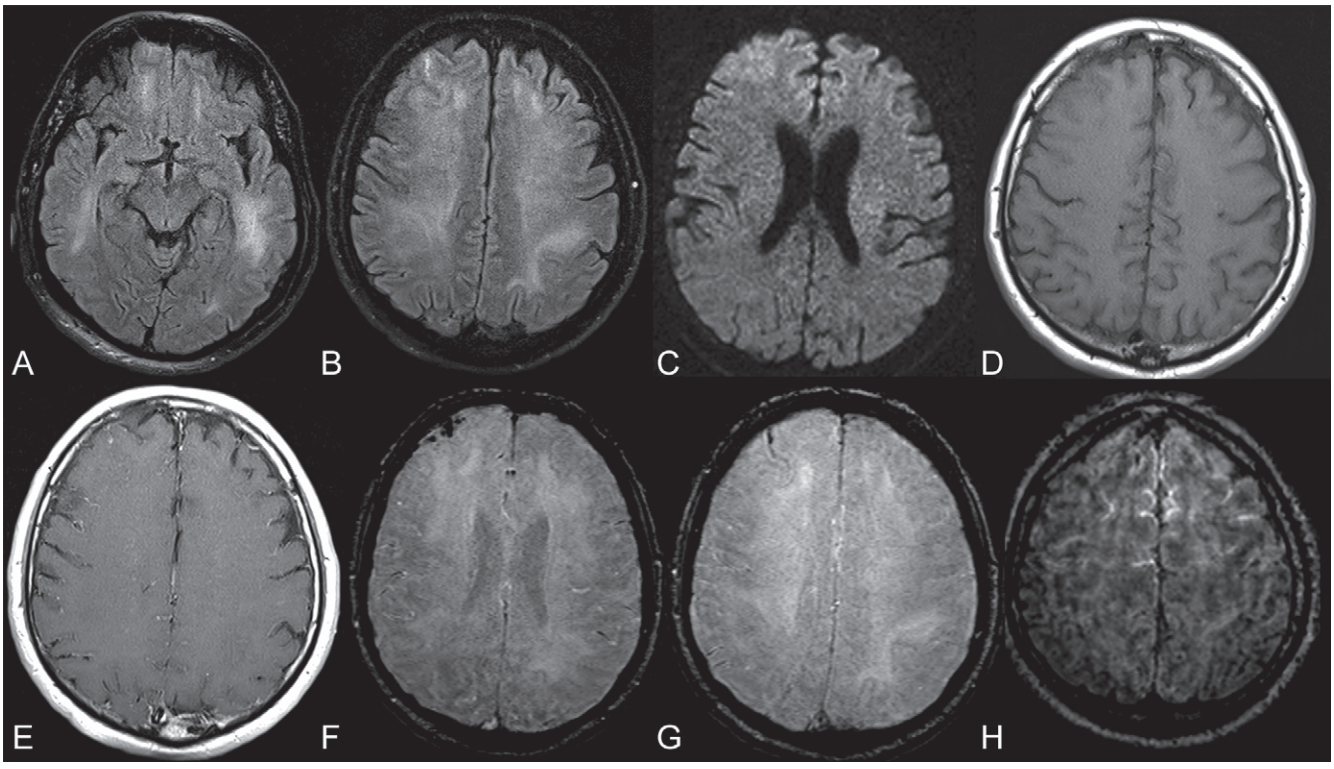

Figure 2: Contrast material–enhanced cranial 1.5-T MRI scans in a 59-year-old intubated man with altered mental status despite tapering of sedoanalgesia. *A*, *B*, Axial fluid-attenuated inversion recovery images at level of, *A*, midbrain and, *B*, centrum semiovale demonstrate prominent symmetric white matter hyperintensity and right frontal cortical hyperintensity. Prominent linear hyperintensity within frontal sulci is also shown. *C*, Axial diffusion-weighted image (b = 2000 sec/mm^2) shows frontal increased signal intensity. There was also a corresponding low apparent diffusion coefficient (not shown) *D*, Axial T1-weighted image shows right frontal sulcal effacement. *E*, Postcontrast T1-weighted image shows mild pial-subarachnoid enhancement. *F*, *G*, Axial susceptibility-weighted images at level of, *F*, corona radiata and, *G*, centrum semiovale demonstrate blooming artifact in the frontal sulci. *H*, Postcontrast fluid-attenuated inversion recovery image depicts bilateral leptomeningeal enhancement.

Disclosures of Conflicts of Interest: S.G.K. disclosed no relevant relationships. **L.D.** disclosed no relevant relationships. **Z.T.S.** disclosed no relevant relationships. **S.K.** disclosed no relevant relationships. **C.A.** disclosed no relevant relationships. **D.K.** disclosed no relevant relationships. **Y.K.** disclosed no relevant relationships. **D.Y.** disclosed no relevant relationships. **F.T.** disclosed no relevant relationships. **M.S.Y.** disclosed no relevant relationships. **E.O.** disclosed no rel-

evant relationships. **B.G.** disclosed no relevant relationships. **E.K.** disclosed no relevant relationships. **I. Koyluoglu** disclosed no relevant relationships. **H.S.D.K.** disclosed no relevant relationships. **O.M.** disclosed no relevant relationships. **I.K.O.** disclosed no relevant relationships. **N.A.** disclosed no relevant relationships. **B.C.Y.** disclosed no relevant relationships. **S.R.** disclosed no relevant relationships. **D.E.G.** disclosed no relevant relationships. **A.K.J.** disclosed no relevant relationships. **A.I.** disclosed no relevant relationships. **V.E.** disclosed no relevant relationships. **M.Y.E.** disclosed no relevant relationships. **N.C.** disclosed no relevant relationships. **S.A.** disclosed no relevant relationships. **B.K.** disclosed no relevant relationships. **S.S.D.** disclosed no relevant relationships. **E.G.** disclosed no relevant relationships. **I. Dikmen** disclosed no relevant relationships. **M.Y.** disclosed no relevant relationships. **S.U.** disclosed no relevant relationships. **T.L.** disclosed no relevant relationships. **I. Demirel** disclosed no relevant relationships. **A.A.** disclosed no relevant relationships. **I. Kesimci** disclosed no relevant relationships. **S.B.D.** disclosed no relevant relationships. **M.T.** disclosed no relevant relationships. **O.K.** disclosed no relevant relationships. **L.T.** disclosed no relevant relationships. **R.Z.** disclosed no relevant relationships. **A.D.** disclosed no relevant relationships. **I.O.A.** disclosed no relevant relationships. **N.K.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed no relevant relationships. Other relationships: has a proctoring and consultancy agreement for interventional neuroradiology procedures with MicroVention.

References

1. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020 Apr 10 [Epub ahead of print].
2. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. Virus Res 2014;194:145–158.
3. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55–58.
4. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology 2020 Mar 31:201187 [Epub ahead of print].
5. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020 Apr 15 [Epub ahead of print] https://doi.org/10.1056/NEJMc2008597.
6. Morfopoulou S, Brown JR, Davies EG, et al. Human Coronavirus OC43 Associated with Fatal Encephalitis. N Engl J Med 2016;375(5):497–498.
7. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan 2005;14(3):113–119.
8. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–1034.
9. Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 2004;251(10):1227–1231.
10. Koeller KK, Shih RY. Viral and Prion Infections of the Central Nervous System: Radiologic-Pathologic Correlation: From the Radiologic Pathology Archives. RadioGraphics 2017;37(1):199–233.
11. Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B. Autoimmune Encephalitis: Pathophysiology and Imaging Review of an Overlooked Diagnosis. AJNR Am J Neuroradiol 2017;38(6):1070–1078.
12. Cianfoni A, Caulo M, Cerase A, et al. Seizure-induced brain lesions: a wide spectrum of variably reversible MRI abnormalities. Eur J Radiol 2013;82(11):1964–1972.
13. Muttikkal TJ, Wintermark M. MRI patterns of global hypoxic-ischemic injury in adults. J Neuroradiol 2013;40(3):164–171.
14. Bathla G, Policeni B, Agarwal A. Neuroimaging in patients with abnormal blood glucose levels. AJNR Am J Neuroradiol 2014;35(5):833–840.
15. McKinney AM, Sarikaya B, Gustafson C, Truwit CL. Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging. AJNR Am J Neuroradiol 2012;33(5):896–903.
16. Fanou EM, Coutinho JM, Shannon P, et al. Critical Illness-Associated Cerebral Microbleeds. Stroke 2017;48(4):1085–1087.