

## CLINICAL AND POPULATION SCIENCES

## Cerebral Microbleeds and Leukoencephalopathy in Critically Ill Patients With COVID-19

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**BACKGROUND AND PURPOSE:** We conducted this study to investigate the prevalence and distribution of cerebral microbleeds and leukoencephalopathy in hospitalized patients with coronavirus disease 2019 (COVID-19) and correlate with clinical, laboratory, and functional outcomes.

**METHODS:** We performed a retrospective chart review of 4131 COVID-19 positive adult patients who were admitted to 3 tertiary care hospitals of an academic medical center at the epicenter of the COVID-19 pandemic in New York City from March 1, 2020, to May 10, 2020, to identify patients who had magnetic resonance imaging (MRI) of the brain. We evaluated the MRIs in detail, and identified a subset of patients with leukoencephalopathy and/or cerebral microbleeds. We compared clinical, laboratory, and functional outcomes for these patients to patients who had a brain MRI that did not show these findings.

**RESULTS:** Of 115 patients who had an MRI of the brain performed, 35 (30.4%) patients had leukoencephalopathy and/or cerebral microbleeds. Patients with leukoencephalopathy and/or cerebral microbleeds had neuroimaging performed later during the hospitalization course (27 versus 10.6 days;  $P<0.001$ ), were clinically sicker at the time of brain MRI (median GCS 6 versus 14;  $P<0.001$ ), and had higher peak D-dimer levels ( $8018\pm6677$  versus  $3183\pm3482$ ;  $P<0.001$ ), lower nadir platelet count ( $116.9\pm62.2$  versus  $158.3\pm76.2$ ;  $P=0.03$ ), higher peak international normalized ratio (2.2 versus 1.57;  $P<0.001$ ) values when compared with patients who had a brain MRI that did not show these findings. They required longer ventilator support (34.6 versus 9.1 days;  $P<0.001$ ) and were more likely to have moderate and severe acute respiratory distress syndrome score (88.6% versus 23.8%,  $P<0.001$ ). These patients had longer hospitalizations (42.1 versus 20.9 days;  $P<0.001$ ), overall worse functional status on discharge (mRS 5 versus 4;  $P=0.001$ ), and higher mortality (20% versus 9%;  $P=0.144$ ).

**CONCLUSIONS:** The presence of leukoencephalopathy and/or cerebral microbleeds is associated with a critical illness, increased mortality, and worse functional outcome in patients with COVID-19.

**Key Words:** coronavirus ■ COVID-19 ■ critical illness ■ leukoencephalopathy ■ microbleeds

Coronavirus disease 2019 (COVID-19) is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) which primarily targets the lungs. There is, however, growing evidence of prominent neurological manifestations.<sup>1-4</sup> There have been reports describing neuroimaging features of COVID-19,<sup>5,6</sup> but data beyond case studies<sup>7-10</sup> is limited. One of the neuroimaging findings described in patients with COVID-19 is leukoencephalopathy with cerebral microbleeds.<sup>8,10</sup>

Leukoencephalopathy and cerebral microbleeds have previously been described in critically ill patients with diseases other than COVID-19.<sup>11-17</sup> Microbleeds may be seen in the brain parenchyma of critically ill patients, especially patients with acute respiratory distress syndrome (ARDS)<sup>14</sup> or disseminated intravascular coagulation.<sup>11-13,17</sup> Cerebral microbleeds can be observed in the subcortical white matter (WM) and splenium of the corpus callosum (CC) in critically ill patients who have had a prolonged course of respiratory failure and periods of hypoxemia.

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## Nonstandard Abbreviations and Acronyms

<b>ACE-2</b>	angiotensin-converting enzyme 2
<b>ARDS</b>	acute respiratory distress syndrome
<b>CC</b>	corpus callosum
<b>COVID-19</b>	coronavirus disease 2019
<b>MRI</b>	magnetic resonance imaging
<b>SARS-COV-2</b>	severe acute respiratory syndrome coronavirus 2
<b>WM</b>	white matter

These cerebral microbleeds are usually identified on susceptibility-weighted magnetic resonance imaging (MRI).<sup>18</sup> Similarly, leukoencephalopathy and WM cytotoxic edema may be observed in a variety of conditions including diffuse hypoxic-ischemic injury, posterior reversible encephalopathy syndrome, acute disseminated encephalomyelitis, and various toxic and metabolic causes.<sup>19</sup>

In this report, we aim to identify and characterize the pattern of leukoencephalopathy and cerebral microbleeds in patients with COVID-19 and compare the clinical, laboratory, and functional outcomes to a control cohort of patients with COVID-19 without these neuroimaging findings. We hypothesized that patients with COVID-19 with leukoencephalopathy and/or cerebral microbleeds will have worse functional outcomes at time of discharge compared with those patients without these neuroimaging findings.

## METHODS

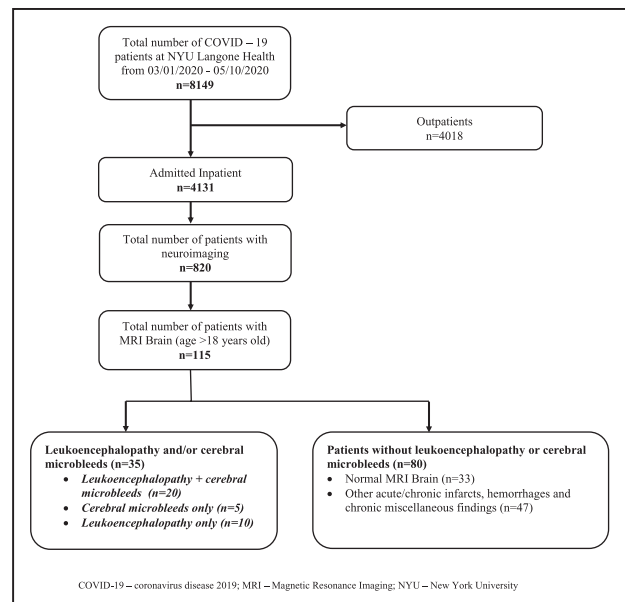
### Data Availability Statement

The study data set has been submitted in the [Data Supplement](#).

We performed a retrospective chart review of COVID-19 positive adult patients (aged  $\geq 18$  years) who were admitted to 3 tertiary care hospitals of an academic medical center at the epicenter of the COVID-19 pandemic in New York City from March 1, 2020, to May 10, 2020 (Figure 1) to determine who had MRI of the brain performed. A confirmed case of COVID-19 was defined as a positive result on SARS-COV-2 real-time reverse transcriptase polymerase chain reaction assay of nasopharyngeal or oropharyngeal swab specimens.<sup>20</sup>

### Imaging Analysis

MRI was performed using a 3.0 T MRI scanner and included susceptibility-weighted imaging for 90 patients. Gradient echo imaging was obtained in 25 patients using a 1.5 T MRI scanner. Two fellowship-trained neuro-radiologists (Drs Jain and Nguyen) evaluated each neuroimaging study for the presence or absence of cerebral microbleeds and leukoencephalopathy. Cerebral microbleeds were characterized as diffuse (bilateral and involvement of  $>5$  brain lobes) or (1) lobar, (2) subcortical, (3) deep, (4) CC, (5) pontine, and/or (6) cerebellar. CC microbleeds were further classified as involving all the segments or



**Figure 1. Study flowchart.**

COVID-19 indicates coronavirus disease 2019; MRI, magnetic resonance imaging; and NYU, New York University.

isolated splenium. Presence or absence of superficial siderosis was noted. Leukoencephalopathy was categorized as diffuse and involvement of peri-rolandic regions was also noted down. The presence of edema in the CC was also noted. The presence or absence of WM restricted diffusion as signal drop out on apparent diffusion coefficient maps was also noted for all patients.

Data were obtained from chart review and included demographics, comorbidities, number of days on a ventilator, hospital length of stay, Glasgow Coma Scale at the time of MRI (if unavailable, Glasgow Coma Scale scores  $\pm 2$  days were used), and ARDS severity score (calculated using the lowest  $\text{PaO}_2/\text{FiO}_2$  ratio available). If Glasgow Coma Scale scores were missing, they were imputed from neurological examination notes by a neurology resident (Dr Agarwal). ARDS severity scores were dichotomized into moderate–severe hypoxemia (ARDS severity score  $<200$ ) and mild hypoxemia (ARDS severity score  $\geq 200$ ). Laboratory variables included platelet count and fibrinogen (at admission and nadir), D-dimer, and international normalized ratio (at admission and peak). Functional outcomes included discharge modified Rankin Scale and death. Modified Rankin Scale scores were obtained from physical therapy notes on the day of discharge (if no physical therapy notes on the day of discharge, then modified Rankin Scale from physical therapy notes from prior 5 days was acceptable). If there was no modified Rankin Scale documented, it was imputed by a neurology resident (Dr Agarwal) from either the physical therapy notes or neurological examination notes performed by either a neurology resident or attending).

This study was approved by the New York University Grossman School of Medicine Institutional Review Board, which granted both a waiver of informed consent and a waiver of the Health Information Portability and Privacy Act (Institutional Review Board No. i20-00567).

## Statistical Analysis

Patients were divided into 2 groups: those with neuroimaging findings of leukoencephalopathy and/or cerebral microbleeds and those without these findings. Descriptive statistics for continuous variables are presented as means plus or minus SD and median with interquartile range for age and ordinal data. Categorical variables are presented as a percentage. Comparison of continuous variables was performed using the independent samples *t* test (Welch) or Wilcoxon rank-sum test as appropriate. Categorical variables were compared using the  $\chi^2$  or Fisher exact test, as appropriate. We examined the relationship between the number of days on the ventilator and the probability of having leukoencephalopathy and/or cerebral microbleeds using logistic regression, adjusting for covariates that were significantly different between the groups. These variables were considered as predictors in building a logistic regression model. Collinearity of the predictors were also explored through their pair-wise correlations to gain an understanding of the roles they play in predicting the MRI results. Associations are presented as odds ratios with corresponding 95% CIs.  $P < 0.05$  were considered statistically significant for all analyses. Statistical analyses were conducted using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Out of 4131 patients admitted with COVID-19, 115 adult patients had an MRI of the brain. Of these, 35 (30.4%) patients had cerebral leukoencephalopathy and/or cerebral microbleeds. Out of the remaining 80 patients, 47 (40.9) had acute/chronic infarcts, hemorrhages, or other chronic findings and 33 patients (28.7%) had normal MRI of the brain (Figure 1).

Patients with cerebral leukoencephalopathy and/or cerebral microbleeds on neuroimaging were younger (median age 61 versus 69;  $P = 0.003$ ) and predominantly males (82.8% versus 66.3%;  $P = 0.078$ ; Table 1). Patients with leukoencephalopathy and/or cerebral microbleeds required longer ventilator support (34.6 versus 9.1 days;  $P < 0.001$ ) and had longer hospitalizations (42.1 versus 20.9 days;  $P < 0.001$ ) when compared with patients without these findings (Table 1). These patients were thrombocytopenic with lower nadir platelet counts ( $P = 0.003$ ), higher peak D-dimer ( $P < 0.001$ ), and higher peak international normalized ratio ( $P < 0.001$ ) values; though the 2 groups were not different in other comorbidities (Table 1). Patients

**Table 1. Comparison Between Patients With MRI Brain Findings of Leukoencephalopathy and/or Cerebral Microbleeds and Without**

Characteristic	Leukoencephalopathy and/or Cerebral Microbleeds, n=35	Other MRI Brain Findings (Without Leukoencephalopathy and/or Cerebral Microbleeds), n=80	P Value
Age, median (IQR), y	61 (50–66)	69 (59.75–75.25)	0.0031
Male gender, n (%)	29 (82.8)	53 (66.3)	0.078
BMI	28.7 (5.9)	27.4 (6.1)	0.257
Hyperlipidemia, n (%)	13 (37.1)	31 (38.8)	1.0
Diabetes mellitus, n (%)	15 (42.9)	31 (38.8)	0.836
Hypertension, n (%)	21 (60)	54 (67.5)	0.573
Day of MRI since admission, mean (SD)	27.0 (10.3)	10.6 (12.9)	<0.001
GCS at the time of MRI, median (IQR)	6 (3–9)	14 (11–15)	<0.001
Number of patients intubated, n (%)	33 (94.3)	23 (28.75)	<0.001
Ventilator days, mean (SD)	34.6 (13.9)	9.1 (15.9)	<0.001
Moderate, severe hypoxemia, n (%)	31 (88.6)	19 (23.75)	<0.001
Length of hospital stay, mean (SD)*	42.1(9.9)	20.9 (18.1)	<0.001
mRS at discharge (IQR)†	5 (4–5)	4 (2–5)	0.0014
Deaths, n (%)	7 (20)	7 (9.0)	0.144
Laboratory parameters			
Platelets on admission, mean (SD)	214.8 (67.7)	223.3 (95.8)	0.589
Platelet count nadir, mean (SD)	116.9 (62.2)	158.3 (76.2)	0.0030
D-dimer on admission, mean (SD)	1963 (2867)	1051 (1672)	0.217
D-dimer peak, mean (SD)	8018 (6677)	3183 (3482)	<0.001
Fibrinogen on admission, mean (SD)	647 (188)	572 (197)	0.090
Fibrinogen nadir, mean (SD)	433.6 (162.1)	469.5 (167.1)	0.354
INR on admission, mean (SD)	1.21 (0.17)	1.28 (0.64)	0.382
INR peak, mean (SD)	2.20 (1.88)	1.57 (1.13)	<0.001

BMI indicates body mass index; GCS, Glasgow Coma Scale; INR, international normalized ratio; IQR, interquartile range; MRI, magnetic resonance imaging; and mRS, modified Rankin Scale.

\*Total length of hospital stay is until May 13, 2020, if a patient was still admitted to the hospital as of data collection/analysis.

†If a patient is still admitted, mRS reflects the status as of May 13, 2020.

with leukoencephalopathy and/or cerebral microbleeds had worse modified Rankin Scale scores at discharge compared to patients without these findings ( $P=0.001$ ; Table 1). Patients with leukoencephalopathy and/or cerebral microbleeds had neuroimaging performed later during the hospitalization course (27 versus 10.6 days;  $P<0.001$ ) and had a worse coma score at the time of MRI of the brain (median Glasgow Coma Scale score 6 versus 14;  $P<0.001$ ) when compared with patients without these findings. Indications for performing neuroimaging in patients with leukoencephalopathy and/or cerebral microbleeds included encephalopathy (82.9%), focal weakness (5.7%), aphasia (2.9%), apneic episodes (2.9%), and seizures (2.9%), whereas the indication for performing neuroimaging in patients without these findings were encephalopathy (48.6%), weakness (25%), headache (4.2%), aphasia (5.6%), seizures (2.8%), dizziness/vertigo (2.8%), dysarthria (2.8%), ataxia (1.4%), diplopia (1.4%), dysmetria (1.4%), memory loss (1.4%), and postoperative (1.4%).

Of the 35 patients with leukoencephalopathy and/or cerebral microbleeds, 30 (85.5%) had leukoencephalopathy; and 16 (53.3%) of these 30 patients showed restricted diffusion on apparent diffusion coefficient maps. 25 (71.5%) of the 35 patients had microbleeds and 20 (57%) patients had both leukoencephalopathy and microbleeds (Figure 2). Peri-rolandic leukoencephalopathy was seen in 24 (80%) of the patients with leukoencephalopathy and 8 (33%) of these 24 also showed restricted diffusion on apparent diffusion coefficient maps (Figure 3). Restricted diffusion on apparent diffusion coefficient maps was seen in the deep WM. Lobar distribution of microbleeds (Figure 4) was seen in 15 (60%) of 25 patients and 10 (40%) had diffuse involvement (Figure 2). Cerebral microbleeds were seen in all the segments of CC in 15 (60%) patients whereas 4 (16%) patients had microbleeds involving only the splenium (Figure 4). No patient with leukoencephalopathy

and/or cerebral microbleeds demonstrated superficial siderosis. The pattern of distribution of leukoencephalopathy and cerebral microbleeds is shown in Table 2.

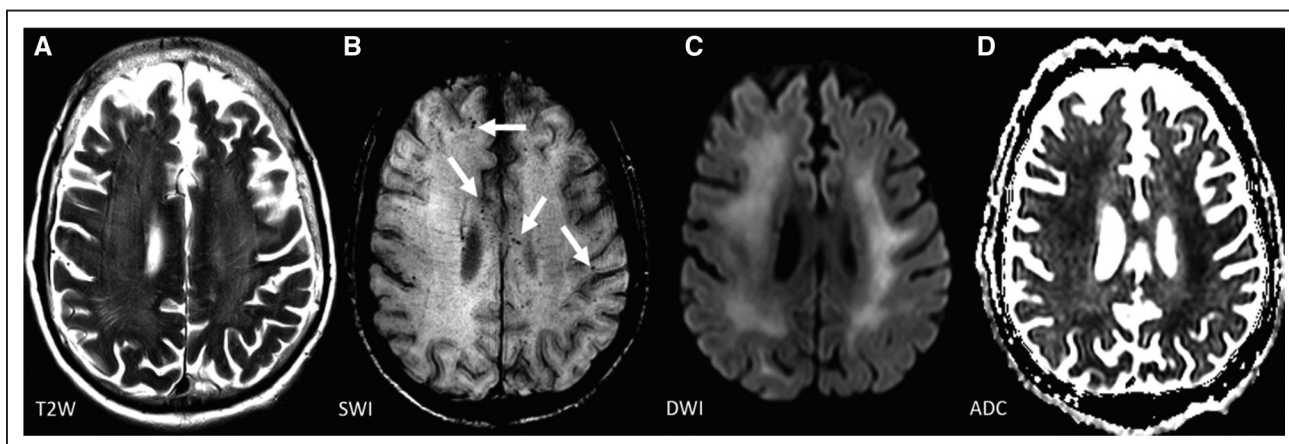
### Association Between the Number of Ventilator Days and Leukoencephalopathy and/or Cerebral Microbleeds on MRI Brain

In an unadjusted model, there was an association between the number of days patients were on a ventilator and the odds of having leukoencephalopathy and/or cerebral microbleeds on MRI brain (odds ratio per day increase, 1.09 [95% CI, 1.06–1.12],  $P<0.0001$ ). In multivariate analysis, after adjusting for platelet nadir count and peak D-dimer levels (adjusted odds ratio per day increase, 1.09 [95% CI, 1.05–1.14],  $P<0.0001$ ), the association between ventilator days and the presence of leukoencephalopathy and/or cerebral microbleeds persisted.

### DISCUSSION

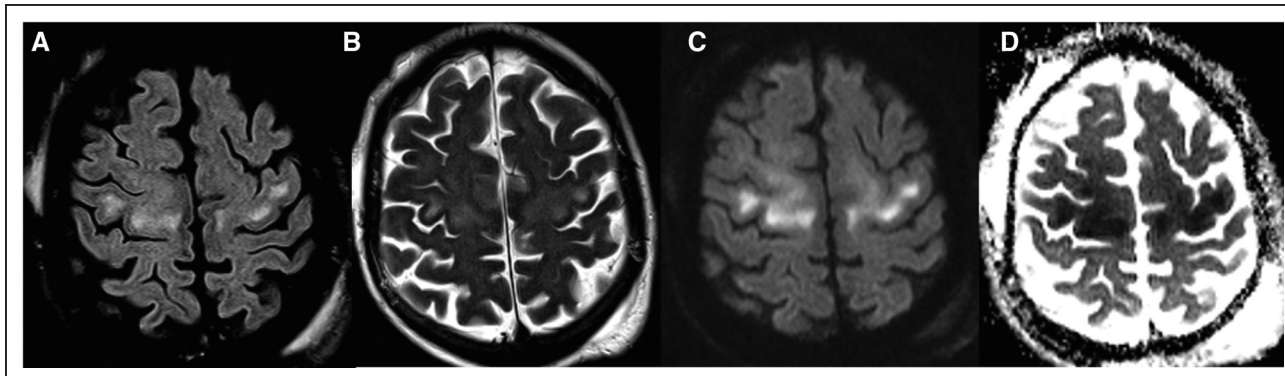
Our findings demonstrate that leukoencephalopathy and/or cerebral microbleeds are seen in patients with COVID-19 with severe illness marked by prolonged ventilator support and hospitalization, thrombocytopenia, and elevated D-dimer. These neuroimaging findings are also associated with worse neurological status and could potentially provide insight into the pathophysiology of brain damage and encephalopathy observed in this disease.

In the current study, the majority of cerebral microbleeds were located in subcortical WM and the CC, similar to the patterns described with high-altitude cerebral edema and ARDS<sup>16,17</sup> and none of our patients demonstrated superficial siderosis. Hypoxemia is common to these disease processes, and hypoxia-induced



**Figure 2. Diffuse leukoencephalopathy and diffuse cerebral microbleeds in subcortical white matter (WM) and corpus callosum: 45-year-old male with coronavirus disease 2019 (COVID-19), ventilated for 28 d, died after 47 d of hospitalization.**

**A**, Axial T2-weighted MR images showing diffuse and confluent WM signal abnormality in both cerebral hemispheres and **(B)** susceptibility-weighted imaging (SWI) showing multiple diffusely scattered cerebral microbleeds in the subcortical WM as well as in corpus callosum (white arrows). **C**, diffusion-weighted imaging and **(D)** apparent diffusion coefficient (ADC) maps showing evidence of restricted diffusion and diffuse cytotoxic edema in the WM.



**Figure 3. Leukoencephalopathy in peri-rolandic regions: 64-year-old male with coronavirus disease 2019 (COVID-19), ventilated for 47 d, died after 49 d of hospitalization.**

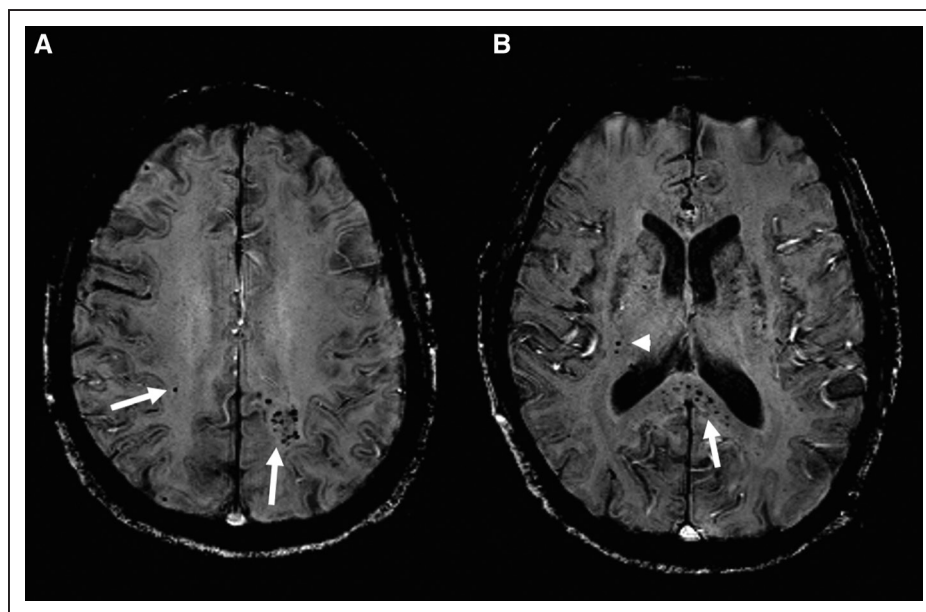
**A**, Axial fluid-attenuated inversion recovery, **(B)** T2-weighted images showing white matter signal abnormality in peri-rolandic regions. **C**, diffusion-weighted imaging and **(D)** apparent diffusion coefficient (ADC) maps showing evidence of restricted diffusion and cytotoxic edema in the peri-rolandic white matter.

hydrostatic or chemical effects on the blood-brain barrier could potentially account for extravasation of erythrocytes and lead to cerebral microbleeds.

However, there are other possible explanations for these findings in patients with COVID-19. Patients with COVID-19 have been noted to have a consumption coagulopathy characterized by elevated D-dimer and fibrinogen degradation products, which can lead to thrombosis in small medullary veins leading to cerebral microbleeds.<sup>21</sup> Accordingly, we found that patients with cerebral microbleeds had lower platelets, higher D-dimer levels, and higher international normalized ratio values. It is also worth noting that the spike protein of the

SARS-COV-2 virus has a strong affinity for the ACE-2 (angiotensin-converting enzyme 2) receptor which has widespread expression in endothelial cells. Microscopic disruption of the endothelium in brain tissue may also be responsible for these small cerebral microbleeds.<sup>21</sup>

Leukoencephalopathy and WM cytotoxic edema can be seen in critically ill patients in a variety of conditions including patients with diffuse hypoxic-ischemic injury, posterior reversible encephalopathy, septic shock, acute disseminated encephalomyelitis, and various toxic metabolic causes.<sup>19,22</sup> Leukoencephalopathy seen in these patients with COVID-19 can be multifactorial. Since COVID-19 is a preinflammatory state,<sup>23</sup> the disruption



**Figure 4. Cerebral microbleeds in a lobar distribution as well as involvement of the splenium of the corpus callosum: 58-year-old male patient with coronavirus disease 2019 (COVID-19), ventilated for 52 d, and remains admitted to the hospital currently.**

**A**, Susceptibility-weighted imaging (SWI) showing cerebral microbleeds in subcortical white matter (WM) in both parietal lobes (white arrows). **B**, SWI showing multiple cerebral microbleeds involving the splenium (white arrow) and sparing of rest of the corpus callosum. A few deep WM cerebral microbleeds are also seen in right cerebral hemisphere (white arrowhead).

**Table 2. Patterns and Distribution of Leukoencephalopathy and Cerebral Microbleeds**

	No. of Patients (%)
Distribution of Leukoencephalopathy, n=30	
Diffuse	18 (60%)
Peri-rolandic involvement	24 (80%)
Distribution of Cerebral Microbleeds, n=25	
Diffuse	10 (40%)
Lobar	15 (60%)
Pons/cerebellum	5 (20%)
Corpus callosum including splenium	15 (60%)
Splenium only	4 (16%)
Subcortical white matter	19 (76%)
Deep white matter	10 (40%)

of the blood-brain barrier by endothelial cell activation<sup>21</sup> can lead to the passage of inflammatory mediators and neurotoxic factors into the brain and cause leukoencephalopathy. Though our patients did not have a neuropathological examination, an alteration of blood-brain barrier has been identified neuropathologically in a patient with diffuse leukoencephalopathy.<sup>24</sup> Since the majority of patients with leukoencephalopathy were critically ill requiring multiple days in the intensive care unit on a ventilator with moderate-severe ARDS scores, they possibly suffered cerebral hypoxia and ischemic injury due to prolonged shock and refractory hypoxia. This could also result in a diffuse leukoencephalopathy similar to delayed post hypoxic leukoencephalopathy. More neuropathological studies are needed to examine the tissue and molecular mechanisms of this injury seen in these patients.

This study has limitations which include a single-center experience that included patients with neuroimaging done over a short course of time (2 months) with a relatively low number of subjects without long-term follow-up. None of the patients in our study have correlative neuropathology for neuroimaging findings. MRI is not universally available, particularly during a pandemic, which could limit the generalizability of these findings. Additionally, MRI detection of cerebral microbleeds is influenced by technical factors such as echo time, spatial resolution, and strength of the magnetic field used. It is also worth noting that susceptibility-weighted imaging is considered the gold standard to assess for cerebral microbleeds, as it has shown more interrater reliability and higher sensitivity for the detection of tiny hemorrhages than gradient echo imaging in previous studies,<sup>18</sup> but majority of the patients included in our study did have susceptibility-weighted imaging sequence for detection of microbleeds. Moreover, though the regression analysis showed an association between the number of days on a ventilator and the finding of leukoencephalopathy and/

or cerebral microbleeds, this should be interpreted with caution as the study sample size was small.

## CONCLUSIONS

Leukoencephalopathy and/or cerebral microbleeds are associated with critical illness, mortality, and worse functional outcome in patients with COVID-19. Although the mechanism of leukoencephalopathy and cerebral microbleeds, its relationship to SARS-CoV-2, as compared with critical illness in general, is uncertain, possibilities include endotheliitis with thrombotic microangiopathy<sup>21</sup> and prolonged respiratory failure and hypoxemia. Identification of these findings in patients with COVID-19 may be helpful for neuroprognostication, however, follow-up studies are needed to better understand this entity and its long-term effects.

## ARTICLE INFORMATION

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### Supplemental Materials

Data set

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