

# MRI of Cerebrovascular Injury Associated With COVID-19 and Non-COVID-19 Acute Respiratory Distress Syndrome: A Matched Case-Control Study

**OBJECTIVES:** Cerebrovascular injury associated with COVID-19 has been recognized, but the mechanisms remain uncertain. Acute respiratory distress syndrome (ARDS) is a severe pulmonary injury, which is associated with both ischemic and hemorrhagic stroke. It remains unclear if cerebrovascular injuries associated with severe COVID-19 are unique to COVID-19 or a consequence of severe respiratory disease or its treatment. The frequency and patterns of cerebrovascular injury on brain MRI were compared among patients with COVID-19 ARDS and non-COVID-19 ARDS.

**DESIGN:** A case-control study.

**SETTING:** A tertiary academic hospital system

**PATIENTS:** Adult patients (>18 yr) with COVID-19 ARDS (March 2020 to July 2021) and non-COVID-19 ARDS (January 2010-October 2018) who underwent brain MRI during their index hospitalization.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Cerebrovascular injury on MRI included cerebral ischemia (ischemic infarct or hypoxic ischemic brain injury) and intracranial hemorrhage (intraparenchymal, subarachnoid, or subdural, and cerebral microbleed [CMB]). Twenty-six patients with COVID-19 ARDS and sixty-six patients with non-COVID ARDS underwent brain MRI during the index hospitalization, resulting in 23 age- and sex-matched pairs. The frequency of overall cerebrovascular injury (57% vs 61%), cerebral ischemia (35% vs 43%), intracranial hemorrhage (43% vs 48%), and CMB (52% vs 41%) between COVID-19 ARDS and non-COVID-19 ARDS patients was similar (all *p* values >0.05). However, four of 26 patients (15%) with COVID-19 and no patients with non-COVID-19 ARDS had disseminated leukoencephalopathy with underlying CMBs, an imaging pattern that has previously been reported in patients with COVID-19.

**CONCLUSIONS:** In a case-control study of selected ARDS patients with brain MRI, the frequencies of ischemic and hemorrhagic cerebrovascular injuries were similar between COVID-19 versus non-COVID-19 ARDS patients. However, the MRI pattern of disseminated hemorrhagic leukoencephalopathy was unique to the COVID-19 ARDS patients in this cohort.

**KEY WORDS:** acute respiratory distress syndrome; cerebral microbleeds; COVID-19; intracranial hemorrhage; ischemic stroke

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Cerebrovascular injury has been comprehensively reported in patients with COVID-19 and is associated with poor functional outcomes and higher mortality (1). Previous studies evaluating neurologic imaging of patients with COVID-19 demonstrated high rates

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of abnormalities on MRI, including ischemic and hemorrhagic stroke (2). Specifically, diffuse leukoencephalopathy and cerebral microbleeds (CMBs) have been reported in prior series of patients with severe COVID-19 (3), with proposed mechanisms including neurotropism or endothelial damage from the virus, respiratory disease and prolonged hypoxia, or treatment complications.

Severe COVID-19 infection frequently results in acute respiratory distress syndrome (ARDS), which is characterized by diffuse lung parenchymal inflammation and noncardiogenic pulmonary edema (4). Prior to the emergence of COVID-19, potential mechanisms for cerebrovascular injury in ARDS included cerebral hypoxia and potential alterations in cerebral hemodynamics related to hypercapnia associated with lung-protective ventilation strategies (5). Although much attention has been paid to the cerebrovascular injury associated with severe COVID-19, it is unknown whether MRI findings differ between patients with COVID-19 ARDS and non-COVID-19 ARDS. In this case-control study, MRI-based imaging was compared in patients with COVID-19 ARDS and non-COVID-19 ARDS to compare the frequency and patterns of cerebrovascular injury.

## **MATERIALS AND METHODS**

### **Case Definition, Inclusion, and Exclusion Criteria**

Cases were patients with COVID-19 ARDS who underwent a brain MRI during their index hospitalization for COVID-19. We performed a retrospective review of all adult patients (>18 yr) hospitalized with COVID-19 ARDS in the Cleveland Clinic health system between March 2020 and July 2021 who underwent a brain MRI during their hospitalization. ARDS was defined and its severity was stratified according to Berlin definition (6).

### **Control Definition, Inclusion, and Exclusion Criteria**

Controls were patients with non-COVID-19 ARDS who underwent a brain MRI during their index hospitalization for ARDS. We reviewed a prospective registry of all adult patients (>18 yr) admitted to the Cleveland Clinic ICU diagnosed with ARDS

between January 2010 and October 2018 to identify patients who underwent an MRI while hospitalized for ARDS.

### **Data Collection**

Extracted information included demographic characteristics including age and sex, past medical history, clinical characteristics including  $Pao_2/FiO_2$  ratio, Glasgow Coma Scale, Sequential Organ Failure Assessment at time of ICU admission, use of antiplatelet medications or therapeutic anticoagulation (IV heparin or therapeutic low molecular weight heparin) at time of MRI, critical care interventions during ICU hospitalization (including vasopressors, dialysis, and paralytics), and hospital outcomes including duration of mechanical ventilation, length of stay, and hospital mortality.

Cerebrovascular injury on MRI was subdivided into cerebral ischemia (including acute ischemic infarct and hypoxic ischemic brain injury) and intracranial hemorrhage (including CMBs, intraparenchymal hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage). CMBs were defined as areas of hypointensity less than 5 mm in diameter on susceptibility-weighted imaging or gradient echo sequences suggestive of hemosiderin deposition. Patients with multiple subtypes of brain injury were included under each category.

This study was approved by the Cleveland Clinic Institutional Review Board (IRB) as part of an ongoing registry database with IRB number 14-1431 on November 16, 2021, entitled "Medical Records: Assessment of Severity of Acute Respiratory Distress Syndrome and its outcome." The need for informed consent was waived by the IRB.

### **Statistical Analysis**

Statistical analyses were performed using IBM SPSS statistics version 28.0 (IBM, Armonk, NY). Data are presented as counts with percentages and medians with interquartile ranges (IQRs). Mann-Whitney *U* test was used for comparison of continuous variables, whereas chi-square and Fisher exact tests were used for comparison of categorical variables. *p* values less than 0.05 were considered statistically significant. Cases and controls were matched 1:1 by age ( $\pm 5$  yr) and sex.

## RESULTS

Twenty-six of 227 COVID-19 ARDS patients (11%) and 66 of 687 non-COVID-19 ARDS patients (10%) had a brain MRI during the index hospitalization (**Supplemental Table 1**, <http://links.lww.com/CCM/H199>). The most common reason for MRI between both COVID-19 and non-COVID-19 cohorts was persistent encephalopathy (54% and 59%) followed by evaluation for stroke (35% and 23%). The median age for patients with COVID-19 ARDS was 69 years (IQR, 57–74), while patients with non-COVID-19 ARDS were younger with a median age 53 (IQR, 41–63,  $p < 0.001$ ). COVID-19 ARDS patients had higher prevalence of several other vascular risk factors including hypertension (92% vs 47%;  $p < 0.001$ ), hyperlipidemia (65% vs 41%;  $p = 0.04$ ), and chronic kidney disease (35% vs 6.1%;  $p < 0.001$ ). In the unmatched cohorts, no differences were seen between cases and controls in the frequency of overall cerebrovascular injury (62% vs 45%;  $p = 0.3$ ) or ischemia (35% vs 33%;  $p = 1.0$ ) detected on MRI. However, intracranial hemorrhage (46% vs 23%;  $p = 0.04$ ), intraparenchymal hemorrhage (15% vs 3%;  $p = 0.02$ ), and CMBs (55% vs 20%;  $p = 0.002$ ) were more prevalent among COVID-19 patients than non-COVID-19 patients (**Supplemental Table 2**, <http://links.lww.com/CCM/H199>).

Patients were matched 1:1 on age ( $\pm 5$  yr) and sex resulting in 23 matched patients in each cohort. Clinical characteristics of the matched case and control populations are included in **Table 1**. COVID-19 patients had a higher prevalence of hypertension (91% vs 43%;  $p = 0.001$ ) and chronic kidney disease (35% vs 6.1%;  $p = 0.04$ ), but ARDS severity, use of antiplatelets or systemic anticoagulation, duration of mechanical ventilation, need for extracorporeal membrane oxygenation (ECMO), and mortality did not differ between the cohorts. There was no difference in the median number of days from ICU admission to obtaining MRI between COVID-19 ARDS and non-COVID-19 ARDS patients (13 vs 10;  $p = 0.56$ ). After matching, the frequency of overall cerebrovascular injury (57% vs 61%), cerebral ischemia (35% vs 43%), intracranial hemorrhage (43% vs 48%), and CMB (52% vs 41%) between COVID-19 ARDS and non-COVID-19 ARDS patients was comparable (all  $p$  values  $> 0.05$ ; **Supplemental Table 2**, <http://links.lww.com/CCM/H199>).

Hemorrhagic leukoencephalopathy (defined as leukoencephalopathy with underlying CMBs) was seen in four patients (15%) with COVID ARDS and no patients with non-COVID ARDS (**Fig. 1**). MRI was obtained in all four patients for persistent encephalopathy. No patients with hemorrhagic leukoencephalopathy had been treated with ECMO. Cerebrospinal fluid (CSF) analysis was performed in two patients with COVID-19 hemorrhagic leukoencephalopathy without evidence of CSF pleocytosis, elevated CSF protein, or elevated CSF immunoglobulin production in either patient.

## DISCUSSION

In this case-control study, cerebrovascular injury was identified in more than half of COVID-19 ARDS patients with MRI, but there was no difference in frequency once compared with age- and sex-matched patients with non-COVID-19 ARDS. However, 15% of COVID-19 ARDS patients demonstrated disseminated hemorrhagic leukoencephalopathy (a radiographic pattern of cerebrovascular injury previously reported in severe COVID-19), whereas this was not observed in patients with non-COVID-19 ARDS.

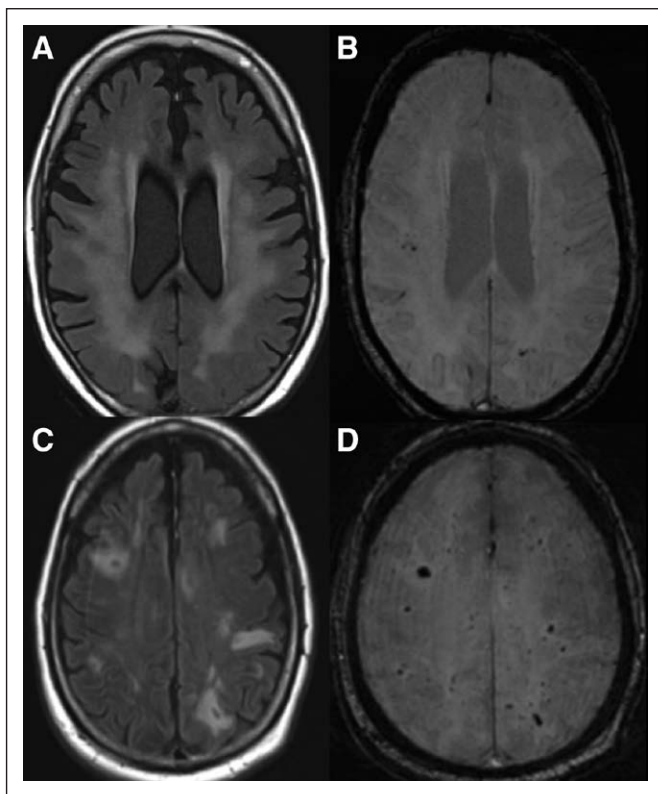
Although the association between severe COVID-19 and stroke has been extensively reported, both COVID-19 ARDS and non-COVID-19 ARDS patients had similar rates of cerebrovascular injury on MRI in our cohort. Part of the association between severe COVID-19 and stroke may not be caused by the virus itself but instead related to pulmonary injury and systemic inflammation present in ARDS regardless of its etiology. Patients with either COVID-19 or non-COVID-19 ARDS may also develop ischemic stroke from watershed hypoperfusion in the setting of sepsis and prolonged hypoxemia. Additionally, ARDS has been associated with the development of CMBs related to endothelial damage (7), which may be at risk for expansion and intracranial hemorrhage especially in the setting of anticoagulant or antithrombotic medications. The cerebrovascular complications of both COVID-19 and ARDS may contribute to the prolonged neurologic and cognitive recovery seen in patients of both conditions, and the identified prevalence in our study suggests that cerebrovascular injury may be underrecognized in patients with ARDS with persistent neurologic dysfunction. Patients in both

**TABLE 1.**  
**Characteristics of Matched Non-COVID and COVID Acute Respiratory Distress Syndrome Patients Who Underwent MRI**

	Non-COVID ARDS With Brain MRI ( <i>n</i> = 23)	COVID ARDS Patients with Brain MRI ( <i>n</i> = 23)	<i>p</i>
<b>Demographics</b>			
Median age (IQR)	66 (57–71)	68 (54–74)	0.72
Median body mass index (IQR)	30 (26–35)	33 (29–40)	0.08
Male, <i>n</i> (%)	14 (61)	14 (61)	1.00
<b>Past medical history, <i>n</i> (%)</b>			
Hypertension	10 (43)	21 (91)	0.001
Hyperlipidemia	9 (39)	16 (70)	0.08
Smoking	10 (43)	13 (57)	0.56
Diabetes	6 (26)	10 (43)	0.35
Congestive heart failure	1 (4)	7 (30)	1.00
Chronic kidney disease	4 (6.1)	9 (35)	0.04
Liver disease	1 (4)	0 (0)	1.00
Active malignancy	2 (9)	1 (4)	1.00
Ischemic stroke	2 (9)	5 (22)	0.41
Hemorrhagic stroke	0 (0)	1 (4)	1.00
<b>Admission characteristics</b>			
ARDS severity on ICU admission			0.57
Mild (P/F ratio 200-300), <i>n</i> (%)	8 (35)	5 (22)	
Moderate (P/F ratio 100-200), <i>n</i> (%)	9 (39)	12 (52)	
Severe (P/F ratio <100), <i>n</i> (%)	6 (26)	6 (26)	
ICU admission Sequential Organ Failure Assessment (IQR)	13 (11–15)	9 (5–13)	0.02
Admission Glasgow Coma Scale (IQR)	7 (3–9)	4 (3–14)	0.70
<b>ICU management, <i>n</i> (%)</b>			
Vasopressors	18 (78)	20 (87)	0.70
Dialysis	9 (39)	11 (48)	0.77
Paralytics	5 (22)	16 (70)	0.003
Antiplatelet use	6 (26)	5 (22)	1.00
Therapeutic anticoagulation	4 (17)	10 (43)	0.11
Extracorporeal membrane oxygenation	3 (4.5)	1 (4)	0.91
<b>Outcomes</b>			
Median mechanical ventilation duration in days (IQR)	20 (11–36)	23 (13–32)	0.81
Median time from presentation to MRI in days (IQR)	10 (4–17)	13 (4–21)	0.56
Hospital length of stay (IQR)	27 (21–41)	26 (19–35)	0.64
ICU length of stay (IQR)	21 (12–31)	26 (13–34)	0.80
Hospital mortality, <i>n</i> (%)	9 (39)	8 (35)	1.00

ARDS = acute respiratory distress syndrome, IQR = interquartile range, P/F =  $P_{aO_2}/F_{iO_2}$ .

Therapeutic anticoagulation referred to the use of continuous heparin or low molecular weight heparin at treatment doses intended for active thrombolysis and did not include the use of anticoagulation for deep vein thrombosis prophylaxis.



**Figure 1.** Representative images of patients with COVID-related leukoencephalopathy with underlying microhemorrhage. Axial T2-weighted fluid attenuation inversion recovery (FLAIR) (A) and susceptibility weighted imaging (B) of a 53-yr-old male with COVID-19 acute respiratory distress syndrome (ARDS) demonstrating diffuse subcortical white matter hyperintensity with underlying microhemorrhage. Axial T2 FLAIR (C) and susceptibility weighted imaging (D) of a 72-yr-old male with COVID-19 ARDS, demonstrating multifocal white matter hyperintensities with underlying microhemorrhage.

populations with persistent encephalopathy or focal neurologic deficit may benefit from neurology consultation and brain imaging with MRI for early detection and management of cerebrovascular injury.

Hemorrhagic leukoencephalopathy has been reported in previous series of patients with COVID-19 (3, 8), but it remains unknown whether this radiographic entity is similar to the parainfectious acute hemorrhagic leukoencephalitis (AHLE) reported in other respiratory infections such as influenza and *Mycoplasma pneumoniae*. CSF analysis in our two patients demonstrated no evidence of acute inflammation, and a previous study of patients with neurologic complications of COVID including stroke did not demonstrate differences in CSF inflammatory changes between COVID patients and controls (9). Additionally, an autopsy of a patient with COVID-associated hemorrhagic

leukoencephalopathy demonstrated diffuse microvascular injury in the regions of radiographic abnormalities with widespread microhemorrhage and ischemia without significant inflammation (10). It is possible that the hemorrhagic leukoencephalopathy in COVID-19 may represent microvascular injury without evidence of the inflammation and demyelination that has been identified in prior cases of para-infectious AHLE.

There are several limitations with the present study. In the unmatched populations, patients with COVID-19 ARDS were older with a higher prevalence of several vascular risk factors, and even after age-sex matching, COVID-19 ARDS patients had higher prevalence of hypertension and chronic kidney disease than non-COVID-19 patients. It is challenging to differentiate between acute and chronic microhemorrhages on MRI. Given this limitation, it is possible that some changes identified on MRI may reflect premorbid vascular disease, especially given the differences in vascular risk factors were not completely balanced after matching. Differences between the pathophysiology of COVID-19 ARDS and non-COVID-19 ARDS as well as the different time intervals of the cohorts may result in changes in management strategies, which could contribute to the risk of cerebrovascular complications. Sample size was overall limited due to the severity of illness, precluding many patients from obtaining MRI. The epoch captured in our study did not include the recent Delta and Omicron variants, which may limit the generalizability to present COVID-19 infections.

## CONCLUSIONS

In this case-control study of ARDS patients with brain MRI, patients with COVID-19 ARDS and non-COVID-19 ARDS had similar prevalence of cerebrovascular injury identified on MRI. However, the MRI pattern of disseminated hemorrhagic leukoencephalopathy was unique to the COVID-19 ARDS patients in this cohort.

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