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Dear Editor,

We present, to our knowledge, the first case series of posterior reversible encephalopathy syndrome (PRES) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We report this possible neurological complication of coronavirus disease 2019 (COVID-19) in two patients hospitalized in a single center in April 2020. Based on this report, we advocate for tight blood pressure control in all Covid-19 patients; as hypertensive encephalopathy, with or without PRES, may be an unrealized contributory factor to the prolonged ventilation times observed in severe Covid-19. Additionally, our patients developed PRES with relatively moderate blood pressure fluctuations, further advocating for tight blood pressure control, as there may be an unrealized element of endothelial dysfunction contributing to hypertensive encephalopathy with relatively milder blood pressure swings in SARS-CoV-2 infection.

A 58-year-old man (Patient-1) and a 67-year-old woman (Patient-2) with medical history and hospitalization courses summarized in Table 1 were diagnosed with COVID-19 via a positive nasopharyngeal swab for SARS-CoV-2 nucleic acid, both requiring mechanical ventilation due to acute hypoxic respiratory failure. Patient-1 received a single 400 mg intravenous dose of tocilizumab for suspicion of COVID-19-induced cytokine release syndrome. He was weaned off sedation and extubated on day 21. His blood pressure range was 86–189/52–122 mmHg and he had developed acute kidney injury with peak creatinine at 2.1 mg/dL during the course of his admission that resolved by his discharge. His post-extubation course was complicated by altered mentation, which improved slowly. Magnetic resonance imaging (MRI) and computerized tomography (CT) of the brain were done on day 26 and revealed findings compatible with PRES, detailed in (Fig. 1). The patient's blood pressure was then managed with an intravenous nicardipine infusion to < 140/90 mmHg for about 24 h before transitioning to an oral regimen. His mentation continued to slowly improve to his baseline, and he was discharged home on hospital day 33. Patient-2 was weaned off sedation on day 21, but her altered mentation remained the principal barrier to extubation. Her blood pressure range was 79–193/44–97 mmHg, and she had developed acute kidney injury requiring hemodialysis during her hospital course that resolved by the time of discharge. On day 25, MRI brain was done and revealed findings compatible with PRES, detailed in (Fig. 2). The patient's blood pressure was managed in the same manner as Patient-1. She was extubated on day 30 and discharged on day 47 to a sub-acute rehabilitation facility having nearly returned to her baseline mentation but requiring physical therapy. Neither patients reported visual disturbances but altered mentation would have beclouded this complaint.

The pathogenesis of PRES remains controversial [1]. Both our patients had prolonged intubation periods with fluctuating blood pressures, which potentially impaired their autoregulatory threshold of cerebral circulation. Their overall mean arterial pressures, however, were in the mild hypertension range and Patient-1's altered consciousness began to improve prior to the initiation of antihypertensives. Endothelial dysfunction in the setting of COVID-19 could have
SARS-CoV-2 binds directly to the angiotensin-converting enzyme 2 (ACE2) receptors. This binding may cause an increase in blood pressure along with weakening of the endothelial layer leading to a weakened blood-brain barrier, which may result in dysfunction of the brain’s autoregulation of cerebral circulation [2,3]. Whether endothelial dysfunction follows a direct toxic insult or is part of an endogenous pathway is unclear. Further supporting an endothelial dysfunction process, one of our patients received tocilizumab, which is known to have endothelial modulation properties and has been previously reported in association with PRES. [4]

We have had on average 1.4 cases of PRES per year over the past 5 years (January 2015 to December 2019) in our hospital. The two patients described here were diagnosed in the same week, 3 weeks after the plateau of COVID-19 cases in our hospital. While it is plausible that the occurrence of PRES in these two patients is only incidentally related to their SARS-CoV-2 infection, the weekly average cases of PRES since the plateau of the cumulative curve of COVID-19 cases in our hospital is significantly higher than over the past 5 years (0.66 vs 0.03; p < .005, Mann-Whitney rank sum test).

A case of COVID-19 associated with a PRES-like syndrome was

Table 1
Patient characteristics and clinical course.

| Variable                                | Patient-1                  | Patient-2                  |
|------------------------------------------|----------------------------|----------------------------|
| Age (years), sex                         | 58, male                   | 67, female                 |
| Medical History                          | Hyperlipidemia             | Hypertension               |
|                                         |                            | Obesity                    |
|                                         |                            | Type 2 diabetes mellitus   |
| Risk Factors for PRES                   | Acute hypertension spells  | Acute Kidney Injury requiring |
|                                         | Tocilizumab                | hemodialysis               |
|                                         | Sepsis                     | Sepsis                     |
| Onset of PRES from Hospitalization (days)| 26                         | 25                         |
| Symptoms of PRES                         | Altered level of consciousness | Altered level of consciousness |
| Symptoms of COVID-19                     | Fever, dry cough, malaise  | Shortness of breath, fever, myalgia, vomiting, diarrhea |
| Mean Arterial Pressure (MAP) Average     | 106 mmHg over 26 days      | 90 mmHg over 25 days       |
| Blood Pressure Range                     | 86–139/52–122 over 26 days| 79–193/44–97 over 25 days  |
| Therapeutic Medication Administered      | Tocilizumab                | Hydroxychloroquine         |
|                                         | Azithromycin               | Ceftriaxone                |
|                                         | Ceftazidime                |                            |
|                                         | Vancomycin                 |                            |
|                                         | Metronidazole              |                            |
| Sedating Medication Administered         | Midazolam                  | Midazolam                  |
|                                         | Lorazepam                  | Lorazepam                  |
|                                         | Hydromorphone              | Hydromorphone              |
|                                         | Propofol                   | Propofol                   |
|                                         | Dexmedetomidine            |                            |
| Hospital Problem List                    | Acute kidney injury not requiring hemodialysis | Acute kidney injury requiring hemodialysis |
|                                         | Acute Hypoxic Respiratory Failure | Acute Hypoxic Respiratory Failure |
|                                         | Acute Respiratory Distress Syndrome | Acute Respiratory Distress Syndrome |
|                                         | Transaminitis              | Fungemia with Candida Dublaniensis |
|                                         |                            | Critical Care Myopathy     |
| WBC Nadir (per mm3)                      | 3.59                       | 6.42                       |
| Platelet Nadir (per mm3)                 | 199                        | 277                        |
| PT (sec)                                 | Peak: 12.7                 | Peak: 1.4                  |
|                                         | Nadir: 12.6                | Nadir: 1.2                 |
| aPTT (sec)                               | 36.8                       | Peak: 81.3                 |
|                                         | Nadir: 41.2                | Nadir: 41.2                |
| Fibrinogen (mg/dL)                       | Peak: 917                  | Peak: 818                  |
|                                         | Nadir: 351                 | Nadir: 692                 |
| Ferritin (ng/mL)                         | Peak: 972                  | Peak: 316                  |
|                                         | Nadir: 463                 | Nadir: 227                 |
| D-Dimer (ng/mL)                          | Peak: 1343                 | Peak: 2946                 |
|                                         | Nadir: 322                 | Nadir: 419                 |
recently described in this journal[6]. That patient also had severe SARS-CoV-2 infection requiring mechanical ventilation. While a definitive etiology was likewise not clear in that case, the patient was noted to have elevated blood pressure around the time of the PRES diagnosis. Our observations add further evidence to this possible important association.

This report describes a case series of two patients with SARS-CoV-2 infection associated with PRES, providing further evidence of the diverse neurological complications potentially associated with COVID-19. We observed PRES in both patients with relatively moderate blood pressure fluctuations, perhaps suggesting that manifestations of hypertensive encephalopathy, such as PRES, may occur at lower blood pressure thresholds in patients with Covid-19, possibly due to cerebral endothelial dysfunction induced by SARS-CoV-2. This observation argues for tight blood pressure control in COVID-19 patients as they may be at more risk for sequelae of hypertensive encephalopathy. Our report also suggests the potential for hypertensive encephalopathy, even without PRES, to be one of the factors contributing to the prolonged ventilator times previously described in severe SARS-CoV-2 infection [5] adding another reason to consider tight blood pressure control in ventilated COVID-19 patients.

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Fig. 1. Patient 1. (A, B, C) Axial T2 FLAIR showing hyperintensity (arrows) involving the subcortical white matter of both occipital lobes and both posterior temporal lobes with effacement of the adjacent sulci, compatible with PRES. (D, E) Axial susceptibility weighted imaging (SWI) and (F) CT head showing characteristic convexal subarachnoid hemorrhage (arrows) often seen with PRES. Of note, diffusion weighted imaging (DWI) and T1 post-contrast imaging were unremarkable.
Declaration of Competing Interest

None.

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