Hyponatremia is frequently associated with atypical pneumonia. One of the underlying mechanisms is inappropriate antidiuretic hormone (ADH) secretion (4). We report the first case series of coronavirus disease (COVID-19)-associated syndrome of inappropriate antidiuretic hormone secretion (SIADH). Additionally, we review pertinent literature and discuss the potential mechanism of this phenomenon.

Case 1 is a 58-yr-old man known to have well-controlled hypertension, asthma, and dyslipidemia. He presented with fever, cough, and sore throat. His sodium level was 116 mmol/L (135–145 mmol/L). The second case is a 20-yr-old man with no comorbidities; he presented with fever, cough, nausea, vomiting, lethargy, and disorientation. His sodium level was 112 mmol/L. Case 3 describes a 47-yr-old man with no comorbidities presenting with abdominal pain, fever, and a sodium level of 117 mmol/L.

The common features across the three cases were fever, evidence of pneumonia (abnormal chest X-ray depicting bilateral infiltrates), and severe hyponatremia. The workup for hyponatremia confirmed SIADH in all three cases (Table 1). The diagnosis was based on euolemic hyponatremia (<135 mmol/L) with concurrent low serum and high urine osmolality (< 280 and >100 osmol/kgH2O, respectively) and high urine sodium (>40 mmol/L) (6, 15). No underlying medication or medical conditions commonly associated with SIADH were identified. The second case was symptomatic; hence, required initial management with hypertonic saline followed by fluid restriction. The other two cases improved with fluid limitation alone. Nasopharyngeal RT-PCR confirmed COVID-19. All three cases were managed in a designated COVID-19 facility in Qatar and had a favorable outcome with the resolution of hyponatremia.

Pulmonary involvement in the form of pneumonia is prevalent among COVID-19-infected individuals as depicted by our cases, and the emerging literature (3). The mechanism of SIADH in pneumonia is not well established; however, animal models determined the role of low intravascular fluid volume and low extracellular fluid osmolality (12, 16). In the setting of intravascular volume depletion, baroreceptors in the carotid sinus, carotid body, and aorta activate the renin-angiotensin system. This, in turn, triggers a baroreceptor-mediated, nonosmotic ADH secretion (1, 17). In the case of decreased intravascular osmolality, osmoreceptors activate and increase the ADH secretion (2).

Emotional, physical, or psychological stresses and pain associated with infections (such as COVID-19) stimulate the hypothalamohypophyseal axis, leading to ADH release. Alternatively, stress activates the cortical neurons, which stimulate the hypothalamus to secrete ADH (9). Additionally, pneumonia-induced lung injury can result in a ventilation-perfusion mismatch. This mismatch results in compensatory hypoxic pulmonary vasoconstriction, leading to an inadequate filling of the left atrium. Consequent on this, a decreased left atrial stretch and increased ADH secretion occur (5, 10).

Marked elevation of inflammatory cytokines is described in COVID-19, leading in certain instances to cytokine storm (8, 11, 14). This increase in cytokines can result in SIADH via two mechanisms. First, inflammatory cytokines, such as IL-6, can directly stimulate the nonosmotic release of ADH (13). Second, these cytokines can injure the lung tissue and alveolar cells, which can induce SIADH via the hypoxic pulmonary vasoconstriction pathway, as previously described (7) (Fig. 1).

This discussion invites a study to explore the association between ADH and inflammatory cytokine levels, measured in COVID-19 patients and controls (with and without pulmonary involvement). This will advance our knowledge about the mechanism of SIADH.

There are additional clinical implications based on the aforementioned discussion. In the time of the pandemic, when medical resources are limited, any additional clue leading to the diagnosis of COVID-19 may prove valuable. Based on this limited evidence, we suggest triaging patients presenting during this pandemic with hyponatremia and fever as a high probability for COVID-19; these patients should be prioritized for testing and isolation whenever possible. A large cross-sectional study exploring the prevalence of hyponatremia and SIADH in this cohort of patients is needed to support our findings and conclusion.

Statement of ethics. Consent was obtained from all three subjects in this study. Approval from a select committee for COVID-19-related publications and ethics in Qatar was obtained.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
Z.Y. conceived and designed research; Z.Y. drafted manuscript; S.D.A.-S. and M.F.M. edited and revised manuscript; H.A.-S. approved final version of manuscript.

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Table 1. Patient summary

| Characteristics | Patient 1 | Patient 2 | Patient 3 |
|-----------------|-----------|-----------|-----------|
| Demography      |           |           |           |
| Age             | 58        | Male      | 20        | Male      | 47        |
| Sex             | Male      | Male      | Male      | Male      | Indian    |
| Nationality     | Sri Lankan| Nepalese  | Indian    |           |           |
| Initial findings|           |           |           |           |           |
| Past medical history | Hypertension, dyslipidemia, asthma | Not significant | 7 | 3 |
| Duration of symptoms, days | 5 | Fever, cough, sore throat | Fever, cough, nausea, vomiting, lethargy | Abdominal pain, fever |
| Symptoms        |           |           |           |           |           |
| GCS             | 15/15     | Disoriented| 12/15     | Oriented  | 15/15     |
| Orientation     |           |           |           |           |           |
| Symptoms of hyponatremia | Lethargy | Lethargy, disorientation, nausea, agitation | None |           |
| Imaging features (X-ray chest) | Bilateral perihilar infiltrates | Increased bronchovascular markings initially, organized infiltrates at 72 h | Bilateral perihilar infiltrates |           |
| Admission to ICU | No | Yes – 24 h | Positive | Positive | No |
| Laboratory findings | | | | | |
| COVID-19 RT-PCR (nasopharyngeal swab) | Positive | Positive | Positive |
| White cells, per mm$^3$ | 4.6 | 7.2 | 4.2 |
| Neutrophils, per mm$^3$ | 2.5 | 5.2 | 3.2 |
| Lymphocytes, per mm$^3$ | 77 | 76 | 61 |
| Eosinophils, per mm$^3$ | 4.0 | 0.8 | 0.7 |
| Monocytes, per mm$^3$ | 0.0 | 0.0 | 0.0 |
| Platelet count, per mm$^3$ | 1.7 | 1.2 | 0.3 |
| Hemoglobin, g/L | 227 | 222 | 110 |
| CRP, mg/L | 15 | 13.5 | 11 |
| Total protein, g/L | 42 | 34 | 24 |
| Alaamn, g/L | 13 | 27 | 34 |
| Glucose, mmol/L | 31 | 31 | 39 |
| Urea, mmol/L | 5.7 | 15.5 | 7.8 |
| Creatinine, μmol/L | 77 | 78 | 81 |
| EGFR, ml·min$^{-1}$·1.73 m$^2$ | 74 | 57 | 65 |
| Serum ferritin, μg/L | 97 | 141 | 110 |
| Potassium, mmol/L | 700 | 379 | 900 |
| Chloride, mmol/L | 3.7 | 3.8 | 3.8 |
| Bicarbonate, mmol/L | 77 | 78 | 81 |
| Corrected calcium, mmol/L | 24 | 22 | 21 |
| Lactate, mmol/L | 2.46 | 2.38 | 2.17 |
| Sodium on day 1, mmol/L | 1.6 | 2.4 | 1.6 |
| Volume status | Euvolemic | Euvolemic | Euvolemic |
| Serum osmolality, osmol/kg H$_2$O | 243 | 253 | 278 |
| Urine osmolality, osmol/kg H$_2$O | 316 | 509 | 769 |
| Urine spot sodium, mmol/L | 145 | 145 | 71 |
| Diagnosis for hyponatremia | SIADH | SIADH | SIADH |
| Total hypotonic saline received, mL | 0 | 300 ml (3 boluses of 100ml each) | 0 |
| Fluid restriction/24 h, mL | 1,200 | 750 | 1,000 |
| Serum sodium level at 24 h, mmol/L | 121 | 120 | 120 |
| Serum sodium level at 48 h, mmol/L | 122 | 126 | 124 |
| Serum sodium level at 72 h, mmol/L | 128 | 129 | 128 |
| AM serum cortisol level, nmol/L | 237 | 523 | Not available |
| TSH level, mIU/L | 2.22 | 1.0 | 2.3 |

COVID-19, coronavirus disease; CRP, C-reactive protein; EGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; ICU, intensive care unit; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TSH, thyroid-stimulating hormone.
Fig. 1. Proposed mechanism for syndrome of inappropriate antidiuretic hormone secretion (SIADH) in coronavirus disease (COVID-19) infection. ADH, antidiuretic hormone secretion; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
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