BRIEF COMMUNICATION

Thrombotic and Hemorrhagic Neurological Complications in Critically Ill COVID-19 Patients

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We report a series of three cases admitted to the intensive care unit (ICU) of Paulo Niemeyer State Brain Institute due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), all developing acute respiratory distress syndrome (ARDS) and acute renal failure, and later in the course of the disease, catastrophic intracerebral hemorrhages.

Clinical characteristics of the patients are described in Table 1.

Patient 1

A 56-year-old woman presented with fever and flu syndrome on March 29th, prompting her to seek medical attention in the emergency department. After 2 days, she developed dyspnea and oxygen desaturation with need of O₂ support by face mask. On April 5th, her symptoms worsened and she was intubated, started on empirical therapy with ceftriaxone, oseltamivir, and azithromycin. A chest computed tomography (CT) scan showed diffuse infiltrates with ground-glass pattern. Severe SARS-CoV-2 was diagnosed through reverse transcription polymerase chain reaction (RT-PCR) of her tracheal aspirate.

She had no prior knowledge of other medical conditions.

She was transferred to our ICU on April 7th and was admitted in septic shock and ARDS, requiring high levels of FiO₂ and vasoactive drug support (norepinephrine).

Her initial PaO₂/FiO₂ ratio was 149, and her chest CT scan showed diffuse ground-glass opacities in both lungs. Antibiotic was changed to piperacillin + tazobactam and hydroxychloroquine was started. Renal function progressively worsened (urea of 254 mg/L), and dialysis was started the following day.

During the first 3 days, she stabilized with a low dose of norepinephrine and daily prolonged hemodialysis. She remained under continuous analgosedation (midazolam and fentanyl) and neuromuscular blockade (cisatracurium) with a PaO₂/FiO₂ ratio of 150–200. Her initial D-dimer was 59,960 mcg/L.

On the fourth day, her pulmonary function worsened and she underwent prone positioning, with limited improvement in gas exchange. Her D-dimer was 53,460 mcg/L.

On the following days, she was not able to undergo prone position or dialysis due to hemodynamic instability. Her PaO₂/FiO₂ ratio was still 150–200.

Fibrinogen level was 575 mg/dl, and D-dimer levels remained elevated throughout her ICU stay with subsequent values of 42,132 mcg/L and 31,610 mcg/L. Prothrombin time and partial thromboplastin time, which were assessed every day, were within normal range and platelet counts progressively reduced after the fifth day in the ICU (114, 99, 74 and finally 59 thousand per milliliter).

She was kept on continuous sedation, analgesia and neuromuscular blockade due to the severity of lung injury, with preserved brainstem reflexes on neurological examination. On April 13th, 16 days after initial symptoms and 9 days after mechanical ventilation was started, she acutely presented with mydriasis, without response to light. A CT scan of the brain was promptly obtained, which showed a large cerebellar hematoma and spontaneous hyperintensity of the right transverse sign, suggestive of acute cerebellar venous thrombosis with secondary hemorrhage (Fig. 1a).

She died on April 14th.

Patient 2

Male patient, in his 40 s was admitted to an emergency service due to dyspnea with a diagnosis of pneumonia on

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Table 1 Clinical characteristics of the three patients

	Patient 1	Patient 2	Patient 3
Sex	Female	Male	Female
Weight (kg)	70	84	90
Medical history	None	Obesity	Obesity, depression
Anticoagulation and medication	Prophylaxis only (enoxaparin)	Prophylaxis only (enoxaparin)	Yes (unfractionated heparin)
COVID-19 onset symptoms	Fever and flu syndrome	Dyspnea	Dyspnea
Time between onset and intubation (days)	7	2	2
Time between onset and dialysis (days)	10	6	12
Time between onset and cerebral hemorrhage (days)	15	16	15
Outcome	Death	Death	Death

Fig. 1 Brain CT scans of the three patients: **a** large cerebellar hematoma and spontaneous hyperdensity of the right sigmoid sign and internal jugular vein (patient 1). **b** Multiple sites of intracerebral hemorrhage (patient 2). **c** Multiple sites of intracerebral hemorrhage (patient 3). **d** Intracerebral hemorrhage and diffuse cerebral edema (patient 2)

April 4th. He was treated with oxygen support via face mask and ceftriaxone, azithromycin, and hydroxychloroquine. Due to worsening symptoms and oxygen need, he was intubated and mechanically ventilated on April 6th.

On April 7th, he was transferred to the ICU and tested for COVID-19, which was confirmed through RT-PCR of the tracheal aspirate.

No known prior medical conditions other than obesity.

Initially, elevated FiO₂ support was required but he was hemodynamically stable with no other organ dysfunction. PaO₂/FiO₂ was 196, and continuous analgesia (midazolam and fentanyl) and neuromuscular blockade (cisatracurium) were started. Due to worsening gas exchange, prone position was initiated with improved oxygenation and tidal volumes.

On the fourth ICU day, renal function deteriorated (urea of 149 mg/L and low urine output) and dialysis was started.

After two 18-hour daily sessions of prone positioning, PaO₂/FiO₂ ratio stabilized between 160 and 200. With improved lung function, cisatracurium was discontinued on day 7 and antibiotic therapy was concluded. Weaning off sedation and mechanical ventilation was initiated. D-dimer levels were 6746 mcg/L.

After 10 days in the ICU, he developed fever and piperacillin/tazobactam was started for suspected ventilation-associated pneumonia (VAP). With no signs of septic shock, he remained hemodynamically stable with normal arterial lactate and PaO₂/FiO₂ ratios above 200.

On April 19th, 16 days after initial symptoms and 13 days of ICU, he presented with mild bleeding through venous catheter insertion points. Platelet count, prothrombin time, and partial thromboplastin time, which were assessed daily, were unremarkable. Fibrinogen was 484.2 mg/dL. He was also neurologically stable, with preserved brainstem reflexes. The next day he acutely presented mydriasis and immediately underwent a brain CT scan, which revealed multiple sites of intracerebral hemorrhage (right frontal lobe, left thalamus, and left occipital lobe) and diffuse cerebral edema (Fig. 1b–d).

He died on the same day.

Patient 3

Female patient, in her earlier 60s, on April 14th, was admitted to an emergency facility due to dyspnea. On April 16th, she developed ARDS and was intubated and mechanically ventilated. Amoxicillin with clavulanate and hydroxychloroquine were initiated. The diagnosis of SARS-CoV-2 infection was confirmed in the outside hospital.

On April 23rd, she was transferred to our ICU. Due to deep vein thrombosis and pulmonary embolism diagnosed on the day of ICU admission, the patient was started on full anticoagulation with IV unfractionated heparin.

She developed septic shock, requiring high doses of norepinephrine. On her PT, the international normalized ratio (INR) varied between 1.6 and 2.15. Her platelet count, fibrinogen, and PTT (even with the use of IV heparin) were within normal values throughout the ICU stay. She also had dialysis started on the fourth day in

the ICU due to acute renal failure. She was kept on sedation and neuromuscular blockade due to worsening gas exchange. With these measures, her P/F ratio was maintained between 100 and 200.

On the seventh day in the ICU, she acutely presented anisocoric pupils without reaction to light and underwent a brain CT scan, which showed multiple sites of hemorrhage (right basal ganglia, left frontal, and left occipital lobes) and diffuse edema (Fig. 1c).

She died on the following day.

Coagulopathy has been considered a frequent characteristic of patients with COVID-19, with high rates of thrombotic phenomena. Abnormal coagulation was described in early reports of COVID-19 probably due to activation of multiple systemic inflammatory response pathways [1]. Even in patients with thromboembolic prophylaxis or full anticoagulation, up to 69% show clinical thrombotic episodes [2].

Evidence of brain hemorrhagic events becomes even more relevant, as protocols worldwide have recommended using isolated D-dimer levels to guide full anticoagulation therapy [3], with a recent multicentric cohort research suggesting even higher anticoagulation targets [4], since, despite the use of anticoagulation, these patients can develop severe thrombotic events, leading to worse outcomes. When considering the high incidence of acute renal failure (25–28%) and the use of low molecular weight heparin with no anti-factor Xa monitoring, clinical management of full anticoagulation becomes even more complicated [5].

We report one case of thrombotic cerebral disease with secondary hemorrhage and two cases of intracerebral hemorrhage—though we cannot rule out completely a chance of hemorrhagic transformation of ischemic stroke, since those patients did not undergo magnetic resonance image. Cerebral hemorrhagic complications in severe COVID-19 patients have been rarely described [6], and the association of these complications with the use of anticoagulation or with previous thrombotic events is still uncertain [3, 4].

Data available is insufficient to imply causality between COVID-19 and cerebral hemorrhagic complications. This case series highlight that brain hemorrhage can occur in this population, which was not described until recently [6]. Morassi et al. reported two cases of intracerebral hemorrhage, both in severe COVID-19 patients. These events were also bilateral and ultimately lead to death. Their series also had a markedly high incidence of acute renal failure, which are remarkably similar to our cases. These findings raise concerns regarding the management of patients with severe disease and organ failure. As anticoagulation therapy is being used in severe COVID-19 in many centers around the world [3, 4], the

evidence of hemorrhagic complications—spontaneous or not—should warn clinicians that full anticoagulation should be indicated with utmost care.

Better understanding of the complex balance between prothrombotic and hemorrhagic states in patients with severe COVID-19 is urgent in order to improve the management of these patients. Moreover, efficacy and safety of anticoagulation strategies should be evaluated in the context of randomized clinical trials to guarantee we are not causing additional harm to patients with a baseline high mortality risk.

Author Contributions

BG, CR, and PK wrote the paper, and it was approved for submission by all authors.

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Conflict of interest

The authors declare they have no conflict of interest.

Ethical Approval

The data acquisition from patients' files was approved by the Ethics Committee (CAAE 30650420.4.1001.0008).

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