CASE SERIES

Critically Ill Patients with Variable Heart Failure in Severe COVID-19 Disease: A Case Series

Joanne Michelle D. Gomez, M.D., Mary Potkonjak, M.D., Maria Isabel Camara Planek, M.D., Prutha Lavani, PharmD, Karolina Marinescu, M.D. and Tisha Suboc, M.D.

Rush University Medical Center, Chicago, Illinois, USA

ABSTRACT
COVID-19 disease, while primarily a respiratory disease, has proven itself a multi-system disorder with profound cardiovascular sequelae. In patients with SARS-CoV-2 infection, effective early diagnosis and management of concomitant cardiovascular manifestations of the disease are key to favorable outcomes. Here we present a case series of three patients with varied cardiovascular presentations of severe COVID-19 illness: cardiogenic shock from Takotsubo cardiomyopathy, arrhythmia in a patient with suspected hydroxychloroquine-associated cardiomyopathy, and right-sided heart failure with obstructive shock in the setting of massive pulmonary embolism. Through our experience, we aim to provide a better understanding of the unique spectrum of the cardiovascular effects of severe COVID-19 disease to guide management of the critically ill.

KEYWORDS: Severe COVID-19 Disease, Cardiovascular Disease, Heart Failure, Critical Care.

INTRODUCTION
While primarily known for its devastating respiratory sequelae, COVID-19 disease has also exhibited significant cardiovascular effects that have complicated the management of the most critically ill. Differentiating between respiratory or cardiac etiologies can be challenging as dyspnea is often the predominant presenting symptom. Furthermore, it is important to identify when cardiac and pulmonary effects coexist to guide the patient’s medical management. The incidence of left ventricular dysfunction, right ventricular dysfunction, and cardiogenic shock has not been well described in patients with COVID-19. One Chinese study reports new or worsening heart failure occurred in 23% of COVID-19 patients overall and 52% in patients who subsequently died from the disease. In addition, heart failure patients do not only have a higher predisposition to COVID-19 disease, but also have worse outcomes as seen in small observational studies published to date.1 In this paper, we present three cases of patients with severe COVID-19 disease requiring intensive care unit admission with various heart failure sequelae. We outline their disease presentation, diagnostic tests that led to diagnosis, and discuss the unique decision-making points made and chosen management strategies in the context of the current pandemic.

CASE SERIES
Case 1: Takotsubo Cardiomyopathy and Combined Septic and Cardiogenic Shock
A 50-year-old male with a past medical history of type 2 diabetes and hypertension presented to the Emergency Department with progressive shortness of breath for 2 days. On arrival, the patient was afebrile, hypotensive with blood pressure (BP) of 80/40 mm Hg, tachycardic with heart rate (HR) of 130-140 beats/minute, and tachypneic with respiratory rate (RR) at 40 breaths/minute. His O2 saturation of 70% on room air and respiratory distress led to urgent endotracheal intubation along with initiation of norepinephrine for vasopressor support given his hemodynamic instability. An arterial blood gas (ABG) was obtained and revealed metabolic acidosis: pH 7.334, CO2 40, O2 54, and HCO3 16. Initial laboratory findings were significant for elevated arterial lactate 2.5 mmol/L, serum creatinine 1.46 mg/dL, WBC 20 per uL, LDH 722

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u/L, ferritin 365 ng/mL, troponin 0.15 ng/mL, and B-type natriuretic peptide (BNP) 101 pg/mL. Electrocardiogram (ECG) was significant only for sinus tachycardia. Chest x-ray revealed scattered bilateral ground glass opacities, and a normal cardiome diastinal silhouette (Image 1).

The patient received antibiotic management with one dose of cefepime, as well as a three-day course of azithromycin 500 mg daily, and was transferred to the medical intensive care unit (ICU) for further management. Testing for SARS-CoV-2 via nasopharyngeal swab polymerase chain reaction test was positive.

On arrival to ICU, patient was placed on low tidal volume ventilation for the diagnosis of COVID-19 acute respiratory distress syndrome (ARDS) per the ARDSNet protocol. Patient subsequently had improvement in tachycardia to HR 98 beats/minute, but a few hours into the course had worsening hypotension that required up-titration of vasopressors up to norepinephrine 60 mcg/min, vasopressin 0.03 units/min, and epinephrine 5 mcg/min to sustain normal mean arterial pressures ≥ 65 mmHg. Subsequent laboratory testing showed troponin elevation which peaked at 0.3 ng/mL; inflammatory makers were also elevated (ferritin 446 ng/mL, C reactive protein 429 mg/L, LDH 807 u/L, CK 224 U/L) and hydroxychloroquine was started. Repeat ECG showed sinus tachycardia, new low voltage QRS in all leads, and nonspecific T wave abnormalities (Image 2).
Bedside echocardiogram showed a depressed left ventricular function with apical hypokinesis with a pattern suggestive of Takotsubo cardiomyopathy (Video 1). Dobutamine 5 mcg/kg/min was initiated, which allowed epinephrine 5 mcg/min to be weaned off and norepinephrine to be weaned from 60 to 25 mcg/kg/min. Dobutamine was later decreased to 2.5 mcg/kg/min, which allowed norepinephrine to be weaned off within a 6-hour time period. One day after bedside echocardiogram, a formal echocardiogram was performed that showed hyperdynamic left ventricular systolic function, ejection fraction (EF) 70-75%, with complete resolution of left ventricular dysfunction confirming the diagnosis of stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy (Video 2).

Additionally, there was new, marked, right ventricular dilation with apical hyperkinesis and vigorous left ventricular systolic function. The differential diagnosis included McConnell’s sign from pulmonary embolism or ARDS complicated by pulmonary hypertension causing right ventricular (RV) failure. The patient was started on empiric therapeutic anticoagulation with intravenous heparin. Computerized tomography (CT) pulmonary angiogram was not obtained due to the patient’s worsening acute kidney injury (creatinine peaked at 2.87 mg/dL) in the background of chronic kidney disease (baseline of 1.4 mg/dL) due to suspected cardiorenal syndrome. Lower extremity Doppler studies were unrevealing for lower extremity deep vein thrombosis. He was then transitioned to prophylactic subcutaneous low molecular weight heparin, as suspicion for pulmonary embolism was deemed lower compared to likelihood of ARDS as the cause of RV dilation in this patient. He was successfully extubated 19 days after admission, and had improvement of his mentation and renal function.

Case 2: Treatment of Severe COVID-19 in a Patient with suspected Hydroxychloroquine-Associated Cardiomyopathy

A 53-year-old female with a history of dilated cardiomyopathy, non-ischemic secondary to presumed hydroxychloroquine-associated cardiomyopathy, with left ventricular EF 30% and Grade 2 diastolic dysfunction, s/p cardiac resynchronization therapy-defibrillator, systemic lupus erythematosus, hypertension, hyperlipidemia, and morbid obesity (BMI 35 kg/m²) presented with fever, cough, and shortness of breath. During initial evaluation in the emergency department, she was febrile to 101.4°F, O₂ saturation was FiO₂ 82% on room air requiring oxygen supplementation with 2 L/min via nasal cannula to maintain normal oxygen saturation, but was otherwise hemodynamically stable. Laboratory examination was notable for elevated troponin 0.12 ng/mL, and ECG showed an atrial-sensed, biventricular-paced rhythm (Image 3), and chest CT angiogram showed bilateral ground-glass opacities with a small pericardial effusion (Image 4).
SARS-CoV-2 nasopharyngeal testing was sent, while ceftriaxone and azithromycin (later changed to doxycycline) were started empirically for treatment of presumed community-acquired pneumonia. On Hospital Day 3, SARS-CoV-2 testing returned positive and patient had a confirmed diagnosis of COVID-19 pneumonia. She developed worsening hypoxia on Hospital Day 5 and required escalation of care to the intensive care unit where she underwent endotracheal intubation and proning for severe ARDS. She was hypotensive from septic shock and treated with norepinephrine to maintain MAP > 65. A multi-disciplinary discussion was held prior to initiation of a short course of hydroxychloroquine therapy given her history of presumed hydroxychloroquine-associated cardiomyopathy. However, in the absence of a prior endomyocardial biopsy for definitive diagnosis of hydroxychloroquine-associated cardiomyopathy, and in the setting of patient’s acute decompensation and poor prognosis from COVID-19, it was deemed that the potential benefit of short course of hydroxychloroquine outweighed anticipated risks, based on available data at that time; thus, hydroxychloroquine was administered on Hospital Days 5-9.

Norepinephrine was weaned within 24 hours of initiation. However, patient developed acute oliguric renal failure, which raised concern for development of low cardiac output state and decompensated heart failure. Dobutamine 5 mcg/kg/min was subsequently started on Hospital Day 7 with improvement in hemodynamics. On Day 9, continuous veno-venous hemofiltration (CVVH) was initiated as a renal replacement strategy due to worsening kidney failure. After optimization of volume status, guided by central venous pressure monitoring, dobutamine was able to be weaned off by Hospital Day 10 after improvement of hemodynamics determined by central venous saturations. Her course was complicated by severe dysautonomia and opioid and benzodiazepine withdrawal with marked lability in her blood pressure and heart rate. She developed a wide-complex tachycardia on Hospital Day 15 (Image 5) during her course, which required short-term intravenous amiodarone.

Patient’s QT interval was prolonged during this time to 525 ms from a baseline of 464 ms earlier in the admission. The Electrophysiology service was consulted, and rhythm was deemed most consistent with sinus tachycardia with aberrancy; anti-arrhythmics were subsequently discontinued. Subsequent transthoracic echocardiograms were performed showing stable left ventricular ejection fraction of 25-35% with moderate pericardial effusion that decreased in size with serial sessions of renal replacement therapy with ultrafiltration (Video 3). She underwent tracheostomy on Hospital Day 25. Prior to discharge, she showed signs of renal recovery, such that RRT was discontinued, and EF improved to 35%. She was discharged to a long-term acute care hospital after a 40-day hospitalization on GDMT with carvedilol 50 mg twice daily, sacubitril-valsartan 97/103 mg BID, hydralazine 100 mg three times daily, isosorbide dinitrate 40 mg three times daily, and spironolactone 12.5 mg daily.
Case 3: Combined Septic and Obstructive Shock from COVID-19-Associated Massive Pulmonary Embolism

A 47-year-old male, with a past medical history of obesity (BMI 36 kg/m²), presented with non-productive cough, chills, and left-sided chest pain. On presentation, he was febrile to 101.5°F, BP 166/71 mmHg, HR 82 bpm, and saturating FiO₂ 98% on room air. Shortly after presentation, he was noted to be hypoxic to as low as FiO₂ 90% on room air, and was placed on 2 L of O₂ supplementation via nasal cannula. Chest x-ray showed bibasilar opacities concerning for infection (Image 6).

Empiric antibiotics with ceftriaxone and azithromycin (changed to doxycycline after 1 dose) were started for presumed pneumonia and nasopharyngeal SARS-CoV-2 testing was sent. Patient was started on enoxaparin 40 mg SQ daily for venous thromboembolism prophylaxis. On Hospital Day 2, SARS-CoV-2 testing returned positive, making the diagnosis of COVID-19 pneumonia. Ceftriaxone and azithromycin were discontinued after two doses, and he was treated with a five-day course of hydroxychloroquine. He had worsening degree of hypoxia on Day 3, necessitating transfer to the intensive care unit, endotracheal intubation, and mechanical ventilation. He was on minimal support from the ventilator until Hospital Day 6 when his PEEP and FiO₂ requirements sharply increased (P/F ratio 115). Patient was placed on the institution’s proning protocol for ARDS to improve oxygenation.

On Hospital Days 7-8, he was noted to have a rapid decline in clinical status associated with hypotension requiring initiation of norepinephrine and vasopressin. Subsequent laboratory findings showed evidence of severe impairment in tissue perfusion with lactic acidosis (pH 7.129, pCO₂ 59, pO₂ 217, lactate 9.9 mmol/L) for which renal replacement therapy was started. Patient also had an uptrending serum troponin that had peaked to 4.66 ng/mL, and an elevated d-dimer above the institution’s assay range >27.5 mg/L. A transthoracic echocardiogram showed a small, vigorous LV with a marked RV dilatation and hypokinesis, with estimated central venous pressure of 20-25 mmHg (Video 4). Bilateral lower extremity Doppler showed acute bilateral deep venous thrombosis. There was a high suspicion for acute pulmonary embolism, however, a chest CT was not able to be accomplished due to his profound hemodynamic instability, and was instead treated empirically with systemic anticoagulation with intravenous heparin. Hypotension persisted despite inotropic support with dobutamine 5 mcg/kg/min and fluid removal with renal replacement therapy. He had increasing vasopressor needs and later developed multi-system organ failure. His marked RV dilatation and hypokinesis was concerning for obstructive shock secondary to a massive pulmonary embolism. He was treated with IV tissue-type plasminogen activator (t-PA) 50 mg, a reduced dose due to perceived bleeding risk from thrombocytopenia. He had subsequent improvement in his oxygen and vasopressor requirements after thrombolysis. He was transitioned to argatroban drip briefly due to concern for heparin-induced thrombocytopenia, and was transitioned back to intravenous heparin at 12 units/kg/hr with an aPTT goal of 50-75 seconds after this was ruled out. By Hospital Day 9, patient was weaned off all vasopressors, but remained on dobutamine. On Hospital Day 10, he had another decompensation with worsening hypotension and hypoxemia. Serial troponin values were uptrending and peaked at 14.06 ng/mL. Repeat transthoracic echocardiogram showed persistent RV dilatation with reduced systolic function consistent with persistent right ventricular failure. Due to high suspicion for significant residual clot burden, chest CT angiography was pursued which revealed a large, saddle-shaped pulmonary embolism with multiple filling defects in the bilateral segmental pulmonary arteries (Image 7).

After multidisciplinary discussion with Interventional Radiology, decision was made to treat the patient with a second round of intravenous t-PA at full dose of 100 mg, administered as a 10 mg IV bolus followed by 90 mg infused over 2 hours. Chest CT angiography performed the following day showed improvement in clot burden (Image 8).
**DISCUSSION**

The first case highlights the development of Takotsubo cardiomyopathy related to COVID-19 infection, a disease association and management not well described in the current literature in light of the ongoing pandemic. Overall, supportive care remains the cornerstone of Takotsubo cardiomyopathy management. A recent systematic review of the association between Takotsubo cardiomyopathy and sepsis found that once initiation of sepsis management started, 92.3% had a favorable outcome. For our patient, the prompt initiation of inotropic support with dobutamine as well as optimization of hypoxemic respiratory failure led to rapid improvement in hemodynamics through improvement in biventricular contractility and treatment of right-sided heart failure from cor pulmonale. Had our patient not improved with these measures, invasive hemodynamic monitoring with the placement of a pulmonary artery catheter would have been indicated and could be placed bedside to limit staff exposure. Additionally, if the patient had refractory shock, a trial of inhaled pulmonary vasodilators and evaluation for mechanical biventricular support candidacy would have been warranted.

Troponin elevation is common in hospitalized COVID-19 patients and has been associated with a higher risk of in hospital mortality; however, the etiology of myocardial injury and manifestation of heart failure is not well elucidated. In this case, the troponin elevation was secondary to type 2 myocardial infarction from multiple factors including hypotension and systemic inflammatory toxicity, leading to Takotsubo cardiomyopathy. The hypercoagulable state associated with COVID-19 patients has been well documented. As such, there is a high suspicion for evaluation of thromboembolism, particularly pulmonary embolism, in setting of RV dysfunction. While commonly seen, the etiology of the hypercoagulable state is unclear. Thromboinflammation, the interaction between thrombosis and inflammation, is thought to contribute to clot formation in severe COVID-19. In our patient, the presence of RV dysfunction and McConnell’s sign on echocardiogram prompted empiric treatment of pulmonary embolism with therapeutic systemic anticoagulation with IV heparin. However, the clinical improvement that followed the optimization of respiratory status and hemodynamics with dobutamine suggests that these findings were more likely from
Takotsubo cardiomyopathy and hypoxic respiratory failure secondary to ARDS from COVID-19, rather than acute pulmonary embolism. The management strategy was then focused on supportive care for the management of COVID-associated ARDS. While our patient was successfully weaned off the ventilator and vasopressor support, the presence of McConnell’s sign that sign of ARDS may have a prognostic impact. In a recent study, a strong trend, albeit not achieving statistical significance, was found towards increased hospital mortality for patients with McConnell’s sign that were not associated with pulmonary embolism. Thus, aggressive treatment of hypoxic respiratory failure, which in this case was the etiology of right ventricular dysfunction, was the center of the management approach.

In the second case, a 53-year-old female with underlying non-ischemic cardiomyopathy, suspected to be secondary to hydroxychloroquine, was diagnosed with SARS-CoV-2 infection and developed hypoxic respiratory failure and cardiogenic shock with acute renal failure requiring inotropic support and renal replacement therapy. This is a unique case given the patient’s presumptive diagnosis of hydroxychloroquine-induced cardiomyopathy. It is a uncommon side effect that has been described in several case reports. Chloroquine-induced cardiomyopathy, has been described more frequently. The classic clinical presentation is that of new arrhythmia, non-ischemic cardiomyopathy, occasionally with concentric left ventricular hypertrophy or restrictive pattern, and histologic findings of lysosomal curvilinear bodies on electron microscopy. At the time of the patient’s diagnosis six years prior, a left heart catheterization showed non-obstructive coronary artery disease, and a cardiac magnetic resonance imaging study that showed dilated cardiomyopathy without late gadolinium enhancement to suggest inflammation. Her diagnosis was not confirmed with an endomyocardial biopsy; however, given her dilated non-ischemic cardiomyopathy and long-term use of hydroxychloroquine for more than 8 years for systemic lupus erythematosus treatment, her previous physician was concerned for hydroxychloroquine induced cardiomyopathy for which reason it was discontinued. The possibility of hydroxychloroquine-induced cardiomyopathy complicated the treatment of SARS-CoV-2 in this patient. The risk of administering hydroxychloroquine was evident; while the potential benefit was unclear. The evidence supporting the use of hydroxychloroquine in treating SARS-CoV-2 is limited. Early in vitro studies showed reductions in viral loads with use, although clinical trials have not demonstrated benefit for patients across any severity of disease. This was an important clinical decision to make for the patient given a propensity for QT prolongation and subsequent malignant arrhythmias and potential worsening cardiomyopathy with the contemplated initiation of the drug. The patient’s clinical course was complicated by wide-complex tachycardia in the setting of QT prolongation. Wang et al. described the clinical characteristics of 138 patients infected with SARS-CoV-2 pneumonia. While the subtype of arrhythmia remained unspecified, in their experience, 16.7% of patients were noted to develop arrhythmias. The risk of developing a ventricular arrhythmia in SARS-CoV-2 patients is largely understood through the risk of developing prolonged QT and subsequent torsade de pointes (TdP). In this patient, several QT prolonging agents were administered throughout the course of her admission including hydroxychloroquine, azithromycin, and methadone. While in this case, her wide-complex tachycardia was ultimately determined not to be a ventricular in origin, this case exemplifies the need for close arrhythmia monitoring in these highest risk patients.

In the third case, Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in critically ill COVID-19 patients despite prophylactic anticoagulation. In this case, a previously healthy 47-year-old male developed severe ARDS secondary to SARS-CoV-2 pneumonia and septic shock. His course was complicated by obstructive shock and right ventricular failure in the setting of a massive pulmonary embolism. The presumptive diagnosis was made on the basis of right ventricular failure, markedly elevated d-dimer, increased oxygen requirements, and acute bilateral lower extremity deep venous thrombosis. A definitive diagnosis was later made with chest CT angiography showing a large saddle pulmonary embolism; intravenous thrombolysis with full dose t-PA offered improvement in hemodynamics. D-dimer elevations have been seen in many patients with SARS-CoV-2 infection and is associated with a higher disease severity. However, the significance of an elevated d-dimer, incidence of thrombotic complications with COVID-19 disease along with the level of d-dimer elevation associated with these complications, have yet to be completely understood. There are now several case series that have documented rates of VTE and PE in critically ill patients at 20-43%. Interestingly, all of these patients received VTE prophylaxis and pulmonary embolism is the most common thrombotic event reported.

This case highlights a case of combined septic and obstructive shock due to massive pulmonary embolism and severe COVID-19 infection. COVID-19 disease predisposes patients to a myriad of thromboembolic complications, including pulmonary embolism, which can further cause respiratory and hemodynamic compromise. Prompt diagnosis and appropriate treatment, in this case with systemic thrombolysis, proved to facilitate recovery. A high index of suspicion for these complications is imperative for the critically ill COVID-19 patients.

CONCLUSION

These three cases demonstrate a variety of manifestations of cardiovascular dysfunction in patients with COVID-19, including Takotsubo cardiomyopathy, right-sided heart failure, arrhythmias, and venous thromboembolism. Additionally, we outline the critical decision-making process done in the course of management of a patient with pre-existing heart failure with reduced ejection fraction from presumed hydroxychloroquine-induced cardiomyopathy, particularly, the risks and benefits of short-course of hydroxychloroquine therapy. These cases show various cardiovascular disorders that complicate severe COVID-19 infection. As demonstrated here, septic shock can coexist with cardiogenic or obstructive shock. In these cases, the addition of inotropic agents, or therapy with anti-coagulation and thrombolysis, were deemed helpful, and should be considered in severely ill patients, if there is
considerable suspicion for concomitant decompensated heart failure or thromboembolism. Heart failure management in the setting of COVID-19 infection, either new-onset such as the case of stress cardiomyopathy, or pre-existing, has important clinical consequences and often portend worse outcomes. Close attention to the risk of concomitant cardiogenic shock, arrhythmias, or thromboembolism, and targeted therapy, in patients with severe COVID-19 infection is imperative.

Abbreviations: BP – blood pressure; HR – heart rate; RR – respiratory rate, ABG – arterial blood gas; ECG – electrocardiogram; ICU - intensive care unit; ARDS - acute respiratory distress syndrome; EF – ejection fraction; RV - right ventricular; CT - computerized tomography; BMI – body mass index; CVVH - continuous veno-venous hemofiltration; TdP - torsade de pointes; t-PA - tissue-type plasminogen activator; DVT - deep vein thrombosis; PE- pulmonary embolism; VTE - venous thromboembolism.

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COMPETING INTERESTS

The authors declare no competing interests with this case.

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REFERENCES

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30566-3/fulltext]
[https://journals.sagepub.com/doi/abs/10.1177/0003319716653886]
[https://jamanetwork.com/journals/jamacardiology/fullarticle/2763524]
[https://jamanetwork.com/journals/jamacardiology/fullarticle/2763845]
[https://pubmed.ncbi.nlm.nih.gov/19454550/]
[https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.120.317055]
[https://pubmed.ncbi.nlm.nih.gov/32364264/]

[10.1161/CIRCRESAHA.120.317055]
[https://pubmed.ncbi.nlm.nih.gov/30649217/]
[https://journal.chestnet.org/article/S0012-3692(17)32165-7/fulltext]
[https://pubmed.ncbi.nlm.nih.gov/24062937/]
[https://pubmed.ncbi.nlm.nih.gov/22550010/]
[https://pubmed.ncbi.nlm.nih.gov/5796692/]
[https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1]
Gomez JMD et al.  

Critically Ill Patients with Heart Failure & COVID-19 Disease


(https://pubmed.ncbi.nlm.nih.gov/32673060/)

(https://pubmed.ncbi.nlm.nih.gov/32205204/)

(https://pubmed.ncbi.nlm.nih.gov/32391667/)

(https://jamanetwork.com/journals/jama/fullarticle/2761044)

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7146714).