

## Study of the effect of high blood pressure on the kidney in children with COVID-19

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### Abstract

Hypertension is considered as a comorbid condition for the novel coronavirus 2019 (COVID-19). However, there are no reports of "Hypertension crisis" as a presentation or comorbidity of the COVID-19 infection in pediatric patients. In this retrospective observational study, we collected data from total six pediatric patients, diagnosed with confirmed COVID-19 positive who had presented with acute severe hypertension. The mean age of patients was 4.2 years. Four cases were with newly diagnosed nephrotic syndrome and two with chronic kidney disease who were on regular dialysis with no edema or sign of fluid overload, were enrolled. The lowest and highest systolic blood pressures at the time of admission were 160 mmHg and 200 mmHg, respectively. The diastolic blood pressures were between 100-155 mmHg. All patients treated with Labetalol infusion titrated to maximum dosage and continued for at least one week. Our reported children had resistant hypertension and their blood pressure had been controlled with four or five antihypertensive medications. It is crucial to consider the diagnosis of COVID-19 in a patient presenting with a hypertension crisis, even in the absence of classic signs of the virus. Thus from our study we strongly recommend the medical practitioners to consider the probability of COVID-19 infection in cases presenting to the hospital with acute severe hypertension.

**Keywords:** COVID-19; pediatric; hypertension; kidney disease; nephrotic syndrome.

### Introduction

The symptoms of COVID-19 viral disease, generally ranging from mild to moderate flu-like conditions to critical situation connected with acute respiratory distress syndrome and cytokine storm with decreased adaptive immune response, portending high morbidity and mortality. On 31 December 2019, a newly emerged pneumonia caused by a novel coronavirus, named SARS-CoV-2, was announced by China [1]. It spread out so rapidly until WHO announced coronavirus 2019 disease (COVID-19) as a pandemic condition on 11 March 2020. The firstly reported presentations of COVID-19 were like other viral respiratory infections, including high fever and dry cough. However, it might lead to acute respiratory distress syndrome and the mortality rate was quite high [2]. Since then, a wide spectrum of clinical manifestations has been described, ranging from the absence of any symptoms to fever, cough, dyspnea, diarrhea, ageusia, anosmia, and even cutaneous lesions [3, 4]. Various dermatologic problems also occurs specifically in Adult COVID-19 positive patients [5]. The Novel Coronavirus 2019 (COVID-19) has emerged and imposed an enormous burden on the world's health care resources and influenced millions of people all around the globe [6]. From the beginning of the pandemic, there was very limited information on the clinical features and the disease course in children [7]. However, as time went on, a large number of reports discussed the characteristics of the disease in adults as well as in children (Figure 1 and 2).

In a recent systematic review and meta-analysis, it was reported that pediatric patients with comorbidities are at a greater risk for more severe infection and mortality [6]. As one of the comorbid conditions, chronic kidney disease (CKD) is associated with a greater risk for disease severity [8]. Since patients with chronic kidney conditions, especially those on hemodialysis, require more hospital visits, they tend

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to be at greater risk for acquiring the virus through contacts with infected people. There are many studies that reported hypertension as a comorbid condition for COVID-19 infection [9]. However, to our knowledge, there are no reports of hypertension crisis as a comorbidity or a presentation sign of COVID-19 infection. Here, we have reported six pediatric patients with renal diseases presenting with hypertension crisis who had tested positive for COVID-19 or had evidence of the infection on Chest computed tomography (CT) imaging (Figure 3 and 4).

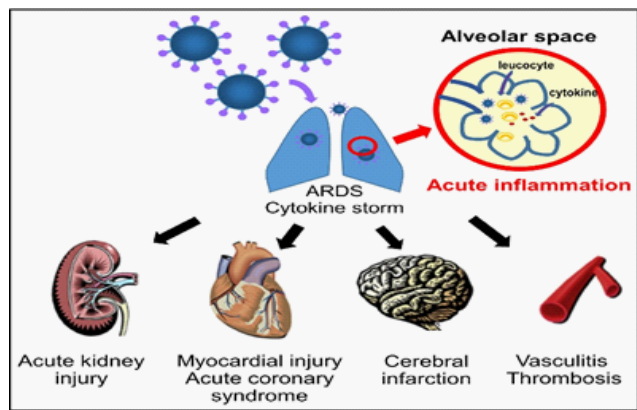


Figure 1: COVID-19 and hypertension-evidence and practical management.

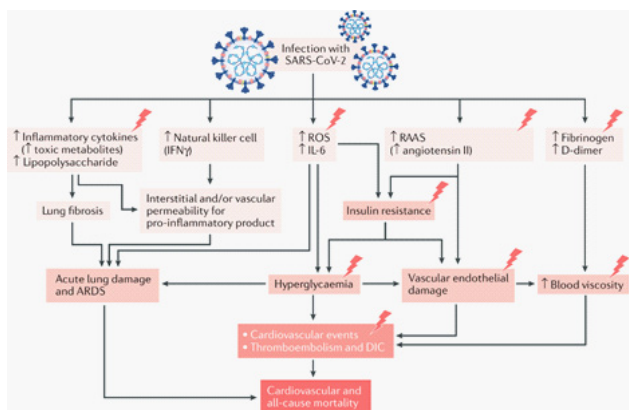


Figure 2: The impact of COVID-19.

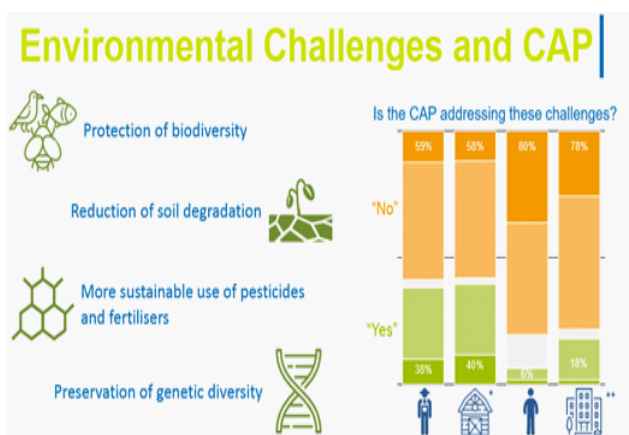


Figure 3: Effect of COVID-19 on Kidney Disease Incidence and Management.

Methods

The pediatric cases with COVID-19 infection and severe hypertension admitted to a pediatric hospital from March 2020 to February 2021 were enrolled in this retrospective observational study. Confirmed cases defined by one or more of the following: a positive SARS-CoV-2

real-time polymerase chain reaction (RT-PCR) test from nasopharyngeal swab specimens, serological examinations using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, and chest CT scan findings in favor of the infection. Hypertensive crisis eluci-

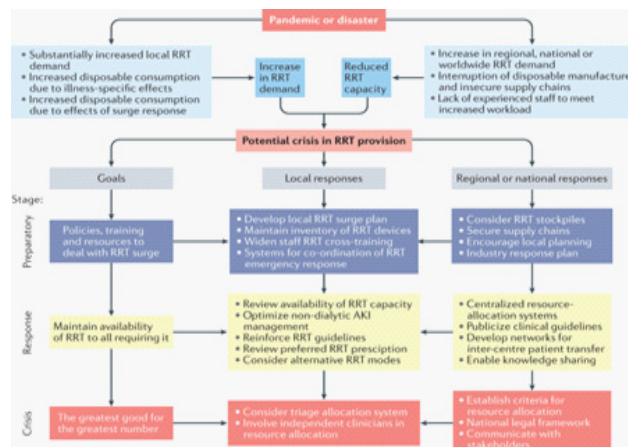


Figure 4: COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality.

dated by an acute rise of blood pressure more than stage 2 cut-off with the potential risk of end-organ damage [10].

Results

Six confirmed SARS-CoV-2 cases with hypertensive crisis, were enrolled. The mean age of patients was 4.1 (range: 1-12) years. The clinical characteristics and laboratory data of the patients are shown in Table 1. Four cases with newly diagnosed nephrotic syndrome who were on prednisolone (2 mg/kg/day), experienced a rapid rise in blood pressure. The remaining two cases were suffered from stage 5 chronic kidney disease (CKD-5) who were on regular hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) with no edema or signs of fluid overload. Patient 5 and 6 were identical twins.

The lowest and highest systolic blood pressure at the time of admission was 160 mmHg and 200 mmHg, respectively. The diastolic blood pressures were between 100-155 mmHg. Five out of six patients had close-contacts with COVID-19 cases. All of the patients had normal or controlled blood pressure prior to admission. Three patients presented with fever, two out of which experienced other COVID-19 symptoms, such as respiratory distress and diarrhea. The remaining three cases presented with acute severe hypertension without any fever, respiratory or gastrointestinal symptoms. All patients treated with labetalol infusion titrated to maximum dosage and continued for at least one week and due to poor control of blood pressure, additional oral antihypertensive medications were added. On follow-up (Table 2), one patient who was on CAPD died following loss of consciousness and multi-organ dysfunction. The patient on HD got complicated with pericardial effusion, pancreatitis, and chronic diarrhea. All nephrotic syndrome patients were resistant to steroid and therefore went on renal biopsy and calcineurin inhibitor was started for massive proteinuria. All reported cases had resistant hypertension, and their blood pressure controlled with four or five antihypertensive medications.

**Table 1:** Clinical and laboratory characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
<i>Clinical features</i>						
Age (y)	3	3	12	1	3	3
sex	Female	Male	Male	Female	Male	Male
Underlying condition	Carnitine palmitoyl-transferase 2 (CPT2) deficiency and End-stage renal disease	Nephrotic Syndrome	End-stage renal disease	Nephrotic Syndrome	Nephrotic Syndrome	Nephrotic Syndrome
Blood pressure on admission (mmHg)	160/110	170/100	200/155	160/115	165/110	160/100
History of close-contact with COVID-19 patients	+	+	-	+	+	+
	(three weeks prior to admission)	(two weeks prior to admission)		(one week prior to admission)	(two week prior to admission)	(two week prior to admission)
Presentation signs and symptoms	tonic-clonic Seizure	Generalized edema, Fever, Gross hematuria	Fever, Respiratory distress, Dyspnea	-	fever, Diarrhea	Tonic-clonic seizure
Imaging studies	Brain MRI: Normal Chest X-ray: Evidence of pulmonary edema	Chest CT scan: small subpleural ground-glass patches in favor of COVID-19	Chest CT scan : patchy peripheral consolidations in favor of COVID-19	Chest CT scan: mild ground-glass opacities in favor of COVID-19	Chest CT scan: Ground-glass opacifications in favor of COVID-19	Brain MRI: in favor of PRES syndrome Chest CT scan: Ground glass opacifications in favor of COVID-19
COVID-19 confirmatory tests	Positive Anti-SARS-CoV-2 IgM Ab	Positive Anti-SARS-CoV-2 IgM Ab, Positive Anti-SARS-CoV-2 IgG Ab	Positive RT-PCR for COVID-19	Positive Anti-SARS-CoV-2 IgM Ab	-	-
Extra-pulmonary Complications	Fluctuations in Consciousness, Multi-organ dysfunction	none	Pericardial effusion, Pancreatitis, chronic Diarrhea	Chronic kidney Disease	none	none
Outcome	Death	Discharge	Discharge	Discharge	Discharge	Discharge
<i>Laboratory tests</i>						
White blood cell count, $\times 10^9/L$	18.1	22.1	22.8	8.1	13.3	16.0
Lymphocyte, %	8	22	35	30	28	22
Hemoglobin, g/dl	9.1	8.3	9.0	7.5	13.6	12.3
Platelet, $\times 10^9/L$	254	898	90	509	641	671
C-reactive protein, mg/L (normal range 0.0-6.0)	108	5	115	7	12	31
Ferritin ng/ml	414	442	1050	40	151	68
D-dimer $\mu g/ml$ (normal range:0.0-2.0)	2	2	2	1.5	2.5	6
Alanine aminotransferase, U/L	18	20	25	10	27	30
Creatinine, mg/dl	4.6	1.4	2.6	1.8	0.4	0.5

**Table 2:** Administered drugs

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Labetalol	+	+	+	+	+	+
	(Maximum dose: 3 mg/kg/h)	(Maximum dose: 2.5 mg/kg/h)	(Maximum dose: 2.5 mg/kg/h)	(Maximum dose: 3 mg/kg/h)	(Maximum dose: 2.5 mg/kg/h)	(Maximum dose: 2.5 mg/kg/h)

Angiotensin-converting enzyme (ACE) inhibitors	+	+	-	+	+	+
Angiotensin II receptor blockers (ARBs)	+	-	+	+	+	-
Beta-blockers	+	-	+	+	-	-
Calcium channel blockers (CCB)	+	+	+	+	+	+
Furosemide	-	+	-	+	+	+
Additional anti-hypertensive drugs	Hydralazine, Terazosin	Hydrochlorothiazide	Terazosin, Clonidine	Prazosin	-	-
Anti-microbial and COVID-19 treatment	Ceftriaxone, Vancomycin	none	Meropenem, piperacillin-tazobactam, Teicoplanin, Remdesivir	Hydroxychloroquine	Meropenem, Teicoplanin	Ceftriaxone

**Discussion**

Herein, we have reported six pediatric cases, presented to hospital with hypertension crisis, without signs of fluid overload and mostly without any classic symptoms of COVID-19, who tested positive for the virus or had evidence of the infection on chest CT imaging. Based on published articles, hypertension has been identified as one of the most prevalent comorbidities in COVID-19 [9, 11]. However to this date, there is no report of “Hypertension crisis” as a presenting sign or comorbid condition of the infection and it is crucial to consider this diagnosis in a patient presenting with a severe rise in blood pressure even in the absence of classic signs of the virus. The importance of this consideration is the initiation of the proper isolation of the patient in the hospital so that other patients who have been admitted for non-infectious causes are kept safe from catching the virus (Figure 5). It was showed that, renal and cardiovascular complications were the second and third most prevalent manifestations of COVID-19 infection in children, respectively [12]. Again there might be a cause-and-effect correlation between hypertension and COVID-19 infection [13]. From renal manifestations, acute kidney injury, uremia, and hematuria were the most frequent complications of SARS-CoV-2 infection in children.

**Conclusion**

Hypotension, shock, and tachycardia were some of the cardiovascular features of the disease. Three of our cases presented with hypertension crisis without any other symptoms of viral infection and surprisingly diagnosed with COVID-19 during the laboratory workup or CT scan. However, whether the virus itself can cause exacerbation of hypertension or not, is yet unknown, and more comprehensive studies are needed to identify this correlation. Most of our patients had not developed severe COVID-19 symptoms, and the reason for their admission was hypertension crisis, and after controlling the blood pressure, they were discharged from the hospital, except for one patient who developed encephalopathy and multi-organ dysfunction and unfortunately passed away. In conclusion, we recommend the medical practitioners to consider the probability of COVID-19 infection in cases presenting to the hospital with hypertension crisis, especially those with controlled blood pressure followed by this acute presentation, and to maintain proper testing and isolation to protect other patients from the disease.

**Declarations**

**Ethics approval and consent to participate:**

- Very initially, written informed consents were obtained from the parents.
- This whole study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee.

**Consent for publication:** Written informed consents were obtained from the parents.

**Availability of data and materials:** The datasets used in the current study are available upon reasonable request.

**Competing interests:** The authors declare no conflicts of interest relevant to this manuscript.

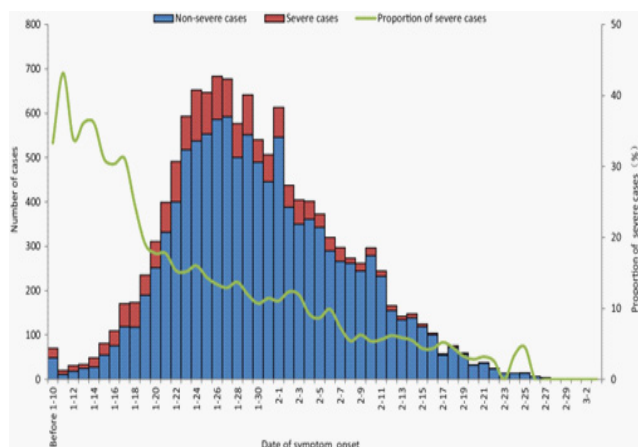


Figure 5: Risk factors for developing severe COVID-19 in China: an analysis of disease surveillance data.

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**Author contributions:** None except listed.

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