

## Case Report

# The Increased Risk of Renal Stones in Patients With COVID-19 Infection



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## ABSTRACT

**Background:** The novel coronavirus disease (caused by SARS-CoV-2) has become a disaster all over the world. Based on available evidence, the main organ infected by this virus is the respiratory system; however, various other vital systems can also be affected by potential outcomes. One of the critical affected organs is the kidney.

**Objectives:** This study aimed to report and reviewed Risk of Renal Stones in Patients With COVID-19 Infection.

**Methods:** In the present study, we reviewed literature about the renal stone in patients with COVID-19 in six databases, including PubMed, Scopus, Web of Science, Springer, Ovid, and Google Scholar. Then, we reported six adult COVID-19 patients with no history of kidney disease and new-onset renal stones.

**Results:** The rate of complicated ureteral stone disease significantly increased during the COVID-19 period. A few studies were available about renal stones, and mostly they were about the management of renal stones in patients infected with the coronavirus. However, in six patients, after being infected with COVID-19, the renal stone was recognized in patients. All the reported patients did not have a history of renal disease or other risk factors for renal stone formation.

**Conclusion:** Kidney injury is a possible complication of coronavirus, but based on our search, renal stone without history was not reported. However, observed cases highlighted the possible effects of COVID-19 infection on kidney function changes. On the other hand, although supplementation with vitamins C and D may be beneficial for the management of COVID-19, is associated with risks. These molecules should be used with caution, particularly in prior stone formers. Physicians should be responsible for understanding the impact of potential treatments for COVID-19 on common pathologies within their scope of practice.

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## Introduction

In the past decade, SARS-CoV and MERS-CoV, known as zoonotic coronaviruses, have caused severe outbreaks and damaged the respiratory tract [1, 2]. The coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, China, and by April 13, 2020, it affected more than 137,000,000 people worldwide, causing more than 2,900,000 deaths [3].

The most common symptoms at the onset of the disease include fever, cough, myalgia, fatigue, dyspnea, and diarrhea [1, 2]. A high percentage of patients with COVID-19 show abnormalities in renal function [4-8], presenting with proteinuria or elevated blood urea nitrogen (BUN) [5].

Renal stone is a typical cause in daily urology practice and might be life-threatening if it is associated with infection and/or renal impairment. This article was written to review and report this case after observing six cases of renal stones in our hospital. In this case series, we reported six confirmed COVID-19 cases with different manifestations at the initial presentation. On admission, all patients underwent initial laboratory tests, including cell blood count (CBC), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urea and creatinine, liver function test (LFT), and coagulation tests. All symptoms were relieved with symptomatic therapy.

## Mechanism of kidney injury in patients with COVID-19

Based on some studies, the rate of acute kidney injury (AKI) and associated outcomes in patients with COVID-19 are not well understood [9-17]. Chen et al. in a systematic review and meta-analysis reported the incidence of AKI as 8.9% (95% CI 4.6-14.5) in COVID-19 patients [18]. Hirsch et al. reported that AKI frequently occurs among patients with COVID-19. Also, they claimed that AKI occurs early and in temporal association with respiratory failure and poor prognosis [17]. Another study showed that SARS-CoV-2 induces a renal tubular lesion compatible with acute tubular necrosis that can lead to acute renal insufficiency and a testicular lesion [19].

Renal injury is associated with COVID-19 infection. Some proposed and reported mechanisms include ischemic injury, cytokine storm, and direct infection [6, 20], but the natural and exact mechanism and effect of this novel virus are unclear until now. We hypothesized that this mechanism can be attributed to renal stone formation.

## Renal and urethral stone

After searching in the selected databases, we found few studies conducted about renal injury and predominantly renal stones. Abolyazid et al. reported two cases with flank pain with COVID-19 diagnosed by CT scan. However, in this article, the relationship between renal stones and COVID-19 was not debated [21]. In another study, Gul et al. reported that during the COVID-19 pandemic, the rate of complicated ureteral stone disease significantly increased [15]. Flammia et al. suggested that urinary stone emergencies are mainly severe, their care needs to be continued, and they were not significantly influenced by this pandemic, but did not mention an increase or no increase in the rate of renal stone in COVID-19 patients [22].

## Case presentation

We reported six cases with renal stones after being infected with COVID-19. Demographic data are shown in Table 1, urinary analysis data of these patients are shown in Table 2, and therapeutic agents administered during the study are presented in Table 3.

Case one was a 53-year-old man who was referred to the emergency department with severe fatigue, chest pain, myalgia, and urticaria for two days. The patient received hydroxychloroquine, naproxen, vitamins C and D, and diphenhydramine as a symptomatic treatment. On the fourth day, he reported flank pain and urinary frequency. He also complained of sand excretion in urine three months ago. The sonography report showed a stone (6 mm) in the inferior calyx of the right kidney and microlithiasis in the left kidney. Flank pain was relieved after naproxen and hyoscine were administered.

Case two was a 44-year-old woman who was referred to the emergency department with initial recognition of COVID-19. The patient had a history of hysterectomy (five years ago) and mitral valve prolapse (two years ago) and was using propranolol, nortriptyline, and vitamin D3. The initial laboratory tests showed a normal range except CRP, ESR, and lymphopenia (490/ $\mu$ L). Hydroxychloroquine, naproxen, diphenhydramine, vitamin C, and doxycycline were administered. On the 14th day, flank pain with dysuria and urine discoloration were reported. Urinalysis (U/A) showed microscopic hematuria, proteinuria, and bacteriuria. Sonography confirmed a stone (4-5 mm) in the inferior calyx of the left kidney.

**Table 1.** Demographic and clinical characteristics of patients

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (y)	53	44	28	48	25	24
Gender	Male	Female	Female	Male	Female	Female
Signs and symptoms	Severe fatigue, chest pain, myalgia, and urticaria	Sore throat, fatigue, chest pain, myalgia, headache, dizziness, nausea, anorexia, and dyspnea	Cough, sore throat, chest pain, and dyspnea	Cough, sore throat, headache, diarrhea, and dyspnea	Cough, sore throat, headache, myalgia, fever, fatigue, nausea, chest pain, and dyspnea	Cough, headache, diarrhea, myalgia, fatigue, nausea, and dyspnea
Onset of symptoms (d)	2	4	5	5	5	3
SPO <sub>2</sub> (%)	96	98	97	96	97	96
Heart rate (beat/min)	75	83	91	85	87	75
Respiratory rate (breath/min)	18	17	16	18	16	17
Blood pressure (mmHg)	120/80	125/86	128/86	130/84	127/75	130/80
Body temperature (C°)	37.8	36.9	37	37.6	38	38
Onset of flank pain (d)	4	14	10	9	3	8
Side of renal stone in kidney (right or left)	Right & left	Left	Left	Right	Left	Right

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**Table 2.** Urinary analysis data of the patients

Cases	Color	Appearance	Specific gravity	pH	Protein	Glucose	Blood	Bilirubin	Urobilinogen
1		Clear	1.015	7			+		Normal
2		Turbid	1.010	5			+		Negative
3		Clear	1.010	8			+		Normal
4	Yellow	Clear	1.030	5	Negative	Negative	+	Negative	Negative
5		Semi-clear	1.016	5			Trace		Negative
6		Semi-clear	1.010	6			+		Negative

Cases	Ketones	Nitrite	WBC	RBC	Epithelial cells	Cast	Bacteria	Mucus	Crystals	Serum creatinine
Case 1			2-3	4-6	2-3	Not seen	Trace		Calcium oxalate crystals	0.9
Case 2			Many	4-6	2-3	WBC cast: 1-2	Few		Not seen	0.6
Case 3	Negative	Negative	1-2	4-5	2-3	Not seen	Few	Not seen	Not seen	1
Case 4			4-6	7-11	1-2	Not seen	Few		Not seen	0.8
Case 5			10-12	3-4	8-10	Not seen	Mild		Not seen	0.85
Case 6			8-10	4-5	4-6	Not seen	Moderate		Not seen	1.1

**PBR**

**Table 3.** Therapeutic agents administered during the study

Drugs	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Hydroxychloroquine	+	+	+	+	+	+
Azithromycin				+	+	+
Doxycycline		+	+			
Naproxen	+	+	+	+	+	+
Diphenhydramine	+	+	+	+	+	+
Vitamin C (1000 mg)	+	+	+	+	+	+
Vitamin D (2000 IU)	+	+	+	+	+	+
Pantoprazole			+	+		+
Atorvastatin				+		
Propranolol		+				
Nortriptyline		+				

**PBR**

Case three was a 38-year-old woman who was referred to the emergency department with cough, sore throat, chest pain, and dyspnea for five days. She had a history of anemia, for which iron supplements had been administered. The initial laboratory tests were normal except for CRP and ESR. Hydroxychloroquine, naproxen, diphenhydramine, doxycycline, vitamins C and D, and pantoprazole were administered for treatment. On the 10<sup>th</sup> day, flank pain was reported. Sonography showed a stone (2-3 mm) in the median calyx of the left kidney.

Case four was a 48-year-old man who was referred to the emergency department with cough, sore throat, headache, diarrhea, and dyspnea for five days. He had a history of hypercholesterolemia and had taken atorvastatin. The initial laboratory tests were normal except for serum levels of CRP, ESR, and lymphopenia (760/ $\mu$ L). He received hydroxychloroquine, naproxen, diphenhydramine, azithromycin, and vitamins C and D3. On the ninth day, the patient reported urine discoloration, flank pain, frequent urination, and dysuria. U/A findings indicated hematuria. Sonography showed a stone (4 mm) in the median calyx of the right kidney.

Case five was a 25-year-old with COVID-19. The Serum level of ESR was abnormal in initial laboratory tests. The patient was given hydroxychloroquine, naproxen, diphenhydramine, vitamins C and D, and azithromycin. On the third day, she reported the fever and frequent urination. Ciprofloxacin was administered according to the results of U/A (bacteriuria and pyuria). On the eighth day, left flank pain was observed. U/A was normal. Sonography confirmed calculus (4 mm) in the inferior calyx of the left kidney.

Case six was a 24-year-old woman who was referred to the emergency department with cough, headache, diarrhea, myalgia, fatigue, nausea, and dyspnea for three days. She had a history of anemia, for which she had taken iron supplements. CRP, ESR, and lymphopenia (992/ $\mu$ L) were reported in initial laboratory tests. Azithromycin, hydroxychloroquine, naproxen, diphenhydramine, vitamins C and D, and pantoprazole were administered for treatment. On day eight, she reported right flank pain and palpitation. U/A indicated pyuria, bacteriuria, and hematuria. Sonography showed a stone (2-3 mm) in the inferior and median calyces of the right kidney.

## Discussion

COVID-19 has rapidly evolved into a pandemic but remains without a well-defined treatment or prevention strategy. The use of vitamin supplements, particularly vitamins C and D, has also garnered great interest. Prior research on respiratory infections suggests that vitamins C and D supplementation may be useful [23, 24].

Vitamin C is a critical antioxidant for the immune system's function [25]. A large meta-analysis found that vitamin C supplementation at  $\geq 200$  mg/d was associated with a shorter duration of the common cold [26]. Furthermore, high-dose intravenous vitamin C improved outcomes in critically ill patients with sepsis and acute respiratory distress syndrome [23].

Vitamin C is associated with adverse effects at higher doses. Of urological interest, vitamin C is metabolized to oxalate and excess consumption may lead to hyperoxaluria [23]. Daily supplementation with 2000 mg/d of vitamin C was associated with increased urinary oxalate [27].

Vitamin D helps regulate calcium and phosphate stores in the body and is required for the proper immune system function. A large meta-analysis found that vitamin D supplementation reduced the risk of acute respiratory infections [28]. A recent analysis of European nations also found that lower vitamin D levels were associated with higher COVID-19 caseload and mortality [24].

The relationship between vitamin D and nephrolithiasis has generated significant interest as most kidney stones are calcium stones. A meta-analysis assessing the general risks of vitamin D supplementation identified an increase in nephrolithiasis risk [29].

Oxalate crystals were found in the urinalysis of case one, indicating a high vitamin C intake during treatment. Patients were prescribed 1000 mg of vitamin C twice daily. It should also be noted that patients in quarantine used foods containing vitamin C, such as citrus fruits, etc. which would increase the intake of vitamin C by more than 2,000 mg per day.

Therefore, supplementation with vitamins C and D, although may be beneficial for the management of COVID-19, is not without risk. These molecules should be used with caution, particularly in prior stone formers.

It should also be noted that a higher ambient temperature has an association with kidney stone disease, and temperatures were indeed unusually high in the summer of COVID-19 in Mazandaran [30].

Review studies demonstrated that kidney injury is reported in some studies, such as case reports from many countries [22, 31, 32], but the exact mechanism is unclear. Renal stone was not reported previously but urethral stone showed in one study [18].

This case series showed that COVID-19 could affect kidneys and lead to renal calculi. Recent studies, such as that by Xia et al. in China [7] and Benedetti et al. in the United States [8], showed that coronavirus can cause AKI at different levels and with different outcomes [9-12]. Evaluating biopsy samples of native and allograft kidneys from patients with COVID-19 by Kudose et al. showed that they developed a wide array

of glomerular and tubular diseases [8]. Another study noted the productive direct infection of the kidneys by SARS-CoV-2 [4]. Ahmed et al. in their study described kidney injury resulting from coronavirus [18].

In the present study, we reported six cases of renal stones in patients with confirmed COVID-19. None of the patients had risk factors or previous history of kidney disease and kidney injury. Flank pain began after (on average) 15 days of symptom onset. The risk factors for renal calculi are divided into four major categories: dietary, genetic, environmental, and lifestyle [13]. Stone formation is affected by demographic characteristics, such as age, race, and BMI > 30 kg/m<sup>2</sup>. Thus, Shin et al. reported that age older than 40 is a significant risk factor [14]. All of our cases had a BMI lower than 25 kg/m<sup>2</sup>, and three were under 40 years old.

Based on previous studies, kidney stones develop about three times more frequently in individuals with positive family history [13, 14]. Also, comorbidities, such as hypertension, diabetes, and CKD can increase the risk of renal stone formation [13]. However, no family history of renal stones was reported in our reported patients. Besides, no one had a history of comorbidities, which increased the risk of stone formation. After lab examination and physical assessments of the cases, no critical risk factors for renal calculi formation were found.

Our study has limitations. Firstly, our sample is relatively small and comes from a single center. The results may be different with more extensive data from multiple centers. Another limitation was the lack of more specialized tests and imaging techniques to assess the kidneys.

## Conclusion

Based on our review, there is no strong evidence about the role of coronavirus infection on the formation of renal stones. Although our data are insufficient to conclude the relationship between COVID-19 and renal calculi, we suggest the possibility of renal stone formation in the patient with COVID-19 and recommend further investigations and observational studies about this hypothesis. Supplementation with vitamins C and D, although may be beneficial for the management of COVID-19, is not without risk. These molecules should be used with caution, particularly in prior stone formers. Physicians should be responsible for understanding the impact that potential treatments of COVID-19 could have on common pathologies within their scope of practice.

## Ethical Considerations

### Compliance with ethical guidelines

This report was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MA-ZUMS.REC.1399.8510).

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### Authors' contributions

Visiting the patients and participated in data acquisition and drafting of the manuscript: Monireh Ghazaeian, Hossein Kasiri; Contribution to acquisition data and writing the manuscript: Hamidreza Samaee, Parisa Moradimaj. Read and approved the contents of the manuscript: All authors.

### Conflict of interest

The authors declared no conflicts of interest or competing for a financial interest in the present study.

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