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How has the COVID-19 disease affected patients with kidney stones?

COVID-19 hastalığı böbrek taşı olan hastaları nasıl etkiledi?

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Abstract

Purpose: To evaluate the relationship between the presence of kidney stones and COVID-19.

Materials and methods: Patients, who were treated for COVID-19 as outpatients as well as inpatients in the ward and/or ICU of two different secondary and tertiary care centers between July 15, 2020, and December 31, 2020, and aged ≥18 years were retrospectively evaluated. The patients were divided into two subgroups based on the presence of kidney stones, and then the patients with kidney stone were categorized into three groups: those who were treated in an outpatient setting (Group 1), those who were treated in the ward (Group 2), and those who were treated in the intensive care unit (Group 3).

Results: The total of 1,335 COVID-19 patients included in the study. Kidney stone was present in 31 (6.9%) of 450 outpatients, 41 (8.9%) of 460 inpatients treated in the ward, and 60 (14.1%) of 425 inpatients treated in the intensive care unit. In Group 1, the duration of COVID-19 treatment was significantly longer in patients with kidney stone than patients without kidney stone (8.1±1.7 vs. 6.8±2.2 days, *p*=0.01). In Group 2 and in Group 3, the mean hospitalization duration was significantly longer in patients with kidney stone than in those without kidney stone (9.1±3.7 vs. 6.2±2.1 days, *p*=0.007; 19.1±8.1 vs. 11.3±6.2 days, *p*=0.001, respectively).

Conclusion: The duration of COVID-19 treatment was longer and the COVID-19 infection was more severe in those with kidney stones.

Key words: COVID-19, kidney stone, nephrolithiasis, pandemic.

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Öz

Amaç: Böbrek taşı varlığı ile COVID-19 hastalığı arasındaki ilişkinin değerlendirilmesi.

Gereç ve yöntem: COVID-19 tanısı ile 15 Kasım-31 Aralık 2020 tarihleri arasında 2. ve 3. basamak 2 farklı merkezde ayaktan, servis ve/veya yoğun bakımda tedavi uygulanan hastalar retrospektif olarak tarandı. Öncelikle hastalar böbrek taşı varlığına göre alt gruplara ayrıldı ve daha sonra böbrek taşı olan olgular, ayaktan tedavi gören hastalar Grup 1, serviste yatarak tedavi gören hastalar Grup 2 ve yoğun bakımda tedavi ihtiyacı doğan olgular ise Grup 3 olarak kategorize edildi.

Bulgular: Çalışmaya toplam 1335 COVID-19 hastası dahil edildi. Ayaktan tedavi edilen 450 hastanın 31'inde (%6,9), serviste yatan 460 hastanın 41'inde (%8,9) ve yoğun bakımda yatan 425 hastanın 60'ında (%14,1) böbrek taşı mevcuttu. Grup 1'de, böbrek taşı olan hastalarda COVID-19 tedavi süresi böbrek taşı olmayan hastalara göre anlamlı olarak daha uzundu (8,1±1,7 ve 6,8±2,2 gün, *p*=0,01). Grup 2 ve Grup 3'te ortalama hastanede kalış süresi böbrek taşı olan hastalarda böbrek taşı olmayanlara göre anlamlı olarak daha uzundu (sırasıyla 9,1±3,7 ve 6,2±2,1 gün, *p*=0,007; 19,1±8,1 ve 11,3±6,2 gün, *p*=0,001).

Sonuç: Böbrek taşı olanlarda COVID-19 tedavi süresinin daha fazla ve COVID-19 enfeksiyonunun daha şiddetli olduğu saptandı.

Anahtar kelimeler: COVID-19, Böbrek taşı, nefrolitiazis, pandemi.

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China [1]. Although COVID-19 primarily affects the respiratory system, it has the potential to affect several other systems with cellular access receptors for the virus, such as the cardiovascular, gastrointestinal, renal, and central nervous systems [2]. COVID-19-associated mortality usually results from coagulopathy, cytokine storm syndrome, and multiorgan failure [3]. Activation of the immune system appears to play a crucial role in both pathogenesis and mortality in COVID-19. As innate immune cells, the dendritic cells and macrophages participate in the immune system–mediated response against the virus until adaptive immunity is activated [4]. The CD4+ Thelper cells activate B cells to facilitate virus-specific antibody production, whereas the CD8+ Tcytotoxic cells destroy the virus-infected cells [5]. Although these cells are involved in immune defense against various infections, they may induce symptoms associated with the infections. These symptoms trigger various levels of antibody response based on the amount and location of the pre-existing immune defense cells. The basal immune response in chronic diseases does not always benefit the required defense; however, it may sometimes lead to severe symptoms due to excessive response.

Chronic diseases are diseases that progress slowly, last for ≥3 months, are caused by ≥1 risk factors, generally have a complicated disease course, and affect the quality of life of the individual. Most chronic diseases such as metabolic syndrome, diabetes mellitus (DM), obesity, hypertension (HT), and cardiovascular diseases aggravate the severity of COVID-19, as in all other infections [6]. The inflammatory response that occurs during the disease course is generated by both the innate and adaptive immune systems. Cytokines, which play a major role in this inflammatory response, are produced by various immune system cells such as the macrophages, dendritic cells, natural killer cells, and T and B lymphocytes [7]. Furthermore, the disruption of mitochondrial function is a key factor in the progression of chronic and age-related diseases [8]. A previous study has shown that mitochondrial dysfunction is a key factor in triggering the cytokine storm associated with the severity of COVID-19 and the devastating symptoms that, ultimately, lead to death in patients with COVID-19 [9].

Urinary stone diseases have a chronic pathophysiology that affects 5%-10% of the population throughout their life [10, 11]. The main components of urinary tract stones are mostly calcium, oxalate and phosphate. A previous study has shown that oxalate causes mitochondrial dysfunction and impairs redox homeostasis in monocytes [12]. As a result of the loss of functions of macrophages due to mitochondrial dysfunction and more than a desired level of reactive oxygen species (ROS) are produced in the cellular environment, an excessive immune response mechanism comes into play. The excessive immune response that occurs in other chronic diseases has also been demonstrated in patients with urinary stones.

This study aimed to evaluate the effect of the presence of kidney stones on disease severity in patients with COVID-19 and to explore prevalence of kidney stones in patients treated at different clinical levels such as outpatient, ward, and intensive care unit (ICU).

Materials and methods

A retrospective analysis was performed with the data of patients who were treated for COVID-19 as outpatients as well as inpatients in the ward and/or ICU of two different secondary and tertiary care centers between July 15, 2020, and December 31, 2020. In total, 1,335 patients aged >18 years were included in this study. Diagnosis was made by using the real-time reverse transcription polymerase chain reaction (rRT-PCR) test with nasopharyngeal swab samples of the patients included in the study. Patients with negative rRT-PCR test results but positive radiological results were also included in this study. In order to standardize the study, the initiation of COVID-19 treatment by the relevant clinician was accepted as the inclusion criterion. Patients who were pregnant, had active ureteral stones and were younger than 18 years of age with COVID-19 infection were excluded from the study. The patient's data were analyzed and they were randomized into the following three groups: those treated in outpatient setting, those hospitalized and treated in the ward and those treated in the ICU. All patients were examined for the presence of urinary stones.

The following data of the patients included to the study were recorded: demographics (age and sex), medical history, medications used, urinary stone location, stone burden, previous stone surgeries, comorbidities, and COVID-19 severity level and the type of treatment (outpatient, ward, or ICU) they received due to COVID-19 was recorded.

At first, the patients were divided into two subgroups based on the presence of kidney stones, and then the data of these patients with kidney stones were analyzed in detail. The patients with kidney stone were further categorized into three groups: those who were treated in an outpatient setting (Group 1), those who were treated in the ward (Group 2), and those who were treated in the ICU (Group 3). The patients included in the study were evaluated cross-sectionally and compared only according to the presence of kidney stones. The course of COVID-19 was investigated in the patients with kidney stones and also the relationship between the presence of kidney stones and COVID-19 and its effect on the severity of COVID-19 were examined. The patient's kidney stone disease was taken as a sufficient criterion for inclusion in the study. Symptomatic or other clinical features were not taken into account. The study was approved by the local ethics committee (Approval number: 2021/230).

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 22 software (SPSS, Inc., Chicago, IL, USA). Descriptive data were presented as frequency (percentage), number and mean ± standard deviation, or median (min–max). Distribution properties of numerical variables were evaluated using the Kolmogorov–Smirnov test. Independent-samples t-test was used for comparing the normally distributed and Mann–Whitney U test was used for comparing the nonnormally distributed numerical variables. Categorical data were evaluated using the chi-square test and *p* values of <0.05 were considered statistically significant.

Results

The mean age of 1,335 patients included in the study was 56±15.1 years and the male/female ratio was 790/545 (Table 1). The mean hospitalization duration was 9.08±4.18 days. In this cross-sectional study, kidney stone was present in 31 (6.9%) of 450 outpatients, 41 (8.9%) of 460 inpatients treated in the ward, and 60 (14.1%) of 425 inpatients treated in the ICU. The distribution of stone location and mean stone burden for a total of 132 patients with a history of kidney stone were as follows: upper calyx (56 mm^2) in 31 patients, middle calyx (36 mm^2) in 28 patients, lower calyx (32 mm^2) in 59

Table 1. Demographic characteristics of the cases

		Kidney stone +	Kidney stone -	Total	*p*
Age (year)		58±17.2	55±14.8	56±15.1	0.200
Gender	Male	79 (59.9%)	711 (59.1%)	790	0.500
	Female	53 (40.1%)	492 (40.9%)	545	
Stone localization/ size (mm^2)	Upper calyx	31 (56 mm^2)	-		
	Middle calyx	28 (36 mm^2)	-		
	Lower calyx	59 (32 mm^2)	-		
	Renal pelvis	14 (81 mm^2)	-		
Previous kidney stone surgery history (%)		49 (37.1%)	-		
History of medical treatment for kidney stone (%)		35 (26.5%)	-		
Patients treated in an outpatient setting		31 (6.9%)	19 (93.1%)	450	
Patients treated in the ward		41 (8.9%)	419 (91.1%)	460	
Patients treated in the ICU		60 (14.1%)	365 (85.9%)	425	**0.010**
Total		132	1203	1335	

ICU: Intensive care unit

patients, and renal pelvis stones in 14 patients (81 mm^2). Among the patients, 49 (37.1%) had a history of previous stone surgery and 35 (26.5%) had a history of potassium citrate treatment for kidney stones.

The patients included in the study were investigated in terms of comorbidities such as DM, HT, coronary artery disease, and obesity. As summarized in Table 2, the presence of at least one of these diseases was considered positive for comorbidities. Although positivity rate for comorbidities was high in Group 3, as expected, no significant correlation was found between the presence of kidney stone and comorbidities in any of the group (p>0.005).

When evaluated in terms of the presence of kidney stones, only 6.9% patients in Group 1 and 14.1% patients in Group 3 had kidney stones, and this result was statistically significant (p=0.01). Long-term post-COVID-19 syndrome (a term used to describe the disease in people who have recovered from COVID-19 but still report persistent effects of infection or have usual symptoms of the infection for much longer than expected, and it is defined as the persistence of symptoms for ≥1 month) was observed in 14 of 31 patients with kidney stones who were treated in an outpatient setting. The duration of treatment was 6.8±2.2 days in the patients without kidney stones, whereas it increased to 8.1±1.7 days in the presence of kidney stones, and the difference was statistically significant (p=0.01) (Table 2). When the comorbidities of the patients were evaluated, no significant difference was observed in patients with and without kidney stones, whereas the presence of kidney stones was found to be the only parameter associated with long-term post-COVID-19 syndrome, and a statistically significant result was obtained (p<0.05).

The mean hospitalization duration for the patients in Group 2 was 6.5±2.2 days. In patients with kidney stones, this period was significantly longer than in those without kidney stones (9.1±3.7 vs. 6.2±2.1 days, p=0.007). A significant relationship was not observed between the presence of kidney stones and age, sex, and comorbidities. However, the presence of kidney stones had a role in increasing the symptom score and prolonging the treatment and hospitalization durations.

In this study, among the 425 patients in Group 3 treated in the ICU, 115 were intubated and 310 were followed up on a mechanical ventilator due to hypoxia. During the follow-up, 76 (17.8%) patients died. In total, 60 (14.1%) patients were positive and 365 (85.9%) were negative for a history of kidney stones. Age, gender, demographics, and comorbidities of the patients were similar in the patients with and without kidney stones. Although there was no relationship between death during follow-up and the presence of kidney stones, the presence of kidney stones was significantly observed higher in patients requiring prolonged treatment. When the mean hospitalization duration in the ICU was compared between the patients with and without kidney stone, a significant difference was observed (19.1±8.1 vs. 11.3±6.2 days, p=0.001). Although the number of intubated patients was 21 (35%) in the group with kidney stones, it was 94 (25.7%) in the group without kidney stones; and, the difference was not statistically significant (p=0.19). There was a significant relationship between the presence of kidney stones and prolonged treatment time, long hospital stay, and increased symptom score (p<0.05, p<0.001, and p<0.05, respectively).

Discussion

Coronavirus disease 2019 rapidly spread all over the world since its first diagnosis and has now become a pandemic. The clinical effects of COVID-19 are associated with widespread inflammatory response [13]. A previous study has reported that it is more common in patients with inflammatory diseases and worse clinical outcomes are observed in patients with comorbidities [14]. Previous studies in the literature suggest that urinary stone diseases trigger the inflammatory activation in such patients [15-17]. To the best of our knowledge, this is the first study to investigate the relationship between the presence of kidney stones and COVID-19. The main finding of this study is that the severity and duration of COVID-19 are significantly higher in those with kidney stone disease. This suggests that the presence of kidney stone adversely affects the course of COVID-19.

The prevalence of urinary tract stone is increasing worldwide. A previous study reported that the prevalence rate of kidney stones in Chinese adults was 5.8% [18]. In another

Table 2. Comparison of the groups according to the presence of kidney stone disease

	Group 1 (n=450)			Group 2 (n=460)			Group 3 (n=425)		
	Kidney stone + n=31 (6.9%) %	**Kidney stone - n=419 (93.1%) %**	***p***	**Kidney stone + n=41 (8.9%) %**	**Kidney stone - n=419 (91.1%) %**	***p***	**Kidney stone + n=60 (14.1%) %**	**Kidney stone - n=365 (85.9%) %**	***p***
Gender									
Male	18 (58.1)	237 (56.5)	0.170	22 (53.6)	268 (63.9)	0.410	37 (61.6)	226 (61.9)	0.230
Female	13 (41.9)	182 (43.5)	0.180	19 (46.4)	151 (36.1)	0.260	23 (38.4)	139 (38.1)	0.240
Age (year)	49±15.4	53±9.8	0.300	54±11.8	50±17.1	0.640	71±20.4	69±14.5	0.220
Presence of the comorbid diseases ≥1 (DM, HT, obesity, cardiovascular diseases etc.)	10 (32.2)	144 (34.3)	0.400	19 (46.3)	198 (47.2)	0.280	36 (60)	289 (79.1)	0.470
Duration of hospital stay (day)	-	-	-	9.1±3.7	6.2±2.1	**0.007**	19.1±8.1	11.3±6.2	**0.001**
Lung involvement	-	-		8 (19.5)	103 (24.5)	0.190	51 (85)	299 (81.9)	0.480
The need for O2 support	3 (9.6)	31 (7.3)	0.110	12 (29.2)	59 (14.08)	**0.050**	43 (71.6)	325 (89.04)	**0.010**
The need for intubation	-	-		-	-		21 (35)	94 (25.7)	0.190
Mortality (Exitus)	-	-		-	-		11 (18.3)	65 (17.8)	0.210

DM: Diabetes mellitus, HT: Hypertension

study conducted between 2007 and 2010, the prevalence rate of kidney stones was 8.8% [11]. Considering all the patients in this study, the overall rate of kidney stones was 9.8%. On the other hand, when subgroups were considered, this rate was 6.9% in those treated in an outpatient setting for COVID-19, 8.9% in those treated in the ward, and 14.1% in those treated in the ICU. The increased rate of kidney stones in patients treated in the ICU was also found to be significant.

Although the pathophysiology of COVID-19 is not clearly understood, it is known to cause aggressive inflammation induced by the viral replication, thereby causing acute lung injury [19]. Although the host's immune response is important for the eradication of the infection, it also plays an important role in the pathogenesis of severe clinical manifestations [20]. The Coronavirus-19 suppresses the antiviral interferon-γ response in the lung tissue in the early period, resulting in the overproduction of proinflammatory cytokines (e.g., interleukin [IL]-1β, IL-2, IL-6, IL-7, IL-8, and tumor necrosis factor-α) and chemokines (e.g., CXC chemokine ligand 10 and CC-chemokine ligand 2). The result is a cytokine storm. Thus, damage to the lung tissue occurs, resulting in pneumonia and acute respiratory distress syndrome. Th1/Th17 cells may also be activated in this process and exacerbate inflammation. These cellular mechanisms reveal that the immune response is a determining factor for the clinical outcomes of COVID-19 [19, 20]. Several studies conducted from this perspective have shown that COVID-19 is more common in patients who are prone to inflammation. Ferri et al. [21] conducted a multicenter study with 1.641 patients and emphasized that there were more patients diagnosed with rRT-PCR in the patient group with ≥1 autoimmune systemic diseases than the normal population or those who were highly likely to have COVID-19 infection based on their symptoms despite the diagnosis not being conformed. In another study, it was shown that pneumonia that developed secondary to COVID-19 was detected more commonly in patients with inflammatory bowel disease than in the group without inflammatory bowel disease [22]. Furthermore, in a population-based study by Doran et al. [23], a total of 609 patients with and without rheumatoid arthritis were compared and patients with rheumatoid arthritis were more likely to be severely symptomatic and hospitalized. Similarly, in a prospective study conducted with 2,108 patients with inflammatory polyarthritis, hospitalized patients had a 2- to 4-fold increased risk of infection compared with the healthy population [24]. In the present study, a significantly higher rate of kidney stones was found in patients with COVID-19 treated in the ICU and the treatment and hospitalization durations of patients with kidney stones in all three groups were significantly longer than those without kidney stones; this was consistent with the aforementioned findings in the literature.

It has been shown that patient admissions to both emergency and urology outpatient clinic decreased during the COVID-19 pandemic period [25]. Urinary system stone disease is one of the presentations of urological diseases to emergencies outpatient clinics. Kidney stones occur in 5%-10% of the general population at least once in their lifetime [26]. Most kidney stones are in the form of calcium oxalate (CaOx) [27]. It has previously been shown that the crystals and oxalate that form kidney stones cause the release of monocyte chemoattractant protein-1 (MCP-1), which plays an important role in the activation and migration of monocytes/macrophages from the renal epithelial cells [12]. The mitochondria regulate intracellular signaling cascades by producing ROS, which is necessary for the macrophages to perform their physiological functions. However, excessive production of ROS impairs the mitochondrial function and causes the activation of cascades that cause excessive inflammatory response [28]. It is known that oxalate crystals, which constitute a major portion of urinary stones, increase ROS production in renal cells [29]. In addition, macrophages exposed to CaOx crystals have been shown to release inflammatory cytokines and chemokines [12]. In a study conducted by Williams et al. [30], a significant decrease was reported in the mitochondrial functions of monocytes circulating in the blood in patients with CaOx stones compared with those in the control group. Monosodium urate crystals also activate inflammatory pathways by stimulating IL-1β production and lead to an innate immune response [16]. Although the metabolic structures of the stones were unknown in the present study,

the finding related to COVID-19 progressing more severely in patients with kidney stones is supported by the abovementioned mechanisms.

Impairment of the mitochondrial function plays a key role in aging and the progression of age-related diseases [8, 9]. Various diseases associated with aging and mitochondrial dysfunction, such as neurodegenerative diseases, diabetes, and atherosclerosis, have been associated with excessive activation of the inflammatory system. In addition, the association of mitochondrial dysfunction with inflammation increases after the fifth decade of one's life, and the severity of COVID-19 and its associated mortality also increase in this age group [9]. This may explain that why excessive inflammatory response cannot be prevented in elderly patients and patients with comorbidities and why life-threatening consequences occur as a result of cytokine storm [31]. The increased need for intensive care and advanced treatment for COVID-19 in elderly patients and patients with comorbidities in the present study is supported by the relationship revealed by the abovementioned mechanisms.

This study has some limitations such as its retrospective design and inability to evaluate the mortality rates for all of the patients because of the lack of data. In addition, as the stone analysis results of the patients were not available, a comparative analysis could not be performed considering the metabolic structure of the stone. It was also another limitation that the severity of the disease was differentiated only according to the treatment setting. Nevertheless, this study is important as, to our knowledge, it is the first study to evaluate the incidence and severity of COVID-19 in patients with kidney stones.

It was determined that the duration of COVID-19 treatment was longer and the COVID-19 infection was more severe in those with kidney stones. This study presents a different perspective in the evaluation of patients with kidney stones during this ongoing pandemic; however, further prospective and randomized controlled studies are needed regarding this issue.

Conflict of interest: No conflict of interest was declared by the authors.

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The authors declare that data and material used for this study is avaliable upon a reasonable request.

Authors' contributions to the article

Conception and design of the study; M.B.D., T.I.D., S.T., T.N.Y. Generation, collection, assembly, analysis and/or interpretation of data; S.S., S.T. Drafting or revision of the manuscript; M.B.D., S.S., T.I.D., T.N.Y., S.T. Approval of the final version of the manuscript; M.B.D., S.S., T.I.D., T.N.Y., S.T.