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CONTENTS

POST-ACUTE COVID-19 SYNDROME AND URINARY TRACT INFECTIONS

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Abstract: The complications in the respiratory tract and cardiovascular events are the leading causes of death and morbidity among COVID-19 patients but it was shown that nearly all other systems might be involved including the urinary system. The post-acute COVID-19 syndrome is defined as the presence and/or persistence of symptoms 8–12 weeks after the onset of COVID-19 unrelated to any other illness. The main pathophysiological mechanisms underlying the post-acute COVID-19 syndrome depend on the organ system involved, virus-specific pathophysiological alterations, immunological and inflammatory alterations, and other common post-infectious sequelae. Urinary tract infections (UTIs) that affect the kidneys, and cause fever, stones, sepsis, urinary obstruction, catheters, or immunocompromised patients are classified as complicated infections.
The objective of this study was to assess complicated urinary tract infections in patients who recently recovered from COVID-19. It is an observational analysis of a case series of ten patients aged 22 to 71 years who had COVID-19 one to six months before the urinary infection. Their radiographic images of the lungs had a finding suggesting sequelae of respiratory infection. Urine cultures were positive for *Escherichia coli* in 5 patients, *Enterococcus spp.* in 3 patients, and 2 patients had sterile findings but their urinalysis revealed the presence of leukocytes and bacteria. Six patients were febrile and two patients had clinical signs of urosepsis (systolic pressure<100mm/hg, tachypnea >22r/min, leukocytosis, and GSC<15) in two patients. All patients had elevated leukocyte counts and high CRP serum levels, confirming acute inflammation. D-dimers were elevated in most patients (n=9), which could signal active clotting issues—important in the context of infections and inflammatory processes. Serum creatine was elevated in 4 patients possibly indicating renal stress or dysfunction. Elevated serum urea levels in more than half of patients (n=6) indicate protein catabolism or decreased renal clearance. The study observed a higher incidence of patients with elevated serum glucose (n=9), which could be stress-induced hyperglycemia or underlying metabolic issues like diabetes.
Treatment was dual antibiotic therapy with intravenous cephalosporin and ciprofloxacin (n=6), intravenous ertapenem and ciprofloxacin (n=3), and intravenous amikacin in one patient. The patients were discharged to home treatment after 5 days (n=1), 10 days (n=4), 15 days (n=3) and 20 days (n=2) respectively. The average hospital stay due to urinary infection was 13 (+/-10) days; male patients had a longer average hospital stay (20 days) compared to female patients (12.22 days). Patients with urinary catheters had a longer hospital stay (15 days) unlike the others (12.5 days), indicating more severe urinary issues or complications that might extend the hospital stay. Patients requiring intensive care (n=2) had a longer average hospital stay (17.5 days) compared to those who did not need intensive care (11.875 days), underscoring the impact of critical care needs on hospitalization length.
This case series concludes that in a certain number of patients, depending on the patient's age, gender, and comorbidities, complicated urinary infections may occur after COVID-19. They should be recognized and treated in time in order not to escalate into a life-threatening condition such as urosepsis.
Keywords: COVID-19, SARS-CoV-2, complicated urinary infections, urosepsis

1. INTRODUCTION

The SARS-CoV-2 coronavirus, which causes COVID-19, is a serious worldwide health threat that spreads as a pandemic with typical initial symptoms being dyspnea, exhaustion, fever, and cough, noticed between days 4 and 5 following exposure (Chams et al., 2020).
The respiratory complications and cardiovascular events are the leading causes of death and morbidity among infected patients; however, autopsy and pathological investigations have shown the involvement of nearly all systems, including the gastrointestinal, musculoskeletal, central and peripheral nervous, and renal systems (Çopur et al., 2020).
Chronic kidney disease (CKD), diabetes mellitus, and immunocompromising disorders are associated with increased hospitalization and mortality rates, in addition to cardiovascular and respiratory comorbidities (Maillard et al., 1990).

Up to 25% of patients with severe COVID-19 had an acute kidney infection and required kidney replacement therapy which was observed especially in patients admitted to the intensive care unit (Gabarre et al., 2020).
Post-COVID syndrome can affect people who had mild symptoms and were self-treated at home, as well as those who went to the emergency wards with alarming symptoms or had severe symptoms that necessitated a short hospital stay. The post-acute COVID-19 syndrome is defined as the presence and/or persistence of symptoms 8–12 weeks after the onset of COVID-19 unrelated to any other illness(Nalbandian et al., 2021).
Depending on the organ system involved, virus-specific pathophysiological alterations, immunological and inflammatory alterations, and other common post-infectious sequelae are the main pathophysiological mechanisms underlying the post-acute COVID-19 syndrome (Copur et al., 2022).

2. MATERIALS AND METHODS

We performed an observational analysis of a series of ten patients aged 28 to 70 years who had symptomatic or asymptomatic COVID-19 before hospitalization due to complicated urinary infections. The research protocol was in ordinance with the Helsinki declaration and all patients signed written consent for data sharing. Variables that were encountered were age, gender, time past from the COVID-19, vital parameters (tachypnea, tachycardia, blood pressure, and body temperature), biochemical blood analyses (leukocyte count, C-reactive protein, creatinine, urea, and serum glycose), urine and blood microbiology culture, D-dimers, the duration of hospitalization and the therapy applied.

3. RESULTS

The ages of the patients ranged from 23 to 88 years, with a mean age of 55.6 years. The average hospital stay was 13 days, with a minimum stay of 3 and a maximum of 28 days. Table 1 shows the descriptive statistics for all numerical variables included in the study.

Table 1. Descriptive statistics for all numerical variables in the study

	Age	TT	TA Systolic	TA Diastolic	LE	Urea	Creatine	Glycemia	CRP	D-dimers	Time after COVID-19	Hospital stays (days)
Mean	53	37.88	111	63	13.21	10.31	157.15	13.24	239.84	3689.1	2.78	13
SD	18.36	1.05	22.34	13.37	4.81	7.47	115.09	9.85	66.02	2512.97	1.86	4.83
Min	22	36.5	70	40	7.5	3	57.3	4.4	154.1	450	1	5
Max	71	39.8	140	80	21.9	27.5	348.8	34.6	320.1	7800	6	20

Source: The authors

Urine cultures were positive for *Escherichia coli* in 5 patients, *Enterococcus spp.* in 3 patients, and 2 patients had sterile findings but their urinalysis revealed the presence of leukocytes and bacteria. Six patients were febrile and two patients had clinical signs of urosepsis (systolic pressure<100mm/hg, tachypnea >22r/min, leukocytosis, and GSC<15) in two patients. All patients had elevated leukocyte counts and high CRP serum levels, confirming acute inflammation. D-dimers were elevated in most patients (n=9), which could signal active clotting issues—important in the context of infections and inflammatory processes. Serum creatine was elevated in 4 patients possibly indicating renal stress or dysfunction. Elevated serum urea levels in more than half of patients (n=6) indicate protein catabolism or decreased renal clearance. The study observed a higher incidence of patients with elevated serum glucose (n=9), which could be stress-induced hyperglycemia or underlying metabolic issues like diabetes. The number of patients with high, low, and normal values of the variables are shown in Table 2.

Table 2: The number of patients with normal, high, and low levels of parameters compared to reference values

		Count	Column N %
Temperature values	High	7	70,0%
	Normal	3	30,0%
Blood pressure (Systolic)	High	1	10,0%
	Low	2	20,0%
	Normal	7	70,0%
Blood pressure (Diastolic)	Low	2	20,0%
	Normal	8	80,0%
Leukocyte count	High	10	100,0%
Creatine serum level	High	4	40,0%
	Normal	6	60,0%
Glucose serum level	High	9	90,0%
	Normal	1	10,0%
CRP level	High	10	100,0%
D-Dimers level	High	9	90,0%
	Normal	1	10,0%
Urea serum level	High	6	60,0%
	Normal	4	40,0%

Source: The authors

Treatment of the included patients was dual antibiotic therapy with intravenous cephalosporin and ciprofloxacin (n=6), intravenous ertapenem and ciprofloxacin (n=3), and intravenous amikacin in one patient. The patients were discharged to home treatment after 5 days (n=1), 10 days (n=4), 15 days (n=3) and 20 days (n=2) respectively.
The strongest positive correlation with hospital stays was seen with D-dimers ($r = .84$, $p < .001$), followed by glycemia ($r = .69$, $p < .01$), serum urea, and creatine. A significant positive correlation was found both between the length of hospital stays and D-dimers and between the length of hospital stays and glycemia. In contrast, the time passed from the initial COVID-19 infection was negatively correlated with hospital stays ($r = -.38$, $p < .05$). Blood pressure readings (TA Systolic and TA Diastolic) show negative correlations with the length of hospital stay. Male patients had a longer average hospital stay (20 days) than female patients (12.22 days). Patients with tachypnea had a significantly longer hospital stay (18.33 days) than those without (10.71 days). Patients with E.coli in their urine culture had an average hospital stay of 13 days, identical to patients with a negative urine culture result. A negative blood culture was associated with an average hospital stay of 13 days. The average hospital stays were 13 days; catheterized patients also had a longer hospital stay (15 days) than those not catheterized (12.5 days) as well as the patients requiring intensive care (17.5 days). Other parameters such as body temperature (TT), leukocyte esterase (LE), and markers of inflammation or liver function (CRP, AST, ALT) show varied degrees of correlation with hospital stay length. The correlations are given in Table 3.

Table 3. Correlations Between Variables

		Age	TT	TA Systolic	TA Diastolic	LE	Urea	Creatine	Glycemia	CRP	D-dimers	Time after COVID-19	Hospital stays (days)
Age	Correlation	1	-0.49	0.2	0.16	0.39	0.5	0.29	-0.36	0.57	0.39	-0.38	-0.24
	p		.268	.667	.733	.383	.253	.535	.432	.18	.383	.398	.599
TT	Correlation	-0.49	1	-0.28	-0.22	-0.14	-0.54	-0.25	0.16	-0.05	0.07	-0.25	0.32
	p	.268		.55	.634	.758	.21	.585	.728	.908	.878	.592	.483
TA Systolic	Correlation	0.2	-0.28	1	0.91	0.22	0.09	0.27	-0.02	-0.47	0.11	-0.12	0.01
	p	.667	.55		.004	.638	.846	.554	.969	.284	.816	.797	.984
TA Diastolic	Correlation	0.16	-0.22	0.91	1	0	0.1	0.1	-0.16	-0.42	0	0.14	-0.09
	p	.733	.634	.004		1	.832	.832	.733	.35	1	.761	.841
LE	Correlation	0.39	-0.14	0.22	0	1	0.68	0.96	0.54	0.5	0.86	-0.78	0.62
	p	.383	.758	.638	1		.094	<.001	.215	.253	.014	.038	.14
Urea	Correlation	0.5	-0.54	0.09	0.1	0.68	1	0.75	0.43	0.54	0.71	-0.15	0.45
	p	.253	.21	.846	.832	.094		.052	.337	.215	.071	.756	.312
Creatine	Correlation	0.29	-0.25	0.27	0.1	0.96	0.75	1	0.57	0.43	0.79	-0.62	0.62
	p	.535	.585	.554	.832	<.001	.052		.18	.337	.036	.139	.14
Glycemia	Correlation	-0.36	0.16	-0.02	-0.16	0.54	0.43	0.57	1	-0.07	0.64	-0.2	0.95
	p	.432	.728	.969	.733	.215	.337	.18		.879	.119	.667	.001
CRP	Correlation	0.57	-0.05	-0.47	-0.42	0.5	0.54	0.43	-0.07	1	0.5	-0.45	0.07
	p	.18	.908	.284	.35	.253	.215	.337	.879		.253	.305	.873
D-dimers	Correlation	0.39	0.07	0.11	0	0.86	0.71	0.79	0.64	0.5	1	-0.64	0.79
	p	.383	.878	.816	1	.014	.071	.036	.119	.253		.124	.036
Time after COVID-19	Correlation	-0.38	-0.25	-0.12	0.14	-0.78	-0.15	-0.62	-0.2	-0.45	-0.64	1	-0.35
	p	.398	.592	.797	.761	.038	.756	.139	.667	.305	.124		.438
Hospital stays (days)	Correlation	-0.24	0.32	0.01	-0.09	0.62	0.45	0.62	0.95	0.07	0.79	-0.35	1
	p	.599	.483	.984	.841	.14	.312	.14	.001	.873	.036	.438	/

Source: The authors

4. DISCUSSIONS

Post-acute COVID-19 otherwise known as “long COVID” affects the urinary tract and is usually manifested with urinary urgency, frequency, and nocturia (Lamb et al., 2022).

An estimated 5–10% of people experience long COVID symptoms following the initial SARS-CoV-2 infection. Female sex, ethnic minority status, socioeconomic hardship, smoking, obesity, a variety of comorbidities, and advancing age were risk factors for long-term COVID-19. Multiple symptoms related to various clinical and sociodemographic risk factors are associated with SARS-CoV-2 infection (Subramanian et al., 2022). A recent study's findings indicate that approximately 33.0% of patients infected with the SARS-Cov-2 virus have a long-term COVID-19 infection, 33.0% are asymptomatic, and 34.0% have never had a COVID-19 infection (Allan-Blitz et al., 2023).

In this case series study, urine cultures were positive for *Escherichia coli* in 50% of patients, *Enterococcus spp.* in 3 patients, and 2 patients had sterile findings but their urinalysis revealed the presence of leukocytes and bacteria. Seven patients (70%) had an elevated body temperature and other patients had normal body temperatures, suggesting either early stages of infection or early effective management. All patients had elevated leukocyte counts, strongly indicating active infections. Most patients maintain normal blood pressure, possibly reflecting either a controlled health status or non-severe cases. Only two patients had low systolic and diastolic pressure, which might be concerning in clinical practice since ii pointe severe urinary infection with raised possibility of urosepsis. Serum creatine was elevated in 4 patients (40%), possibly indicating renal stress or dysfunction. More than half of the patients had normal creatinine serum levels, suggesting adequate kidney function. Elevated serum urea levels in more than half of patients (60%) indicate protein catabolism or decreased renal clearance. The study observed a higher incidence of patients with elevated serum glucose (n=9), which could be stress-induced hyperglycemia or underlying metabolic issues like diabetes. All patients had high CRP serum levels, confirming acute inflammation. D-dimers were elevated in most patients (n=9), which could signal active clotting issues—important in the context of infections and inflammatory processes.

There are several possible ways that COVID-19 may impact the kidney, and these factors' relative contributions may change over time. Many of the direct and secondary consequences of SARS-CoV-2 could recur after hospital discharge and continue to cause sepsis episodes. The renal features observed during the post-acute COVID-19

period have been attributed to several pathophysiological mechanisms, including tubular injury, endothelial damage, inflammatory mediators, complement activation, micro- or macrovascular injury, and podocyte injury (Parmar, 2021). The studies showed that when compared to asymptomatic and recovered individuals, those with long-COVID-19 had significantly higher urinary leukotriene E4 levels (Allan-Blitz et al., 2023). It is unknown whether the clinical kidney outcomes are brought on by direct cytopathic effects, indirect mechanisms, or both, although direct viral entry into the renal tissue has been demonstrated in numerous studies and is supported by the presence of viral inclusion bodies on biopsy specimens (Fehr & Perlman, 2015; Parmar, 2021).

Bladder urothelial cells contain ACE2 receptors, which may be the mechanism of action since SARS-CoV-2 shows high-affinity bonding after them and this reaction causes cellular chain reaction followed by urothelial cell dysregulation (Lin et al., 2021). This theory is supported by the validation of SARS-CoV-2 in the urinary tract and the detection of the virus in urine (Frithiof et al., 2020).

It was also shown that an unbalanced host response between the pro-inflammatory and anti-inflammatory response to SARS-CoV-2 infection induces sepsis which endures the inflammatory basis of COVID-19 and emphasizes the current definition of sepsis (Faix, 2013; Rello et al., 2017).

The Renin-Angiotensin System is. Besides the pulmonary, renal, and immune systems,

Urinary tract infections in long-term COVID-19 patients may be caused by modifications in the gut microbiome, in addition to the inflammatory changes impacting the urinary system since the renin-angiotensin system which is directly attacked by SARS-CoV-2 virus due to its attachment to the angiotensin-converting enzyme-2 (ACE2) (El-Arif et al., 2021) also controls the intestinal microbiome and cardiovascular homeostasis (Perlot & Penninger, 2013; Rysz et al., 2021).

Our study showed that patients with urinary infections after COVID-19 have different treatment options depending on the etiological factors. Catheterized patients had longer hospital stays which is in alignment with some study's conclusions of increased frequency and morbidity of catheter-associated cystitis in patients especially when associated with previous COVID-19 (Dhawan et al., 2023).

5. CONCLUSIONS

This case series is a practical contribution to the impact of SARS-CoV-2 on the urinary system, including clinical aspects of patients with urinary tract infections who were not hospitalized due to COVID-19. Certain factors such as age, gender, and comorbidities, can lead to complicated uroinfections after COVID-19. Therefore, we recommend thorough follow-up to be recognized and treated in time so that they would not pass into a life-threatening condition such as urosepsis.

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