Kidney Involvement in Pediatric COVID-19 Cases: A Single-Center Experience

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What is already known on this topic?

 Kidney involvement including transient or severe hematuria, proteinuria, or acute kidney injury has been documented in adults with coronavirus disease 2019. However, data in the pediatric age group are limited.

What this study adds on this topic?

• The incidence of hematuria, proteinuria, and elevated serum creatinine was 15.8%, 6%, and 3%, respectively. Overall kidney involvement (at least 1 of the 3 conditions) was 23.2%, which was significantly high in patients with moderate-tosevere disease (i.e., 43.5%).

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ABSTRACT

Objective: The kidney is the second most commonly affected organ by severe acute respiratory syndrome coronavirus-2, characterized by hematuria, proteinuria, and acute kidney injury. There are few studies describing renal involvement in pediatric cases.

Materials and Methods: This retrospective study evaluated the prevalence of hematuria, proteinuria, and acute kidney injury in severe acute respiratory syndrome coronavirus-2-positive pediatric cases (1-18 years old) who visited emergency department between March and November 2020. Patients with urinary tract infections were excluded. An age-specific upper limit of reference interval was used to define "elevated serum creatinine" (greater than upper limit of reference interval) and acute kidney injury (>1.5 times upper limit of reference interval).

Results: A total of 228 patients were evaluated, median age was 12.7 years (interquartile range: 7.5; 16.1), and 51.3% were male. The prevalence of asymptomatic, mild, and moderate-to-severe disease was 12.7% (29/228), 77.2% (176/228), and 10.1% (23/228), respectively. The prevalence of hematuria, proteinuria, and elevated serum creatinine was 15.8% (36/228), 6% (14/228), and 3% (7/228), respectively. Kidney involvement (i.e., at least 1 of these findings) was 23.2% (53/228) and significantly higher in the moderate-to-severe disease (43.5%). None of the patients met the acute kidney injury criterion. In logistic regression analysis, female sex (odds ratio: 1.97, 95 Cl%: 1.03; 3.70, P = .040) and fever (odds ratio: 2.28, 95% Cl: 1.19; 4.36, P = .012) were independent predictors of kidney involvement. Three patients demonstrated a kidney presentation (macroscopic hematuria) on admission, and another patient was diagnosed with C3 glomerulonephritis during hospitalization.

Conclusion: Kidney involvement was found about in 1 quarter of children with coronavirus disease 2019. Awareness and recognition of kidney involvement and follow-up are important in the management.

Keywords: Children, COVID-19, SARS-CoV-2, kidney, proteinuria, hematuria, acute kidney injury, C3 glomerulonephritis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was announced as a pandemic in March 2020.^{1,2} A wide clinical spectrum has been observed, ranging from asymptomatic children to severely ill patients.³

Cite this article as: Ağbaş A, Akkoç G, Kızılırmak C, Çalışkan Dolu N, Bayramoğlu E, Elevli M. Kidney involvement in pediatric COVID-19 cases: A single-center experience. *Turk Arch Pediatr.* 2022;57(5):558-562. There is tropism of SARS-CoV-2 for the kidneys, podocytes, and proximal renal tubule epithelium.⁴ Hematuria, proteinuria, and acute kidney injury have been reported in adults with COVID-19,⁵⁻⁸ but data are still limited in the pediatric age group.⁹⁻¹⁴ The pathophysiology has been thought to be direct viral toxicity to these cells or the effects of systemic inflammation or ischemia on the kidneys. Finally, several cases of glomerulonephritis have been reported that had COVID-19.¹⁵⁻²⁰ However, it is not clear whether SARS-CoV-2 is the cause or whether it is just a coincidence.

In this study, we aimed to evaluate the prevalence of kidney involvement in terms of hematuria, proteinuria, elevated serum creatinine, and acute kidney injury (AKI) in SARS-CoV-2-positive children and adolescents with a wide range of clinical presentation. We also reported 3 COVID-19 cases presented with fever and macroscopic hematuria on admission and 1 adolescent who was diagnosed with C3 glomerulonephritis during hospitalization due to acute severe COVID-19.

MATERIAL AND METHODS

Study Population

This is a retrospective study conducted in Haseki Training and Research Hospital, Department of Pediatrics between March and November 2020, during the first 8 months of the pandemic in Turkey. The inclusion criteria were: children and adolescents aged 1-18 years, who visited the emergency department, who had a positive oro-nasopharyngeal swap polymerase chain reaction (PCR) test for SARS-CoV-2, and who had a urinalysis and serum creatinine measurement. Exclusion criteria were urinary tract infection (positive urine culture) or known kidney disease with persistent hematuria, proteinuria, or elevated serum creatinine or multisystem inflammatory syndrome in children. This study was approved by the local ethics committee of Haseki Training and Research Hospital, 2020-135, September 9, 2020).

Clinical and laboratory findings on admission were recorded retrospectively. Based on the clinical findings, patients were divided into 3 groups: (1) asymptomatic group: patients who underwent PCR testing based only on a contact history without any symptoms; (2) mild group: patients with nonspecific symptoms such as cough, fever, malaise, and myalgia; and (3) moderate-to-severe group: patients whose pneumonia was confirmed by physical examination and imaging (chest X-ray and/or computed tomography) with or without oxygen requirements. The moderate-to-severe group consisted of hospitalized patients. Asymptomatic and mild cases were followed by telephone or outpatient clinic visits. None of the patients experienced clinical deterioration or required intensive care.

Laboratory Parameters and Definitions

Complete blood count, C-reactive protein, procalcitonin, fibrinogen, D-dimer, kidney function tests, and urinalysis were performed in all possible COVID-19 cases. The presence of more than 5 erythrocytes per high-power field was defined as *hematuria*. *Proteinuria* was defined as urine dipstick test demonstrating \geq 2 positive protein and/or urine protein-to-creatinin e ratio higher than 0.2 mg/mg. *Elevated serum creatinine* was defined as a serum creatinine above the age-specific upper limit of reference interval (ULRI) values.²¹ Acute kidney injury was defined as a serum creatinine 1.5 times higher than the

ULRI.²¹ *Kidney involvement* was defined as having at least 1 of the followings: hematuria, proteinuria, and/or elevated serum creatinine. Severe acute respiratory syndrome coronavirus 2 was assessed by quantitative reverse-transcriptase PCR through a nasopharyngeal swab detection kit (Bioksen ArGe Teknik Co., Ltd., Turkey; Biospeedy®).

Statistical Analysis

Statistical Package for Social Sciences, version 20.0 software (SPSS Inc.; Chicago, IL, USA) was used for analysis. Normality of data was analyzed by Kolmogorov–Smirnov test. Continuous data that were not normally distributed were expressed as median (25th and 75th percentile) and analyzed with the Mann–Whitney U test for comparison of 2 groups or the Kruskal– Wallis test for comparison of more than 2 groups. Categorical variables were expressed as numbers (percentages) and analyzed with the Chi-square test or Fischer's exact test. To identify predictors of kidney involvement, all parameters that had a P-value of ≤ .25 in univariate analysis, and clinically relevant parameters were tested using backward multivariable logistic regression analysis. A 2-sided P-value of \leq .05 was defined as statistically significant. The patient diagnosed with C3 glomerulonephritis was not included in the statistical analyses and was reported separately.

RESULTS

A total of 228 SARS-CoV-2 PCR-positive children were included. The median age was 12.7 years (7.5; 16.1), and 117 (51.3%) were male. The ratios of asymptomatic, mild, and moderate-tosevere clinical courses were 12.7% (29/228), 77.2% (176/228), and 10.1% (23/228), respectively. Clinical and laboratory findings are shown in Table 1.

Assessment of the Kidney Involvement on Admission

The prevalence of hematuria, proteinuria, and elevated serum creatinine was 15.8% (36/228), 6% (14/228), and 3% (7/228), respectively. Kidney involvement (at least 1 of hematuria, proteinuria, and/or elevated serum creatinine) was observed in 23.2% of patients (53/228). Among the patient groups (Table 1), kidney involvement was significantly higher in the moderate-to-severe (hospitalized) group (43.5%), which was 21.6% in the mild group and 17.2% in the asymptomatic group (P = .047). Patients with kidney involvement were significantly of female sex and had fever, higher fibrinogen levels, and significantly lower hemoglobin levels (Table 2, P < .05 for all). In logistic regression analysis, female sex (odds ratio (OR): 1.97, 95% CI: 1.03; 3.70, P = .040) and fever (OR: 2.28, 95% CI: 1.19; 4.36, P = .012) were independent predictors of kidney involvement.

A second urinalysis was available in 14 of 36 patients with hematuria and in 5 of 14 patients with proteinuria; none of them had persistent hematuria or proteinuria. Lastly, 52% (119/228) of patients had urine density >1020 on admission.

Coronavirus Disease 2019 Patients with a Kidney Presentation on Admission or Hospitalization

During the study period, 2 patients with an underlying kidney disease presented with fever and macroscopic hematuria and were hospitalized with suspected urinary tract infection: a 2-year-old girl with neurogenic bladder and a 5-year-old

Variables	Asymptomatic (n = 29)	Mild (n = 176)	Moderate-to-severe (n = 23)	P*
Age, years	11.8 (4.43; 14.7)	12.7 (7.99; .0)	15.1 (6.03; 16.9)	.200
Sex, male	18/29 (62.0)	87/176 (49.4)	12/23 (52.2)	.450
Symptoms				
Fever	NA	80/175 (45.7)	19/23 (82.6)	.001
Diarrhea	NA	14/176 (8.0)	1/23 (4.3)	1.000
Vomiting	NA	7/176 (4.0)	0	1.000
Urea, mg/dL	23 (18; 26)	23 (19; 27)	19 (16; 23)	.025
Creatinine, mg/dL	0.43 (0.32; 0.59)	0.52 (0.40; 0.63)	0.57 (0.46; 0.69)	.061
Scr/ULRI >1	0	6/175 (3.4)	1/23 (4.3)	.507
Urinalysis				
Urine density				.885
>1015	11	50	7	
1015-1020	6	30	5	
1020-1030	9	76	9	
>1030	3	20	2	
Proteinuria				.065
No	25	140	15	
Trace	-	20	3	
1+	2	7	3	
2+	-	5	2	
3+	1	2	-	
Jrine prt/cr >0.2	2/4	1/10	3/11	.263
Proteinuria ^c	2/29 (6.9)ª	8/174 (4.6)ª	4/23 (17.4) ^b	.056
Hematuria	3/29 (10.3)	26/176 (14.8)	7/23 (30.4)	.129
Proteinuria and/or hematuria	5/29 (17.2)°	33/176 (18.8)°	10/23 (43.5) ^b	.033
Kidney involvement ^d	5/29 (17.2)°	38/176 (21.6)ª	10/23 (43.5) ^b	.047
Leucocyte, ×10³/µL	6.1 (5.2; 8.6)	6.3 (4.8; 7.9)	4.6 (4.2; 5.9)	.014
Lymphocyte, 8 × 10³/µL	2.3 (1.9; 3.9)	2.0 (1.6; 2.7)	1.6 (1.4; 2.2)	.001
Hemoglobin, g/dL	13.5 (12.2; 14.3)	13.0 (12.2; 14.0)	13.0 (12.4; 15.2)	.809
Platelet, ×10³/µL	254 (221; 329)	231 (205; 275)	221 (188; 288)	.136
Elevated C-reactive protein	5/29 (17.2)°	47/176 (26.7)°	15/23 (65.2) ^b	<.001
Elevated procalcitonin	4/27 (14.8)°	38/158 (24.1)°	10/22 (45.5) ^b	.040
D-dimer, ng/mL	390 (260; 700)	350 (250; 520)	700 (310; 1.020)	.053
Fibrinogen, mg/dL	274 (239; 316)	285 (247; 329)	379 (329; 440)	<.00'

*Data are given as median (25th; 75th percentile) and analyzed with Mann–Whitney U-test for comparison of 2 groups or Kruskal–Wallis test for comparison of 3 groups. Categorical data are given as n (%) and analyzed with Pearson Chi-square test or Fisher's exact test.

^cProteinuria; urine dipstick protein ≥2(+) and/or spot urine protein-to-creatinine ratio > 0.2; ^dKidney involvement; at least 1 of proteinuria, hematuria, and/or elevated serum creatinine; *P* values <0.05 were presented in bold.

NA, not applicable; ULRI, upper limit of reference interval.

boy with vesicoureteral reflux. However, no bacterial growth was detected in the urine cultures. Blood pressure, kidney function tests, and urinary tract ultrasonography were unremarkable. Severe acute respiratory syndrome coronavirus 2 PCR tests were positive and hematuria resolved within a few days. A 4-year-old girl presented with macroscopic hematuria. History revealed recurrent macroscopic hematuria but was not evaluated. Blood pressure, kidney function tests, complement C3 and C4, anti-nuclear antibody (ANA), anti-double stranded DNA, anti-neutrophil cytoplasmic antibody (ANCA), and urinary tract ultrasonography were unremarkable. The SARS-CoV-2 PCR test was positive and hematuria was resolved within a few days; urinalysis at discharge was negative for hematuria or proteinuria. Further investigation could not be performed because the patient did not return for follow-up. Lastly, a 17-year-old boy was admitted with fever and fatigue. His medical history was unremarkable. He was diagnosed with acute severe COVID-19 syndrome with high inflammatory markers, lymphopenia, and pulmonary involvement. Urinalysis on admission revealed microscopic hematuria and proteinuria (+++ positive). The 24-hour urine protein level was 1800 mg/ day. Serum creatinine (0.8 mg/dL) and albumin (4 g/dL) were within normal range, serum complement C3 was low (0.5 mg/ dL), C4, ANA, anti-dsDNA, and ANCA were unremarkable. A kidney biopsy was performed after recovery from COVID-19 and revealed C3 glomerulonephritis with subepithelial and mesangial immune deposits that were C3 (+++) and IgG (-). No chronic findings were noted on biopsy. C3 nephritic factor was slightly positive but could be analyzed in the second week of steroid treatment. No mutation was detected in C3,

Involvement						
	Kidney	Kidney				
	Involvement	involvement				
Variables	(+) (n = 53)	(–) (n = 175)	P*			
Age, years	12.7 (5.8; 16.5)	12.6 (8.2; 15.9)	.961			
Sex, female	33/53 (62.3)	78/175 (44.6)	.024			
Symptoms						
Fever	30/53 (56.6)	69/175 (39.4)	.020			
Diarrhea	3/53 (5.7)	12/175 (6.9)	1.000			
Vomiting	2/51 (3.9)	5/175 (2.9)	.657			
Leucocyte, ×10³/µL	6.0 (4.3; 8.0)	6.0 (4.9; 7.6)	.682			
Lymphocyte, $8 \times 10^{3}/\mu L$	2.0 (1.4; 2.7)	2.0 (1.6; 2.8)	.885			
Hemoglobin, g/dL	12.8 (12.2; 13.3)	13.3 (12.3; 14.3)	.018			
Platelet, ×10³/µL	227 (201; 271)	233 (203; 281)	.799			
Elevated C-reactive	15/53 (28.3)	52/175 (29.7)	.843			
protein Elevated procalcitonin	11/46 (23.9)	41/161 (25.5)	.830			
D-dimer, ng/mL	380 (290; 550)	360 (245; 560)	.320			
Fibrinogen, mg/dL	317 (254; 374)	287 (247; 332)	.037			
*Data are given as median (25th; 75th percentile) and compared with						

Table 2. Comparison of Patients With and Without Kidney

Mann–Whitney U test or n (%) and compared with Pearson's Chi-square or

Fischer's exact tests.

complement factor H, B, I, and thrombomodulin genes. In the sixth month of steroid treatment, the C3 level was in the normal range and proteinuria was 240 mg/day.

DISCUSSION

The main findings of our study were as follows: the prevalence of hematuria was 15.8%, proteinuria was 6%, and elevated serum creatinine was 3% at admission. Kidney involvement, which was defined as the presence of at least 1 of these 3 findings, was 23.2% in the entire cohort and was significantly higher in hospitalized children (43.5%).

There are several mechanisms that contribute to kidney involvement in terms of hematuria, proteinuria, elevated serum creatinine, or AKI. Angiotensin-converting enzyme 2 is the host receptor for SARS-CoV-2 cell entry and is highly expressed in the kidneys.⁴ Immunofluorescence of kidney samples showed SARS-CoV-2 protein in areas of glomerular epithelial, endothelial, and tubular cells, with preferential targeting of glomerular cells.⁴ Therefore, SARS-CoV-2 has a selective tropism for the kidney with a direct cytopathic effect.⁴ Second, the immune response to virus-infected cells and a cytokine storm also play a role. Other factors such as hypovolemia and/or hypoperfusion (gastrointestinal involvement [GIS] involvement and cardiomyopathy),^{6,22} toxic tubular damage (rhabdomyolysis and nephrotoxic agents), and organ cross-talk between lung-kidney (cytokines, acure respiratory distress syndrome [ARDS], and hypoxia) and heart-kidney (cardio-renal syndrome) axis may also contribute to AKI.²² The most common injury observed in biopsy and autopsy studies is acute tubular injury,^{18,19} which is the result of a cytopathic effect and/or immune injury caused by interstitial macrophages and activation of the complement system.

The incidence of AKI in the adult COVID-19 population has been reported between 1.3% and 44%. In a meta-analysis of approximately 40 000 adult patients, the cumulative incidence of AKI was reported to be 19%.7 Acute kidney injury is a negative prognostic factor and is associated with an increased risk of mortality.⁷ However, a recent meta-analysis found that the incidence of AKI and kidney replacement therapy was not significantly different in COVID-19 patients compared to other respiratory viruses-related critically ill patients.⁵ Although children have a milder disease course, the incidence of AKI has been reported between 0% and 29% in hospitalized children⁹⁻¹⁴ and as high as 44% in critically ill children.¹⁰ Low albumin and high leukocyte counts were reported as risk factors for AKI, and AKI was associated with longer hospital stay.9 None of our patients met the criteria for AKI. Only 7 patients had elevated serum creatinine on admission.

The prevalence of significant proteinuria has been reported as 34% at the time of admission and 63% during hospitalization in adults with COVID-19.7 Massive proteinuria may occur because of epithelial cell damage (collapsing glomerulopathy) and endothelial damage (thrombotic microangiopathy), or moderate proteinuria may be seen due to transient febrile illness, acute tubular necrosis, and acute interstitial nephritis. The prevalence of hematuria has been reported to be about 35% in adults.⁷ There are limited data on the prevalence of proteinuria and hematuria in the pediatric population.^{12,14} Stewart et al¹² reported a prevalence of proteinuria of 10% and hematuria of 23% in hospitalized pediatric patients. In the current study, the incidence of proteinuria and hematuria was 6% and 15.8% in the whole cohort and 17.4% and 30.4% in hospitalized children, respectively. In addition, during the study period, 2 children with a known kidney disease, 1 with vesicoureteral reflux (VUR), and 1 with neurogenic bladder presented with fever and macroscopic hematuria. These symptoms were thought to be related to COVID-19 but not with the underlying kidney disease.

The prevalence of kidney involvement was 23.2% in the entire cohort and 43.5% in hospitalized children. Patients with kidney involvement were significantly more likely to be of female sex and have fever, higher fibrinogen levels, and lower hemoglobin levels. In logistic regression analysis, female sex and fever were the independent predictors of kidney involvement. In addition, about half of the children had high urine density on admission to emergency department, which suggests lower hydration status of the patients on admission. Overall, these findings emphasize the importance of nephroprotective measures such as hydration and avoidance of nephrotoxic medication.

Several cases with SARS-CoV-2-positive glomerulonephritis have been reported such as collapsing glomerulopathy^{15,17} and ANCA-positive pauci-immune vasculitis.^{18,20} New-onset or relapsing idiopathic nephrotic syndrome have also been reported during infection with SARS-CoV-2 with a good prognosis and response to steroids.¹⁶ There is evidence of endothelitis, intravascular coagulation, thrombotic microangiopathy (TMA), disseminated intravascular coagulation (DIC), thrombotic events, and even areas of infarction on kidney specimens with COVID-19.23-25 In addition, activation of the complement system has been demonstrated on kidney biopsy and autopsy specimens.²⁶ We diagnosed C3 glomerulonephritis in an adolescent during hospitalization for acute severe COVID-19. However, we could not distinguish whether it was related to SARS-CoV-2 or just a coincidence.

Our study had several limitations. Unfortunately, there was no measured basal creatinine in the patients before or after the COVID-19. Therefore, we used the upper limit of the reference value to evaluate the creatinine levels, which could lead to underestimation of AKI cases. Second, proteinuria was determined with urine dipstick test, which is sensitive to albuminuria. The prevalence of proteinuria might be higher because we could not assess tubular proteinuria in all patients by quantitative measurement of urine total protein or tubular proteins. Third, urine culture could not be performed in all patients with pyuria and/or hematuria. Finally, our cohort consisted of mostly cases with mild disease course. The strength of our study is that a relatively high number of patients with a positive SARS-CoV-2 PCR test were consecutively included.

CONCLUSION

The kidney is affected in children and adolescents with COVID-19. Kidney involvement is generally subtle and mild; however, about a quarter have hematuria, proteinuria, and/or elevated serum creatinine. About half of the patients were found to have findings suggesting low hydration status on admission. Although rare, patients may present with a kidney symptom such as macroscopic hematuria and may have glomerulonephritis associated with COVID-19. Therefore, awareness and recognition of kidney involvement, follow-up of these patients, and taking protective measures such as hydration and avoidance of nephrotoxic medications are important in the management of COVID-19.

Ethics Committee Approval: This study was approved by Haseki Training and Research Hospital, (Approval No: 2020-135, 09/09/2020).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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