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Renal Involvement in Hospitalized Children with COVID-19

Mahmoud Alhandi Omar Helal[1, 2, *], Abubakr Imam[3, 4], Shaikha Nasser Al-Thani[4], Wadha Al-Shafi[5], Lujain Loay[1], Farid Fatnassi[1], Mahmoud Abdul Majid[1], Malek Almoustafa[1], Fatin A. Moussa[1], Mohammed Sultan[1], Moustafa Ezz[1], Limia Altaj Sati Seed[6]

[1]Pediatric Department, Hamad General Hospital, Doha, Qatar

[2]Pediatric Nephrology Department, Alkindi University Hospital, Aleppo, Syria

[3]Pediatric Nephrology Department, Sidra Hospital, Doha, Qatar

[4]Faculty of Medicine, Weil Cornell University, Doha, Qatar

[5]Department of Dermatology, Hamad Medical Corporation, Doha, Qatar

[6]Pediatric Nephrology Department, Madina Maternity and Children Hospital, Al Madinah Al Munawwarah, Saudi Arabia

Email address:

dr.mahmoud.helal@gmail.com (Mahmoud Alhandi Omar Helal), aimam@sidra.org (Abubakr Imam), SAlthani7@hamad.qa (Shaikha Nasser Al-Thani), WAlshafi@hamad.qa (Wadha Al-Shafi), LLoay@hamad.qa (Lujain Loay), FFATNASSI@hamad.qa (Farid Fatnassi), MAbdulmajid@hamad.qa (Mahmoud Abdul Majid), malmoustafa@hamad.qa (Malek Almoustafa), FMOUSSA@hamad.qa (Fatin A. Moussa), MSULTAN1@hamad.qa (Mohammed Sultan), MEZZ@hamad.qa (Moustafa Ezz), limiaseed5@gmail.com (Limia Altaj Sati Seed)

[*]Corresponding author

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Abstract: *Background:* Coronavirus disease 2019 (COVID-19), usually causes respiratory and gastrointestinal symptoms in children. While the clinical features range from upper respiratory tract infections to severe diseases. Kidney involvement in these children has been reported in different parts of the world, with different prevalence and acuity. To date, data are still accumulating to characterize kidney involvement in this disease and its impact on these children. Objective: We aimed to determine the prevalence of renal involvement in hospitalized children with COVID-19 in the state of Qatar and describe their clinical presentation and outcome. Methods: We retrospectively reviewed all children (age 0–14 years) with COVID-19 admitted to Hamad General Hospital, from March 1, 2020, to January 1, 2021. The diagnosis was confirmed by positive PCR results for the virus. We reviewed kidney involvement in these children at presentation, during hospitalization, and at 6 weeks follow-up. Results: A total of 2586 patients who were positive by PCR were reviewed, of which 584 were excluded due to missing data, and 1602 were completely asymptomatic at presentation. A total of 400 patients were then included in this study and were divided into two groups: patients without renal involvement (non-renal group) 282 patients (70.5%), and patients with renal involvement (renal group) 118 patients (29.5%). In the renal group, the median age was 16.7 months, and 90 patients (76.3%) were female. Fever was present in 107 patients (90.7%), and the median duration of hospitalization was 3.3 days. In this group, 84 patients (71.2%) presented with respiratory symptoms, and 34 patients (28.8%) presented with gastroenterological symptoms. The most frequent manifestation of renal involvement in these patients was microscopic hematuria, followed by leukocyturia, and acute kidney injury (AKI) was present in 14 patients (12%). During the reported period and follow-up of 6 weeks, children with AKI were at an early stage, and none of them required kidney replacement therapy. Conclusion: Kidney involvement in children with COVID-19 infection in our patients was noted in almost one-third of the patients and varied from urinary findings without any clinical symptoms to early-stage AKI. Electrolyte abnormalities with metabolic acidosis can present at presentation and require careful attention and management.

Keywords: Coronavirus Disease 2019 (COVID-19), Acute Kidney Injury (AKI), Urinary Tract Infections (UTIs)

1. Introduction

COVID-19 infection usually causes respiratory and gastrointestinal symptoms with clinical features ranging from a common cold to severe disease, such as bronchitis, pneumonia, severe acute respiratory distress syndrome, multi-organ failure, and even death. SARS-CoV, MERS-CoV, and SARS-CoV-2 seem to affect children less commonly and cause fewer symptoms with less severe disease than adults, and are also associated with much lower case-fatality rates [1]. Clinicians have observed several extrapulmonary manifestations of COVID-19. Many systems have been reported to be affected ranged from hematological findings to cardiovascular, renal, gastrointestinal, hepatobiliary, endocrinological, neurological, ophthalmological, and dermatological involvement [2- 6].

In adults, acute kidney injury (AKI) is a frequent complication of COVID-19 and is associated with higher mortality rates [7, 8]. The incidence of AKI in hospitalized patients with COVID-19, ranges from 0.5% to 29% and occurs within a median of 7–14 days after admission [3, 5, 8]. Studies from the USA have reported significantly higher AKI rates. In a study of nearly 5,500 patients admitted with COVID-19 in a New York City hospital system, AKI occurred in 37%, with 14% of the patients requiring dialysis [9]. Moreover, AKI occurred at much higher rates in critically ill patients ranging from 78% to 90% [9-13]. Of 257 adult patients admitted to ICUs, 31% received renal replacement therapy (RRT) [11]. Urinary findings of hematuria have been reported in nearly half of patients with COVID-19 [9], and proteinuria has been reported in up to 87% of critically ill patients with COVID-19 [11]. Hyperkalemia and acidosis were the most common electrolyte abnormalities observed in these patients, even among patients without AKI. COVID-19 is also increasingly reported among patients with end-stage renal disease and kidney transplant recipients, with higher mortality rates than those seen in the general population [14-16].

Children and adolescents with COVID-19 infection have considerably better outcomes than adults, with mortality rates in pediatric patients (age <18 years) of less than 1% reported in early studies [17, 18]. The most common clinical features in children described in the literature are fever, dry cough, and pneumonia [3]. However, multisystem involvement, including the development of hyperinflammatory shock, is increasingly being recognized. In other studies, AKI has been reported in adult patients with COVID-19, with a high prevalence across inpatient admissions (≤7%) and admissions to adult intensive care units (ICUs; ≤23%), as first reported in Wuhan, China [19]. In adult COVID-19 patients, AKI is associated with an increased mortality risk, even after adjusting for age, sex, and comorbidities [5]. In addition, a large proportion of adults have proteinuria (44%) and hematuria (27%) at presentation, despite an elevated serum creatinine prevalence of only 16% [20].

Overall, in children, there are scanty data when compared to adults; however, the data are accumulating from different parts of the world. Douglas et al. [21] studied 52 pediatric patients (aged 0–16 years) admitted to the Great Ormond Street Hospital for Children NHS Foundation Trust (London, UK) with confirmed severe acute respiratory syndrome coronavirus infection and diagnosed by either a positive PCR result or seropositivity. Of the 52 inpatients, 24 (46%) had a serum creatinine greater than the upper limit of reference interval (ULRI), 22 [42%] had proteinuria, and hematuria was observed in 40 [77%] patients. Qui et al. [18] did not find any renal dysfunction in 36 hospitalized pediatric patients (aged 0–16 years) with COVID-19 in China.

In this retrospective, exploratory, descriptive study, we aimed to determine renal involvement in all pediatric patients hospitalized with COVID-19.

2. Study Methodology

2.1. Design

We included all children (age 0–14 years) with COVID-19 admitted to Hamad General Hospital, pediatric division- Doha, Qatar from March 1, 2020, to January 1, 2021, who were diagnosed by positive PCR results. We examined the clinical presentations and kidney involvement in these patients.

Clinical classification of COVID-19 in children: [22]

1. Mild disease: Upper respiratory symptoms (e.g. pharyngeal congestion, sore throat, and fever) for a short duration or asymptomatic infection, positive RT-PCR test for SARS-CoV-2, and no abnormal radiographic and septic presentation.
2. Moderate disease: Mild pneumonia; symptoms such as fever, cough, fatigue, headache, and myalgia; and no complications or manifestations related to severe conditions.
3. Severe disease: Mild or moderate clinical features plus any manifestations that suggest disease progression.

1) Rapid breathing (≥70 breaths per minute for infants aged <1 year; ≥50 breaths per minute for children aged >1 year)
2) Hypoxia
3) Lack of consciousness, depression, coma, and convulsions
4) Dehydration, feeding difficulty, and gastrointestinal dysfunction
5) Myocardial injury
6) Elevated liver enzyme levels.
7) Coagulation dysfunction, rhabdomyolysis, and any other manifestations suggesting injuries to vital organs.

4. Critical illness: Rapid disease progression and any other condition

1) Respiratory failure requiring mechanical ventilation (e.g., ARDS, persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or masks)
2) Septic shock
3) Organ failure requiring ICU monitoring

2.2. Renal Manifestations of COVID-19

The clinical presentations may include AKI, Electrolyte abnormalities (hyperkalemia, hyponatremia, and hypernatremia, among others), Proteinuria, Hematuria, and Metabolic acidosis.

Criteria for Kidney Disease Improving Global Outcomes (KDIGO) acute kidney injury in children [23].

Stage 1:

Increase to 1.5 1.9 times baseline, an OR increase of ≥0.3 mg/dL (≥26.5 mcmol/L),

The time frames for the increases in serum creatinine are:

Increase of SCr ≥0.3 mg/dL (≥26.5 mcmol/L) within 48 hours

Increase in SCr >1.5 times the baseline within the prior seven days

Urine output <0.5 mL/kg per hour for 6 to 12 h.

Stage 2:

Increase to 2 to 2.9 times baseline,

Urine output <0.5 mL/kg per hour for ≥12 h

Stage 3:

Increase greater than 3 times baseline, OR

SCr ≥4 mg/dL (≥353.6 mcmol/L), OR

Initiation of renal replacement therapy, OR

EGFR <35 mL/min per 1.73 m^2 (<18 years).

Urine output <0.3 mL/kg per hour for ≥24 h, OR

Anuria for ≥12 h

2.3. Inclusion Criteria

All pediatric patients with COVID-19 (detected by polymerase chain reaction performed on nasopharyngeal aspirates) were admitted to Hamad Hospital from (0 to 14) years, using electronic medical records (Cerner) over that time period (from March 1 to January 1, 2021), with one of the following:

a) Proteinuria: (≥1+) on dipstick analysis or urine protein/creatinine ratio in spot urine samples > 0.2.
b) Hematuria: ≥ 5 RBC/HPF.
c) Sterile Pyuria: ≥ 5 WBC/HPF or ≥10 WBC/mm^3 with negative urine culture [24].
d) Hypernatremia:> 145meq/l.
e) Hyponatremia: < 135 meq/l.
f) Hypokalemia:< 3.5meq/l.
g) Metabolic acidosis (ph <7.35).
h) Elevated serum creatinine:> 1.5 times greater than (ULRI) values.
i) Elevated serum urea level: > 7 mmol/l.
j) Urine specific gravity (SG) <1.003.

2.4. Exclusion Criteria

Patients with previous chronic kidney diseases.

2.5. Data Collection

Children who met inclusion criteria, data were collected from electronic medical records such as symptoms at presentation, duration of symptoms, comorbid conditions (infancy, asthma, obesity, and immunosuppression), and the severity of disease, physical examination findings, laboratory investigations, radiologic findings, therapies, clinical course during hospitalization, and demographic data.

2.6. Statistical Consideration and Data Analysis

Descriptive statistics in the form of mean and standard deviation or median and interquartile range were used to present the sample demographics and other clinical features. Categorical data are presented as frequencies and percentages. Bivariate analysis was performed to compare comorbidities and laboratory parameters between the patients with and without severe disease. This was performed using nonparametric tests (Wilcoxon rank sum) or parametric tests (t-test) for continuous variables, as appropriate. Fisher's exact test or the $\chi 2$ test was used to compare categorical variables between patients with and without severe disease. Regression analysis was used to assess the relationship between dependent and independent variables. A α of 0.05 (two tailed) was predetermined as the level of significance. All analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 25 (SPSS Inc., Chicago, IL). No sample size calculation was performed because this was an exploratory descriptive study. Statistical Consideration and Data Analysis were performed by a member of the Medical Research Center.

3. Results

The electronic medical records of 2586 patients aged 0-14 years who presented with COVID-19-related infections at all the facilities of Hamad Medical Corporation, Qatar, from March 1, 2020, to January 1, 2021, were reviewed. A total of 2186 patients were excluded due to missing data (584 patients) or asymptomatic presentation (1602 patients). A total of 400 patients were included in this study and were divided into two groups: patients with renal involvement (renal group), 118 patients (29.5%); and patients without renal involvement (non-renal group), 282 patients (70.5%), as shown in Figure 1. The demographic characteristics, clinical features at presentation, and laboratory findings of both the groups are shown in Table 1. In the renal group, 90 patients (76.3%) were female, the median age was 16.7 months, fever was present in 107 patients (90.7%), and median duration of hospitalization was 3.3 days. 84 patients (71.2%) presented with respiratory symptoms and 34 patients (28.8%) presented with gastroenterological symptoms. The most frequent manifestation of renal involvement was microscopic hematuria, which was observed in 44 patients (38.3), followed by leukocyturia (39 patients, 33.1). AKI was found in 14 patients (12%), while proteinuria was present in 3 patients (2.6%). All AKI cases were stage 1 according to KDIGO staging. Metabolic acidosis was noted in 16 patients (13.6%) and serum electrolyte abnormalities were observed in 47 patients (39.8%). None of the patients required renal replacement therapy or developed hypertension. During hospitalization, chemistry values were corrected for all

patients. Urine tests were performed on patients every second day during hospitalization. After discharge, urine tests were performed weekly. All urinary findings completely resolved during the first 6 weeks of the follow-up period. In this group, four patients were admitted to the pediatric intensive care unit (PICU) and five patients were associated with multisystem inflammatory syndrome in children (MIS-C). In the non-renal group, 170 patients were female (60.3%), the median age was 27.8 months, fever was found in 167 patients (70.5%) and median duration of hospitalization was 2.8 days. 202 patients (71.6%) presented with respiratory symptoms and 80 patients (28.4%) presented with gastroenterological symptoms. Table 2 shows the markers of renal involvement in hospitalized children with covid-19 according to the disease severity. Table 3 shows the markers of renal involvement according to the symptoms of presentation.

Table 1. *Shows demographic characteristics, clinical features at presentation, and laboratory findings, of both groups.*

	Overall (n=400)	**Renal-involvement (n=118)**	**Non-renal involvement N=282**	**P Value**
Demographics				
Age (year)				
≤1	201 (52.2)	53 (44.9)	148 (52.5)	
1-2	118 (29.5)	56 (47.5)	62 (22.0)	0.001
>2	81 (20.3)	9 (7.6)	72 (25.5)	
Sex				
male	140 (35)	28 (23.7)	112 (39.7)	0.002
female	260 (65)	90 (76.3)	170 (60.3)	
Month of admission				
March,	6 (1.5)	1 (0.8)	5 (1.8)	
April	21 (5.3)	4 (3.4)	17 (6.0)	
May,	62 (15.5)	14 (11.9)	48 (17.0)	
June	109 (27.3)	35 (29.7)	74 (26.2)	
July,	63 (15.8)	20 (16.9)	43 (15.2)	0.590
August	61 (15.3)	24 (20.3)	37 (13.1)	
Sep,	43 (10.8)	10 (8.5)	33 (11.7)	
Oct	21 (5.3)	6 (5.1)	15 (5.3)	
Nov,	9 (2.3)	3 (2.5)	6 (2.1)	
Dec	5 (1.3)	1 (0.8)	4 (1.4)	
Race				
Asian	125 (31.3)	38 (32.2)	87 (30.9)	
Arab	235 (58.8)	69 (58.5)	166 (58.9)	0.226
Africa	31 (7.8)	11 (9.3)	20 (7.1)	
Europe, America	9 (2.3)	0 (0)	9 (3.2)	
Underlying comorbidities				
Asthma	22 (5.5)	7 (5.9)	15 (5.3)	0.806
Obese	26 (6.5)	4 (3.4)	22 (7.8)	0.103
immunosuppression	12 (3.0)	6 (5.0)	6 (2.2)	0.12
Blood group				
O	174 (43.5)	49 (41.5)	125 (44.3)	
A	129 (32.3)	39 (33.1)	90 (31.9)	0.816
B	73 (18.3)	21 (17.8)	52 (18.4)	
AB	24 (6.0)	9 (7.6)	15 (5.3)	
Clinical features at presentation				
Coagulopathy	32 (8.0)	18 (15.3)	14 (5.0)	0.001
Fever	274 (77.2)	107 (90.7)	167 (70.5)	0.001
duration of fever				
1-2	225 (65.8)	81 (74.3)	144 (61.8)	
3-5	105 (30.7)	24 (22.0)	81 (34.8)	0.058
> 5	12 (3.5)	4 (3.7)	8 (3.4)	
severity of fever				
38-39	290 (85.5)	75 (70.1)	215 (92.7)	0.001
>39	49 (14.5)	32 (29.9)	17 (7.3)	
SEVERITY OF DISEASE:				
MODERATE	143 (35.8)	53 (44.9)	90 (31.9)	0.013
SEVERE	257 (64.3)	65 (55.1)	192 (68.1)	
Diarrhea	156 (39.8)	53 (44.9)	103 (37.6)	0.174
Vomiting	87 (22.3)	31 (26.3)	56 (20.5)	0.209
poor appetite	94 (23.6)	40 (34.2)	54 (19.1)	0.001
Tachypnea	19 (4.8)	9 (6.0)	10 (3.6)	0.004
TACHYCARDIA	94 (23.5)	54 (45.8)	40 (14.2)	0.001
Cough	305 (76.3)	84 (71.2)	221 (78.4)	0.12
Dehydration	26 (6.5)	14 (11.9)	12 (4.3)	0.005
headache	27 (6.8)	3 (2.5)	24 (8.5)	0.001
Seizures	5 (1.3)	4 (3.4)	1 (0.4)	0.01

	Overall (n=400)	Renal-involvement (n=118)	Non-renal involvement N=282	P Value
Sore throat	53 (13.3)	8 (6.8)	45 (16.0)	0.04
MUSCLE PAIN	13 (3.3)	0 (0)	13 (4.6)	0.007
duration of hospitalization				
1-2 day	219 (54.8)	65 (55.1)	39 (33.1)	
3-5 day	148 (37)	14 (11.9)	154 (54.6)	0.18
>5 day	33 (8.3)	109 (38.7)	19 (6.7)	
Ventilation	2 (0.5)	2 (1.7)	0 (0.0)	0.03
PICU	7 (1.8)	4 (4.1)	3 (1.1)	0.05
Laboratory Features				
CT				
10-20	170 (42.5)	49 (41.5)	121 (42.9)	
21-30	156 (39)	37 (31.4)	119 (42.2)	0.01
> 30	74 (18.5)	32 (27.1)	42 (14.9)	
Wbc		10.3 ± 5.1	8.6 ± 3.8	0.001
Hg	-	12.2 ± 1.8	12.0 ±0.98	0.46
Platelets	-	317.4 ± 117	327.1 ± 83.4	0.35
CRP	-	12.5 ± 18.9	16.6 ± 23.5	0.07
ALT	-	71.7 ± 130	68 ± 111	0.95
AST	-	81.8 ± 95.9	76 ± 101	0.89
elevated Liver enzymes	45 (113)	20 (16.9)	25 (8.9)	0.02
Low Albumin	-	42.3 ± 5.4	43.5 ± 2.7	0.009
Multisystem inflammatory syndrome	14 (3.5)	5 (4.2)	9 (3.2)	0.60

Table 2. *Markers of renal involvement in hospitalized children with COVID-19, according to the severity of disease.*

Markers of renal involvement	Overall (400)	Overall (118)	Severe cases	Moderate cases	P value
Age (year)					
≤1	201 (52.2)	53 (44.9)	35 (53.8)	18 (34)	
1-2	118 (29.5)	56 (47.5)	26 (40)	30 (56.6)	0.10
>2	81 (20.3)	9 (7.6)	4 (6.2)	5 (9.4)	
Sex					
M	140 (35)	28 (23.7)	16 (24.6)	12 (22.6)	0.80
F	260 (65)	90 (76.3)	49 (75.4)	41 (77.4)	
Elevated Creatinine	14 (3.5)	14 (12.0)	9 (14.1)	5 (9.4)	0.44
Elevated Urea	33 (8.2)	33 (28.7)	23 (36.5)	10 (19.2)	0.04
Proteinuria	3 (0.75)	3 (2.6)	2 (3.1)	1 (1.9)	0.70
Hematuria	44 (11)	44 (38.3)	23 (36.5)	21 (40.4)	0.67
pyuria	39 (9.7)	39 (33.1)	25 (38.5)	14 (26.4)	0.17
Urine SG < 1.005	15 (3.7)	15 (12.7)	9 (13.8)	6 (11.3)	0.68
HYPERNATREMIA	1 (0.25)	1 (0.8)	1 (1.5)	0 (0)	0.36
HYPONATREMIA	7 (1.75)	7 (6.0)	5 (7.8)	2 (3.8)	0.36
HYPOKALEMIA	13 (3.25)	13 (11.0)	8 (12.3)	5 (9.4)	0.62
HYPERKALEMIA	26 (6.5)	26 (22)	16 (24.6)	10 (18.8)	0.62
METABOLIC ACIDOSIS	16 (4)	16 (13.6)	9 (13.8)	7 (13.2)	0.92
HYPOTENSION	11 (2.75)	11 (9.3)	8 (12.3)	3 (5.7)	
CT					
10-20	170 (42.5)	49 (41.5)	23 (35.4)	26 (49.1)	
21-30	156 (39)	37 (31.4)	21 (32.3)	16 (30.2)	0.25
> 30	74 (18.5)	32 (27.1)	21 (32.3)	11 (20.8)	
Blood Group					
A	174 (43.5)	39 (33.1)	19 (29.2)	20 (37.1)	
B	129 (32.3)	21 (17.8)	9 (13.8)	12 (22.6)	0.26
AB	73 (18.3)	9 (7.6)	5 (7.7)	4 (7.5)	
O	24 (6.0)	49 (41.5)	32 (49.2)	17 (32.1)	
Coagulopathy	32 (8)	18 (15.3)	11 (16.9)	7 (13.2)	0.58

Table 3. *Markers of renal involvement in hospitalized children with COVID-19, according to the presentation symptoms.*

Markers of renal involvement	Overall (118)	Gastroenterological presentation (34)	Respiratory presentation (84)	P Value
Sex				
M	28 (23.7)	9 (26.5)	19 (22.6)	0.66
F	90 (76.3)	25 (73.5)	65 (77.4)	
Age (year)				

Markers of renal involvement	Overall (118)	Gastroenterological presentation (34)	Respiratory presentation (84)	P Value
≤1	53 (44.9)	16 (47.1)	37 (44)	
1-2	56 (47.5)	17 (50)	39 (46.4)	0.48
>2	9 (7.6)	1 (2.9)	8 (9.5)	
Elevated Creatinine	14 (12)	6 (17.6)	8 (57.1)	0.23
Elevated Urea	33 (28.7)	15 (44.1)	18 (22.2)	0.02
Proteinuria	3 (2.6)	0 (0)	3 (3.6)	0.26
Hematuria	44 (38.3)	8 (23.5)	36 (44.4)	0.04
pyuria	39 (30.1)	8 (23.5)	31 (36.9)	0.16
Urine SG < 1.005	15 (12.7)	0 (0)	15 (17.9)	0.008
HYPERNATREMIA	1 (0.8)	1 (2.9)	0 (0)	0.11
HYPONATREMIA	7 (6)	2 (6.1)	5 (6)	0.98
HYPOKALEMIA	13 (11)	3 (8.8)	10 (11.9)	0.63
METABOLIC ACIDOSIS	16 (13.6)	3 (8.8)	13 (15.5)	0.33
HYPOTENSION	11 (9.3)	5 (14.7)	6 (7.1)	0.20
CT				
10-20	49 (41.5)	11 (32.4)	38 (45.2)	
21-30	37 (31.4)	14 (41.2)	23 (27.4)	0.30
> 30	32 (27.1)	9 (26.5)	23 (27.4)	
Blood Group				
A	39 (33.1)	12 (35.3)	27 (32.1)	
B	21 (7.8)	9 (26.5)	12 (14.3)	0.27
AB	9 (7.6)	1 (2.9)	8 (9.5)	
O	49 (41.5)	12 (35.3)	37 (44)	

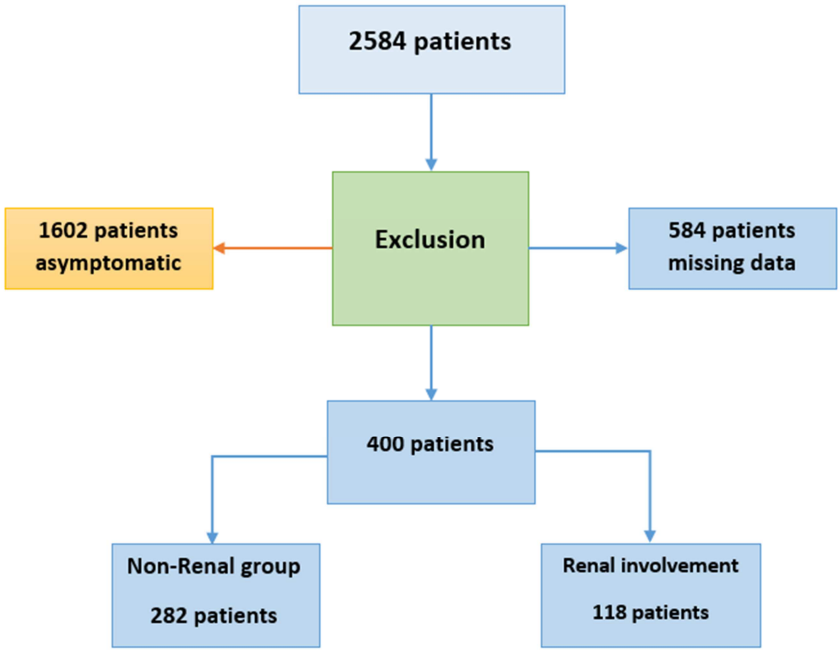

Figure 1. *Flow diagram of study selection.*

4. Discussion

The results of this retrospective study revealed a relatively high prevalence of renal involvement in hospitalized pediatric patients with COVID-19. Renal involvement was associated with a longer duration of hospitalization. Compared to patients who did not develop renal manifestations, patients who developed AKI had more severe disease and even showed failure of other organs. AKI was found in 14 patients (3.5%), which is lower than other studies who reported 29% and 21% [21, 25]. This difference between our study and those studies maybe due to the severity of cases, where in other studies high number of patients admitted to PICU, but in our study only 7 (1.8%) were admitted to PICU. Another reason that could explain the lower prevalence of AKI in our cohort, that we reported lower incidence of MIS-C in our study 14 (3.5%), while in the in these studies it was 73% and 15%. All AKI cases in our patients were stage 1 according to KDIGO staging. Remarkably, AKI was asymptomatic without significant oliguria or severe hypovolemia, and none of the patients required renal replacement therapy (RRT). All AKI patients returned to the normal range during the first week of infection.

Different parts of the world have reported during the pandemic their experience with this disease. In children, AKI

was reported to be present in 10.8% and 12.9% of patients [26, 27]. Other studies found much higher incidences of AKI at range of 20% and as high as 70% [25, 28, 29, 30]. Contrarily, other studies reported significantly lower rates at 1.2%, 1.3%, 8.2%, and 2.7% [31-34]. A recent study by Basu et al. reported an AKI incidence of 37.5% in 311 pediatric patients with COVID-19 [33]. Kari et al. hypothesized that some discrepancy in AKI incidence may also be attributed to differences in the AKI definitions used [25].

Other than AKI, in our study, among 400 patients, three children (0.7%) developed proteinuria, while hematuria was in 11% of the patients. In a study, proteinuria was found in 44 % and hematuria in 77% of the patients [21] and another study, of 346 patients, hematuria was seen in 6 (1.7%) and proteinuria was in 10 (2.9%) [35].

Comparing the renal and non-renal groups, the patients were predominantly younger in the renal group than in the non-renal group; remarkably, females were dominant in the renal group. Furthermore, coagulopathy, elevated liver enzymes, fever, fever severity, poor appetite, dehydration, tachycardia, tachypnea, seizure, ventilation, MIS-C, and PICU were higher in the renal group than in the non-renal group. In contrast, headache, throat pain, and muscle pain were lower than those in the renal group. AKI resolved in all patients before discharge. Lower albumin levels and higher WBC counts are associated with AKI in children. There was a good outcome following COVID-19 infection in children with kidney involvement, so all renal manifestations resolved over a short follow-up period of 6 weeks.

Descriptions of renal dysfunction caused by COVID-19 in pediatrics will help clinical practices to prevent and treat these abnormalities in a timely manner. In COVID-19, proteinuria and hematuria seem to be associated with a more severe clinical course and higher mortality, which would provide an opportunity for early risk stratification [8, 36]. In patients with suspected or confirmed COVID-19, emphasis should be placed on the optimization of volume status to prevent pre-renal AKI, while avoiding hypervolemia, which may worsen the patient's respiratory status.

A conservative regime of fluid resuscitation is recommended by the Surviving Sepsis guidelines for critical illness in COVID-19 [37]. A significant increase in critical cases in adult patients may increase the need for RRT, and using acute peritoneal dialysis in select cases [38]. The prothrombotic complication is considered an additional challenge in the use of the extracorporeal circuits required for RRT. In a French study, circuit clotting was found in 97% of patients receiving RRT [39]. Systemic anticoagulation is required in patients with COVID-19 who are treated with RRT [40].

Several possible explanations for the mechanisms of kidney involvement in COVID-19 are suggested. The first is the direct infection of kidney cells with the virus. The virus spike (S) protein of COVID-19 binds to angiotensin-converting enzyme 2 (ACE2), which is attached to the outer surface of cells in the lungs, vascular endothelium, kidneys, heart, and intestine. This possibility is supported by histopathological findings of the presence of ACE2 receptors and viral inclusion particles with distinctive spikes in the tubular epithelium, podocytes, and endothelial cells of the glomerular capillary loops, visualized by electron microscopy [41, 42, 43]. Histopathological findings include prominent acute tubular injury and diffuse erythrocyte aggregation and obstruction in peritubular and glomerular capillary loops [41, 42]. Secondly, the damage is caused by microvascular dysfunction secondary to endothelial damage. This possibility is supported by the demonstration of lymphocytic endothelialitis in the kidney in addition to viral inclusion particles in glomerular capillary endothelial cells [43]. Thirdly, similar to other severe infection with influenza virus, cytokine storm may be playing an important role in the immunopathology of COVID-19 kidney involvement in these patients [44]. In fact, it has been speculated that this is an underlying mechanism of the clinical 'viral sepsis' and multiple-organ dysfunction, including AKI, in patients with COVID-19 [45]. Glomerular injury mediated by immunocomplexes of viral antigens or virus-induced specific immunological effector mechanisms is also possible, and this is reflected in the development of collapsing focal segmental glomerulosclerosis in patients with SARS-CoV-2 who have two high-risk variants of APOL1 (the gene that encodes apolipoprotein L1), indicating genetic or ethnic variable response or susceptibility towards these viruses involvement's of kidney [46- 48]. Finally, transient albuminuria may occur secondary to endothelial dysfunction or direct podocyte injury. It is also possible that the pattern of severe proximal tubular injury may lead to a defect in receptor-mediated endocytosis, resulting in proteinuria [42]. In critically ill patients, other potential etiologies, such as rhabdomyolysis, volume depletion, and interstitial nephritis can be risk factors [48].

Studies on children with COVID-19 showed electrolyte abnormalities such as potassium, sodium, chlorine, and calcium [34, 49]. Hyponatremia is the most common electrolyte disorder, which is related to an elevated risk of mortality in hospitalized children [50]. A case-control study found that electrolyte abnormalities such as hypokalemia, hypochloremia, and hyponatremia are more common in the COVID-19 group than in the control group [51). Urine formation, blood pressure regulation, osmolality regulation, acid-base balance, and hormone secretion are essential functions of the kidneys [52]. As suggested, coronaviruses bind to ACE2 receptors to enter cells [53, 54]. Therefore, the imaginable mechanisms that cause renal insufficiency in COVID-19 patients can be low fluid intake or fluid loss due to fever. Additionally, AKI can be caused by the cytopathic effects of COVID-19 on proximal tubular straight cells and podocytes. Furthermore, significant mortality in COVID-19 patients is associated with AKI. [55] The involvement of pathogens in the kidneys can damage many mechanisms and cause several consequences such as fluid and electrolyte disturbances. Hence, controlling renal function can reduce or prevent severe complications in COVID-19 patients and play a significant role in reducing mortality. Current studies found that electrolyte disorders, especially hyperkalemia are the

most common renal issue in COVID-19 hospitalized children [56]. Decreased kidney function can drive fluid and electrolyte imbalances [57]. As well, gastrointestinal involvement can also cause fluid and electrolyte disturbances [58]. Therefore, monitoring fluid and electrolyte balance play an essential role in the management of these patients [59].

5. Conclusion

Kidney involvement in children with COVID 19 infection can range from mild symptoms with incidental urinary findings to AKI. Electrolyte abnormalities with metabolic acidosis can present at presentation and require careful and immediate attention and management. Although we had a relatively high prevalence of kidney involvement during the reported period of our study, we had a lower number of children with AKI, and none of them required kidney replacement therapy. Further studies with longer follow-up periods are needed to characterize the short- and long-term effects of renal manifestations in children.

Abbreviations

COVID 19: Coronavirus disease 2019;
AKI: Acute Kidney injury;
PCR: Polymerase Chain Reaction

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of the Medical Research Center at Hamad Medical Corporation, on 17/02/2021, approval No: MRC-01-21-089.

It was registered in ClinicalTrials. gov Identifier: (NCT04788394).

This retrospective study was conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP), and within the laws and regulations of MOPH in Qatar.

All methods were performed in accordance with the relevant guidelines and regulations.

Consent for Publication

Not required

Availability of Data and Materials

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

MAOH: proposal and protocol development, data acquisition, drafting, and writing of the manuscript. AI: Writing the manuscript. FF: acquiring of data. MA: acquiring of data. FA: acquiring of data. LA: acquiring of data. WA: acquiring of data. SA: Writing the manuscript. MS: acquiring of data. ME: acquiring of data. LASS: manuscript review.

All authors read and approved the final manuscript.

ORCID

Mahmoud Alhandi Omar Helal: https://orcid.org/0000-0002-4026-3169

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