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ORIGINAL ARTICLE

Acute kidney injury in children with moderate-severe COVID-19 and multisystem inflammatory syndrome in children: a referral center experience

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Abstract

Background Data on the characteristics of acute kidney injury (AKI) in pediatric COVID-19 and MIS-C are limited. We aimed to define the frequency, associated factors and early outcome of AKI in moderate, severe or critical COVID-19 and MIS-C; and to present a tertiary referral center experience from Türkiye.

Methods Hospitalized patients ≤ 18 years of age with confirmed COVID-19 or MIS-C at İhsan Doğramacı Children's Hospital, Hacettepe University, between March 2020—December 2021 were enrolled. The characteristics of AKI in the COVID-19 group were investigated in moderate, severe and critically ill patients; patients with mild COVID-19 were excluded.

Results The median (Q1-Q3) age in the COVID-19 ($n = 66$) and MIS-C ($n = 111$) groups was 10.7 years (3.9–15.2) and 8.7 years (4.5–12.7), respectively. The frequency of AKI was 22.7% (15/66) in COVID-19 and 15.3% (17/111) in MIS-C; all MIS-C patients with AKI and 73.3% (11/15) of COVID-19 patients with AKI had AKI at the time of admission. Multivariate analyses revealed need for vasoactive/inotropic agents [Odds ratio (OR) 19.233, $p = 0.002$] and presence of vomiting and/or diarrhea (OR 4.465, $p = 0.036$) as independent risk factors of AKI in COVID-19 patients; and need for vasoactive/inotropic agents (OR 22.542, $p = 0.020$), procalcitonin and ferritin levels as independent risk factors of AKI in the MIS-C group. Age was correlated with lymphocyte count ($r = -0.513$, $p < 0.001$) and troponin level ($r = 0.518$, $p < 0.001$) in MIS-C patients. Length of hospital stay was significantly longer in both groups with AKI, compared to those without AKI. Mortality was 9.1% in the COVID-19 group; and was associated with AKI ($p = 0.021$). There was no mortality in MIS-C patients. AKI recovery at discharge was 63.6% in COVID-19 survivors and 100% in MIS-C patients.

Conclusions Independent risk factors for AKI were need for vasoactive/inotropic agents and vomiting/diarrhea in moderate, severe or critical COVID-19 patients; and need for vasoactive/inotropic agents and severe inflammation in MIS-C patients. Our findings suggest that inflammation and cardiac dysfunction are associated with AKI in MIS-C patients; and the association with age in this group merits further studies in larger groups. Early outcome is favorable; long-term follow-up for kidney functions is needed.

Keywords Children · Kidney · Acute kidney injury · COVID-19 · Multisystem inflammatory syndrome in children

Introduction

The coronavirus disease-19 (COVID-19), caused by SARS-CoV-2, which first appeared in Wuhan, China in 2019, quickly turned into a global pandemic. Although the lungs are the primary organs affected by COVID-19, studies with both adult and pediatric patients have shown that the kidneys are one of the organs frequently affected by COVID-19. Acute kidney injury (AKI) is a common complication

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in adults with COVID-19 and is associated with increased mortality [1]. In the pediatric population, the prevalence of AKI is highly variable. Studies reported a frequency of AKI between 1.26% and 29% in hospitalized children [2, 3]. On the other hand, in a multicenter study of critically ill children with COVID-19, the point prevalence of AKI was documented as high as 44% [4]. The pathophysiology of AKI in COVID-19 patients is multifactorial and may develop as a result of dehydration, cytokine storm, direct kidney tubular damage by virus, hemodynamic instability, cardiac dysfunction, and nephrotoxic drugs [5, 6]. The association of AKI with mortality has also been reported in pediatric patients [7, 8].

In April 2020, a new syndrome affecting children was reported with features similar to Kawasaki disease or toxic shock syndrome [9]. Subsequently, cases were reported worldwide. This condition, which was associated with a recent SARS-CoV-2 infection, was termed multisystem inflammatory syndrome in children (MIS-C). Recent studies with MIS-C draw attention to the frequency of AKI in this new condition. Toraih et al. reported the frequency of AKI as 41% in a meta-analysis of 15 studies [10]. In another meta-analysis, the pooled proportion of AKI in MIS-C patients was 20% [11].

Although information on pediatric AKI in COVID-19 and MIS-C has been increasing since the beginning of the pandemic, studies determining the characteristics of AKI in the pediatric population are still needed. Therefore, we retrospectively examined the frequency and associated factors for AKI in hospitalized patients with moderate-severe and critically ill COVID-19 and MIS-C; and aimed to present the experience from a tertiary center in Türkiye.

Methods

Study design and population

We retrospectively analyzed patients under the age of 18 who were hospitalized with the diagnosis of COVID-19 and MIS-C at Hacettepe University İhsan Doğramacı Children's Hospital between March 2020 – December 2021. Medical records of 220 patients with a confirmed diagnosis of SARS-CoV-2 by positive reverse transcriptase-polymerase chain reaction (RT-PCR) and 112 MIS-C patients diagnosed according to Centers for Disease Control and Prevention's (CDC) diagnostic criteria were reviewed [12].

Patients with chronic kidney disease and patients who developed SARS-CoV-2 infection after hospitalization for AKI were excluded. The characteristics of AKI in the COVID-19 group were investigated in moderate, severe and critically ill patients categorized according to the National Institutes of Health's classification; mild cases that did not have shortness of breath, dyspnea, or abnormal chest imaging were excluded [13]. The patient inclusion flow diagram is given in Fig. 1; 66 moderate-severe-critically ill patients with COVID-19 and 111 MIS-C patients which fulfilled inclusion criteria composed the study group.

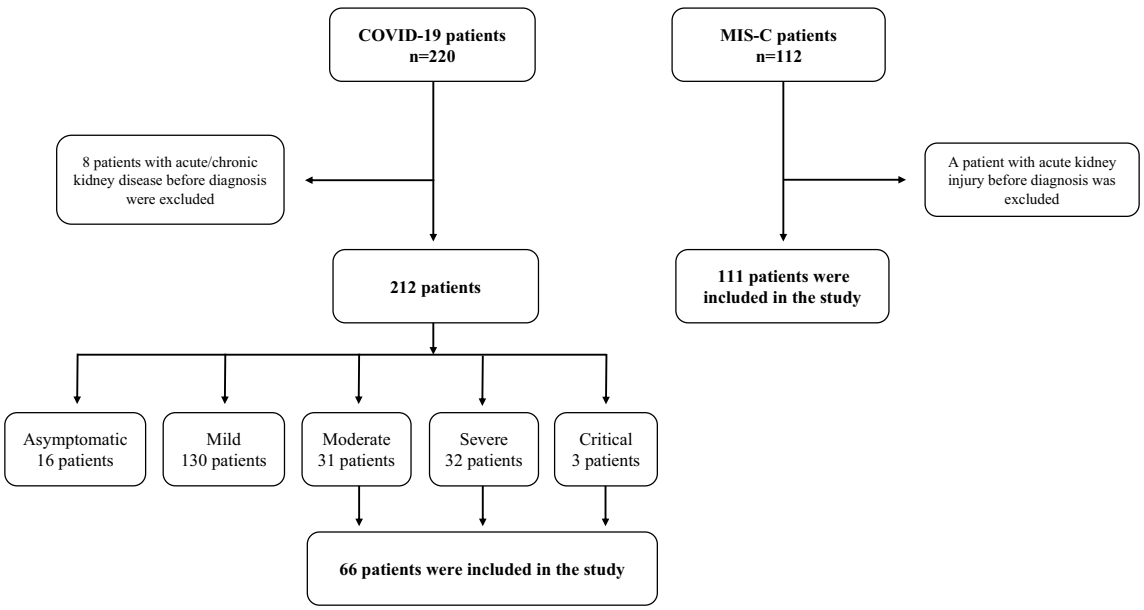

Fig. 1 Patient inclusion flow diagram

Data collection

We retrospectively collected data from medical records for demographic characteristics, underlying disease(s), complaints and findings at presentation, laboratory characteristics (including procalcitonin, IL-6, BNP, troponin and echocardiography in MIS-C group) at admission, treatment, clinical course, outcome and laboratory data at discharge.

The study protocol was approved by the Hacettepe University Clinical Research Ethics Committee (KA-21092).

Definitions

Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were used for definition and staging of AKI [14]. KDIGO defines AKI as an increase in serum creatinine of 0.3 mg/dL within 48 h or an increase in serum creatinine by 1.5 times the initial value within 7 days. The staging of AKI is expressed by the rate of increase of serum creatinine level relative to baseline creatinine. Stage 1, 2, and 3 AKI are a 1.5–1.9, 2.0–2.9 and ≥ 3 times increase in serum creatinine level from the baseline value, respectively. Estimated baseline creatinine value was calculated ["back-calculate" serum baseline creatinine by setting the estimated glomerular filtration rate (eGFR) to 120 ml/min/1.73m^2] using the modified Schwartz formula in patients who did not have a baseline creatinine value in the last one year [15]. AKI recovery was defined as eGFR above 90 ml/min/1.73 m^2. Since it was a retrospective analysis we defined proteinuria as follows according to the specific gravity in the spot urine analysis of the patients: if the specific gravity was below 1020, 1 + protein; when it was between 1020–1035, 2 + protein; when it was above 1035, 3 + protein presence [16]. Hematuria was defined as red blood cells > 5/hpf on urine microscopy. Hypertension was defined as systolic and/or diastolic blood pressure ≥ 95th percentile (in medical records during hospitalization) for gender, age, and height; and staged as stage 1 or 2 according to the European Society of Hypertension Guideline [17]. Echocardiographic evaluation was performed in all MIS-C patients as soon as possible at the time of admission. Systolic function was classified as normal (> 55%), mild (41–55%), moderate (31–40%) or severe (≤ 30%) dysfunction according to ejection fraction [18].

Obesity was defined as BMI ≥ 95th percentile for age on the CDC gender-specific growth charts in children over 2 years of age, and gender-specific weight for recumbent length ≥ 97.7th percentile on the World Health Organization (WHO) charts in children under 2 years of age [19].

Statistical analysis

Statistical Package for Social Sciences for Windows 22 program was used for analysis. Variables with normal distribution in descriptive statistics were presented as mean ± standard deviation; those without normal distribution, median (interquartile range: 25th–75th percentiles); and categorical variables, number of cases and percentage (%). Student's t-test was used to compare numerical variables with normal distribution; the Mann–Whitney U test was used to compare numerical variables without normal distribution. Categorical variables were assessed using Pearson's chi-square or Fisher's exact test. Logistic regression analyses were performed to define independent risk factors for AKI in COVID-19 and MIS-C groups. Variables associated by univariate analysis at p value of 0.20 or less were further entered into the logistic regression analysis. Parameters with high correlation were removed. Hosmer–Lemeshow goodness of fit statistics were used to assess model fit. P value ≤ 0.05 was considered statistically significant.

Results

The study included 66 moderate-severe-critically ill patients with COVID-19 and 111 MIS-C patients. Thirty-nine of the COVID-19 patients (59.1%) and 67 of the MIS-C patients (60.4%) were male ($p = 0.868$). Although median age of the patients with COVID-19 was higher, compared to the MIS-C group, it did not reach statistical significance [10.71 years (3.93–15.17; range: 0.16–17.96) vs. 8.65 years (4.52–12.68; range: 0.18–17.69); $p = 0.214$]. Other demographic characteristics of the patients at the time of admission are presented in Table 1. Frequency of fever, vomiting/diarrhea and rash was higher in the MIS-C group; and presence of chronic disease and cough was higher in the COVID-19 group.

The frequency of AKI was 22.7% (15/66) in COVID-19 patients and 15.3% (17/111) in MIS-C patients ($p = 0.215$).

AKI in moderate-severe-critically ill COVID-19 patients

Thirty-one patients (47.0%) had moderate, 32 patients (48.5%) had severe, 3 patients (4.5%) had critical COVID-19. There was no significant difference for age, gender, BMI z-scores and presence of obesity of patients with and without AKI. Patients with AKI were more likely to have vomiting and/or diarrhea at presentation than those without AKI ($p = 0.052$) (Table 1). Patients with AKI had higher uric acid ($p = 0.013$), LDH ($p = 0.009$), procalcitonin ($p = 0.004$), D-dimer ($p = 0.019$), BNP ($p = 0.006$) and troponin ($p = 0.001$) levels at presentation, compared to patients without AKI (Table 2).

AKI was present on admission in 11 patients (73.3%). In the remaining 4 patients, AKI developed within the first

Table 1 Demographic and clinical characteristics of COVID-19 and MIS-C patients

Variables	COVID-19 (*N* = 66)				MIS-C (*N* = 111)			
	Overall	AKI (*N* = 15)	No AKI (*N* = 51)	*p* value	Overall	AKI (*N* = 17)	No AKI (*N* = 94)	*p* value
Age, years	10.71 (3.93–15.17)	10.00 (0.79–15.08)	11.09 (4.76–15.42)	0.295	8.65 (4.52–12.68)	11.98 (7.71–15.20)	8.45 (4.00–11.49)	0.006
Male, *n* (%)	39 (59.1)	11 (73.3)	28 (54.9)	0.202	67 (60.4)	9 (52.9)	58 (61.7)	0.497
BMI z-score ($n_1 = 65$, $n_2 = 106$)	1.06 (-0.73–1.58)	1.11 (-1.64–2.15)	0.82 (-0.67–1.53)	0.405	0.49 (-0.94–1.38)	0.27 (-0.73–1.70)	0.50 (-1.05–1.36)	0.853
Obesity, *n* (%)	12/65 (18.5)	5 (33.3)	7 (14.0)	0.128	21/106 (19.8)	4 (23.5)	17 (19.1)	0.741
Symptoms, *n* (%)								
Fever	47 (71.2)	10 (66.7)	37 (72.5)	0.748	111 (100.0)	17 (100.0)	94 (100.0)	
Vomiting/diarrhea	20 (30.3)	8 (53.3)	12 (23.5)	0.052	67 (60.4)	11 (64.7)	56 (59.6)	0.691
Cough	39 (59.1)	6 (40.0)	33 (64.7)	0.087	9 (8.1)	1 (5.9)	8 (8.5)	1.000
Myalgia	9 (13.6)	1 (6.7)	8 (15.7)	0.672	6 (5.4)	2 (11.8)	4 (4.3)	0.228
Rash	–	–	–		49 (44.1)	6 (35.3)	43 (45.7)	0.425
Chronic disease, *n* (%)	33 (50.0)	9 (60.0)	24 (47.1)	0.378	10 (9.0)	1 (5.9)	9 (9.6)	1.000
Neurological	7 (10.6)	1 (6.7)	6 (11.8)		–	–	–	
Cardiac	5 (7.6)	2 (13.3)	3 (5.8)		–	–	–	
Hemato-oncological	5 (7.6)	1 (6.7)	5 (9.8)		–	–	–	
Endocrine	5 (7.6)	2 (13.3)	3 (5.8)		1 (0.9)	–	1 (1.1)	
Pulmonary	4 (6.1)	1 (6.7)	3 (5.8)		5 (4.5)	–	5 (5.3)	
Immunodeficiency	4 (6.1)	–	4 (7.8)		–	–	–	
Metabolic disease	2 (3.0)	1 (6.7)	1 (1.9)		2 (1.8)	1 (5.9)	1 (1.1)	
Gastrointestinal	1 (1.5)	1 (6.7)	–		–	–	–	
Rheumatological	–	–	–		2 (1.8)	–	2 (2.1)	
COVID-19 stage, *n* (%)				0.538				
Moderate	31 (47.0)	6 (40.0)	25 (49.0)					
Severe-critical*	35 (53.0)	9 (60.0)	26 (51.0)					
Ejection fraction, % ($n_2 = 98$)					61.88 ± 12.08	52.00 ± 14.14	63.52 ± 10.96	0.001
Normal (> 55%)					82/104 (78.8)	8/16 (50.0)	74/88 (84.1)	
Mild dysfunction (41–55%)					13/104 (12.5)	5/16 (31.3)	8/88 (9.1)	
Moderate dysfunction (31–40%)					6/104 (5.8)	1/16 (6.3)	5/88 (5.7)	
Severe dysfunction (≤ 30%)					3/104 (2.9)	2/16 (12.5)	1/88 (1.1)	

AKI, acute kidney injury; BMI, body mass index, MIS-C, multisystem inflammatory syndrome in children

Data are presented as n (%) or median (25th and 75th percentiles) or mean ± standard deviation. n_1 = number of COVID-19 patients, n_2 = number of MIS-C patients

*Of the 35 patients whose COVID-19 stage was severe–critical, only 3 patients were in the critical stage. Acute kidney injury developed in 2 of these 3 patients

10 days. Seven patients had stage 1, 2 had stage 2 and 6 had stage 3 AKI (Table 3). Proteinuria was present at admission in 8 of 14 patients (57.1%) with AKI, which was significantly higher than in patients without AKI ($p = 0.031$); the difference for the presence of hematuria at admission did not reach statistical significance (Table 2).

AKI in MIS-C patients

Older age, low albumin, hemoglobin, thrombocyte; and high CRP, procalcitonin, ferritin, D-dimer, troponin, and BNP levels and low ejection fraction on echocardiography on admission were associated with AKI in

Table 2 Laboratory findings in COVID-19 and MIS-C patients with and without acute kidney injury

Variables	COVID-19 ($N=66$)			MIS-C ($N=111$)		
	AKI ($N=15$)	No AKI ($N=51$)	p value	AKI ($N=17$)	No AKI ($N=94$)	p value
Creatinine, mg/dl	0.74 (0.40–1.03)	0.41 (0.25–0.54)	0.002	0.92 (0.69–1.15)	0.42 (0.30–0.55)	< 0.001
eGFR, ml/min/1.73m^2 ($n_1=65$, $n_2=108$)	72.9 (33.3–98.8)	139.0 (116.9–169.4)	< 0.001	63.8 (51.9–79.3)	125.69 (108.57–146.68)	< 0.001
BUN, mg/dl	12.20 (9.56–17.90)	9.64 (7.30–13.55)	0.063	26.4 (16.86–42.14)	10.51 (8.15–14.17)	< 0.001
Sodium, mEq/L	135.0 (132.0–141.0)	137.0 (135.0–140.0)	0.385	133.0 (130.5–138.5)	134.0 (133.0–136.0)	0.375
Potassium, mEq/L	4.18 ± 0.89	4.29 ± 0.51	0.567	3.39 ± 0.58	3.90 ± 0.51	< 0.001
Chloride, mEq/L	102 (100–106)	104 (101–105.25)	0.731	102.29 ± 5.07	100.81 ± 3.77	0.161
Uric acid, mg/dl	5.50 (3.70–7.71)	4.01 (2.72–4.82)	0.013	7.16 (5.33–8.24)	3.69 (2.80–4.80)	< 0.001
Albumin, g/dl	3.68 ± 0.62	3.85 ± 0.47	0.249	2.76 ± 0.63	3.34 ± 0.58	< 0.001
Calcium, mg/dl	9.46 ± 1.13	9.22 ± 0.54	0.266	9.03 ± 0.36	9.30 ± 0.46	0.028
Phosphorus, mg/dl	3.43 (2.69–5.82)	3.76 (3.27–4.36)	0.815	3.40 ± 1.25	3.31 ± 0.95	0.741
Magnesium, mg/dl	2.07 (1.82–2.42)	2.03 (1.93–2.17)	0.405	2.13 ± 0.32	2.06 ± 0.25	0.307
Hemoglobin, g/dl	12.84 ± 2.55	12.66 ± 1.87	0.771	10.90 (9.60–11.95)	11.80 (10.77–12.90)	0.041
White blood cell, /mm^3	7,500 (4,600–13,300)	6,100 (3,800–9,300)	0.196	11,100 (6,500–19,500)	10,000 (6,600–13,975)	0.434
Lymphocyte, /mm^3	1,120 (740–3,020)	1,055 (667.5–1,982.5)	0.533	870 (565–1,320)	1,105 (692.5–1,847.5)	0.090
Neutrophil, /mm^3	4,420 (1,860–10,020)	3,635 (2,465–5,820)	0.222	9,790 (5,385–18,120)	7,270 (4,800–11,650)	0.143
Platelets, × 10^3/mm^3	153 (134–279)	212 (150–291)	0.525	136 (85.5–170)	184 (123.25–290.5)	0.010
LDH, U/L ($n_1=31$)	899 (413–1,971)	391 (257–491)	0.009	342 (243–410)	314 (259–394)	0.609
ESR, mm/h ($n_1=48$, $n_2=107$)	11 (6–23)	19 (8–34.5)	0.219	31 (8–50)	36.5 (17–54.5)	0.575
CRP, mg/dl ($n_1=63$)	2.20 (0.36–16.90)	1.42 (0.52–6.81)	0.580	23.04 ± 9.50	16.05 ± 9.27	0.005
Procalcitonin, ng/ml ($n_1=49$)	0.83 (0.32–16.73)	0.14 (0.05–0.38)	0.004	16.76 (8.55–47.51)	2.54 (1.11–10.53)	< 0.001
IL-6, pg/ml ($n_2=108$)				123.21 (32.06–289.61)	56.69 (20.59–155.76)	0.168
Ferritin, µg/L ($n_1=32$)	278.9 (60.5–1,426.1)	111.6 (64.2–380.1)	0.516	761.5 (440.6–1,434.5)	296.1 (153.4–619.7)	0.001
D-dimer, mg/L ($n_1=48$)	3.20 (0.84–6.16)	0.91 (0.52–1.50)	0.019	6.82 (3.60–12.49)	3.37 (1.83–5.66)	0.006
Fibrinogen, mg/dl ($n_1=48$)	347.01 ± 173.84	369.04 ± 129.32	0.658	538.83 ± 186.03	511.11 ± 191.24	0.582
BNP, pg/ml ($n_1=34$)	32.0 (20.5–205.6)	10.0 (10.0–34.6)	0.006	1,499.1 (183.1–2,840.65)	138.70 (43.37–602.52)	0.001
> 100 pg/ml, n (%)	4 (26.7)	1 (2.0)	0.008	15 (88.2)	53 (56.4)	0.013
Troponin, ng/L ($n_1=45$)	56.30 (14.10–494.37)	2.80 (2.30–7.10)	0.001	177.00 (30.45–396.55)	20.45 (4.45–133.60)	0.007
Urine density ($n_1=40$, $n_2=78$)	1,015.86 ± 8.82	1,019.69 ± 8.48	0.187	1,012.73 ± 4.77	1,015.84 ± 7.95	0.213
Proteinuria, n (%)	8/14 (57.1)	5/26 (19.2)	0.031	5/11 (45.5)	22/67 (32.8)	0.499
Hematuria, n (%)	2/14 (14.3)	1/26 (3.8)	0.276	3/11 (27.3)	10/67 (14.9)	0.380

AKI, acute kidney injury; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; LDH, lactate dehydrogenase; MIS-C, multisystem inflammatory syndrome in children

Data are presented as n (%) or median (25th and 75th percentiles) or mean ± standard deviation. n_1 = number of COVID-19 patients, n_2 = number of MIS-C patients

the MIS-C group (Table 1 and 2). The mean ejection fractions at admission of patients with and without AKI were 52.00 ± 14.14% and 63.52 ± 10.96%, respectively ($p=0.001$). Ejection fraction was low (≤ 55%) in 50% of patients with AKI and 15.9% of patients without AKI ($p=0.005$).

All AKI patients had AKI on admission, and none of the patients developed AKI during follow-up. Almost two-thirds of the patients (64.7%) had stage 1 AKI, and only 2 patients had stage 3 AKI (Table 3). No association was observed between the presence of proteinuria or hematuria and AKI (Table 2).

Table 3 Acute kidney injury stage and characteristics of the patients

Variables	COVID-19 ($N=15$)	MIS-C ($N=17$)	p value
AKI stage			0.179
Stage 1, n (%)	7 (46.7)	11 (64.7)	
Stage 2, n (%)	2 (13.3)	4 (23.5)	
Stage 3, n (%)	6 (40.0)	2 (11.8)	
Hospitalization day of AKI diagnosis	0 (0–3)	0 (0–0)	0.202
Peak serum creatinine, mg/dl	0.94 (0.44–1.65)	0.93 (0.72–1.31)	0.571
Kidney replacement therapy, n (%)	3 (20.0)	3 (17.6)	1.000
CVVHDF	3 (20.0)	2 (11.7)	0.645
Hemodialysis	1 (6.67)	1 (5.8)	1.000
AKI duration, days	2 (1–9), (range: 1–27)	2 (1–2) (range: 1–8)	0.366
Discharge serum creatinine, mg/dl	0.62 (0.25–0.84)	0.39 ± 0.12	0.052
Discharge eGFR	100.02 (80.7–120.45)	159.04 (133.43–181.83)	0.001

AKI, acute kidney injury; CVVHDF; continuous venovenous hemodiafiltration; eGFR, estimated glomerular filtration rate; MIS-C, multisystem inflammatory syndrome in children

Data are presented as n (%) or median (25th and 75th percentiles)

Multivariate analysis for independent factors of AKI

Logistic regression analyses revealed need for vasoactive/inotropic agents [odds ratio (OR) 19.233] and presence of vomiting and/or diarrhea (OR 4.465) as independent risk factors of AKI in the COVID-19 group; and need for vasoactive/inotropic agents (OR 22.542), procalcitonin and ferritin levels as independent risk factors of AKI in the MIS-C group (Table 4). Odds ratio for log-transformed procalcitonin level was 7.124 [95% confidence interval (CI), 1.723–29.456]; each 100 µg/L increase of ferritin level was associated with a 1.142-fold (95% CI, 1.016–1.297) increase for AKI in the MIS-C group.

Although we were not able to identify age as an independent factor, we also found a moderate correlation between age and lymphocyte count ($r=$ -0.513, $p<0.001$) and troponin level ($r=0.518$, $p<0.001$) in MIS-C patients.

Clinical course and outcome

In the COVID-19 group hypertension was observed in 16.7% of patients (11/66); there was no significant difference according to presence of AKI. Five patients had stage 1 hypertension and 6 patients had stage 2 hypertension. Twenty-seven patients (40.9%) with COVID-19 required intensive care unit (ICU) admission. The need for ICU, use of vasoactive/inotropic agents, and follow-up on mechanical ventilation were significantly higher in patients with AKI (Table 5). Two patients with AKI in the COVID-19 group needed extracorporeal membrane oxygenation (ECMO) support and three patients required kidney replacement therapy (KRT). The median AKI duration of COVID-19 patients was 2 days (range 1–27 days) (Table 3). Continuous venovenous hemodiafiltration and/or hemodialysis were performed in three patients for 6, 9, and 27 days.

Table 4 Results of logistic regression analysis for independent risk factors associated with acute kidney injury in COVID-19 and MIS-C patients

Risk factors for AKI according to disease group	Odds Ratio (95% Cl)	p value
COVID-19		
Need for vasoactive/inotropic agents	19.233 (2.958–125.039)	0.002
Vomiting/diarrhea	4.465 (1.105–18.049)	0.036
MIS-C		
Need for vasoactive/inotropic agents	22.542 (1.649–308.097)	0.020
Log10 procalcitonin (ng/ml)	7.124 (1.723–29.456)	0.007
Ferritin (each 100 µg/L increase)	1.142 (1.016–1.297)	0.040

AKI, acute kidney injury; MIS-C, multisystem inflammatory syndrome in children

Log10 procalcitonin: Log transformed procalcitonin

The independent variables for the COVID-19 group were sex, obesity, vomiting/diarrhea, cough, need for intensive care unit, use of vasoactive/inotropic agents, mechanical ventilation support, white blood cell. The independent variables for the MIS-C group were age, ejection fraction, hemoglobin, lymphocyte, neutrophil, platelets, C-reactive protein, procalcitonin, IL-6, ferritin, D-dimer, brain natriuretic peptide (albumin and troponin were removed due to high correlation), mechanical ventilation support, and use of vasoactive/inotropic agents

Hypertension was observed during hospitalization in 7 patients (6.3%) in the MIS-C group (4 patients had stage 1, and 3 patients had stage 2 hypertension). Forty-one patients (36.9%) were followed up in the ICU. Biological agent use, plasma exchange, non-invasive and invasive mechanical ventilation requirement, need for vasoactive/inotropic agent, and ICU admission were higher in patients with AKI (Table 5). ECMO support was performed in one patient. Median AKI duration was also 2 days in MIS-C patients (range 1–8 days). Three patients required KRT; the duration of KRT was 1–2 days in the affected patients.

Length of hospital stay was significantly longer in patients with AKI, compared to those without AKI ($p = 0.005$ and $p = 0.001$, respectively), in COVID-19 and MIS-C groups. Mortality was 9.1% in the COVID-19 group; there was no mortality in MIS-C patients (Table 5). Acute kidney injury was associated with mortality in COVID-19 patients ($p = 0.021$). While all patients with AKI in the MIS-C group had an eGFR above 90 ml/min/1.73m^2 at discharge, 4 of the patients with AKI who survived in the COVID-19 group (4/11, %36.4) had an eGFR below 90 ml/min/1.73m^2 at discharge.

Table 5 The clinical course, treatments applied, and outcomes in COVID-19 and MIS-C patients with and without acute kidney injury

Variables	COVID-19 ($N=66$)				MIS-C ($N=111$)			
	Overall	AKI ($N=15$)	No AKI ($N=51$)	p value	Overall	AKI ($N=17$)	No AKI ($N=94$)	p value
Hypertension, n (%)	11 (16.7)	4 (26.7)	7 (13.7)	0.254	7 (6.3)	1 (5.9)	6 (6.4)	1.000
Antihypertensive requirement, n (%)	8 (12.1)	2 (13.3)	6 (11.7)	0.491	5 (4.5)	–	5 (5.3)	0.375
Treatment, n (%)								
Antibiotic	63 (95.5)	14 (93.3)	49 (96.1)	0.545	101 (90.9)	17 (100)	84 (89.4)	0.355
Antiviral	52 (78.8)	12 (80.0)	40 (78.4)	1.000	100 (90.1)	16 (94.1)	84 (89.4)	1.000
Favipiravir	52 (78.8)	12 (80.0)	40 (78.4)	1.000	100 (90.1)	16 (94.1)	84 (89.4)	1.000
Remdesivir	1 (1.5)	1 (6.7)	–	0.227	6 (5.4)	2 (11.8)	4 (4.3)	0.228
Methylprednisolone	40 (60.6)	7 (46.7)	33 (64.7)	0.209	107 (96.4)	17 (100)	90 (95.7)	1.000
Hydroxychloroquine	3 (4.5)	1 (6.7)	2 (3.9)	0.545	0 (0.0)	–	–	
IVIG	10 (15.2)	5 (33.3)	5 (9.8)	0.040	111 (100)	17 (100)	94 (100)	0 (0)
Biologic agent	4 (6.1)	4 (26.7)	–	0.002	76 (68.5)	16 (94.1)	60 (63.8)	0.013
Anakinra	4 (6.1)	4 (26.7)	–	0.002	74 (69.8)	15 (88.2)	59 (66.3)	0.071
Tocilizumab	–	–	–		3 (2.8)	1 (5.9)	2 (2.2)	0.411
Plasma exchange, n (%)	3 (4.5)	3 (20.0)	–	0.010	27 (24.3)	11 (64.7)	16 (17.0)	<0.001
Oxygen requirement, n (%)	47 (71.2)	12 (80.0)	35 (68.6)	0.524	30 (27.0)	9 (52.9)	21 (22.3)	0.016
ICU, n (%)	27 (40.9)	10 (66.7)	17 (33.3)	0.021	41 (36.9)	14 (82.4)	27 (28.7)	<0.001
Length of ICU stay, days	6.0 (3.0–8.0)	7.5 (4.8–18.8)	6.0 (2.1–7.0)	0.077	3 (2–5.5)	3 (2–6.5)	4 (2–6)	0.425
Vasoactive/inotropic agent, n (%)	8 (12.1)	6 (40.0)	2 (3.9)	0.001	38 (34.2)	13 (76.5)	25 (26.6)	<0.001
Non-invasive mechanical ventilation, n (%)	17 (25.8)	6 (40.0)	11 (21.6)	0.185	14 (12.6)	6 (35.3)	8 (8.5)	0.008
Mechanical ventilation, n (%)	14 (21.2)	7 (46.7)	7 (13.7)	0.011	8 (7.2)	5 (29.4)	3 (3.2)	0.002
Length of mechanical ventilation, days	7.0 (2.0–10.8)	9.0 (7.0–27.0)	3.0 (2.0–7.0)	0.062	5.5 (2.3–7.0)	3.0 (2.0–11.5)	5, 6 and 7 days*	0.546
ECMO, n (%)	2 (3.0)	2 (13.3)	0 (0.0)	0.049	1 (0.9)	1 (5.9)	0 (0.0)	0.153
Length of hospital stay, days	8 (5–11)	11 (7–20)	7 (4–10)	0.005	7 (5–9)	9 (7–10)	7 (5–8)	0.001
Exitus, n (%)	6 (9.1)	4 (26.7)	2 (3.9)	0.021	–	–	–	

AKI, acute kidney injury; ECMO, extracorporeal membranous oxygenation; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MIS-C, multisystem inflammatory syndrome in children

Data are presented as n (%) or median (25th and 75th percentiles). *There were only 3 patients in this category

Extended data comparing COVID-19 vs. MIS-C and COVID-19 AKI vs. MIS-C AKI are presented as an Online Resource.

Discussion

In this study, AKI developed in 22.7% of moderate, severe or critical COVID-19 patients and 15.3% of MIS-C patients. In studies consisting entirely of data from the first year of the pandemic, the frequency of AKI in hospitalized patients with COVID-19 ranged from 1.26% to 29% [2, 3, 7, 16, 20]. However, our study was conducted at a single center, covered a wider time period of the pandemic and also included only moderate, severe and critically ill patients. Relatively higher incidence of AKI in our single center experience can be attributed to the fact that our hospital is a tertiary referral center. Studies have shown that the frequency of AKI in MIS-C varies between 18.2% and 54% [10, 16, 20–22]. Some of these studies had a small number of patients, and the definitions of AKI and MIS-C used in the studies were highly variable.

In this study, we identified vomiting and/or diarrhea as an independent risk factor for AKI in COVID-19 patients. Previously, it was suggested that gastrointestinal findings increase the susceptibility to AKI in COVID-19 patients [2, 3]. Although there are studies that do not support the relationship of AKI and gastrointestinal symptoms, gastrointestinal findings are quite common in both COVID-19 and MIS-C [20]. Although the groups were comparable for white blood cell, thrombocyte, ESR and CRP; elevated levels of LDH, procalcitonin, and D-dimer in our series suggest that inflammation may play a role in the pathogenesis of AKI associated with COVID-19. In addition, elevated BNP and troponin levels indicate that cardiac dysfunction may also play a role in the pathogenesis. As a matter of fact, it is known that cardiac involvement (e.g. fulminant myocarditis) may accompany pediatric COVID-19 patients [23–25]. Multivariate analysis revealed presence of vomiting and/or diarrhea and need for vasoactive/inotropic agents as independent risk factor for AKI in patients with COVID-19; suggesting that the severity of the illness is the real risk factor for AKI, instead of the infection per se. In fact, it has been reported that COVID-19 has a good prognosis in children, even in special conditions such as nephrotic syndrome and chronic kidney disease [26, 27].

In multivariate analysis, we showed that need for vasoactive/inotropic agents and inflammation (presented with procalcitonin and ferritin in the model) were the independent risk factors for AKI in MIS-C patients. Increased capillary permeability secondary to inflammation, as well as cytokine-related hypotension and kidney hypoperfusion are among the conditions thought to be associated with the pathogenesis of AKI in MIS-C patients [20, 28]. In addition, the lower left ventricular ejection fraction in patients with AKI may contribute to the AKI pathogenesis due to decreased cardiac output [20].

Interestingly, we found a significant relationship between older age and AKI in MIS-C patients in univariate analysis. To our knowledge, no similar association has been identified with AKI in patients with MIS-C before. In a recent study, in contrast to our study, the median age of patients with AKI was more likely to be younger than those without AKI (9 years vs. 10.5 years; $p = 0.08$) [22]. While Abrams et al. showed that patients older than 5 years and certain parameters such as BNP, pro-BNP, ferritin, D-dimer, and CRP elevation were associated with severe clinical courses such as ICU admission, shock and decreased cardiac function; in another study, searching for risk factors of severe course in MIS-C, age was not found as a risk factor [29, 30]. Older age was also reported to be associated with thrombotic events in children with COVID-19 or MIS-C [31]. Although the association between age and AKI in MIS-C patients disappeared in multivariate analysis; moderate correlation between age and lymphocyte count ($r = -0.513$, $p < 0.001$) and troponin level ($r = 0.518$, $p < 0.001$) indicate that the association between age and higher level of inflammation and organ damage merits further analyses in larger series.

COVID-19-associated AKI has also been related with severe course in children (ICU admission, inotropic and mechanical ventilatory support, prolonged hospital stay and mortality), as we observed in our study [4, 7, 8, 20, 32]. Moreover, we showed a relationship between AKI and ECMO support in the COVID-19 group. In the MIS-C group, as in the COVID group, we found associations with AKI and ICU admission, inotropic and mechanical ventilatory support, and prolonged hospital stay. We had no mortality in the MIS-C group. Mortality has not been reported in many other studies; however, in a multicenter study which included 322 patients, conducted in Türkiye searching for the factors affecting the mortality of MIS-C patients in the pediatric ICU, mortality was reported as 5% and a correlation was shown between mortality and kidney dysfunction [20, 22, 33].

AKI improved at discharge in all MIS-C patients and in the majority of COVID-19 survivors (63.6%). In previous studies, kidney recovery rate at discharge was reported to be 75–93% in COVID-19 patients and 90% in MIS-C patients [3, 20]. However, among these studies, which had a higher rate of kidney recovery rate in COVID-19 patients, KRT was not used in one study, while the number of patients with AKI was quite low (8.2%, 8/97 patients) in the other [3, 20]. Lower recovery rate in our series in patients with COVID-19 may be attributed to severity of AKI. In the MIS-C group of our study, the use of intravenous immunoglobulin (IVIG), methylprednisolone, and biological agents was higher compared to series reported by Basalely et al. (100% vs. 89% for

IVIG, 96.4% vs. 63.6% for methylprednisolone, and 68.5% vs. 11% for biological agents) [20]. A better recovery rate in our series may indicate that measures to suppress inflammation in MIS-C patients with AKI has a positive effect. Long-term outcomes of patients who had AKI in both the COVID-19 and MIS-C groups merits further studies.

In addition to some limitations due to the retrospective design of our study, there are several other notable limitations. These are the back-calculation of the basal creatinine for the patient's basal creatinine levels, the changes in the virus virulence and emergence of new variants in this process due to the long period in which the patients were included, and the changes in the treatments applied. Only using serum creatinine value in the definition and staging of AKI was also among the limitations. Since urine output was not followed closely in every patient, it could not be used for diagnosis and staging; this condition might have resulted in missing certain cases with AKI. The strengths of our study are the relatively high number of patients with moderate to severe/critical features, treatment practices are more homogeneous due to its single-center nature, and that it covers the widest range of pandemics in the literature. Mild cases of COVID-19 were excluded as they required almost no hospitalization, lacked laboratory data, and serial creatinine follow-up. Hence, AKI rates in our series represent AKI in moderate-severe-critical COVID-19 patients; but not in all patients with COVID-19.

In conclusion, the frequency of AKI in moderate-severe-critical COVID-19 and MIS-C patients is high and AKI often presents at admission; early kidney outcome is excellent in MIS-C, and good in the COVID-19 patients. Independent risk factors for AKI were dehydration (vomiting/diarrhea) and cardiac dysfunction (need for vasoactive/inotropic agents) in COVID-19 patients; and severe inflammation and cardiac dysfunction in MIS-C patients. Older age was correlated with inflammation in MIS-C patients. Further studies evaluating direct and indirect effect of inflammation on cardiac and kidney function in COVID-19 and MIS-C patients may be helpful to develop treatment strategies. Finally, studies on long-term kidney outcome in these groups are needed.

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Data analysis/interpretation: AD, TTO; all authors reviewed the results.
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Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval The study protocol was approved by the Hacettepe University Clinical Research Ethics Committee (KA-21092). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Not applicable.

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