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Review article

Kidney complications associated with COVID-19 infection and vaccination in children and adolescents: a brief review

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Coronavirus disease 2019 (COVID-19) has spread considerably across the globe, affecting numerous children and adolescents besides adults. Despite its relatively lower incidence rates in children and adolescents than in adults, some infected children and adolescents exhibit a severe postinflammatory response known as multisystem inflammatory syndrome in children, followed by acute kidney injury, a common complication. Meanwhile, few reports have been available regarding kidney complications such as idiopathic nephrotic syndrome and other glomerulopathies associated with COVID-19 infection and vaccination in children and adolescents. However, the morbidity and mortality of these complications are not exceptionally high; more importantly, causality has yet to be clearly established. Finally, vaccine hesitancy in these age groups should be addressed, considering the strong evidence of COVID-19 vaccine safety and efficacy.

Key words: COVID-19, Child, Acute kidney injury, Nephrotic syndrome, Vaccination

Key message

Several observational studies have shown that acute kidney injury affects up to 46% of children and adolescents who develop severe postinflammatory responses, such as multisystem inflammatory syndrome in childhood, due to coronavirus disease 2019 (COVID-19). Although causality has not been established, some cases of glomerulopathy or nephrotic syndrome occurring after COVID-19 infection or vaccination have been reported. Therefore, kidney complications associated with these conditions in children and adolescents warrant attention.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions worldwide, including children and adolescents. Although most infected children experience mild to moderate symptoms or remain asymptomatic, some exhibit a severe postinflammatory response known as multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome temporally associated with COVID-19.[1)] This condition reportedly occurs within 2–6 weeks after COVID-19 infection or exposure to an infected person and is characterized by persistent fever, inflammation, and dysfunction of multiple organs, including the heart, kidneys, and lungs. Despite the relatively lower incidence rate of MIS-C (1 of every approximately 3,000–4,000) than that of COVID-19 in adults and its risk of mortality and serious complications, it requires immediate recognition and management.[1-6)]

Since the beginning of the pandemic, reports have shown that acute kidney injury (AKI) in children with MIS-C or critically ill children requiring hospitalization is significantly associated with intensive care unit (ICU) admission.[7,8)] Furthermore, several studies reported other kidney complications, including idiopathic nephrotic syndrome (INS) and various types of glomerulonephritis (GN), in populations with COVID-19 who received the vaccination.[9)] Understanding the epidemiology and pathophysiology of AKI and other kidney complications in relation to COVID-19 infection and vaccination can aid the establishment of treatment strategies and improve clinical outcomes.

This review provided a brief overview of our current understanding of the epidemiology, pathogenesis, and clinical characteristics of AKI, nephrotic syndrome, and GN in children and adolescents who experienced COVID-19 infection and received vaccination.

Kidney complications associated with COVID-19 infection in children and adolescents

1. Acute kidney injury

The Kidney Disease: Improving Global Outcomes defines AKI as one or more of the following criteria: increase in serum creatinine by ≥0.3 mg/dL within 48 hours, increase in serum

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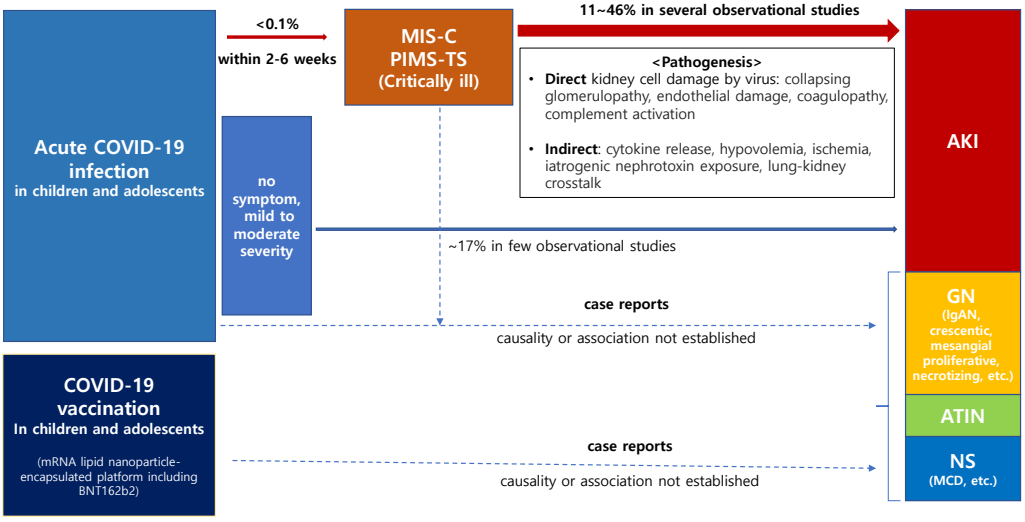

Graphic Abstract. Kidney complications associated with coronavirus disease 2019 (COVID-19) infection and vaccination in children and adolescents. MIS-C, multisystem inflammatory syndrome in children; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with COVID-19; AKI, acute kidney injury; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; ATIN, acute tubulointerstitial nephritis; NS, nephrotic syndrome; MCD, minimal change disease.

creatinine to ≥1.5 times the baseline value within the preceding 7 days, or a urine volume of ≤0.5 mL/kg/hr for 6 hours.[10]

The pathogenesis of COVID-19-associated AKI is multifactorial. First, the virus binds to the angiotensin-converting enzyme 2 receptors distributed across the proximal tubules, podocytes, epithelial cells, and endothelial cells of the kidneys, subsequently causing direct cell damage, resulting in glomerular collapse, endothelial damage, coagulopathy, and complement activation, leading to AKI. In addition, systemic consequences of viral infection, such as cytokine release, hypovolemia, ischemia, or iatrogenic nephrotoxin exposure, or the presence of viruses in distant organs such as the lungs (i.e., lung-kidney cross-talk) can indirectly cause AKI.[1,11]

Studies in adults reported that AKI affects more than 20% of hospitalized patients with COVID-19 and more than 50% of ICU patients.[11] Moreover, several observational studies of various sizes conducted from the beginning of the pandemic reported AKI incidence rates as high as approximately 11%–46% in children and adolescents with COVID-19 who are critically ill or developed MIS-C, similar to those observed in adults.[8,12-20] In contrast, only a few studies reported the incidence of AKI in those with mild to moderate COVID-19. A multicenter cross-sectional study conducted in Turkey reported incidence rates of 16.9% for AKI and 31% for subclinical AKI. Subclinical AKI was defined when at least one of 3 urine biomarkers—neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and interleukin-18—was positive without an elevated serum creatinine level.[21]

A small number of systematic reviews and meta-analyses recently reported the pooled incidence of AKI as 20%–30% in children and adolescents with severe COVID-19 infection such as MIS-C or ICU admission.[22,23] In a meta-analysis by Tripathi et al.,[22] the pooled proportion of death in children with MIS-C was approximately 4% (95% confidence interval [CI], 1%–14%), whereas MIS-C patients with AKI had a 4.68 (95% CI, 1.06%–20.7%) higher odds of death than those without AKI. Moreover, evidence suggests that nearly 15% (95% CI, 4%–42%) of AKI patients with MIS-C require renal replacement therapy (RRT). In contrast, a meta-analysis by Raina et al.[23] revealed that the mortality rate of ICU children with COVID-19 was 2.55% (95 % CI, 1.67%–3.73%) and that the pooled proportion of AKI patients requiring RRT was 0.56% (95% CI, 0.16%–1.43%), significantly lower than that reported by Tripathi et al.[22]

AKI associated with COVID-19 was diagnosed in the early stages of hospitalization in most patients, and they were reportedly infected with COVID-19 approximately 33 days (27.5–46 days) before ICU admission. This appears consistent with reports that MIS-C develops a mean 2–6 weeks after infection with COVID-19. In addition, children with AKI have significantly lower serum albumin levels and higher white blood cell counts than those without AKI at admission.[6,14,18]

A large-scale retrospective study (n=2,546) conducted on pediatric ICU inpatients in North America found that COVID-19 patients with AKI had a 6.29-day (95% CI, 3.95–8.64) longer length of hospital stay, 2.69 times greater odds for mortality (95% CI, 1.48–4.88), and 5.34 times greater odds for kidney support (95% CI, 2.15–13.25) than COVID-19 patients without AKI.[24] Therefore, evidence suggests that AKI after COVID-19 infection in children should be considered a major risk factor for increased severity and mortality.

Table 1 summarizes the major observational studies to date of AKI development in children and adolescents with COVID-19.

2. Idiopathic nephrotic syndrome

INS in children is defined as nephrotic-range proteinuria

Table 1. Summary of studies of AKI development in children and adolescents with COVID-19 infection

Study, country	Study type	No.	Age (yr), median (range)	Kidney complications	Conditions related to COVID-19	Comorbidities	Clinical details	Management	Outcomes
Deep et al.[12] (2020), United Kingdom	Multicenter observational study	116	11 (7–14)	AKI (n=41; 41.4%)	PIMS-TS	Asthma (n=5), cystic fibrosis (3), T1DM (1), autism (1)	Vasodilated shock (49%), inflammatory markers ↑ (CRP, lactate, ferritin, LDH, and CK), cardiac involvement markers ↑ (troponin, CK, and NT-pro-BNP)	PICU admission, vasoactive medication (54%), IMV (35%), ECMO (3/116), CRRT (4/116)	Death (n=2; 1.7%)
González-Dambrauskas et al.[13] (2020), 5 countries	Case series	17	4 (0.08–18)	AKI (3; 18%)	Severe or critical COVID-19	Respiratory (n=1), cardiac (2), cancer or immune (2), obesity (8)	Pneumonia (76%), ARDS (47%), myocarditis (24 %), cardiac arrest (18 %)	PICU admission, antibiotics (88%), corticosteroids (53%), vasoactive infusion (53%), IMV (47%)	Death (1; 6%)
Basalely et al.[14] 2021), United States	Retrospective study	152	8.2 (1.5–13.8) for acute COVID-19, 7.5 (1.5–13.8) for MIS-C	AKI (18; 11.8%)	Acute COVID-19 (97; 63%), MIS-C (55; 36.2%)	HTN (n=1), DM (1), asthma (13), cancer (4), CHD (9), immunosuppressed (5)	Gastrointestinal, fever, rash	PICU admission (60/152), Vasopressor (35/152), ECMO (2/152), MV (11/152), CRRT (2/152)	Death (2; 1.3%)
Bjornstad et al.[8] (2021), United States	Multicenter cross-sectional	106	11.0 (0.1–17.8)	AKI (47; 44%)	Critically ill	Seizure/epilepsy (n=16), CHD (11), asthma (11)	Shock/hemodynamic instability (n=39), sepsis/infection (30), respiratory distress (52), CNS (10)	ICU admission, invasive respiratory support (28 %), vasopressor (29%), ECMO (2%),	Death (6; 6%)
Lipton et al.[15] (2021), United States	Retrospective study	57	7 (8 months–20 years old)	AKI (26; 46%)	MIS-C	Obese (58% for the A KI group, 43% for the non-AKI group)	LV systolic dysfunction, lymphopenia, IL-6, peak CRP, peak ferritin, peak procalcitonin were more prominent in the AKI group	ICU admission (81%), vasopressor (70%), MV (4 %), dialysis (4%), steroids (100%), IVIG (81%) for AKI group	No death, all patients with AKI recovered renal function.
Chopra et al.[16] (2021), India	Cross-sectional	105	6 (1.04–10)	AKI (24; 22.8%)	MIS-C (20; 19.0 %)	CNS (9.5%), tuberculosis (17.1%), hematological/malignancy (14.3 %), sepsis (44.8%), bacterial pneumonia (20.0 %), liver abscess (9.5%)	Leukocytosis, lower platelet count for the AKI group	Invasive respiratory support (34.3%) and vasopressor (25.7%) were significantly higher in the AKI group	Death (n=10; 41.7 % for AKI group vs. n=17; 20.9% for non-AKI group)
Kari et al.[17] (2021), Saudi Arabia	Multicenter retrospective cohort study	89	24 Months (11.5–111.4 months) for the AKI group 72 Months (36.0–92.7 months) for control	AKI (19; 21%)	MIS-C (15% in the AKI group vs. 1.5% in the control group)	63.2% for the AKI group 18.6% for the control group	high RAI scores were correlated with the severity of AKI.	PICU admission (32 %) in the AKI group, use of RRT (n=0)	Oliguria (n=1), use of RRT (n=0), Residual renal impairment at discharge (n=8)
Ricci et al.[18] (2022), Italy	Multicenter retrospective study	38	12.3 (10.6–14.1) for the AKI group, 9.8 (4.3–11.5) for the non-AKI group	AKI (8; 21%)	MIS-C	Not specified	fever >38.0°C (n=34), gastrointestinal (30), rash (16)	PICU admission, fluid replacement, vasoactive drug, IVIG, methylprednisolone bolus, no kidney support	All cases except one recovered renal function within the first week. AKI transient (4), persisted (4)
Basu et al.[19] (2021), 15 countries	Multinational, prospective, point-prevalence study	331	11 (3–16)	AKI (124; 37.4%)	Critically ill	Asthma (12.7%), seizure/epilepsy (13.3%), CHD (9.1%), cancer (8.8%), cerebral palsy/encephalopathy (10.3%)	Respiratory distress (48.0 %), shock/hemodynamic instability (27.5%), sepsis/infection (23.3%), CNS symptoms (11.8%)	ICU admission, invasive respiratory support (26.3 %), vasopressor use (23.5 %) ECMO (2.2%) for confirmed infection	28-Day hospital mortality; 9.5% for confirmed infection with AKI
Stewart et al.[20] (2021), United Kingdom	A single-center observational study	110	10.2 (7.6–12.6)	AKI (33; 30%)	PIMS-TS	T1DM (n=2), sickle cell disease (2), VP shunt (2)	Fever (100%), abdominal pain (72%), vomiting (60 %), diarrhea (59%), respiratory distress (29%)	PICU admission (89%), intubation (20%), inotropic support (76%), methylprednisolone (82%), IVIG (70%)	None had macroalbuminuria or hematuria at follow-up (6-8 weeks, 6 months)
Saygili et al.[21] (2022), Turkey	Cross-sectional	71	mean 9.4 ± 6.2	AKI (12; 16.9%), subclinical AKI (22; 31%)	Mild to moderate severity	Obesity (n=3), asthma (5), developmental delay (5), malignancy (2)	Cough (62%), fever (59 %), sore throat (23%), SOB (20%) Neutrophil count was significantly higher in the AKI group.	No respiratory support (90%), O_2 (7%), high-flow nasal cannula O_2 (3%)	At follow-up (4.3 months), all of AKI group had normal SCr level.
Raina et al.[24] (2022), United States	Retrospective study	2,597	5 (4–5) for the AKI group, 4 (3–5) for the non-AKI group	AKI (274; 10.8%)	Critically ill	Respiratory (64.2%), cardiovascular (58.8%), obesity (54.1%), hematology (45.3%), neurologic (31.8%)	WBC count ↑, serum glucose ↑, bicarbonate ↓ in AKI group.	ICU admission, airway/respiratory support (55.5 %), cardio-respiratory support (2.9%), kidney support (4.7%), vascular access (67.2%)	Death (n=21; 7.7% for the AKI group vs. n=37; 1.6% for the non-AKI group)

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with COVID-19; T1DM, type 1 diabetes mellitus; CRP, C reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase; NT-pro-BNP, N-terminal pro B-type natriuretic peptide; PICU, pediatric intensive care unit; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; ARDS, acute respiratory distress syndrome; MIS-C, multisystem inflammatory syndrome in children; HTN, hypertension; DM, diabetes mellitus; CHD, congenital heart disease; MV, mechanical ventilation; LV, left ventricle; IL-6, interleukin-6; ICU, intensive care unit; IVIG, intravenous immunoglobulin; CNS, central nervous system; RAI, renal angina index; RRT, renal replacement therapy; VP, ventriculoperitoneal; SOB, shortness of breath; SCr, serum creatinine; WBC, white blood cell.

(≥40 mg/m²/hr or a urine protein/creatinine ratio of ≥2 or 3+ protein on a urine dipstick) of unknown etiology plus hypoalbuminemia, edema, or hyperlipidemia.[25] Most children with INS receive chronic immunosuppressive therapy to control the disease activity, which is known to increase the risk of infectious diseases including viral infections.[26]

Morello et al.[26] conducted a systematic review of COVID-19 cases in children with INS. In this comprehensive review of 13 studies (43 children with COVID-19 of 1,126 children with INS) children with INS did not have a particularly high COVID-19 infection rate. Moreover, despite COVID-19 infection, they generally showed a mild clinical course, with low ICU hospitalization rates and a need for respiratory support. They also recommended that immunosuppressive therapy be continued regardless of the pandemic situation. In addition, despite the few cases of INS relapse during the COVID-19 infection period (n=5), they showed a good response to steroids, even de novo cases (n=2) showing typical symptoms and clinical improvement with steroid treatment.

A recent retrospective study of 59 pediatric INS patients from a single center in Korea reported that 20 were infected with COVID-19 during the study period (34%). Consistent with other studies, this study showed that all patients had mild clinical symptoms that improved with symptomatic treatment comprising antipyretic or cold medications and did not require hospitalization or antiviral therapy. Furthermore, the relapse rate among INS patients with COVID-19 (3 of 20 [15%]) did not differ significantly from that of INS patients without COVID-19 (8 of 39 [20.5%]).[27]

Chiodini et al.[28] performed a retrospective cohort analysis of 218 children with INS in Belgium and Italy. Comparison of the relapse rate between the 5 years immediately preceding the COVID-19 outbreak (i.e., 2015–2019) and the first year of the outbreak (i.e., 2020) showed no statistically significant difference, with an incidence rate ratio of 0.9 (95% CI, 0.76–1.06). Moreover, no severe complications among the study participants, such as death or hospitalization due to COVID-19, were reported.

Morello et al.[29] retrospectively analyzed a cohort of 176 children with INS from the beginning of the pandemic to May 31, 2022. A total of 61 (34.7%) were infected with COVID-19 during the study period. After the spread of the omicron variant, children with INS showed a significantly higher COVID-19 infection rate than previously reported. However, the clinical symptoms were mild in children with INS taking immunosuppressive medication or had proteinuria. Moreover, none of the patients required immunosuppressive therapy discontinuation due to the COVID-19 infection.

3. Glomerulopathy

In adults with COVID-19, several pathological findings of kidney biopsies, such as podocytopathies (collapsing glomerulopathies), immune-mediated glomerular diseases (membranous glomerulopathy), tubulointerstitial diseases (acute tubular injury), and thrombotic microangiopathy, have been reported.[1,30,31] In contrast, pathological data in children and adolescents are lacking.[32]

A recent case report showed that a previously healthy 11-year-old boy hospitalized with gross hematuria and generalized edema 2 weeks after contracting the COVID-19 infection in Korea was diagnosed with crescentic immune-complex GN through a kidney biopsy. Steroid therapy, immunosuppressants, including cyclophosphamide and azathioprine, and antihypertensive treatment clinically improved his condition.[33]

Another case study reported on 2 patients (13- and 16-year-old boys) who developed severe, rapidly progressive GN and end-stage renal disease after COVID-19 in India. A kidney biopsy confirmed immunoglobulin A (IgA) nephropathy with crescentic GN, acute tubular injury, and focal medium-artery vasculitis.[34]

In Italy, 2 consecutive renal biopsies were performed in a 10-year-old girl after a COVID-19 infection; the first revealed diffuse and segmental mesangial-proliferative GN, while the second revealed crescentic GN. The same case study also confirmed acute tubulointerstitial nephritis (TIN) through a kidney biopsy in a 12-year-old girl infected with COVID-19.[32]

Furthermore, case reports showed the presence of acute necrotizing GN in 17- and 16-year-old boys infected with COVID-19 in Iran, whereas another report from the United States showed the presence of necrotizing GN in a 17-year-old boy with perinuclear antineutrophil cytoplasmic antibodies/myeloperoxidase vasculitis.[35,36]

Kidney complications associated with COVID-19 vaccination in children and adolescents

Research has demonstrated the safety and efficacy of COVID-19 vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273) in children and adolescents, and the eligibility age for vaccination has been gradually expanded. Since June 2022, vaccination has become available for infants over 6 months of age. A well-known side effect of vaccination is the increased risk of myocarditis and pericarditis after the second dose in young men aged 12–24 years. However, most of these patients improved with conservative treatment, and the condition had no significant impact on their quality of life.[37] In contrast, several cases of renal side effects, such as minimal change disease (MCD), IgA nephropathy (IgAN), and vasculitis, have been reported after vaccination in adults. Nevertheless, causality has yet to be clearly established, with large population-based observational studies suggesting no increase in the risk of occurrence.[9]

Novel mRNA vaccines for SARS-CoV-2, including BNT162B2 (Pfizer), are based on an mRNA lipid nanoparticle-encapsulated platform and induce a stronger cell-mediated response by upregulating CD4+ and CD8+ T cells. Therefore, studies have suggested that the pathogenic mechanism involves the sequential production of proinflammatory cytokines, such as interferon-γ

and tumor necrosis factor-α, which can exacerbate existing immune-mediated glomerular disease or cause de novo GN, including IgAN.[38-40]

In developed countries such as the United States and Japan, the eligibility age for COVID-19 vaccination, especially the Pfizer-BioNTech vaccine, has gradually expanded to include those aged 16+ years (December 2020), 12–15 years (May 2021), 5–11 years (October 2021), and 6 months to 4 years (June 2022). Therefore, case reports on kidney side effects in children and adolescents have been reported mainly in these countries and adolescents aged 12+ years with *de novo* or relapsed forms of glomerular disease (primarily IgAN and INS). Cases of IgAN mainly occurred de novo within 1–2 days after the second dose of the Pfizer-BioNTech vaccine, manifesting as gross hematuria and proteinuria of varying degrees. In most cases, the symptoms improved with intravenous/oral steroid therapy, angiotensin receptor blockers, and supportive care.[39-45]

In contrast to cases of IgAN, there have been cases in which kidney failure and oliguria were severe enough to require hemodialysis. A case report of a 16-year-old girl in Korea showed a relatively long interval between vaccination and symptom onset. She experienced nonspecific symptoms, such as respiratory distress and headache, for 6 weeks after receiving her second dose of the vaccine and was diagnosed with crescentic GN through a kidney biopsy after receiving hemodialysis for acute kidney failure.[46] In Luxembourg, a case of rapidly progressive GN was reported; a 13-year-old girl developed systemic symptoms, including gross hematuria, just 1 d after the first dose of the vaccine and rapidly progressed to AKI, requiring hemodialysis.[47]

Among patients with INS, most had a de novo occurrence than a relapse, and the interval between vaccination and symptom onset was 1–19 days. MCD was the main pathological finding in patients who underwent kidney biopsy, all of whom responded well to steroid treatment.[48-52] On the other hand, 2 reports showed cases of new-onset acute TIN after the second vaccination in Korea that reportedly responded well to oral steroid treatment (a 12-year-old boy) and supportive care (a 17-year-old boy).[53]

Several case reports of kidney complications, such as IgAN and INS after COVID-19 vaccination in children and adolescents are summarized in Table 2.

Management of kidney complications and vaccine hesitancy in children and adolescents with COVID-19

Children and adolescents hospitalized with COVID-19 are at a high risk of developing AKI regardless of disease severity, thereby increasing their morbidity and mortality. In fact, evidence has shown that kidney disease in childhood and adolescence significantly impacted long-term outcomes, such as adult health status, social and behavioral adjustment, educational success, and employment security.[1,54] Therefore, the medical staff caring for these patients should pay special attention to their respiratory and systemic symptoms besides their urinary symptoms and kidney function. If AKI or other kidney complications are diagnosed, a referral to a pediatric nephrologist for active treatment is recommended.

Table 2. Summary of studies of kidney complications in children and adolescents with COVID-19 vaccination

Study, country	Study type	Age (yr)	Sex	Kidney complications	Onset type	Kidney biopsy	Comorbidities	Vaccine brand & dose	Onset interval (day)	Clinical details	Management	Outcomes
Udagawa et al.[41] (2022), Japan	Case report (letter)	15	F	IgAN	Relapse	-	IgAN in remission	Pfizer, 2nd	1	Gross hematuria, fever (38.5 °C), mild proteinuria	Not specified	Urinary findings persisted for 3 days; kidney dysfunction was not observed.
		16	F	IgAN	Relapse	-	IgAN in remission	Pfizer, 2nd	1.5	Gross hematuria, fever (37.7 °C), headache	Not specified	5 Days later, SCr level did not increase, and urinalysis results had normalized.
Uchiyama et al.[39] (2022), Japan	Case series	15	M	IgAN	*De novo*	+	6-Month history of microscopic hematuria	Pfizer, 2nd	1	Gross hematuria, fever (37.7 °C), moderate proteinuria, SCr of 0.97, eGFR of 92, morphological abnormality (–) in the kidneys on CT	Not specified	Gross hematuria spontaneously resolved within 6 days without any treatment, although his microscopic hematuria and proteinuria persisted.
		18	M	IgAN	*De novo*	+	3-Year history of microscopic hematuria	Pfizer, 2nd	2	Gross hematuria, fever (38.6°C), mild proteinuria, SCr of 0.82, eGFR of 99, morphological abnormality (–) in the kidneys on CT	Not specified	Gross hematuria spontaneously resolved within 7 days without any treatment, and microscopic hematuria and proteinuria disappeared gradually.
Okada et al.[42] (2022), Japan	Case report	17	F	IgAN	*De novo*	+	10-Year history of microscopic hematuria	Pfizer, 1st	4	Gross hematuria, proteinuria (0.37 g/gCr), Scr of 0.58, eGFR of 109	Not specified	Macroscopic hematuria changed to microscopic hematuria, and proteinuria resolved spontaneously.
Horino et al.[40] (2022), Japan	Case report	17	M	IgAN	*De novo*	+	5 Months prior to presentation, microhematuria (2+)	Pfizer, 2nd	0.5	Fever, headache, macrohematuria, CRP 1 , SCr of 0.7, marked proteinuria (1.0 g/gCr)	Not specified	Proteinuria and microhematuria persisted for 2 months.

(Continued)

Table 2. Summary of studies of kidney complications in children and adolescents with COVID-19 vaccination (Contuned)

Study, country	Study type	Age (yr)	Sex	Kidney complications	Onset type	Kidney biopsy	Comorbidities	Vaccine brand & dose	Onset interval (day)	Clinical details	Management	Outcomes
Morisawa et al.[43] (2022), Japan	Case series (letter)	16	M	IgAN	*De novo*	+	Asymptomatic hematuria for 2 years, family history of IgAN (mother)	Not specified, 2nd	1	Fever, gross hematuria, peak SCr of 1.26, proteinuria (0.28 g/gCr)	Methylprednisolone pulse followed by oral prednisolone	Gross hematuria resolved 3 days after vaccination. Scr decreased to 1.05 3 months later.
		13	F	IgAN	*De novo*	+	Asymptomatic hematuria for 2 months	Not specified, 2nd	1	Fever, gross hematuria, peak UPCR of 1.99 g/gCr	No treatment	Gross hematuria and proteinuria spontaneously resolved.
Abdel-Qader et al.[44] (2022), Jordan	Case report (letter)	12	M	IgAN, AKI	*De novo*	+	No medical history	Pfizer, 1st	<1	Gross hematuria, proteinuria	Methylprednisolone pulse	Gross hematuria resolved spontaneously, SCr improved at follow-up.
Niel and Florescu[47] (2021), Luxembourg	Case report (letter)	13	F	IgAN presenting RPGN, AKI	*De novo*	+	No medical history	Pfizer, 1st	<1	Fever, asthenia, muscle pain, pharyngitis, SCr of 3.57, macroscopic hematuria, nephrotic-range proteinuria (3.88 g/L), Oliguria	HD for 5 days, IV methylprednisolone pulse followed by oral prednisolone	Kidney function improved progressively. Microscopic hematuria and slight proteinuria persisted.
Hanna et al.[45] (2021), United States	Case series (letter)	13	M	IgAN, AKI	Relapse	-	IgAN, T1DM	Pfizer, 2nd	<1	Gross hematuria	Lisinopril	Gross hematuria resolved spontaneously, and kidney function recovered without intervention within 1 week.
		17	M	IgAN, AKI	*De novo*	+	No medical history	Pfizer, 2nd	<1	Gross hematuria, proteinuria	Methylprednisolone pulse	Gross hematuria resolved spontaneously, but kidney insufficiency persisted.
Kim et al.[46] (2023), Korea	Case report	16	F	CrGN presenting RPGN, AKI	*De novo*	+	No medical history	Pfizer, 2nd	6 Weeks	Dyspnea, headache, BP (155/89), edema, hematuria, proteinuria, swelling and increased echogenicity of both kidneys on renal doppler sonography, peak SCr of 12.7	HD start, methylprednisolone pulse, followed by oral steroid, MMF	HD stopped. Remained in CKD stage at the 3-month follow-up.
Nakazawa et al.[48] (2022), Japan	Case report	15	M	NS	*De novo*	-	No medical history	Pfizer, 1st	4	Eyelid and peripheral edema, urine protein (4+), SCr of 0.64, eGFR of 116, UPCR (7.71 g/gCr), bilateral pleural effusions on chest x-ray, edema of the intestinal wall and ascites	Oral prednisolone	Complete remission
Pella et al.[49] (2022), Greece	Case report	18	M	NS (MCD)	*De novo*	+	No medical history	Pfizer, 1st	11	Gastrointestinal symptoms, ascites, lower extremity edema, hypoalbuminemia (1.8 g/dL), peak nephrotic-range proteinuria (23.4 g/24 hr), total cholesterol (432 mg/dL)	Oral steroid	Complete remission
Jongvilaikasem et al.[50] (2022), Thailand	Case report (letter)	14	M	NS (MCD, AIN), AKI	*De novo*	+	No medical history	Pfizer, 1st	5	Bilateral leg edema, hypertension, urine protein (4+), UPCR of 9 g/gCr, hypoalbuminemia, cholesterol (257 mg/dL)	Methylprednisolone pulse followed by oral prednisolone, HD for 3 weeks	Partial remission
Güngör et al.[51] (2022), Turkey	Case series (letter)	17	F	NS	Relapse	-	INS (MCD) in remission for 4.5 years	Not specified, 2nd	19	Lower extremity and pretibial edema, urea of 5 mmol/L, creatinine of 44.2 μmol/L, albumin of 12 g/L, spot UPCR of 8.7 mg/mg	Oral corticosteroid	Remission achieved 2 weeks after treatment.
		18	F	NS	Relapse	-	INS in remission	Not specified, 2nd	12	Lower extremity edema, urea of 5 mmol/L, creatinine of 42.4 umol/L, albumin of 23 g/L, spot UPCR of 4.1 mg/mg	Oral corticosteroid	Remission achieved
Alhosaini[52] (2022), United Arab Emirates	Case report	16	M	NS (MCD)	*De novo*	+	No medical history	Pfizer, 2nd	7	Bilateral leg pitting edema, nausea, SCr of 0.85, hypoalbuminemia, urine protein (4+), UPCR of 5.6 g/gCr, ascites, pleural effusion	Oral prednisone along with furosemide and olmesartan	After 1 week, edema resolved. proteinuria and serum albumin started to improve.
Choi et al.[53] (2022), Korea	Case series	17	M	ATIN	*De novo*	+	No medical history	Pfizer, 2nd	3	Epigastric pain, nausea, SCr 3, BP (150/85), SCr of 3.1, eGFR of 24, CRP of 3.23, urine blood (–), urine protein (–)	Supportive care	Renal insufficiency gradually improved, discharged after 1 week.
		12	M	ATIN	*De novo*	+	No medical history	Pfizer, 2nd	1	Nausea, vomiting, SCr of 2.28, eGFR of 27, CRP of 6.05, urine protein (2+), UPCR of 1.95 g/gCr	Oral steroid	Remarkable improvement in renal insufficiency on day 10 of hospitalization.

COVID-19, coronavirus disease 2019; IgAN, Immunoglobulin A nephropathy; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CT, computed tomography; HD, hemodialysis,; IV, intravenous; CKD, chronic kidney disease; AIN, acute interstitial nephritis; T1DM, type 1 diabetes mellitus; CRP, C reactive protein; CrGN, crescentic glomerulonephritis; RPGN, rapidly progressive glomerulonephritis; AKI, acute kidney injury; MMF, mycophenolate mofetil; BP, blood pressure; UPCR, urine protein to creatinine ratio; NS, nephrotic syndrome; MCD, minimal change disease; INS, idiopathic nephrotic syndrome; ATIN, acute tubulointerstitial nephritis.

Despite strong evidence of the safety and effectiveness of COVID-19 vaccines, hesitancy remains widespread.[55,56] Wang et al.[57] analyzed vaccine hesitancy and current attitudes toward vaccines among parents of children with chronic kidney disease (n=207). Accordingly, approximately two-thirds of parents were hesitant or unsure about vaccinating their children, and parents with higher education levels were more willing to vaccinate their children. The main reasons for vaccine hesitancy were concerns about vaccine safety, a lack of sufficient information, and a lack of communication with medical experts. Therefore, medical professionals who frequently interact with parents must provide consistent and standardized COVID-19 vaccination information tailored to the parents' level of understanding and maintain consistent communication to increase the COVID-19 vaccination rate.

Conclusion

The current review briefly examined the existing literature on kidney complications reportedly associated with COVID-19 infection and vaccination. A high incidence of AKI is shown in children and adolescents diagnosed with MIS-C or are critically ill because of infection, similar to that in adults. However, INS and other glomerulopathies did not appear to have particularly high morbidity or mortality rates. Vaccine hesitancy in these age groups should be addressed through consistent communication with the parents or guardians based on strong evidence regarding the safety and efficacy of COVID-19 vaccines.

Footnotes

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