Review Article

Renal manifestations of COVID 19 in children

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Abstract

Acute kidney injury (AKI) is an important factor affecting the outcome of hospitalized patients under any disease condition. While a lot has been said and studied about pulmonary manifestations of COVID-19 and multisystem inflammatory syndrome in children, this review focuses on its renal manifestations in children with and its complications. For the collection of data, the patient intervention control outcome model was applied to determine all eligible studies. The data was extracted using PubMed/Medline, Embase, and Google Scholar databases using a combination of keywords (AKI, renal failure, kidney disease, children, pediatric, covid-19, SARS COv2). Studies were reviewed after the exclusion of duplicates. The incidence of renal involvement in COVID 19 is up to 10–15%, which is higher than SARS. Both direct and indirect pathogenic mechanisms operate in patients with COVID 19 leading to varied manifestations. While AKI remains the most common manifestation in children admitted to intensive care units, other manifestations like, proteinuria, hematuria, rhabdomyolysis, and thrombotic microangiopathy have also been described in the literature. The children already on immunosuppression due to transplant or immune-mediated renal disorders do not seem to have more severe illness than those without it. The principles of management of AKI in COVID have not been different than other patient groups.

Keywords: Acute kidney injury, COVID-19, immunosuppression, thrombotic microangiopathy

Introduction

Children constituted less than 12-14% of all lab confirmed cases of COVID 19 and only about 2.5–4% required hospital admission.[1,2] While most pediatric cases are asymptomatic, there have been reports of critical illness including multisystem inflammatory syndrome in children (MIS-C) occurring in all ages of pediatric groups.[3-6]

Although SARS-CoV-2 mainly affects the lungs causing pneumonia, it can, however, affect different organ systems including the myocardium, intestines, kidney, hepatobiliary system, central nervous sytem.[7] Renal involvement remains an important extra-pulmonary manifestation, which has a critical impact on the prognosis and mortality in COVID-19 cases.[8] COVID is expected to become an endemic illness just like other viral illnesses in the future. Diseases like dengue or flu are largely managed by primary care physicians, therefore, it is of utmost importance for them to be aware of complications that may be expected in the natural course of the disease and when to refer the patients to specialty care. In this regard, the present review focuses on renal issues in COVID, especially in children.

Epidemiology

Kidney impairment is more common in SARS-CoV-2.[9,10] The average incidence of acute kidney injury (AKI) as reported in adult patients with SARS-CoV-2 has been between 5.1 and 29%.[11] It is also attributed to comorbidities like hypertension, type 2 diabetes mellitus, cardiac failure, chronic kidney disease, and other chronic diseases in adults, which are almost non-existent in children.

However, children with comorbidities like congenital heart diseases, some urological disorders, and post-renal transplant recipients and infected with SARS-CoV-2 have higher chances of renal involvement and complications [Figure 1].

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Received: 06-09-2021 **Revised:** 06-12-2021
Accepted: 21-12-2021 **Published:** 30-06-2022

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1777_21

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How to cite this article: Mittal A, Nadig P, Singh K. Renal manifestations of COVID 19 in children. J Family Med Prim Care 2022;11:2302-10.

Acute kidney injury

Wang *et al.*[12] reported that 3/238 COVID 19 critically ill children had developed AKI, all of whom required continuous renal replacement therapy. These associations described in this study were gastrointestinal manifestations like vomiting, diarrhea, pain abdomen, elevated IL-6 levels, and complement activation, which could have contributed to AKI. A multi-center study from China reported an incidence of AKI of up to 20%, in SARS-CoV-2 infected children from 25 centers. The incidence increased to 50% in the subset of patients with respiratory failure.[13] Children may present with shock or severe dehydration and need aggressive fluid resuscitation which places them at a higher risk of volume overload and developing renal complications.[14] The incidence of AKI in critically ill pediatric patients infected with SARS-CoV-2 is comparable to data from the Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE) study which reports an incidence of 27% in critically ill children.[15]

Basalely *et al.*[16] described AKI in 18 out of 152 (11%) children with acute COVID 19 infection and MISC related to COVID. It was associated with lower albumin levels and higher WBC counts. Another retrospective observational study on children (N = 70). Nine children (12.9%) met the AKI criteria, five in the no acute respiratory distress syndrome (ARDS) cohort and four in the ARDS cohort, and among them 1 (1.4%) required RRT.[17] A study showed that around 1/3rd of patients either had AKI on presentation or developed it within 24 h of admission.[18] There is also a temporal association between the onset of AKI and the need for intubation. Acute renal impairment in SARS reportedly has high mortality of up to 92%.[10] In general, children with SARS-CoV-2 and AKI have increased chances of ICU admission and require mechanical ventilation, vasopressors than those patients who do not develop AKI.

Table 1 Risk factors for Renal Involvement in COVID-19 in children

Pathophysiology

Coronavirus carried the spike protein (s protein) on its surface, binds to ACE2 receptor on the cell surface, and gets internalized.[19-21] ACE2 is present on the alveolar epithelial cells, lining of the intestine, endothelial cells of both arteries and veins, and also arterial smooth muscle cells of various organs.

The pathophysiology of AKI in patients affected with SARS-CoV2 has been recently hypothesized and multiple mechanisms may be involved in the causation of renal injury [Figures 1 and 2].

Viral tropism

The immunohistochemistry results indicate that the expression of ACE2 protein is quite high in renal tubular cells.[22] The analysis of co-localization of ACE2 and Transmembrane serine protease 2 (TMPRSS) genes showed its mainly concentrated in podocytes and proximal straight tubule cells, making them the candidate host cells for COVID-19 infection.[23] In one post-mortem study consisting of 26 patients who succumbed to COVID-19 and associated AKI showed that there was a prominent tubular injury on light microscopy.[24]

The presence of viral material within both epithelial lining of tubules and podocytes on electron microscopy has been shown implying direct cytopathic involvement of kidney by SARS-CoV-2.[25,26] In a retrospective analysis of 85 patients of confirmed COVID-19 cases, 27% of patients exhibited acute renal failure. On hematoxylin and eosin staining showed severe acute tubular necrosis (ATN) and immunohistochemistry showed viral antigen accumulation in kidney tubules.[8]

Dehydration and GI infection

Dehydration secondary to reduced intake of fluids, vomiting, diarrhea, and sometimes overuse of diuretics in children (such as those with severe lung involvement), can predispose the child to AKI. Among 52 pediatric patients with COVID-19, 46% had

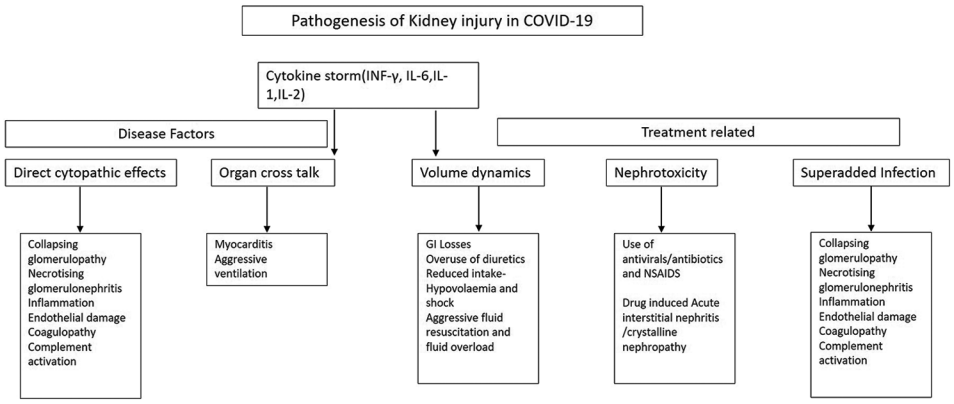

Figure 1: Pathogenic factors leading to renal injury in COVID-19. The flow diagram depicts direct disease factors as well as treatment-related factors that may cause renal injury

Table 1: Potential risk factors for AKI in COVID-19 in children

Pre-existing comorbidities	At admission	During hospitalization
Congenital Heart disease	GI Losses	Fluid overload
Congenital kidney disease	Requirement of ventilation	Nephrotoxic drugs
Diabetes	Dehydration	High PEEP requirement
Post-transplant state/immunosuppression	Rhabdomyolysis	Worsening pneumonia or myocarditis (organ cross talk)
Urological disorders	Elevated inflammatory markers- Hypercoagulability, microangiopathy, and endothelial dysfunction	Requirement of vasopressors
Genetic factors (APOL1, African ancestry)	Severe SARS-CoV2 Pneumonia	Medication-induced Interstitial nephritis/crystalline nephropathy

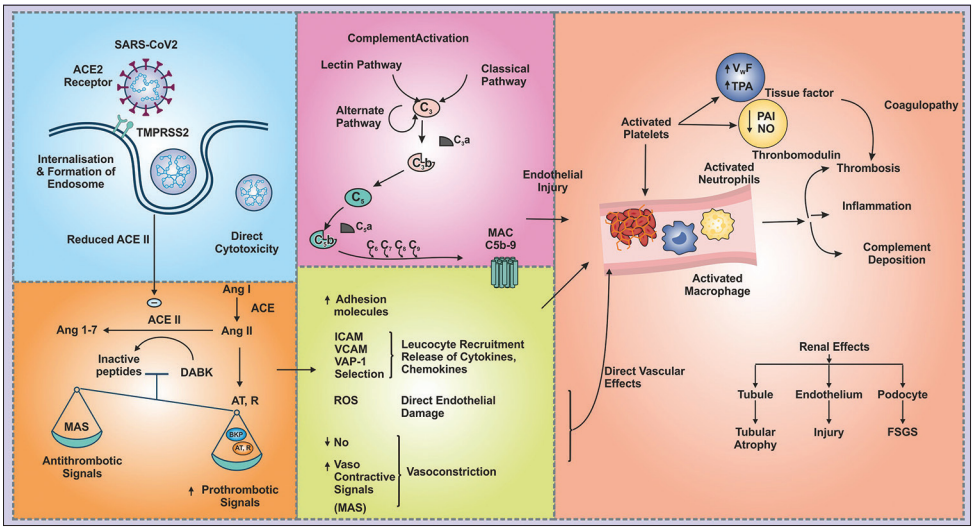

Figure 2: SARS-CoV2 directly infects cells bearing the ACE2 receptors (endothelial cells, alveolar cells, intestinal cells, and smooth muscles.) and the TMPRSS2 (Transmembrane serine protease 2) receptors (located in podocytes and proximal straight tubular cells) and is internalized into the host cell. The virus then uses the host machinery and replicates within the host cell leading to direct viral tropic damage. In the kidneys, it has a propensity for tubular cells. ACE 2 depletion inhibits the conversion of Angiotensin 2 to Angiotensin 1-7 (Ang 1-7), the vasoactive ligand for the MAS receptor and is responsible for Antithrombotic signals. Increased activation of Type 1 Angiotensin receptor occurs due to pro-inflammatory signals produced by reduced MAS. Additionally, reduction in ACE 2 that limits the formation of Ang 1-7 from Ang 2 leads to increased activation of AT1R (Angiotensin 1 receptor). Also, there is reduced conversion of Des-Arginine Bradykinin to inactive peptides, and hence activation of Bradykinin receptors takes place, all of which tilts the balance towards a pro-thrombotic milieu. SARS-CoV2 activates the complement system by classical, lectin as well as alternate pathway. Hence, the generation of C3 convertases and downstream pathways leads to membrane attack complex formation on the target cells. The release of adhesion molecules like ICAM, VCAM, VAP-1, and selectins lead to leucocyte recruitment, and the release of cytokines and chemokines accentuates endothelial injury. AT1R produces reactive oxygen species, which can cause direct endothelial damage, while reduced production of NO and MAS lead to vasoconstriction. This conglomeration of endothelial damage, vasoconstriction, and leucocyte recruitment leads to endothelial dysfunction. The activated endothelial cells initiate coagulation and massive platelet binding, formation of fibrin, and clotting of RBC's leading to systemic thrombosis and Disseminated Intravascular Coagulation

serum creatinine more than the upper limit of the reference interval and 29% met the criteria for AKI. Most cases occurred in children with MIS-C and those admitted to intensive care areas. It was seen that children who developed AKI were more likely to have diarrhea and vomiting suggesting that a pre-renal component was operative in the causation of AKI.[26]

Cytokine storm and organ cross talk

AKI can occur due to the cytokine storm seen in these patients and due to organ cross-talk, in patients with multiorgan dysfunction.[27] There has been evidence of elevated levels of interleukin-6, more so in children with acute respiratory distress syndrome (ARDS). The cytokine storm leads to renal inflammation, vascular leakage, fluid loss in third space, hypovolemia, increased pressure in the abdomen, and the subsequent development of shock, all of which can precipitate and aggravate kidney injury.[28] Aggressive ventilation can cause renal impairment due to organ cross-talk. The possible etiology hypothesized is oxygen toxicity and capillary endothelial damage with continuing high pressure in the lungs from mechanical ventilation, which triggered an inflammatory cascade and thrombotic state leading to hypotension, sepsis, and subsequent AKI.[29] High Positive End Expiratory Pressure (PEEP) during ventilation leads to high systemic venous pressure and consequent reduction in perfusion of kidneys leading to decreased glomerular filtration.

Genetics

A likely genetic predisposition exists which increases the susceptibility to AKI in children with SARS-CoV-2. Polymorphisms in ACE2 might alter the ability of the virus to

enter the cells. Wan *et al.*[30] showed that the receptor-binding domain present on SARS-CoV-2 is structurally similar to SARS-CoV. However, a single mutation improves the binding affinity of SARS-COV-2 to ACE2, leading to an enhanced ability to replicate and transmit among hosts. High-risk APOL1 alleles have also been described as a genetic risk factor for collapsing glomerulopathy. African ancestry has increased susceptibility to the development of AKI.[31]

Endothelial dysfunction

Mechanisms of endothelial dysfunction include direct and indirect activation of endothelial cells by proinflammatory cytokines, adhesion molecules (like ICAM-1, VCAM -1, VAP-1, VEGF), and chemokines, which may result in a cytokine storm, local inflammation, and vascular leakage [Figure 2]. Also, a dysfunctional endothelium brings imbalance of homeostasis in the coagulation pathway, leading to elevated d – dimer, fibrinogen, and enhanced platelet activation, especially in severe cases. Observations of nitric oxide deficiency in COVID 19 contribute to vascular smooth muscle contraction and also reduce the ability to neutralize reactive oxygen species (ROS) [Figure 2].[32]

In line with these manifestations, various case reports have shown that COVID -19 infections may lead to relapse of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.[33]

Nephrotoxicity

Finally, the use of nephrotoxic drugs like antivirals used for the treatment of COVID19, inadvertent use of antibiotics and antifungals, and immunomodulators can lead to AKI in some patients.

Hemodynamic instability

Increased expression of ACE 2 in myocardial smooth muscle may predispose to cardiac injury. Again in order to tackle the hemodynamics, one may resort to the aggressive volume replacement leading to a positive fluid balance and hence worsening AKI.[34] In some patients super added infection with bacterial pathogens causing septic shock can involve kidneys in form of septic ATN.

Clinical Manifestations

The prevalence of renal manifestations is found to be 13.9%.[35] Data from the adult population showed the prevalence of AKI in about half of the hospitalized patients with laboratory-confirmed COVID-19 of whom 25% required ICU admission and 1/5th required dialysis with high mortality of 50%.[36] The incidence of rhabdomyolysis is seen in 7–20% of patients with COVID-19 AKI. Hyperkalemia is observed in ¼th of patients with COVID-19 AKI and is accompanied by metabolic acidosis.[37] There have been reports of presentations similar to thrombotic microangiopathy.[33]

A meta-analysis on children reported that 5% (22/139) had increased urea and 4% (48/184) had increased creatinine.[38] In another study increased serum creatinine was seen in about 50%, and only a third of admitted patients met the diagnostic criteria for acute kidney injury. Of these, 93% were admitted to the pediatric intensive care unit (PICU) and 3/4th were associated with MIS-C. AKI itself may be the cause of PICU admissions in most pediatric cases.[26] In another study on 89 children, about 20% developed AKI and half of these were at stage I. The incidence of AKI among children with MISC was 15% with none requiring renal replacement therapy. Residual renal impairment at discharge occurred in 9% of patients.[39]

Few adult studies have described the prevalence of manifestations such as hematuria (27-53%), proteinuria (36-66%), and oliguria (10%).[11,40,41] Alvarado *et al.*[42] described a complete picture of the onset of nephrotic syndrome along with respiratory symptoms in a pediatric patient which resolved with treatment with steroids. Collapsing focal segmental glomerulosclerosis (FSGS) has been described in a few case reports in adults. Gross hematuria has been described in a case report in a child with respiratory complaints, which was not associated with deranged renal functions.[43] Another report has described, a complete picture of acute glomerulonephritis in two adolescent boys with rapidly progressing renal failure requiring hemodialysis support and pulse methylprednisolone, one of whom had complete recovery of renal functions with normalization of urinalysis, and the other had chronic dependence on dialysis. The histology yielded acute necrotizing glomerulonephritis in both the children with tubular damage and diffuse glomerulosclerosis in the later child.[44] Few studies have also shown adults presenting with AKI and nephrotic range proteinuria, whose renal biopsy have shown a spectrum of changes like minimal change disease, collapsing FSGS, membranous glomerulopathy, cresentric transformation of Lupus nephritis and anti-GBM nephritis, and isolated tubular injury. Among the three of those with collapsing glomerulopathy and a patient with minimal change disease also had APOL1 high risk gene variant.[45] Thrombotic microangiopathy in form of TTP or HUS may present or relapse in the setting of COVID-19.

AKI is also seen in Kawasaki disease patients and is reported in about 1/3rd of them. MISC which has a clinical presentation similar to Kawasaki disease, the cause of AKI is hypothesized to the low cardiac output state, fluid leak, and vasculitis.

Diagnosis

Defining AKI

Acute Disease Quality Initiative working group recommends the use of the Kidney Disease: Improving Global Outcomes (KDIGO) consensus definition for the diagnosis of AKI, including serum creatinine (SCr) level and urine output, in clinical practice [evidence level 1A]. They also suggest using kidney-specific tests along with measures of kidney function to characterize clinical presentations, courses, and outcomes of AKI [evidence level: 2B].[46,47]

Laboratory criteria

Urine analysis in adults, around 46.1% showed proteinuria (2+/3+), with White Blood Cells (WBCs) in urine in 1/3rd of cases and 40% also had hematuria.[18] Urinary sediment analysis helps where more than one possible etiology for kidney injury may exist which can alter the medical approach significantly.[48]

Biomarkers- The role of other kidney injury markers is not very convincing. Many patients do show high levels of insulin-like growth factor binding protein-7 (IGFBP-7) and tissue inhibitors of metalloproteinases-2 (TIMP-2). These patients with increased TIMP-2 and IGFBP-7 had more chances of progression to dialysis than other patients with low levels of these markers. There are studies that have shown that increased urinary α1-microglobulin in admitted patients can help in predicting the development of kidney injury during the course of hospital stay.[49] Some patients with kidney injury also show higher levels of inflammatory markers like ferritin, C- reactive protein, procalcitonin, and lactate dehydrogenase.[18]

Treatment

The management of AKI in children is based on the same principles as AKI in non-COVID patients, however, there are important practical points to be considered.

Conservative management and volume replacement

The fluid and hemodynamic assessment and exclusion of nephrotoxic medications is the first step of management. A randomized clinical trial showed that fluid and vasopressor resuscitation when done early and adequately based on proper hemodynamic assessment significantly reduces the risk of AKI and also a respiratory failure in patients with septic shock.[50] Early institution of the adequate enteral mode of nutrition, proper management of electrolyte and acid-base abnormalities as per KDIGO guidelines, and the surviving sepsis guidelines is an important aspect of management in AKI patients.[51] The role of antivirals, immunomodulatory agents, corticosteroids, renin–angiotensin inhibitors, statins, and anticoagulants in the prevention of AKI is not clear.[52,53] The ventilation strategies if properly selected reduce the risk of AKI like avoiding the use of high PEEP and preferential use of high flow oxygen. The use of oxygen should also be optimized to avoid damage caused by the formation of ROS.

Renal replacement therapy

Deciding the need for RRT is another important consideration in view of the increased exposure to the healthcare staff involved in it, and also the need for additional machinery and manpower.[54] Children when presenting with AKI are likely to be volume depleted owing to fever, reduced fluid intake before hospitalization, and then fluid restriction and diuretic therapy after hospital admission. Once the volume status is optimized, indications for starting RRT are the same as for non-COVID patients—electrolyte imbalance, azotemia, fluid overload, and acid–base disturbances not responding to the medical management.

Timing of RRT

A meta-analysis of randomized clinical trials by Gaudry *et al.*[55] showed that the timing of RRT initiation does not have any impact on survival in severely ill patients with AKI in the absence of other urgent indications for starting RRT. Hence the decision to initiate RRT should be based on the well thought risk-benefit ratio for both patient and healthcare staff.

Mode of RRT

Any form of RRT (intermittent and continuous) may be used depending on patient fluid status and available logistics. Hemodialysis may be used provided the patient's hemodynamic status is stable.[56] Continuous RRT may also aid in the removal of cytokines and fulfill the needs of a child with severely compromised hemodynamics. It is recommended for all the dialysis-equipped centers to continue using the technique that they are most comfortable with.[57]

Role of peritoneal dialysis

Peritoneal dialysis appears to be the most feasible alternative to hemotherapies in children with AKI, especially in resource-limited settings. There is sufficient evidence to prove that PD is equally effective as other forms of renal replacement therapies.[58-60]

Special Groups

Nephrotic syndrome

Various case reports have described, new-onset and relapse of NS triggered by SARS-COV-2.[42,61] Lower relapse rate was noted in the Italian cohort in 2020 compared to 2019 and no difference in the severity of relapses between the two periods.

Children on immunosuppressive medication for kidney disease

A global study collected data of children with COVID-19 taking immunosuppressive medication for various renal disorders included 113 children from 30 countries which comprised 50% renal transplant cases, 25% of nephrotic syndrome cases, and 10% cases included Systemic Lupus Erythematosus (SLE) on immunosuppression. It was found that in up to 80% of cases no respiratory support was required and only 5% required bi-level positive airway pressure or ventilation and also found no significant difference in the severity of COVID-19 based on gender, dialysis status, underlying kidney condition, and type or number of immunosuppressive medications.[62] Another study that prospectively reviewed 159 children with multi-relapsing nephrotic syndrome on therapy with anti-CD20 antibodies found no difference in the severity of illness among those receiving the medication.[63]

These studies suggest that most children with kidney disease taking immunosuppressive medication have mild disease with SARS-CoV-2 infection.

End stage renal disease

COVID-19 in children with existing chronic kidney disease can precipitate acute kidney injury and worsen the renal function. About 21% of patients who succumbed to COVID-19 in Italy had pre-existing chronic renal failure. Studies have reported that patients on dialysis experience a milder pathology due to reduced function of the immune system and less prominent cytokine storm. A meta-analysis found a significant association between chronic renal pathology and the severity of COVID-19.[64] Brioni *et al.* concluded that dialysis patients are fragile, due to the risk of overlapping multiple pathologies and hence are high-risk category for contracting the disease.[65]

Urological disorders

The treating surgeon makes a critical decision of immediate surgery in pandemic versus delaying the procedure while risking the loss of renal function based on the condition of the patient that may require emergent care like Posterior Urethral Valves (PUV) or obstructive megaureter.[66]

Renal transplant recipients

A large multicenter cohort study from 13 transplant centers in India included 250 adult transplant recipients with confirmed COVID 19 infection. A total of 2/3rd cases were mild infection, with about 15% having a severe infection, mortality of up to 11% in immunosuppressed, and those requiring ventilator support.[67] A study from New York that examined the pediatric kidney transplant population infected with SARS-CoV-2 shows that the clinical course was mild and comparable to the healthy pediatric population.[68]

Thus careful consideration of the degree of immunosuppression is required in patients with a kidney transplant to avoid under- or over-immunosuppression. The limited evidence in immunosuppressed children suggests that they may not be at increased risk of severe COVID-19 disease. Also, it has been observed that, in spite of the COVID 19 pandemic, the transplant programs could continue their activities in various centers with specific case selection, accurate screening methods, and following protective protocols.[69]

Prognosis

COVID-19 associated with AKI is usually associated with a poorer prognosis when compared to patients without kidney injury. It was observed that when compared to non-AKI patients, the COVID-19 AKI group had a higher need for PICU admission and two-fold increase in mortality.[70,71]

Sequelae

The incidence of AKI was higher when compared to historical cohorts and it may not behave in the same way as other etiologies (56.9% versus 25.1%, respectively). Patients with AKI and COVID-19 were more likely to require RRT and were less likely to recover their kidney function.[72]

Patients with SARS-CoV-2 AKI had a greater reduction in eGFR even after matching for previous comorbidities. The peak creatinine level and in-hospital dialysis requirement were higher in SARS-CoV-2 patients. In the subset of patients who failed to recover from AKI at the time of discharge, SARS-CoV-2 AKI patients had reduced chances of kidney recovery during outpatient follow-up.[73]

Factors associated with residual renal impairment (seen in up to 9%) were either related to decreased tissue perfusion, sepsis, worsening clinical condition, or comorbidities. Although it is not yet clear whether kidney fibrosis occurs in patients who recover from COVID-19 AKI, the development of fibrosis and progression to Chronic Kidney Disease (CKD) may be likely and such children should be followed for at least 2–3 months post-discharge to evaluate kidney recovery.[74]

Summary and Key Messages

Renal involvement in COVID-19 is emerging as an important marker of severity of disease directly correlating to morbidity and mortality of the patient. While AKI remains the most commonly encountered renal manifestation, other factors like proteinuria, hematuria, nephrotic syndrome, glomerulonephritis, and thrombotic microangiopathy have been instrumental in increased morbidity. The need for identification of exact etiology for AKI is important to define treatment strategy for each patient. Utmost care of fluid balance and appropriate use of potentially nephrotoxic medications goes a long way in reducing the disease burden caused by indirect mechanisms. The timely decision for RRT may be instrumental in improving the prognosis in sicker children, the modality of which, needs to be individualized based on expertise available locally.

List of abbreviations

AKI- Acute kidney Injury

COVID-19- Corona Virus Disease 2019

MISC- Multisystem inflammatory syndrome in children

PICO- Patient intervention control outcomes

SARS Co V 2- Severe acute respiratory syndrome Coronavirus 2

CDC- Centre for disease control

CNS- Central Nervous system

ACE-2- Angiotensin convertase enzyme- 2

CRRT- Continuous renal replacement Therapy

IL-6- Interleukin-6

AWARE- Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology

WBC- white blood cells

ARDS- Acute respiratory distress syndrome

RRT- Renal Replacement Therapy

TMPRS-2- Transmembrane serine protease

ARF- Acute renal failure

TTP- Thrombotic thrombocytopenic purpura

HUS- Hemolytic uremic syndrome

ATN- Acute Tubular Necrosis

PICU- Pediatric Intensive care unit

FSGS- Focal segmental Glomerulosclerosis

ADQI- acute dialysis quality initiative

KDIGO-Kidney disease Improving global outcomes

ULRI- the upper limit of the reference interval

BAPN- British Association of Pediatric Nephrology

IGFBP-7- Insulin-like growth factor binding protein-7

TIMP-2- Tissue inhibitor of metalloproteinases

RCT- Randomised Controlled Trial

PIRRT- Prolonged intermittent renal replacement therapy

SLED- Sustained low-efficiency daily dialysis

PD- Peritoneal dialysis

CVVHD-Continuous venovenous hemodialysis

CVVHDF- Continous venovenous hemodiafiltration

ICAM- Intracellular adhesion molecule

VCAM- vascular cell adhesion molecule

VAP-1 – Vascular adhesion protein 1

VEGF- Vascular endothelial growth factor

Authors' contribution

KS conceptualized the idea, provided intellectual inputs, and edited the final manuscript. AM and PN conducted the literature search. AM prepared the outline of the manuscript, and PN prepared the primary draft of the manuscript, which was edited and corrected by AM. All authors read and edited the final manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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