Review Article

The Impact of COVID-19 on Kidney-Related Diseases in Adults and Children: A Comprehensive Review

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ABSTRACT

A global epidemic of health problems has resulted from the advent of an entirely new coronavirus illness (COVID-19) caused by the SARS-CoV-2 virus. COVID-19 has been linked to a wide range of multi-organ problems, including considerable effects on the kidneys while being primarily known for its ventilation requirements. The key studies on patients, case reports, and recent developments regarding studies show how our understanding of the impact of COVID-19 on kidney-related disorders in adults and children is evolving. Adults who have been affected by COVID-19 are found to be at an elevated risk for Acute Kidney Injury (AKI), frequently occurring in conjunction with severe illness. AKI is linked to greater rates of morbidity and mortality in COVID-19 patients. Direct connections, viral infection, invading inflammation throughout the body, intravascular embolism, and cytokine storms are some of the mechanisms by which the kidneys are affected. Additionally, there is an increasing concern over long-term consequences such as chronic kidney disease (CKD). The effect of COVID-19 on kidney-related diseases in children is generally considered less prominent, but studies show the impact. This review emphasizes the significance of ongoing research into how COVID-19 affects kidney-related disorders in both adults and children and the importance of early kidney problem detection, monitoring, and therapy in COVID-19 affected patients.

Keywords: SARS-CoV-2; COVID-19; Kidney Disease; Acute Kidney Injury; Chronic Kidney Injury.

INTRODUCTION

The coronavirus Disease-2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has dramatically affected human lives worldwide. It has created unprecedented challenges to public health with hitherto unheard difficulties. As of May 5, 2024, 775,431,269 confirmed COVID-19 cases globally, including 7,047,741 deaths as can be found online.[1] Although COVID-19 is primarily considered a respiratory illness, the kidney could be one of the target organs of SARS-CoV-2 infection since the virus enters cells through Angiotensin-Converting Enzyme-2 (ACE-2) receptor, which is abundant in kidneys as well as the lungs, heart, and intestinal cells.[2-4] Studies have reported that the Cluster of Differentiation-147 (CD-147) protein expressed in the coronary tree, epicardial nerves, and renal tubular cells mediate SARS-CoV-2 entering host cells through endocytosis,[5-7] making it reasonable for heart and kidneys being the potential targeting organs. The kidneys have become a major target associated with the virus' pathogenicity because they are crucial for maintaining fluid balance, controlling electrolytes, and removing waste from the body. A Johns Hopkins Medicine news report published online on March 1, 2022, highlights that 30% of the patients hospitalized with COVID-19 develop kidney injury, and more than 50% of the patients in the intensive care unit with kidney injury may require dialysis.[8] Moreover, organs like the heart, liver, and kidneys rely on and support each other's functions, so when the new coronavirus causes damage to one organ, the other organs might be at risk. The essential functions of kidneys impact the performance of the heart, lungs, and other organs. A thorough study is required to clarify the growing interest in understanding the complex interactions underlying COVID-19 and kidney-related disorders. This has sparked a rising body of research as well as clinical observations published in the literature[9-17] and available online.[18] Below are some clinical manifestations reported for kidney damage in COVID-19 patients.

(i) Acute Kidney Injury (AKI): COVID-19 can lead to acute kidney injury, which is a sudden loss of kidney function. This is associated with a higher risk of morbidity and mortality. AKI in COVID-19 patients can result from various factors, including direct viral infection of kidney cells, systemic inflammation, and the effects of mechanical ventilation and medications used in treatments.

(ii) Chronic Kidney Disease (CKD): This involves a gradual loss of kidney function. With pre-existing kidney conditions or risk factors for kidney disease, COVID-19 may accelerate the progression of CKD. Advanced CKD can cause dangerous fluid, electrolytes, and waste levels to build up in our bodies. For the best patient management, future outcomes, and public health measures, it is essential to comprehend how COVID-19 impacts existing illnesses or causes new renal issues.

(iii) Proteinuria and Hematuria: Some COVID-19 patients experience elevated levels of protein (proteinuria) and blood (hematuria) in their urine. These indicators of kidney damage can be seen even in patients with mild or moderate cases of the disease.

(iv) Thrombotic Microangiopathy: In some severe COVID-19 cases, a condition known as thrombotic microangiopathy can occur. This condition is associated with small blood clots in kidneys, which can lead to kidney damage and impaired function.

(v) Electrolyte Imbalances: COVID-19 can disrupt the balance of electrolytes in the body, including sodium, potassium, and calcium. These imbalances can affect kidney function and can lead to complications.

(v) Long COVID and Kidney Disease: Some COVID-19 survivors experience persistent symptoms, often referred to as "long COVID." Kidney-related symptoms, including proteinuria, hematuria, and decreased kidney function, have been reported in some long COVID patients.

(vi) Immunosuppression: Immunosuppressive medications sometimes manage the immune response in severe COVID-19 patients. These medications can affect the kidney and may increase the risk of kidney injury.

It is important to note that the severity of kidney involvement in COVID-19 can vary widely among individuals. Some may experience mild kidney disease, while others may develop severe kidney complications. Early detection and management of kidney-related issues are critical to improving recovery in COVID-19 patients. While the research and understanding of the consequences of the COVID-19 pandemic on human health are still ongoing, this review attempts to summarize the outcome of the investigations conducted so far and shed more light on the distinctive features of kidney-related illnesses, especially AKI and CKD. While several review articles on similar topics have been published in recent literature, the impact of COVID-19 on children's populations is scarce. This study aims to offer a relevant and useful summary of the state-of-the-art knowledge and understanding of the effects of COVID-19 on kidney-related disorders in children and adults. This study also highlights the significance of continuing research, early detection, and efficient therapy for kidney complications in COVID-19 patients, as well as the crucial role of public health actions, such as vaccination, in reducing the pandemic's overall impact on kidney functions for people across all age groups.

DISCUSSION

In this review, the impact of COVID-19 on AKI and CKD in children and adults is analyzed from the published literature and discussed in detail. In addition, the effect of long-term COVID-19 on kidney disease, the risk factors, the preventive measures, and potential biomarkers recommended in recent literature are also summarized.

Acute Kidney Injury (AKI)

Many research articles have been published on the relationship between COVID-19 and AKI in adults.[2,9-16,19] These studies have emphasized the increased risk of AKI in COVID-19 patients with severe illness and have looked into complex theories underlying this phenomenon. Figure 1 shows AKI's pathophysiology involving SARS-CoV-2 targeting ACE2, resulting in angiotensin dysregulation, innate and adaptive immune pathway activation, and hypercoagulation leading to organ damage and AKI associated with COVID-19. In addition, organ crosstalk between COVID-19-affected lungs, the heart, and the kidney may further propagate the AKI.[2, 20]

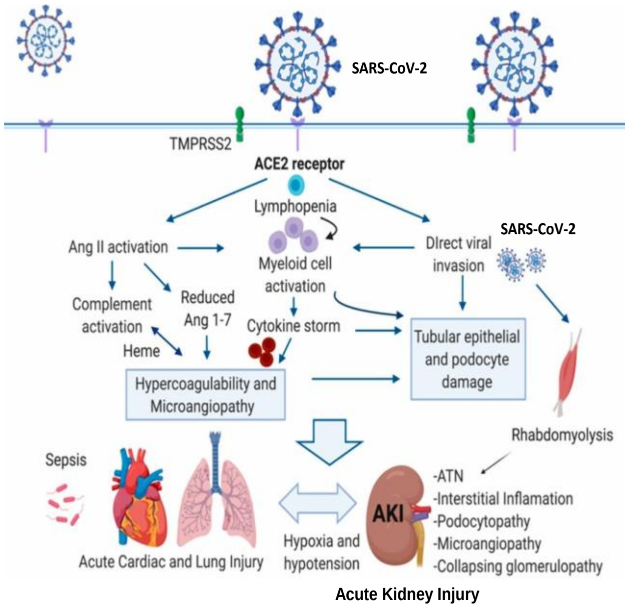

Figure 1: Pathophysiology of acute kidney injury (AKI) in COVID-19.[20]

AKI in Adults

Studies have shown that the incidence of AKI in COVID-19 patients was found to vary between 5 to 57% in different case reports. Studies performed in China have shown that AKI occurred in 5 to 29% within 7–14 days after admission in hospitals. In contrast, reports from the United States have shown greater rates of AKI, in the range between 37% and 57% in COVID-19-positive patients.[21, 22] Also, the onset of AKI in the US was observed much earlier either upon admission or within a day of admission.

Molly *et al.*[23] presented a comparison report between 3,345 patients with COVID-19 and 1,265 patients without COVID-19 during the same hospitalization period. They found a higher AKI incidence among patients with COVID-19 compared with the historical cohort (56.9% with COVID-19 patients versus 25.1% without COVID-19 patients). Patients with AKI and COVID-19 were more likely than those without COVID-19 to require renal replacement therapy (RRT) and were less likely to recover kidney function. The report also indicated that the development of AKI was significantly associated with male sex, black race, and older age (>50 years). Male sex and age >50 years are associated with the composite outcome of RRT or mortality, regardless of COVID-19 status.

Some early studies indicating COVID-19 tends to cause less severe respiratory symptoms in children than it does in adults have sparked worries about the possibility of renal involvement.[24, 25] It has been reported that AKI can occur in children with COVID-19, but the impact may be less than in adults.[17, 25-27] The long-term effects of COVID-19 on young children with kidney issues is still ongoing. Many studies on the impact of COVID-19 on AKI in adult patients have been published in the literature. Table 1 summarizes the results of some of the recently reported studies.[29-35]

Table 1: Summary of some recent studies showing the impact of COVID-19 on AKI of adults.

Number of COVID-19 Adults	% of adults with AKI	Age group (Years)	Reference
80	31.25	52	Diwakar, et.al.[29]
153600	18.23	38-72	Jialing, et.al.[30]
1248	39.0	71	Paul, et.al.[31]
1734	6.1	50-68	Xiaoying, et.al.[32]
3345	56.9	> 50	Molly, et.al.[23]
3993	46	61-81	Lili, et.al.[33]
5449	36.6	58-79	Jamie, et.al.[34]
41294	31.5	58-83	Michael, et.al.[35]

Acute Kidney Injury in Children

Although pediatric COVID-19 patients usually have less severe kidney damage than adult COVID-19 patients, COVID-19-associated AKI has been reported to develop in as many as 29% of hospitalized children and 44% of children admitted to the ICU.[36-38] In addition, a large multicenter study of pediatric critical care units has identified that 37% of critically ill children with SARS-CoV2 developed AKI. These rates are comparable to those in children with sepsis.[39] Similarly, a recent study from the UK discovered that critically ill children with SARS-CoV2 and clinical characteristics of MIS-C (Multisystem Inflammatory Syndrome in Children) were most at risk for AKI.[37] On the other hand, a study from New York hospitals reported that all hospitalized children with SARS-CoV2 are at high risk of AKI, not just the critically ill or those with MIS-C.[40] Table 2 gathers some of the recently reported studies on the impact of COVID-19 on AKI in children published by researchers from different parts of the world.[41-56]

Figure 2 depicts a bimodal distribution of AKI risk by age, with those young adolescents (10–15 years) having a higher risk than both very young children (< 5 years) and older adolescents/young adults (15–35 years), while those over age 65 years also have a high risk of AKI and in a population with no pre-existing comorbidities. The data consistently show an almost 2.5-fold increased odds of developing SARS-CoV2-related AKI for 10–15-year-old children and for 70–75-year-old adults when compared to young adults (30–35 years old).[44,57]

Table 2: Recent studies worldwide show the impact of COVID-19 on AKI in Children.

Number of COVID-19 Children	% of Children with AKI	Age group (Years)	Reference
89	21	4-5	Jameela, et.al.[41]
2546	10.8	21 <	Rupesh, et.al.[42]
71	47.9	15 <	Seha, et.al.[43]
6974	28	< 20	Hannah.[44]
57	46	2-20	Lipton, et.al.[45]
238	1.3	< 20	Xiaowen, et.al.[46]
152	11.8	< 18	Abby, et.al.[47]
52	29	0-16	Douglas, et.al.[37]
92	23.9	1.8-21	Manpreet, et.al.[48]
1247	30.51	9.1*	Raina, et.al.[49]
157	8	ND	Bridget, M.K.[50]
57	50	ND	Bridget, M.K.[50]
98	40.8	< 18	Hasan, et.al.[51]
152	8.2	< 18	Matthew L.[52]
187	38.5	2-10	Masoumeh, et.al.[53]
342	9.1	1-10	Neha, et.al.[54]
179	37.5	< 25	Ranjit, et.al.[55]
110	30	< 18	Douglas, et.al.[56]

* Median age. ND = Children age group not disclosed

Classification, Severity, and Management of AKI

The system for classifying AKI is typically based on changes in serum creatinine levels and urine output, and it is commonly classified using the RIFLE, AKIN, and KDIGO criteria, which are described below:[58,59]

<u>RIFLE Criteria:</u> RIFLE stands for Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (ESKD). These criteria are used to classify the severity of AKI based on changes in serum creatinine levels and urine output. According to these criteria, the risk is increased serum creatinine by 1.5 times the baseline or decreased the estimated glomerular filtration rate (eGFR) by 25% or urine output less than 0.5 mL/kg/h for 6 hours. Injury increases serum creatinine twice the baseline or decreases eGFR by 50% or urine output by less than 0.5 mL/kg/h for 12 hours. Failure increases the serum creatinine three times the baseline, serum creatinine greater than 4.0 mg/dL, urine output less than 0.3 mL/kg/h for 24 hours, or anuria (absence of urine) for 12 hours.

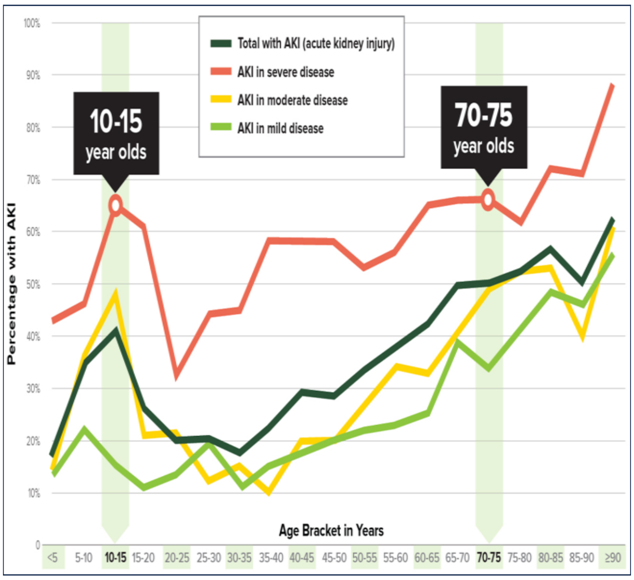

Figure 2: Age distribution of hospitalized patients with SARS-CoV2 who experienced AKI within the first seven days of hospitalization[44,57]

<u>AKIN Criteria:</u> The Acute Kidney Injury Network (AKIN) criteria were developed to modify and refine the RIFLE criteria. They classify AKI into three stages:

Stage 1: Increased serum creatinine by 0.3 mg/dL within 48 hours or increased by 150-200% from baseline, or urine output less than 0.5 mL/kg/h for 6-12 hours.

Stage 2: Increased serum creatinine by over 200% from baseline or urine output less than 0.5 mL/kg/h for over 12 hours.

Stage 3: Increased serum creatinine to more than 4.0 mg/dL, initiation of renal replacement therapy, urine output less than 0.3 mL/kg/h for 24 hours, or anuria for 12 hours.

<u>KDIGO Criteria:</u>

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria further refined the classification of AKI. Like AKIN, it classifies AKI into three stages based on changes in serum creatinine and urine output.

Stage 1:

- Serum creatinine >26 µmol/L higher than the lowest creatinine within 48 h.
- Serum creatinine ≥1.5–1.9 times more elevated than the lowest creatinine within seven days.
- Serum creatinine ≥1.5–1.9 times higher than the median of all creatinine values 8–365 days ago.

Stage 2:

- Serum creatinine is ≥ 2–2.9 times higher than the lowest within seven days.
- Serum creatinine ≥2–2.9 times higher than the median of all creatinine values 8–365 days ago

Stage 3:

- Serum creatinine ≥3 times higher than the lowest creatinine within seven days.
- Serum creatinine ≥3 times higher than the median of all creatinine values 8–365 days ago

The above criteria also emphasize the importance of considering the time frame for AKI diagnosis and the baseline creatinine level. The choice of criteria may depend on clinical practice, research purposes, or local guidelines.

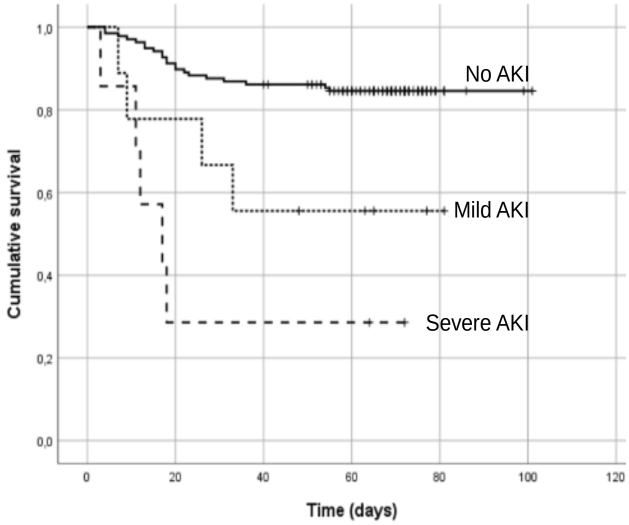

Figure 3: Kaplan–Meier plots of mortality of COVID-19 patients without and with mild (stage 1) and severe AKI (stages 2 and 3)[60]

Figure 3 shows the Kaplan–Meier plots of mortality of COVID-19 patients without and with mild (stage 1) and severe AKI (stage 2 and 3) from a study of 174 hospitalized COVID-19 patients with a broad age group in Italy from March 3rd to May 21, 2020, to investigate the role of kidney dysfunction on COVID-19 severity and mortality.[60] As can be seen, the onset of mortality is shortened with increasing severity of AKI. Other studies have also reported similar mortality trends with AKI severity.[61-63]

The management of AKI involves identifying and treating the underlying cause, providing supportive care, and closely monitoring the patient's condition.[64-66] Treatment may include addressing fluid and electrolyte imbalances, optimizing blood pressure, discontinuing nephrotoxic medications, and, in severe cases, initiating renal replacement therapy such as haemodialysis or continuous renal replacement therapy. Early detection and intervention are crucial in improving outcomes for patients with AKI. Patients at risk of AKI should be closely monitored, and healthcare providers should be vigilant in recognizing the signs and symptoms of this condition. AKI was more likely to occur in individuals with severe COVID-19, especially those who needed intensive care. In-hospital AKI is associated with high mortality, and AKI severity is correlated with death in an AKI stage-dependent manner. Hence, early recognition of AKI and providing appropriate interventions are important to avoid further kidney damage and may help improving the prognosis of patients with COVID-19.[67] Anti-inflammatory drugs (for example, steroids and IL-6 receptor blockers) seem to limit the development of severe AKI in patients with COVID-19.[68]

Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) involves a gradual loss of kidney function. In the early stages of CKD, one might exhibit signs or symptoms such as nausea, vomiting, loss of appetite, etc. Sometimes, the individual may recognize signs of kidney disease once the condition has progressed to an advanced stage. Advanced CKD can cause dangerous fluid, electrolytes, and waste levels to accumulate in the body. CKD can progress to End-Stage Kidney Disease (ESKD), which is fatal without artificial filtering (dialysis) or a kidney transplant.

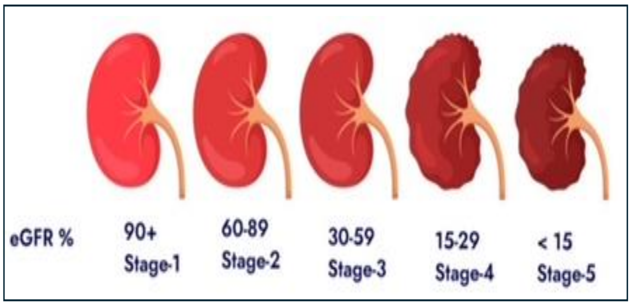

Figure 4: The Five stages of chronic kidney disease (CKD). eGFR = Estimated Glomerular Filtration Rate that reads in mL/min/1.73m^2

The National Kidney Foundation (NKF) classified CKD into five stages, as highlighted in Figure 4. These stages are typically determined based on the Glomerular Filtration Rate (GFR), a math formula using the patient's age, gender, and serum creatinine level (identified through a blood test). Creatinine, a waste product from muscle activity, is a key indicator of kidney function. When kidneys work well, they remove creatinine from the blood, but as kidney function slows, blood levels of creatinine rise. An eGFR value of 90 or above (Stage 1) indicates mild kidney damage, but a person's kidney works well. On the other hand, an eGFR value of below 15 indicates kidney failure and the kidney function is below 15%. This stage is the most serious and can be life-threatening. The patient will need dialysis or a kidney transplant.

CKD has been a global concern even before the COVID-19 pandemic in 2019 because CKD affects approximately 12% of the worldwide population, and it is estimated to increase to over 20% by 2040, primarily due to aging and an increased prevalence of associated diseases such as diabetes, obesity, and hypertension.[69-71] In the pandemic scenario, the rate of CKD further increased because the COVID-19 severity increased in patients with CKD. It has been reported that CKD is the most common risk factor for death in patients with COVID-19 worldwide, and the risk increases with higher CKD stage, with the highest risk occurring in those with kidney failure and receiving replacement therapy (KFRT) and kidney transplant recipients (KTR).[72-74]

In a very recent review, Borja *et al*.[75] have highlighted that CKD is the most prevalent risk factor for severe COVID-19 worldwide, and CKD accounts for the increased risk of severe COVID-19 in 5.1% of the global population, or 23% of the worldwide population at increased risk of severe COVID-19 deaths (Figure 5). It has also been shown in Figure 5 that CKD G4/G5 is one of the highest contributors to COVID-19 deaths after dialysis and organ transplants.[76] Even CKD G3 has been reported to be a higher risk of COVID-19 deaths than heart disease and hypertension. Sara *et al.*[77], in their review article on COVID-19 and CKD, indicated the prevalence among patients with COVID-19, ranging from 0.4 to 49.0%. The review also identified a statistically significant increase in hospitalization and mortality in patients with CKD and COVID-19. Based on the study, they have recommended developing strategies to prevent COVID-19 infection among patients with CKD.

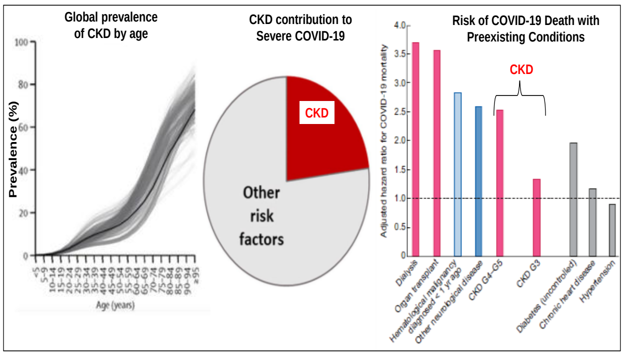

Figure 5: Global prevalence of chronic kidney disease (CKD) and its impact on COVID-19 mortality.[75,76]

Marilia et al.[13] have also recently published a review article summarizing the literature on the impact of COVID-19 on CKD severity. Based on the literature review, the authors have concluded that patients with CKD are more prone to developing severe complications from infection due to several factors, such as an imbalance in immune response, comorbidities, and immunosuppression. Gradually, understanding the effects of the COVID-19 virus by direct cytotoxicity and kidney tropism effects and the emergence of specific treatments by antiviral drugs and monoclonal antibodies is still advancing. The review concluded that although much progress has been made in understanding COVID-19 in CKD, many challenges remain.

A large, nationally representative cohort study from the UK demonstrated a CKD incidence and prevalence ranging from 0.5% to 37% and reported that CKD is associated with a high co-morbidity burden and high 1-year mortality.[78] CKD, including ESKD, is associated with an increased risk of COVID-19 and subsequent adverse outcomes, including hospitalization, respiratory failure, and mortality, with risk proportional to kidney dysfunction.

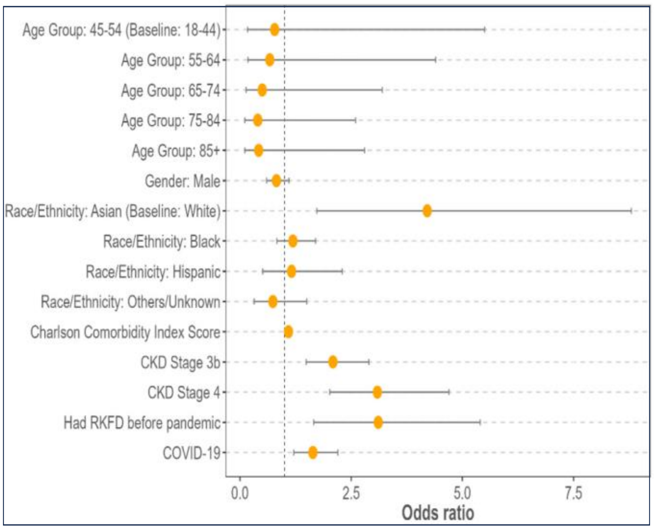

Figure 6: Factors associated with rapid kidney function decline in the COVID-19 pandemic.[79]

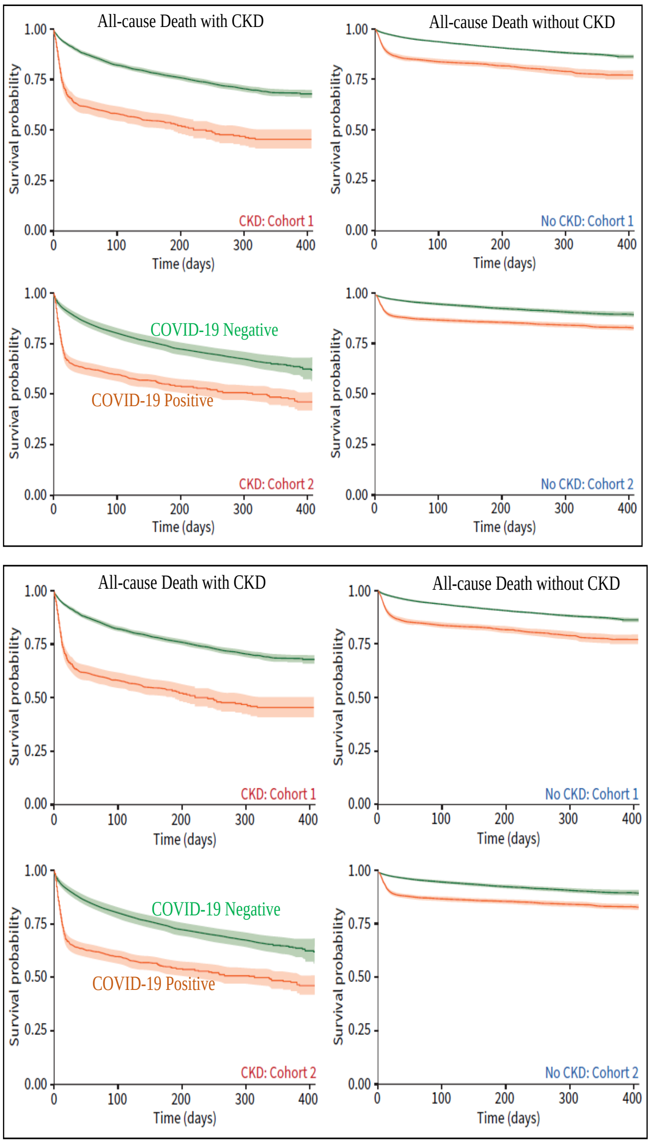

Figure 7: Top panel: Cardiovascular death survival curves for patients with and without COVID-19. Bottom panel: All-cause death survival curves for patients with and without COVID-19.[80]

Yet another study published in Kidney Medicine 2023 employed a cohort of insured individuals with moderate to severe CKD to compare the rates of rapid kidney function decline in pre-pandemic and pandemic periods and to evaluate the impact of COVID-19 on kidney function decline.[79] Based on the screening, the study identified 4475 cohorts with an average age group of around 70. Rapid kidney function decline was observed in 1.9% and 2.0% of enrollees in the pre-pandemic and pandemic periods, respectively. Rapid kidney function decline was observed in 2.5% of those with COVID-19 infection and 1.5% without COVID-19 infection. As CKD severity increased, rates of both rapid kidney function declined, and COVID-19 increased. The study also evaluated factors associated with rapid kidney function decline during the pandemic, including race and ethnicity. As can be seen in Figure 6, Asian members had higher odds of rapid kidney function decline during the pandemic than White members. Compared to members with CKD stage G3a (eGFR between 45 and 59), those with CKD stage G3b (eGFR between 30 and 44) and G4 were more likely to experience rapid kidney function decline during the pandemic. Similarly, members who experienced rapid kidney function decline in the pre-pandemic period had higher odds of rapid kidney function decline during the pandemic than those without pre-pandemic rapid kidney function decline. Members with COVID-19 infection also had greater odds of rapid kidney function decline. Based on the results, the study suggested closely monitoring individuals with CKD and COVID-19.

Emilie et al.[80] have performed a multi-regional data-linkage study utilizing individual patient-level data from two Scottish cohorts aged 50-90 years with and without CKD. The study identified that for patients possessing CKD, COVID-19 increased the risk of cardiovascular death by more than two-fold within 30 days (Figure 7). Similarly, the risk of all-cause death in COVID-19-positive versus negative CKD patients was greatest within 30 days. Compared with patients without CKD, those with CKD had a higher risk of testing positive for COVID-19 (11.5% versus 9.3%). Following a positive test, CKD patients had higher rates of cardiovascular death (11.1% versus 2.7%), cardiovascular complications, and cardiovascular hospitalizations (7.1% versus 3.3%) than those without CKD. The study, therefore, concluded that COVID-19 increases the risk of cardiovascular and all-cause death in CKD patients, especially in the short term. CKD patients with COVID-19 are also at a disproportionate risk of cardiovascular complications than those without CKD.

Nihal *et al.*[81] have evaluated the mortality risk of CKD patients infected with COVID-19 from a New York hospital in the USA. Of 7624 COVID-19 assessed patients, 7.8% had CKD on hospital admission, and 11.2% died of COVID-19 infection. CKD patients were older, more likely to have diabetes, hypertension, and chronic obstructive pulmonary disease (COPD), were current or former smokers, had a longer time to discharge, and had worse survival compared to non-CKD patients. COVID-19 mortality rate was significantly higher in CKD patients (23.1% vs 10.2%) with 1.51 greater odds of dying. A Renal & Urology News published online on August 23, 2023, highlighted that the rapid decline in kidney function often follows COVID-19 infection, including in patients with moderate to severe CKD.[82] Based on a study of 97203 patients, the rapid kidney function declined in 2.5% of the COVID-19 patients compared with 1.5% of the uninfected patients. The COVID-19-infected patients had significant 1.6-fold increased odds of rapid kidney function decline. Trishala *et al*.[83], in their review and meta-analysis of 4350 patients from different countries, identified 212 (4.9%) patients with CKD. The study also concluded that CKD patients had a significantly increased risk of severe disease and death as compared to non-CKD patients and that CKD is manifested as a common underlying disease in COVID-19 patients who had a worse prognosis, including mortality.

Although the Global Burden Disease (GBD) collaboration data shown in Figure 5 indicates no significant CKD in children, a few reports highlight the impact of CKD on the severity of COVID-19 in the children's population.[24,78,84-91] Sudarsan *et al*.[86] based on a study of 88 children with an age group of 6-15 years admitted to four paediatric nephrology centers in New Delhi, India, from April 2020 to June 2021 concluded that children with CKD presenting with moderate-to-severe COVID-19 or in nephrotic syndrome relapse are at risk of severe complications, including severe AKI and mortality. On the other hand, Jenny *et al*.[87] in their study with 197 children and 63 young adults with CKD stage 3-5, glomerular disease treated with immunosuppression and kidney transplant recipients, concluded that unlike COVID-19 in adult patients with kidney disease, the cohort of children and young adults, COVID-19 incidence was similar to the general population and all cases were mild. It may be unnecessary to impose severe restrictions on this patient population during the pandemic. As mentioned earlier, several factors, including race, play a key role in the severity of kidney disease influenced by COVID-19. Consequently, more data need to be gathered to understand better the impact of CKD on the severity of COVID-19 in children.

Clinical studies indicate that AKI accelerates the progression to CKD.[88] Evidence from animal models of AKI suggests several potential mechanisms of progression to CKD, including fibrosis, microvascular rarefaction, tubular and interstitial damage, and glomerulosclerosis. In addition, older age is a risk factor for COVID-19-associated AKI, and kidney aging is a risk factor for CKD. Thus, elderly patients with COVID-19 have a double risk of kidney aging coupled with COVID-19-associated AKI for progression to CKD. AKI and CKD are known to share several pathophysiological mechanisms, including glomerular and tubular cell death, local and systemic inflammation, and fibrosis. In addition, several epidemiological studies reported that elderly patients possessing diseases such as diabetes, hypertension, heart failure, and obesity are at increased risk for COVID-19-associated AKI. All these parameters are also risk factors for CKD. Thus, there is a reciprocal relationship between AKI and CKD. Joshua *et al*.[92] in their review article on COVID-19 survival and its impact on CKD, have reported that both AKI and CKD are associated with severe COVID-19 and risk of death. COVID-19 may lead to CKD in survivors via unresolved acute tubular injury that occurs in patients with severe disease because of podocytopathy, which has been strongly linked to high risk of APOL1 (Apolipoprotein L1) genotypes or by causing endothelial or vascular injury, which promotes CKD progression.

Long-Term COVID-19 and Kidney Disease

Studies have shown that people who have been infected with COVID-19 can experience long-term effects on their kidney functions.[11,19,93-96] An analysis of 1,726,683 US veterans identified from March 1, 2020 to March 15, 2021, showed that after the acute phase of COVID-19, 30-day survivors exhibited higher risks for acute kidney injury (AKI), a steep decline in established glomerular filtration rate (eGFR), end-stage kidney disease (ESKD), and major adverse kidney events (MAKE), which is defined as eGFR decline ≥ 50%.[93] The most surprising finding was that the risk was evident even among people whose COVID-19 disease was mild and did not necessitate hospitalization. The study cohort included 89,216 30-day COVID-19 survivors and 1,637,467 uninfected controls. Patients were categorized by care setting into non-hospitalized and hospitalized patients and those admitted to an intensive care unit (ICU). The COVID-19 patients in the study were primarily men in their late 60s. However, the researchers also analyzed data from 151,289 women (8,817 with COVID-19) and adults of all ages. Among the COVID-19 patients, 12,376 (13.9%) required hospitalization, including 4146 (4.6%) admitted to ICUs. They have applied a median follow-up time of 164 days for the COVID-19 group and 172 days for the control group. After the initial 30 days of COVID-19 infection, 4,757 (5.3%) patients experienced an eGFR decrease of 30% or more. Compared with uninfected controls, patients with milder COVID-19 cases (not hospitalized) had a 9% increased risk for an eGFR decline of 30% or more. The risk for an eGFR decrease of 30% or more increased 2-fold and 3-fold for hospitalized patients not in ICUs and those admitted to ICUs, respectively. Patients with COVID-19 who did not require hospitalization had a significant 30%, 15%, and 215% higher risks for AKI, MAKE, and ESKD, respectively. The risk increased for patients hospitalized for COVID-19, especially for those admitted to an ICU. The ICU patients had significant, 8-fold, 7-fold, and 13-fold higher risks for AKI, MAKE, and ESKD, respectively, compared with controls.

Sachin and Chirag[19] have reported a conceptual model of trajectories of kidney function after SARS-CoV2 infection, as shown in Figure 8. Accordingly, patients with a high burden of frailty, chronic diseases, disability, and immunosenescence are at increased risk of kidney disease and progression to kidney failure, and SARS-CoV2 infection can further increase this risk. The Figure shows that kidney function declines gradually without SARS-CoV2 infection (line 1). Still, patients who are hospitalized with COVID-19 might experience a rapid loss of kidney function, resulting in acute kidney injury during the acute phase of the disease (line 2). Post-infection kidney function trajectories can vary and might include complete recovery (line 3), as indicated by no change in trajectory compared with patients who are not infected, slow progressive decline owing to subclinical inflammation (line 4), relapsing or recurrent acute kidney injury and hospitalizations (line 5) or incomplete recovery and rapidly progressive kidney disease (line 6).

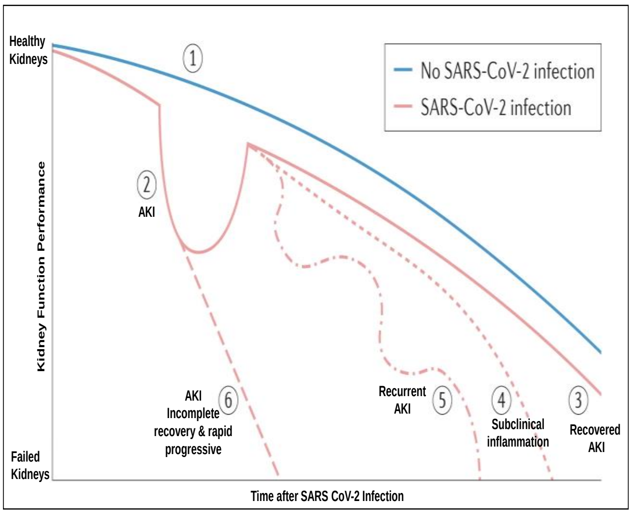

Figure 8: Conceptual model of trajectories of kidney function after SARS-CoV-2 infection.[19]

Helmut and Lang[11] have reported a bidirectional relationship between CKD and COVID-19. CKD due to primary kidney disease or chronic conditions affecting kidneys increases the susceptibility to COVID-19 infection, the risks for progression and critical COVID-19 disease (with acute or acute-on-chronic kidney damage), and death. Patients who have survived COVID-19 face an increased risk of worse kidney outcomes in the post-acute phase of the disease. Of clinical significance, COVID-19 may predispose surviving patients to chronic kidney disease, independently of clinically apparent AKI. The increased risk of post-acute renal dysfunction in COVID-19 patients can be graded according to the severity of the acute infection (non-hospitalized, hospitalized, or ICU patients). The burden of CKD developing after COVID-19 is currently unknown. Based on this study, the authors have concluded that post-acute COVID-19 care should include close attention to kidney function. Future prospective large-scale studies with long and complete follow-up periods are needed to assess kidney function using kidney function/damage markers, urinalysis, and biopsy studies.

Very recently, a research team from British Columbia, Canada[95], has reported that people who have long-term COVID-19 and, especially those who were hospitalized from the virus or have diabetes, show a significant decline in kidney function in the 12 months following infection. The results suggest that such patients may be at higher risk of developing CKD later in their life and should be monitored closely. In their study, the team analyzed data capturing 2,212 long COVID-19 patients 18 years and older referred to the post-COVID recovery clinics between July 2020 and April 2022. All patients included in the study had their kidney function measured within three months of COVID-19 infection, using eGFR and at different intervals following diagnosis (e.g., six months, 12 months). The results revealed that long COVID-19 patients experienced an estimated 2.96 mL/min/1.73 m^2 decrease in eGFR (3.39% reduction from baseline) one year after COVID-19 infection. While everyone naturally loses some kidney function over time, a 1 mL/min/1.73 m2 decline over such a period is more typical in healthy people. The decline in kidney function was highest in patients hospitalized for COVID-19, at 6.72%, followed by diabetic patients, at 6.15%. The study further indicated that most long COVID-19 patients did not develop advanced kidney disease, but less than 5% had a GFR below 30 across all the timepoints. Indeed, more of them fit into the 'less than normal' GFR category. More than a third of patients (36%) also had protein in the urine at some point in their follow-up, another indicator of kidney disease. Medical professionals, therefore, continue to study the long-term effects of COVID-19, including its impact on various organs, to understand better and manage the health consequences of the disease.

Risk Factors for Kidney-Related Complications in COVID-19

Based on the literature data discussed in the preceding sections of this review, below are some of the risk factors associated with COVID-19.[15, 30,31,64, 97-99]

- Age, gender, and race are substantial risk factors for kidney-related problems in COVID-19 patients. AKI, CKD, and the aggravation of existing kidney disorders are more common in older people.
- Pre-existing kidney disease: People who already have kidney conditions, including CKD, are more likely to have serious kidney consequences from COVID-19. Their underlying condition may get worse due to this virus.
- Risk factors for severe COVID-19 and issues with kidneys include comorbidities like diabetes and hypertension. Both separately and in combination with the virus, these illnesses can cause kidney injury.
- Compromised immunity: People with compromised immune systems, whether because of illnesses or immunosuppressive drugs, are more likely to experience severe COVID-19 and the ensuing kidney problems.
- Dehydration can make renal problems worse, and COVID-19's severe symptoms or fever can cause fluid loss, which could increase the chance of kidney damage.

Preventive Measures for Kidney-Related Complications in COVID-19

Minimizing the effect of the virus on renal health in children and adults requires understanding the risk factors and the application of preventative measures for kidney-related disorders in the context of COVID-19. Immunization, individual health management, and public health initiatives are essential in this endeavor.[12, 16,100, 101] These preventive measures are summarized below.

- Immunization: The COVID-19 vaccine has successfully lowered the severity of the disease and its related consequences, such as kidney issues. Promoting immunization among those who qualify is a crucial preventive intervention.
- Hydration: Keeping well-hydrated is important, especially for people experiencing COVID-19 symptoms, including fever and breathing difficulties. Dehydration can be avoided with proper fluid consumption, which may lower the risk of renal problems.
- Comorbidity management: Reducing one's likelihood of kidney-related problems requires effective care of underlying diseases such as diabetes and hypertension. This includes maintaining a medication regimen and routine supervision.
- Prevention of Infection: Adhering to public health recommendations, including mask use, hand washing, and social seclusion, can lower the chance of severe COVID-19 transmission and, as a result, the risk of renal problems.
- Early Medical Care: Early medical evaluation and treatment of COVID-19 symptoms, particularly in high-risk patients, can aid in the early detection and management of complications, including AKI, and possibly stop additional kidney damage.
- Medication Review: It's crucial to check drugs for potential interactions or adverse effects on renal function, especially for people with kidney issues.
- Factors related to lifestyle: Promoting a healthy lifestyle that includes a balanced diet, frequent exercise, and abstaining from excessive alcohol and cigarette use might improve general health and lower the risk of kidney problems.
- Monitoring: Regular blood testing for kidney function can help detect abnormalities.

Stages of Kidney Disease

Understanding the course and seriousness of kidney involvement among COVID-19 victims requires staging the effect of the virus on renal-related disorders. Below are suggested staging methods that impact both children's and adults' kidneys.

- Stage 1: No Kidney Involvement: Patients do not exhibit any symptoms of kidney involvement. There are no signs of kidney damage in clinical or laboratory settings, and kidney function is still within normal ranges.
- Stage 2: Mild Kidney Involvement: Mild kidney involvement is represented by this stage, which is frequently characterized by minor alterations in renal function. Mild proteinuria (excess protein in the urine) or haematuria (blood in the urine) are examples of clinical symptoms. Although they may be slightly increased, serum creatinine levels are still within the normal range. AKI or substantial renal damage is not seen.
- Stage 3: Moderate Kidney Involvement: With more noticeable alterations in kidney function, patients in this stage have moderate kidney involvement. AKI may exist; however, it is typically temporary and reversible. Haematuria and proteinuria might be more apparent. The results of imaging tests, such as ultrasounds, may reveal moderate structural anomalies or indications of renal inflammation.
- Stage 4: Significant Kidney Involvement: This stage denotes a serious kidney infection with severe renal function impairment. Dialysis or other forms of renal replacement therapy may be necessary when AKI is present. Haematuria and proteinuria are frequently noticeable. More significant structural abnormalities may be seen in imaging investigations, and microvascular thrombosis may also be present.
- Stage 5: Chronic Kidney Disease (CKD): Patients in this stage have COVID-19-related chronic renal disease. Even when the sickness has passed its acute phase, kidney function is still reduced. Haematuria, chronic proteinuria, and increased blood creatinine levels are possible. For these people, long-term treatment and kidney disease care are required.
- Stage 6: End-Stage Kidney Disease (ESKD): The development from CKD to kidney failure in its latter stages, which is the most severe, is represented by this stage. To preserve life, patients at this stage frequently need persistent kidney replacement, such as kidney transplantation.

COVID-19 Biological Markers for Kidney Disease

The biochemical markers linked to COVID-19's effects on kidney-related illnesses affecting children and adults are examined in this section to provide information on diagnosis, prognosis, and prospective treatment targets.[103-107] The new coronavirus SARS-CoV2 that produced the COVID-19 epidemic has brought attention to the illness's multisystemic nature. Several biomarkers have become significant indicators of renal involvement in COVID-19 in adults. AKI can still be diagnosed using the creatinine level in the serum, blood urea nitrogen, and approximate glomerular filtration rate (eGFR). However, new indicators, including cystatin C, kidney injury molecule-1 (KIM-1), mononuclear gelatinase-associated lipocalin (NGAL), and NGAL, show promise in early diagnosis and severity evaluation.

Additionally, in severe COVID-19 instances, inflammatory markers such as C-reactive proteins (CRP) and IL-6 (interleukin-6) shed light on the comprehensive inflammatory response linked to kidney impairment. Recently, Steven *et.al*[108] have reported that plasma biomarkers soluble tumor necrosis factor receptor 1 (sTNFR1) and sTNFR2 measured in hospitalized patients with COVID-19 were associated with a greater risk of adverse kidney outcomes. Along with clinical variables previously shown to predict adverse kidney events in patients with COVID-19, both sTNFR1 and sTNFR2 are also reported to be strong factors for adverse kidney outcomes.

Biological indicators are critical when evaluating the effects of COVID-19 on kidney-related disorders in children and adults. These biomarkers support clinical decision-making by diagnosing kidney involvement, tracking the course of the disease, and assessing therapy efficacy.

Some important and more common biological indicators are listed below:

- Serum Creatinine: A crucial indicator of renal function is the level of serum creatinine. Children, as well as adults, may have acute kidney damage (AKI), which is indicated by a rise in serum creatinine. It's an increasingly common marker to gauge kidney injury severity and track healing.
- Blood Urea Nitrogen also known as BUN levels, is another sign of healthy kidneys. Monitoring BUN fluctuations can help track kidney-related concerns because elevated BUN levels have been linked to renal dysfunction.
- Proteinuria: Excessive protein in the urine indicates renal injury. The urine protein-to-creatinine ratio can be used to determine whether a person has proteinuria. Proteinuria that doesn't go away could mean kidney disease.
- Albuminuria: Similar to proteinuria, albuminuria is a sign of renal disease indicated by the presence of albumin, a particular form of protein, in the urine. An early indicator of kidney injury is microalbuminuria or an elevated albumin-to-creatinine ratio.
- Estimated-Globular Filtration Rate (eGFR): Based on the creatinine level in the serum levels, eGFR calculates an estimate of the rate at which the kidneys filter blood. A decline in eGFR indicates diminished kidney function.
- Cytokine Levels: Interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-) levels can be measured to determine the level of the systemic inflammation reaction, which is frequently linked to renal problems in severe COVID-19 cases.
- D-dimer: Excessive D-dimer levels could indicate a hypercoagulable condition that could result in kidney microvascular thrombosis. The risk of thrombotic problems in COVID-19 patients can be assessed by monitoring D-dimer levels.
- Angiotensin II: Kidney damage brought on by COVID-19 has been linked to renin-angiotensin system dysregulation. Monitoring angiotensin II levels to determine how they affect kidney-related pathophysiology is possible.
- Ferritin: Elevated ferritin concentrations are connected to aggravation and may be responsible for renal damage brought on by cytokine storms. Evaluating ferritin levels can reveal information about the inflammatory response at the systemic level.
- Urinary Sediment Examination: Examining urine sediment under a microscope can show the abundance of red and white blood cells, including cellular casts, which might point to the glomerular or spherical involvement in kidney injury.
- Novel Biomarkers: Continued investigations may discover additional biomarkers that are specific to COVID-19-related disorders of the kidney, such as mononuclear gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1).

CONCLUSIONS

In conclusion, the effect of COVID-19 on kidney-related illnesses in both adults and children are a complex and developing topic of concern. Despite the focus on the virus's respiratory symptoms, it is becoming more apparent that SARS-CoV2 can also affect kidneys. In severe COVID-19 instances, there is a significant risk of acute kidney injury (AKI), which increases morbidity and mortality. Diverse mechanisms underline kidney involvement, including persistent inflammation, thrombotic events, direct viral impacts, and cytokine dysregulation. The possibility of long-term kidney issues, such as chronic kidney disorder (CKD), emphasizes how crucial it is to be vigilant when managing and monitoring renal conditions in COVID-19 patients. The effect of COVID-19 on kidneys in children is less prominent than in adulthood, but it is still present. AKI can happen, albeit less frequently, and continued research is necessary to comprehend the long-term repercussions and the possible impacts on young individuals with kidney disease. Importantly, mounting evidence points to the possibility that such COVID-19 vaccination may protect against kidney problems, underscoring the crucial role of extensive vaccination programs in lowering these disease's overall burden. Based on these observations, it is crucial that medical professionals keep an eye out for bladder-related difficulties among COVID-19 patients of any demographic and that public health campaigns, such as immunization, continue to suppress the virus's overall influence on kidney health. Further studies are therefore necessary to better understand the biological processes of kidney functions and provide specialized preventative and therapeutic approaches. A thorough and multidisciplinary strategy is ultimately required to address the intricate interactions throughout COVID-19 and kidney-related disorders, ensuring the most significant outcomes for those impacted.

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