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Histopathological Findings of Acute Kidney Injury in Pediatric Coronavirus Disease-19 Patients: A Systematic Review

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INTRODUCTION

Coronavirus disease-19 (COVID-19) is a contagious infectious disease that is becoming a worldwide problem and has spread. The disease was first detected at the end of 2019 in Wuhan, China, with the alleged spread of the virus from animals to humans for the first time in the Huanan seafood market. COVID-19 has a very broad spectrum of symptoms with characteristics such as fever, sore throat, fatigue, cough, and shortness of breath.¹ COVID-19 has a broad spectrum of symptoms, ranging from asymptomatic to severe symptoms, namely, respiratory failure. Research shows that 81% of patients were asymptomatic or with mild pneumonia symptoms, 14% of cases had severe symptoms, including shortness

ABSTRACT

Introduction: Acute kidney injury (AKI) is a complication of coronavirus disease-19 (COVID-19), and the pathophysiology of AKI in COVID-19 could be determined as multifactorial. The exact prevalence of AKI in COVID-19 patients is growing over time. Due to the difficulties, kidney biopsy is performed in a small minority of AKI patients infected with COVID-19. **Materials and Methods:** This systematic review was conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Keywords used in this study were: “acute kidney injury” AND “histology” AND “children” OR “pediatric” AND “COVID” and searched from databases such as PubMed/MEDLINE, ScienceDirect, Scopus, and SpringerLink. After obtaining eligible studies, the articles were assessed with the Joanna Briggs Institute checklist for case report. **Results:** Seven eligible studies were obtained and assessed. The clinical data showed variable initial symptoms; however, fever, abdominal pain, and respiratory disturbances were shown to be the common comorbidities aligning with the pattern of the COVID-19 symptoms themselves. In the histopathological report from the data, 88.8% (8/9) of patients were found with acute tubular necrosis (ATN). The second-most commonly found pathological data from the histology report were congestion and thrombosis; both of which were present in 55.5% (5/9) of patients each, followed by focal segmental glomerulosclerosis in 80% (4/5) of patients. It should be noted that more than one pathology is found in each patient. **Conclusion:** The findings of the review indicate that ATN followed by congestion and thrombosis are the most common histopathological manifestations in pediatric AKI patients due to COVID-19.

KEYWORDS: *Acute kidney injury, COVID-19, histopathology, pediatric*

of breath to hypoxia, and 5% of cases with critically ill disease, like respiratory failure and shock to multi-organ dysfunction. It has been reported that the exposure to SARS-CoV-2 virus in pediatric patients can lead to a multisystem inflammatory syndrome in children that can potentially result in multi-organ damage, dysfunction, and death.²

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Acute kidney injury (AKI) is a complication of COVID-19, and the pathophysiology of AKI in COVID-19 could be determined as a multifactor. COVID-19 infection targets angiotensin-converting enzyme 2 (ACE2) which triggers angiotensin dysregulation, resulting in the activation of innate immune pathways, adaptive immune pathways, and subsequent hypercoagulation that causes organ damage and leads to acute renal failure.³ The exact prevalence of AKI in COVID-19 patients is unknown. Although some studies report a low incidence rate, with more thorough data collection, the incidence of AKI appears to be even higher.⁴ AKI can be defined as a rapid and sudden or severe decrease in renal filtration function. This condition is usually characterized by an increase in serum creatinine or blood urea nitrogen concentration. Due to the level of blood urea nitrogen concentration returning to normal, not long after it occurs, the benchmark for kidney damage, therefore, was marked by a decrease in urine production.⁵

Due to logistical challenges and the danger of infection, a kidney biopsy is still only performed in a small minority of patients with COVID-19-associated AKI. Since most biopsies are only performed for diagnostic purposes, the true prevalence of abnormal alterations may still be unknown. As of now, the majority of the information on the pathophysiology of COVID-19-related AKI comes from case reports and case series studies.⁶ In the adult studies, the most commonly encountered pathologies are glomerular and tubular diseases such as focal segmental glomerulosclerosis (FSGS) and acute tubular injury.⁷ While glomerular and tubular diseases are commonly encountered in adult studies, the specific pathologies of COVID-19-associated AKI in children may be different, and it is important to understand these differences to develop more effective strategies for prevention, diagnosis, and treatment in this population. In addition, emphasizing the potential long-term consequences of COVID-19-associated AKI in children, such as the impact on future kidney function and overall health, can further underscore the importance of studying this disease in this vulnerable population. By focusing on children, we can gain a more comprehensive understanding of the disease and develop more targeted and effective interventions for this population. In addition, since children have a longer life expectancy than adults, the long-term effects of COVID-19-associated AKI may have a greater impact on their overall health and well-being.

Therefore, this research was proposed to study the alterations that occur in the kidney tissue due to AKI

in children diagnosed with COVID-19 to advance the knowledge of the pathology of the disease.

MATERIALS AND METHODS

Data collection begins with selecting keywords first. In this research, the keywords are as follows: “acute kidney injury” AND “histology” AND “children” OR “pediatric” AND “COVID.” The keywords then were manually searched using the advanced search option from each database. The databases used are PubMed/MEDLINE, ScienceDirect, Scopus, and SpringerLink. Data in the form of articles that have been collected are managed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method.

This study included only case report studies of COVID-19 patients aged 0–18 years with reported AKI based on the available laboratory result or clinical diagnostic with available histopathological data of the kidney. Non-English studies and studies with no full-text access were excluded from this study.

After obtaining eligible studies, the articles were assessed with the Joanna Briggs Institute critical appraisal checklist for case report study. After the study assessment, articles can be read and extracted for each datum in the study.

RESULTS

The flowchart above is a PRISMA flowchart that explains the flow of the data collection and selection process for this systematic review that produces the seven studies that are included in the review [Figure 1].

Table 1 shows the baseline data of each study, with the study type, study method, and database source. The studies consist of seven case reports. Methods that are used in the studies do not have that much of a difference as the clinical history is obtained from the medical charts, and the tissues are later observed with standard pathologic tools.

The demographic data [Table 2] show that the patients come from the 6–11 years age group and 12–18 years age group, both with 46.67% (7/15) followed by 6.66% (1/15) of patients in their infancy. There are more female patients than male patients from the pooled data of the study with 53.34% (8/15) and 46.66% (7/15), respectively. The studies reported that 61.5% (8/13) of the patients were previously healthy as there was no history of past illness in these patients. However, asthma was found in 33.3% (2/6) of patients. On a unique note, one of the patients had a history of Edward’s syndrome 20% (1/5), sickle cell trait 20% (1/5), congenital heart disease 20% (1/5), and also a recipient of a kidney

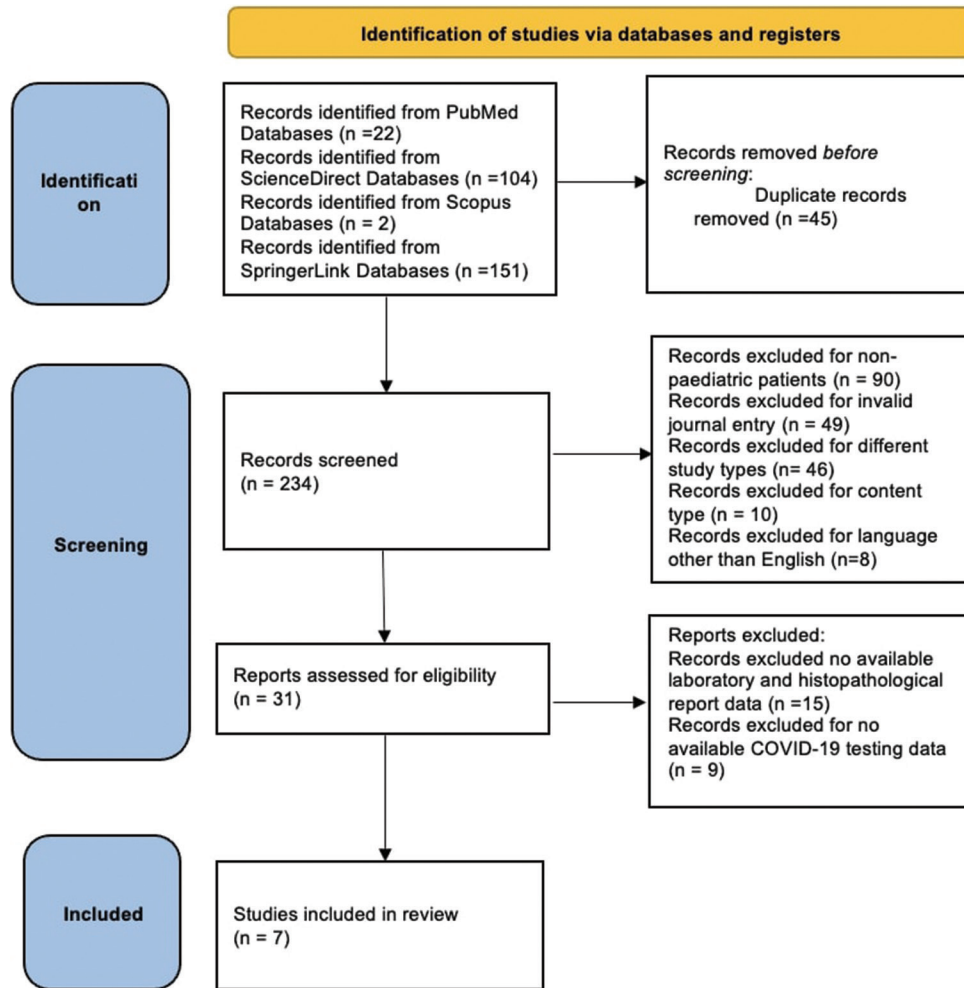


Figure 1: The PRISMA flowchart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

transplant as the patient has a history of end-stage renal disease 100% (1/1). On admission, fever is commonly found in the patients, with 63.6% (7/11), followed by kidney function impairment, abdominal pain, nausea, andodynophagia, with 100% (5/5), 44.4% (4/9), 60% (3/5), and 50% (3/6). New-onset diabetic ketoacidosis, new-onset nephrotic syndrome, and Henoch–Schönlein purpura were also found in the patient from the pooled data of the studies. In the outcome of the studies, 53.34% (8/15) of the patients managed to recover and be alive compared to 46.66% (7/15) who did not manage to result in death.

In the Table 3, the hispathological report from the data, eight patients were found with acute tubular necrosis (ATN), with 88.8% (8/9). The second-most commonly found pathological data from the histology report are congestion and thrombosis with both being present in five patients each (both 55.5% in 5/9 patients). Following the above findings, FSGS and interstitial fibrosis are found in 80% (4/5) and 60% (3/5) of patients, respectively. Acute thrombotic

microangiopathy, mesangiolysis, and tubular atrophy were also found with 66.6% (2/3) each.

DISCUSSION

In this systematic review, the writer has identified seven studies of pediatric COVID-19 patients with manifestations of AKI with histological reports in 15 participants. The studies were case reports. Clinical information such as history of sickness, initial symptoms of the patients, and outcomes were found although data regarding the comorbidities were not universally reported, and data regarding the laboratory result were not all reported.

Although some of the patients can recover from the AKI and return to normal function, not all the baseline levels for the patients were not able to be measured since most of them still had kidney dysfunction at discharge or when they passed away. This is consistent with the study done by Xia *et al.*,¹⁵ which shows that the urea and creatinine levels are correlated with disease progression in hospitalization.

Table 1: Study baseline data

Author	Title	Studied patients	Age/gender	Year published	Country
Dolhnikoff et al. ⁸	SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome	1	11 years/female	2020	Brazil
Duarte-Neto et al. ⁹	An autopsy study of the spectrum of severe COVID-19 in children: From SARS to different phenotypes of MIS-C	5	15 years/female 7 months/female 8–12 years/female 8–12 years/male 8–12/female	2021	Brazil
Nomura et al. ¹⁰	Pathology findings in pediatric patients with COVID-19 and kidney dysfunction	3	12 years/female 6 years/male 9 years/male 5 years/male 18 years/female	2022	USA
Levenson et al. ¹¹	<i>De novo</i> collapsing glomerulopathy in a pediatric kidney transplant recipient with COVID-19 infection	1	17 years/male	2021	USA
Fireizen et al. ¹²	Pediatric P-ANCA vasculitis following COVID-19	1	17 years/male	2021	USA
Basiratnia et al. ¹³	Acute necrotizing glomerulonephritis associated with COVID-19 infection: A report of two pediatric cases	2	16 years/male 15 years/male	2021	Iran
Serafinelli et al. ¹⁴	Kidney involvement and histological findings in two pediatric COVID-19 patients	2	10 years/female 12 years/female	2021	Italy

COVID-19: Coronavirus disease-19, MIS-C: Multisystem inflammatory syndrome in children, SARS: Severe acute respiratory syndrome, P-ANCA: Perinuclear anti-neutrophil cytoplasmic antibody

Table 2: Patient demographic data

	Number of study	Number of patients	n/N	Percentage
Age				
28 days–12 months	1	1	1/15	6.66
6–11 years	4	7	7/15	46.67
12–18 years	6	7	7/15	46.67
Gender				
Female	4	8	8/15	53.34
Male	5	7	7/15	46.66
Past illness				
No past illness	5	8	8/15	61.5
Asthma	2	2	2/7	5.5
Congenital heart disease	1	1	1/7	2.75
Cholestasis	1	1	1/7	2.75
Cytomegalovirus	1	1	1/7	2.75
Sickle cell trait	1	1	1/7	2.75
Edward's syndrome	1	1	1/7	2.75
Herpes	1	1	1/7	2.75
Sleep apnea	1	1	1/7	2.75
COVID-19 pneumonia	1	1	1/7	2.75
Gastroenteritis	1	1	1/7	2.75
Rhinitis	1	1	1/7	2.75
Recurrent urinary tract infection	1	1	1/7	2.75
End-stage kidney disease	1	1	1/7	2.75
Outcome				
Alive	5	8	8/15	53.34
Dead	3	7	7/15	46.66

n: Patient with variable, N: Total patients studied, DKA: Diabetic ketoacidosis, COVID-19: Coronavirus disease-19

Table 3: Histopathological data

Histopathology findings	Number of study	Number of patients	n/N	Percentage
ATN	3	8	8/9	88.8
Thrombosis	3	5	5/9	55.5
Congestion	3	5	5/9	55.5
FSGS	3	4	4/5	80
Interstitial fibrosis	3	3	3/5	60
Acute thrombotic microangiopathy	1	2	2/3	66.6
Mesangiolysis	1	2	2/3	66.6
Tubular atrophy	2	2	2/3	66.6
Acute necrotizing glomerulonephritis	1	1	1/1	100
Acute tubulointerstitial nephritis	1	1	1/2	50
Exudate in Bowman's space	1	1	1/5	20
Mesangial cell hyperplasia	1	1	1/5	20
Mesangial proliferative glomerulonephritis	1	1	1/2	50
Nephrocalcinosis	1	1	1/5	20
Peritubular capillaritis	1	1	1/1	100

ATN: Acute tubular necrosis, FSGS: Focal segmental glomerulosclerosis

The study's notable finding was that ATN was the major pathologic finding associated with a history of AKI. This is in line with common clinical practice in which ATN is the most common cause of AKI. Although there are no studies that have yet to prove whether the mechanism of this pathology is different from the adult and pediatric patients, it has been suggested that the damage in the tubules is caused by the high level of ACE2 expression that can cause cytokine storm, direct viral tropism, hemodynamic instability, or hypoperfusion in COVID-19 patients that correlates to the damage or inflammation in the kidney and progression of AKI in the patients.⁶ Patients with ATN also accompanied with other kidney pathology. The same studies in adult patients showed similarities supporting these findings. A study revealed that in addition to glomerular and vascular alterations suggestive of underlying diabetic or hypertensive illness, they discovered significant ATN, where the obstruction of microvascular lumens is mostly by erythrocytes with subsequent endothelial injury. They also provide data that point to multiple mechanisms for this unique coronavirus infection, possibly including secondary endothelial damage and direct kidney parenchyma infection.¹⁶ Another study also reported that ATN is mostly present in the biopsy with widened tubular lumina, flattened tubular epithelium, and interstitial edema. They also found that three of 18 patients showed signs of disseminated intravascular coagulation, with small fibrin thrombi in the glomerular capillaries.¹⁷

In critically ill patients with COVID-19 illness, there are numerous potentials and probably connected causes of AKI. All patients had elevated inflammatory

markers, which would be suggestive of cytokine release syndrome, a well-known side effect of a severe COVID-19 infection. The most frequent cause of AKI in the critical care unit setting is distributive septic shock, which can generate cytokine storms as a side effect. The exposure of tubular epithelial cells to a pathogen or damage-related molecular patterns, dysfunctional intrarenal microcirculation, and metabolic reprogramming are additional pathways of septic shock-related AKI. The need for mechanical ventilation due to suspected acute respiratory distress syndrome (ARDS) is also something to consider as it is a way of treating one of the main complications of COVID-19. In critically sick patients, ARDS is a known risk factor for the development of AKI, and AKI in the presence of ARDS carries a sizable mortality risk. Complex interactions between the lungs and kidneys, a decreased gas exchange that results in tissue hypoxia, the hemodynamic effects of forceful volume evacuation, and secondary right heart failure are some of the potential causes.¹⁸

Following ATN, congestion was also commonly found in the patient's kidney results. Previous studies had noted that the use of ventilators decreased cardiac output by reducing venous return, which in turn causes reduced blood flow to the kidneys. This is accompanied by an increase in sodium reabsorption and glomerular filtration rate. Sodium reabsorption requires a lot of oxygen, which is impeded by the low blood flow caused by mechanical ventilation.¹⁹ This has been addressed by introducing a more personalized ventilator system that could limit or detect early injury to the kidneys.²⁰ In a reported study, further strengthened the findings of this study, where they

found that ATN and congestion are associated with COVID-19-associated nephropathy.²¹

The finding of FSGS was also found in four of the patients. This finding is also supported by the study that FSGS can be found in COVID-19-related nephropathy.²² In the adult setting, an AKI with hematuria and proteinuria was found, and infection with SARS-CoV-2 was confirmed. The study reported that due to the patient's worsening kidney function, renal replacement therapy with dialysis was started, and later on, a kidney biopsy was performed, and FSGS with epithelial cell hypertrophy and signs of proximal tubular cell injury was found.²³

Lastly, it should be noted that there was more finding of vessel damage like acute thrombotic microangiopathy. In one of the cases, the patient had disseminated intravascular coagulation; the two other cases that the author presented were suspected to be caused by multiple inflammatory syndromes in children.¹⁰

It is important to note that this study has some limitations. The first is that the search terms used were specific and may unintentionally exclude some studies. Next is that the descriptive analysis of a small number of patients in this study limits the pathological conclusions and the generalizability of the findings to the general population. In addition, there is limited laboratory data available to determine the baseline kidney function and assess the severity of kidney function parameters and post-treatment laboratory results. Furthermore, anthropometric data, as well as information about the patient's past illness and comorbidity, are currently unavailable.

CONCLUSION

The findings of the study indicate that ATN followed by congestion and thrombosis are the main histopathological manifestations in pediatric patients with COVID-19-associated AKI.

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Conflicts of interest

There are no conflicts of interest.

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