



Critical analysis of acute kidney injury in pediatric COVID-19 patients in the intensive care unit

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Abstract

Background and objectives COVID-19 is responsible for the 2019 novel coronavirus disease pandemic. Despite the vast research about the adult population, there has been little data collected on acute kidney injury (AKI) epidemiology, associated risk factors, treatments, and mortality in pediatric COVID-19 patients admitted to the ICU. AKI is a severe complication of COVID-19 among children and adolescents.

Methods A comprehensive literature search was conducted in PubMed/MEDLINE and Cochrane Center Trials to find all published literature related to AKI in COVID-19 patients, including incidence and outcomes.

Results Twenty-four studies reporting the outcomes of interest were included. Across all studies, the overall sample size of COVID positive children was 1,247 and the median age of this population was 9.1 years old. Among COVID positive pediatric patients, there was an AKI incidence of 30.51%, with only 0.56% of these patients receiving KRT. The mortality was 2.55% among all COVID positive pediatric patients. The incidence of multisystem inflammatory syndrome in children (MIS-C) among COVID positive patients was 74.29%.

Conclusion AKI has shown to be a negative prognostic factor in adult patients with COVID-19 and now also in the pediatric cohort with high incidence and mortality rates. Additionally, our findings show a strong comparison in epidemiology between adult and pediatric COVID-19 patients; however, they need to be confirmed with additional data and studies.

Keywords COVID-19 · Acute kidney injury · Kidney replacement therapy · Adult · Pediatric · MIS-C

Introduction

Since January 30, 2020, the virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 was declared a global health emergency of international concern by the World Health Organizations (WHO) and has continued to evolve into a devastating pandemic [1]. COVID-19 has infected more than 103 million people of all ages and has a mortality of 2.3 million people globally as of February 2020 (John Hopkins Coronavirus Tracker). We have extensively developed our knowledge on the pathophysiology, diagnosis, management, and post infection complications of COVID-19 in the past year; however, this knowledge continues to evolve. While the majority (approximately 80%) of adult patients with COVID-19 have mild symptoms, the virus may produce severe illness, multiorgan failure, and death in a small portion of the population [2]. Kidney manifestations of COVID-19, such as acute kidney injury (AKI), are typically considered negative prognostic factors and may appear in up

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to 25% of adult patients. The disease is most severe among those who have comorbidities or those who are elderly [3, 4].

Limited research on the epidemiology and manifestations of COVID-19 among pediatric patients has been reported to be much different than that of adults. As reported recently, children only comprise about 1–2% of COVID-19 cases documented worldwide [5]. In a recent meta-analysis of 9,335 pediatric COVID-19 patients, 13.1% of the patients presented asymptotically through contact exposure in family clusters [6]. Overall, 57.4% of patients were hospitalized and at least one underlying comorbidity was reported in 27.1% of cases [6]. The neonatal age group, male gender, lower respiratory tract disease, and pre-existing medical conditions have all been associated with severe disease among children [5]. The most common clinical features of COVID-19 in pediatric patients are fever, dry cough, and pneumonia along with an increasing prevalence of multisystem involvement, including AKI among other kidney manifestations [7]. Thus far, among pediatric COVID cases presenting with the same severity of illness as adults, a similar clinical picture of kidney involvement may be expected [8].

Furthermore, multisystem inflammatory syndrome in children (MIS-C) is a life-threatening complication of the virus specifically among children. MIS-C is associated with SARS-CoV-2 and has been shown to occur within 2–4 weeks, most commonly after an infection [9, 10]. Children with MIS-C have been reported to exhibit symptoms similar to those of Kawasaki disease including fever, toxic shock syndrome, macrophage activation syndrome, secondary hemophagocytic lymphohistiocytosis, and multisystem organ involvement, which commonly includes AKI [9, 11, 12].

Despite this data, there is a lack of large-scale studies analyzing the extent of AKI in pediatric patients. Thus, this systematic review aims to evaluate the incidence of AKI, associated mortality, the need for kidney replacement therapy (KRT), and outcomes in the pediatric COVID-19 population through the analysis of published literature.

Method

Database sources and search strategy

This study was registered with the International Prospective Register for Systematic Reviews (PROSPERO: CRD42021237695). In this study, a systemic search was performed in PubMed/MEDLINE and Cochrane Center Trials databases to find all published literature related to AKI in COVID-19 patients, including incidence and outcomes. The search terms for the pediatric population included “COVID-19”, “Coronavirus”, “Betacoronavirus”, “kidney”, “renal”, “pediatric”, “acute kidney injury”, and “MISC” in the search criteria (Appendix A). All literature from the search strategy was then imported into Rayyan QCRI using EndNote. In addition, the reference lists of the selected studies were further

reviewed for any additional publications that were relevant to the search criteria. The search for the pediatric literature spanned from November 1, 2019 to December 24, 2020. Language restriction of only English studies was applied. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses “PRISMA” checklist (Appendix B).

Literature selection

The pediatric literature was independently reviewed by two reviewers using the inclusion and exclusion criteria with a third reviewer to settle any disputes. The inclusion criteria for the publications of pediatric populations included prospective, retrospective, and case series studies assessing AKI in COVID-19 positive patients. All included studies needed to contain laboratory-confirmed SARS-CoV-2 diagnosis (via detection of SARS-CoV-2 nucleic acid via polymerase-chain-reaction), demographic and epidemiological data (incidence of AKI, severity, and comorbidities), and outcome. Males and females ≤ 24 years were the criteria for the pediatric population. Studies exclusively on kidney transplant patients or a negative SARS-CoV-2 status were excluded along with systematic reviews, meta-analyses, animal studies, and letters not presenting any original data (Table 1).

Quality assessment

All included studies were evaluated for study quality independently using a quality assessment tool from the National Heart Lung and Brain Institute (NHLBI) (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>). This tool is designed to validate the internal studies designed for critical appraisal. The study quality had eight questions: study objective, study population, case definition, consecutive cases, outcome validity, adequate length of follow-up, statistical methods, and results. Studies were scored out of 8 points, where 6–8 points were considered good quality, 4–5 as fair quality, and < 4 were regarded as poor quality.

Data extraction and statistical analysis

Data regarding patient demographics, the presence of comorbidities, AKI incidence, mortality rates, need for KRT, and outcomes were recorded electronically. The pooled proportions for these outcomes and their respective 95% confidence intervals (95% CI) were assessed for each study or calculated when not reported. The degree of between-study statistical heterogeneity was assessed using the I^2 test, where $I^2 \geq 50\%$ indicated high heterogeneity. A meta-analysis of the outcomes was performed with overall pooled estimates calculated with a

Table 1 PICO table

Criteria	Inclusion criteria	Exclusion criteria
Population	Any pediatrics population (< 24 years)	
Intervention/input exposure	SARS-CoV-2 diagnostic test	Negative SARS-CoV-2 test
Comparison	AKI incidence in COVID positive children population.	
Outcomes	Pediatric patients who are COVID + and have AKI	
Study types	Prospective/retrospective studies, case studies	Systematic review, meta analyses, animal studies

random effects model and fixed effects model to assess for high and low heterogeneity, respectively. Forest plots were utilized to visualize the outcomes of each study, including the combined estimated outcomes with their 95% CI. Funnel plots were created to graphically assess publication bias in each study. A p value ≤ 0.05 was used to consider statistical significance. All statistical analyses were performed with R software version 3.1.0.

Results

Study selection and details

The database search for the pediatric population yielded a total of 42 studies with 24 studies included that reported the outcomes of interest (Fig. 1). Of these studies, 10 were retrospective cohort studies, 7 were case reports, 4 were case series, 2 were cross-sectional studies, and one was a prospective cohort study [12–35]. There were 23 studies that were determined to be of good quality while one study was of fair quality [S. Table 1]. However, only a total of 14 pediatric studies were used for our meta-analysis as the other studies had total sample sizes less than 10. The overall sample size of COVID positive children across the studies was 1,247 (ranging from 17 to 570 across 14 different studies). The pooled median age of children was 9.1 years (median of 6.5–14.5 years across all studies) and 56.2% of patients were male. The values pertaining to the distribution of race among the pediatric patients was reported to be African American (29.1%), Caucasian (16.4%), Asian (3.4%), and a category for unknown/missing patients (51.1%). A total of 26.7% of children had at least 1 pre-existing co-morbidity (based on 20 studies). The data for various lab parameters among these patients were very limited including glomerular filtration rate (1 study), serum creatinine (median: 62.5 μmol/L (0.71 mg/dL); 6 studies), blood urea nitrogen, D-dimer (median 2.7 mg/L (0.27 mg/dL); 8 studies), sodium (median 132.5 mEq/L; 3 studies), and potassium (1 study). Also, only one study reported the data for uremia, proteinuria, and hematuria. The details of the studies are provided in Tables 2 and 3.

Data analysis

This meta-analysis for the outcomes of interest was conducted for studies with total sample sizes ≥ 10 (14 studies; n = 1,247). Through our analysis, the pooled (95% CI) AKI incidence in COVID positive pediatric patients was 30.51% (21.84–39.94%) [I² = 89.8% (84.65 to 93.21%); p < 0.0001; random effects; 14 studies; n = 1,247] [Table 4; Figs. 2 and 3]. Additionally, our analysis showed a pooled mortality (95% CI) of 2.55% (1.67–3.73%) [I² = 38.72% (0.00 to 70.77%); p = 0.0999; fixed effects; 10 studies; n = 989] in COVID positive patients [Table 5; Figs. 4 and 5]. Only four studies reported the use of KRT in COVID pediatric

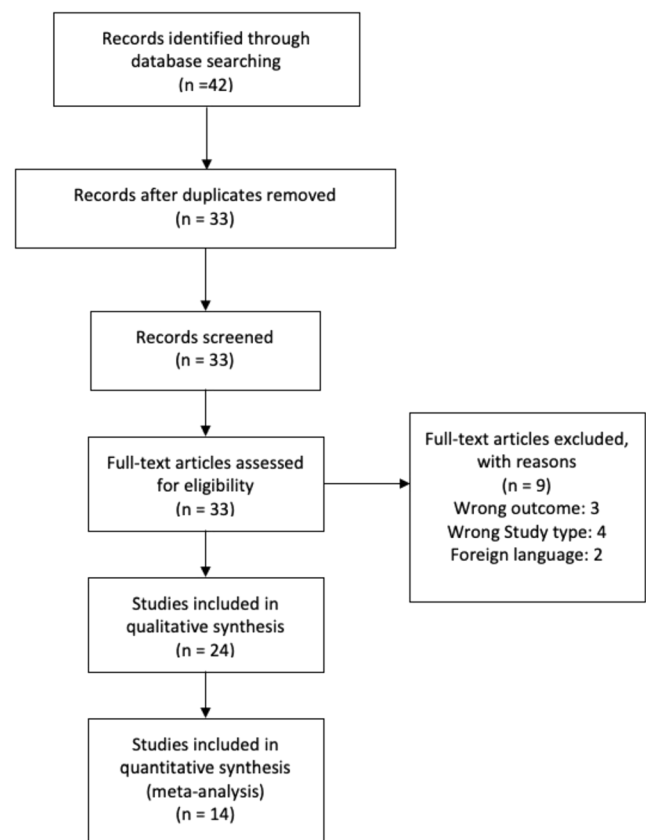


Fig. 1 Prisma flowchart for pediatric studies

Table 2 Summary table for pediatric studies

Study	Study design	Location	Age (years) (mean \pm SD)	COVID+ with AKI	Treatment
*González-Dambrauskas S et al.	Retrospective observational multicenter	Chile, Colombia, Italy, Spain, United States	6.52 \pm 2.99	3	Antibiotics, 15 (88%); remdesivir, 4 (24%); lopinavir and/or ritonavir, 1 (6%); corticosteroids, 9 (53%); tocilizumab, 7 (41%); hydroxychloroquine, 8 (47%)
*Whittaker E et al.	Uncontrolled case series multicenter	England	10 \pm 1.3	11	IVIG, 33 (75%); corticosteroids, 33 (75%); anakinra, 2 (5%); infliximab, 7 (16%)
*Dufort EM et al.	Retrospective observational multicenter	New York, USA	9.33 \pm 1	10	Systemic glucocorticoids, 63 (64%); IVIG, 69 (70%)
*Lee PY et al.	Retrospective single center	Boston, USA	8.77 \pm 2.82	6	Immunomodulatory therapy, 22 (79%); antimicrobial therapy, 22 (79%); anticoagulation therapy, 24 (86%)
*Capone CA et al.	Case series, single center	New York, USA	8.83 \pm 1.183	23	IVIG, 33 (100%); second dose IVIG, 11 (33%); methylprednisolone, 23 (70%); aspirin, 29 (88%); anakinra, 4 (12); tocilizumab, 3 (9%); infliximab, 1 (3); enoxaparin, 14 (42)
Wang X et al.	Retrospective observational	Wuhan, China	1.08	3	Meropenem + linezolid, 3 (100%); oseltamivir, 1 (33%); ribavirin, 2 (67%); corticosteroids, 3 (100%); IVIG, 3 (100%)
Tram N et al.	Case report	Brussels, Belgium	15	1	N/A
Samies NL et al.	Case report	Alabama, USA	16	1	IV fluids and hemodialysis for 5 days
Repper DC et al.	Case report	California, USA	15	1	IVIG, corticosteroids
Qiu L et al.	Case report	China	0.67	1	IVIG, methylprednisolone, fluid and electrolyte therapy, low dose diuretics and dopamine
Niño-Taravilla C et al.	Case report	Chile	8	1	Cefotaxime, fluid resuscitation, tocilizumab, IVIG, 18 (48%); steroids, 27 (60)
*Mamishi S et al.	Retrospective multicenter	Iran	6.98 \pm 0.98	13	Normal saline, clindamycin, ceftriaxone, doxycycline, IVIG, methylprednisolone
Lee M et al.	Case report	California, USA	15	1	All participants (20) received IVIG with adjuvant corticosteroids, IL-1 receptor antagonist, or a monoclonal antibody against IL-6
*Grimaud M et al.	Retrospective observational	France	N/A	14	
Oberweis ML et al.	Case report	Belgium	8	1	IVIG, dobutamine, milrinone
*Toubiana J et al.	Prospective observational	Paris, France	9.03 \pm 2.15	11	IVIG, 21 (100%), 10 (48%) corticosteroids
Shahbaznejad L et al.	Case series	Iran	5.32 \pm 4.10	2	Antibiotics (7); hydroxychloroquine (6); packed cell (6); albumin (6); IVIG 1 g/kg (5); IVIG 2 g/kg (1); steroids (2); vasoactive drugs (4); infliximab (1)

Table 2 (continued)

Study	Study design	Location	Age (years) (mean ± SD)	COVID+ with AKI	Treatment
*Godfred-Cato S et al.	Retrospective report	District of Columbia and New York, USA	9.01 ± 3.33	105	IVIG (424), steroids (334), antiplatelet meds (309), anticoagulation meds (233), vasoactive (221), immune modulators (119)
*Dionne A et al.	Retrospective cohort, single center	Boston, USA	9.28 ± 2.05	2	IVIG (16, 64%), steroids (13, 52%), anakinra (4, 16%), aspirin (14, 56%), remdesivir (9, 36%)
*Derespina KR et al.	Retrospective observational, multicenter	New York, USA	14.5 ± 1.67	9	Hydroxychloroquine (27, 38.6%), azithromycin (23, 32.9%), remdesivir (13, 18.6%), corticosteroids (23, 32.9%), antibiotics (48, 68.6%)
*Stewart DJ et al.	Retrospective observational, single center	London, UK	9.33 ± 1.22	15	N/A
*Bjornstad EC et al.	Multicenter cross-sectional analysis	United States, Western Europe, Eastern Europe/Russia	9.98 ± 2.95	47	N/A
Deep A et al.	Multicenter observational study	United Kingdom	N/A	N/A	N/A
Joshi K et al.	Case series	New York, USA	11.25 ± 1.17	2	Tocilizumab (2), remdesivir (1), IVIG (1), steroids (1), hydroxychloroquine (2)

N/A Not applicable. * The studies included in the meta-analysis

patients with AKI. The pooled proportion (95% CI) of AKI COVID positive patients receiving KRT was 0.56% (0.16–1.43%) [$I^2 = 0\%$ (0.00 to 76.45%); $p = 0.6493$; fixed effects; 4 studies; $n = 712$].

The distribution of various treatments and intervention modalities was also assessed in this study. The analysis showed that the pooled proportion (95% CI) of COVID positive patients receiving respiratory support was 46.33% (24.99–68.40%) [$p < 0.0001$; random effects; 12 studies; $n = 1,086$] while 53.96% (34.43–72.88%) of patients received inotropic support [$p < 0.0001$; random effects; 6 studies; $n = 191$]. The other supportive treatments are described in Table 2. It was evaluated that the median duration of hospital stay among COVID positive patients was 6 days (median of 4–8 days across 7 studies providing the data). Lastly, this meta-analysis evaluated the incidence of MIS-C among COVID-positive patients and found a pooled incidence (95% CI) of 74.29% (41.24–96.43%) [$I^2 = 99.16\%$ (98.98 to 99.32%); $p < 0.0001$; random effect; 12 studies; $n = 1,206$].

Discussion

A multitude of studies have made it clear that COVID-19 has significantly affected individuals of all ages. Although the virus is known to particularly target the lungs, it is not uncommon for the disease to manifest in other organ systems, especially in severe cases. More specifically, various pathological studies have particularly highlighted the kidneys as a target of COVID-19 with the development of AKI in critically ill COVID-19 adult patients. There have also been instances of AKI occurrence in pediatric COVID-19 patients. However, there has been no consensus regarding the accurate incidence, outcomes, and associated mortality among this population. Therefore, our systematic review and meta-analysis was performed to specifically address the incidence, mortality, outcomes, and various treatment modalities utilized in COVID-positive pediatric patients with AKI.

Table 3 Quality criteria checklist assessment for the studies

Study	Inclusion and exclusion specified	Study type	Sample size specified	COVID test mentioned	AKI related labs	Management mentioned
*González-Damrauskas S et al.	Y	R	Y	Y	N	Y
*Whittaker E et al.	N/A	CS	Y	Y	Y	Y
*Dufort EM et al.	Y	R	Y	Y	N	Y
*Lee PY et al.	Y	R	Y	Y	Y	Y
Capone CA et al.	N/A	CS	Y	Y	N	Y
Wang X et al.		R	Y	Y	Y	Y
Tram N et al.	N/A	CR	Y	Y	Y	Y
Samies NL et al.	N/A	CR	Y	Y	Y	Y
Repper DC et al.	N/A	CR	Y	Y	Y	Y
Qiu L et al.	N/A	CR	Y	Y	Y	Y
Niño-Taravilla C et al.	N/A	CR	Y	Y	Y	Y
*Mamishi S et al.	Y	R	Y	Y	Y	Y
Lee M et al.	N/A	CR	Y	Y	Y	Y
Grimaud M et al.	Y	R	N	Y	Y	Y
Oberweis ML et al.	N/A	CR	Y	Y	Y	Y
*Toubiana J et al.	Y	P	Y	Y	Y	Y
Shahbaznejad, L et al.	N/A	CS	Y	Y	N	Y
*Godfred-Cato S et al.	Y	R	Y	Y	N	Y
*Dionne A et al.	Y	R	Y	Y	N	Y
*Derespina KR et al.	Y	R	Y	Y	Y	Y
Stewart DJ et al.	Y	R	Y	Y	Y	N
*Bjornstad EC et al.	Y	CrS	Y	Y	Y	N
Deep A et al.	Y	R	N	N	N	N
Joshi K et al.	N/A	CS	Y	Y	N	Y

Y yes, N no, R retrospective, P prospective, CS case series, CR case report, CrS cross sectional, N/A not applicable

*The studies included in the meta-analysis

Table 4 Meta-analysis of pediatric AKI incidence among COVID positive patients across different studies

Study	Event/sample size	Proportion (%) (95% CI)	Random weight (%)
Bjornstad EC et al., 2020	47/106	44.34 (34.69–54.31)	7.95
Capone CA et al., 2020	23/33	69.70 (51.29–84.41)	6.87
Deep A et al., 2020	48/116	41.38 (32.31–50.90)	8.00
Derespina KR et al., 2020	9/70	12.86 (6.05–23.01)	7.66
Dionne et al., 2020	2/25	8.00 (0.98–26.03)	6.48
Dufort EM et al., 2020	10/99	10.10 (4.95–17.79)	7.91
Godfred-Cato S et al., 2020	105/570	18.42 (15.32–21.85)	8.45
González-Dambrauskas S et al., 2020	3/17	17.65 (3.80–43.43)	5.84
Grimaud M et al., 2020	14/20	70.00 (45.72–88.11)	6.12
Lee PY et al., 2020	6/28	21.43 (8.30–40.95)	6.64
Mamishi S et al., 2020	13/45	28.89 (16.37–44.32)	7.25
Stewart DJ et al., 2020	15/52	28.85 (17.13–43.08)	7.40
Toubiana J et al., 2020	11/21	52.38 (29.78–74.29)	6.20
Whittaker E et al., 2020	11/45	24.44 (12.88–39.54)	7.25
Total (random effects)	317/1,247	30.51 (21.84–39.94)	100

In our meta-analysis, we found an AKI incidence of 30.51% (21.84–39.94%). The higher incidence among pediatric patients was higher than we expected, however, in the multicenter cohort study (the Critical Coronavirus and Kids Epidemiologic [CAKE] study) of critically ill children with COVID-19, the incidence of AKI was reported to be 18% [13]. Additionally, in a multicenter AKI study among critically ill children with COVID-19 by Bjornstad et al. (n = 106), AKI was found to occur in 44% (n = 47) of patients [14]. We also found a mortality of 2.55% (1.67–3.73%) in COVID AKI patients with 0.56% of patients requiring KRT (0.16–1.43%). This is similar to the data reported by the Virtual Pediatric Systems (VPS) from North American pediatric ICUs as of February 2020. Based on the 2,030 COVID-19 positive patients reported by VPS, there was a mortality rate of 3.3%

(Fig. 6c). Additionally, in the 281 (13.8%) of COVID-19 patients with kidney systems involved, there was a mortality rate of 10.3% (n = 29) with 13.9% (n = 39) requiring organ support via KRT. Lastly, it had been reported by various studies that some pediatric patients uniquely exhibited MIS-C. A recent systematic review by Abrams et al. analyzing the clinical features of 440 children with MIS-C revealed that the proportion of patients who received a positive SARS-CoV-2 RT-PCR test ranged from 13 to 60% while the proportion of positive serology tests ranged from 75 to 100% [36]. Additionally, Feldstein et al. reported that out of 186 children with MIS-C, 70% were COVID-positive by RT-PCR or antibody testing [10]. Based on our review, we found that the pooled incidence (95% CI) of MIS-C among COVID-positive patients was 74.29% (41.24–96.43%) [p < 0.0001; random effect; 12

Fig. 2 Forest plot of the meta-analysis of pediatric AKI incidence among COVID-positive patients across different studies. The lower diamond in the graph represents the pooled estimate

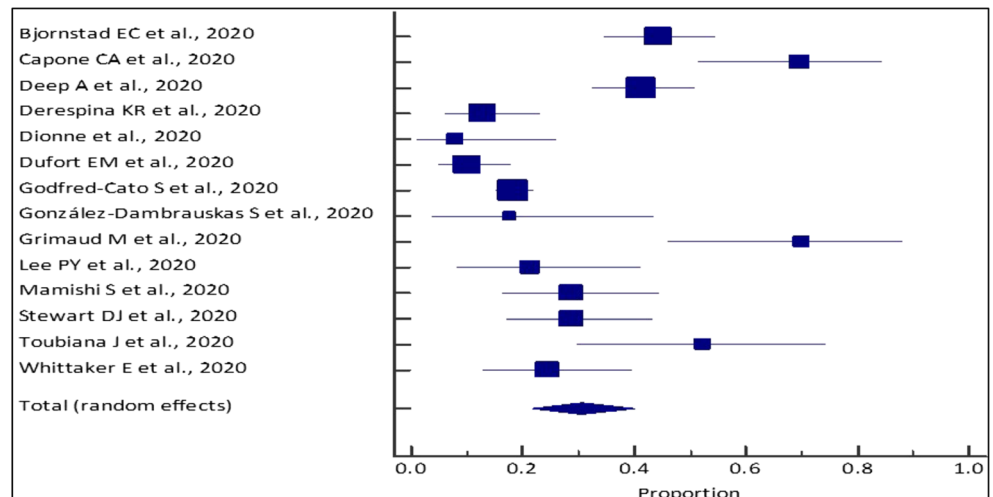
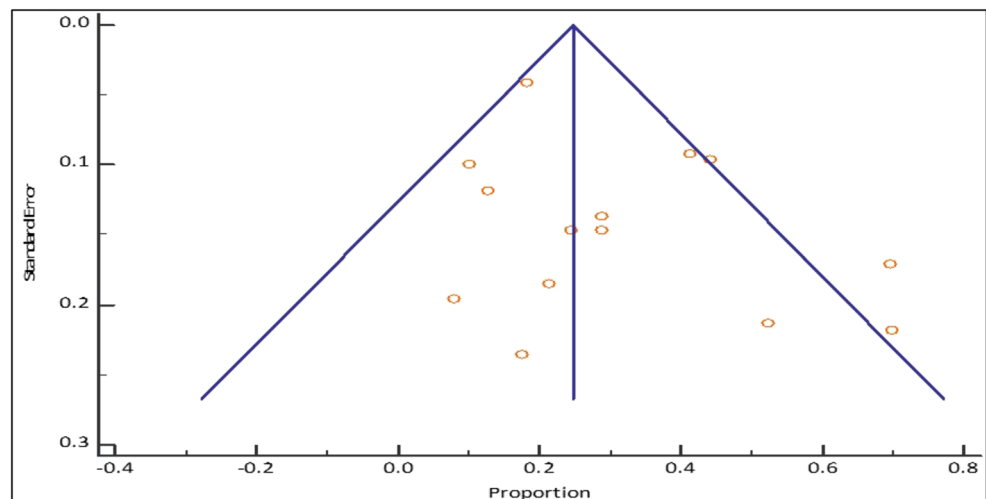


Fig. 3 Funnel plot for pediatric AKI incidence among COVID-positive patients



studies; $n = 1,206$]. This is much higher than reported by VPS, which reported a total of 23.9% of pediatric patients with MIS-C (485 out of 2,030 patients). These differences may potentially be attributed to variations in the definition and clinical knowledge of the syndrome due to its novelty [7].

To bring our pediatric data into comparison with adult data regarding AKI in COVID-positive patients, a sub-analysis was performed with our systematic review which assessed AKI incidence in the majority of adult COVID patients. The parameters of our adult systematic review are highlighted in Appendix C. Our comparison analysis was performed by calculating medians and utilizing the Mann–Whitney U-test with a p value ≤ 0.05 considered for statistical significance (Fig. 6a). The pooled median age of children was 9.1 years (ranging from median of 6.5–14.5 years across all studies) and adults was 61 years (median of 45.6–73 years). The proportion of males was almost equal for children (56.2%) and adult (60.9%) studies. However, there was a lower proportion of children (26.7%) with at least 1 pre-existing co-morbidity than that of adults (40.9%).

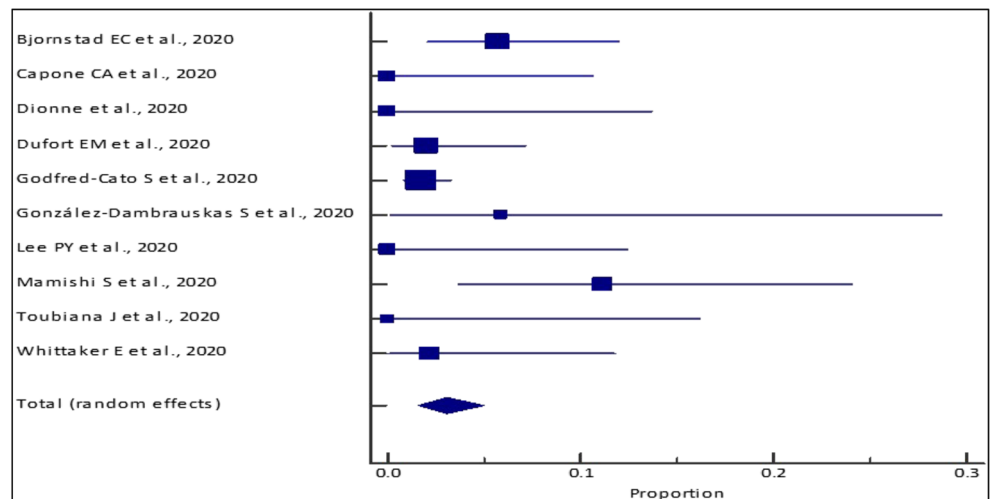
The median (IQR) AKI incidence was calculated for both populations and was found to be higher among pediatric patients [26.6% (17.8–43.6%); $n = 14$] compared to the adult population [15.6% (5.7–31.7%); $n = 53$] ($p = 0.07$). Mortality was also compared and the median (IQR) mortality among COVID-positive patients was observed to be significantly lower among pediatric patients [1.9% (0.0–4.8%); $n = 10$] compared to adults [14.6% (5.4–39.3%); $n = 25$] ($p < 0.001$) (Fig. 6b). In respect to the utilization of KRT among COVID-positive patients, the median utilization was significantly lower among pediatric patients [0.2% (0.0–0.6%); $n = 4$] when compared to adults [8.0% (3.3–16.7%); $n = 33$] ($p < 0.001$) (Fig. 6b).

Overall, this suggests that children may have less severe symptoms from SARS-CoV-2 as compared to adults. The observed outcomes among children may be attributed to a more active innate immune response, generally being overprotected by parents, engaging in fewer outdoor activities, undertaking less international

Table 5 Meta-analysis of pediatric mortality among COVID positive patients across different studies

Study	Event/sample size	Proportion (%) (95% CI)	Fixed weight (%)
Bjornstad EC et al., 2020	6/106	5.66 (2.11–11.91)	10.71
Capone CA et al., 2020	0/33	0 (0–10.58)	3.40
Dionne et al., 2020	0/25	0 (0–13.72)	2.60
Dufort EM et al., 2020	2/99	2.02 (0.25–7.11)	10.01
Godfred-Cato S et al., 2020	10/570	1.75 (0.84–3.2)	57.16
González-Dambrauskas S et al., 2020	1/17	5.88 (0.15–28.69)	1.80
Lee PY et al., 2020	0/28	0 (0–12.34)	2.90
Mamishi S et al., 2020	5/45	11.11 (3.71–24.05)	4.60
Toubiana J et al., 2020	0/21	0 (0–16.11)	2.20
Whittaker E et al., 2020	1/45	2.22 (0.06–11.77)	4.60
Total (fixed effects)	25/989	2.55 (1.67–3.73)	100

Fig. 4 Forest plot of the meta-analysis of pediatric mortality among COVID-positive patients across different studies. The lower diamond in the graph represents the pooled estimate

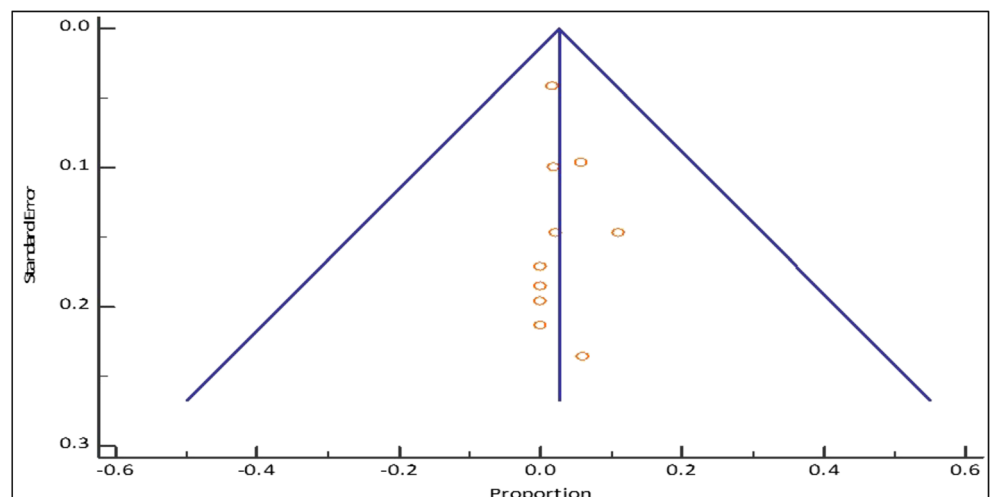


travel, and having less comorbidities. Additionally, children have a difference in the distribution, maturation, and functioning of viral receptors. Differences in the receptors in the renin–angiotensin system (RAS) and altered inflammatory responses to pathogens could also account for age-induced disease differences. Angiotensin II receptors (ACE2) have been shown to have a strong interaction with the receptor-binding domain of the COVID-19 spike-protein. Children have fewer ACE2 receptors than adults, which may potentially contribute to the reduced susceptibility to severe disease in children [37–40]. Despite these reasons providing a case why children are less likely to progress to severe disease, increasing pediatric cases and newer reports are starting to show the opposite. In the study by Bjornstad et al., the investigators reported a mortality of 6% and suggested the possibility of severe disease within the pediatric population [14]. Furthermore, there is a significant difference among the outcomes of

children with COVID-19 receiving care in high-income countries versus low- and middle-income countries. In comparison to high-income countries, low- and middle-income countries report lower proportions of admissions to the ICU (9.9% vs. 26.0%), yet higher numbers of deaths (relative risk 2.14, 95% CI: 1.43 to 3.20) [9]. This suggests that more large-scale global studies are required to fully assess the extent of AKI in pediatric COVID patients.

Although our study was able to accurately determine outcomes in COVID patients, one of the main limitations in our study was the sample size, as COVID and AKI incidence reports are still new. Due to a paucity of literature, it restricted us from doing a detailed analysis. Additionally, some studies presented insufficient data, forcing us to exclude them from our analysis despite meeting our inclusion criteria. It is also important to note that in our analysis, only studies with a sample size greater than 10 were included to remove the influence on outcome by studies with small sample sizes.

Fig. 5 Funnel plot for pediatric mortality among COVID-positive patients

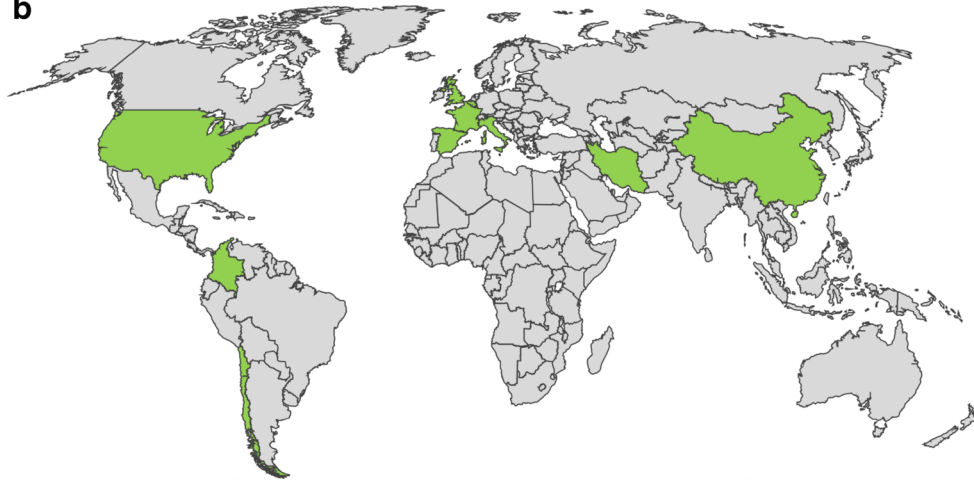


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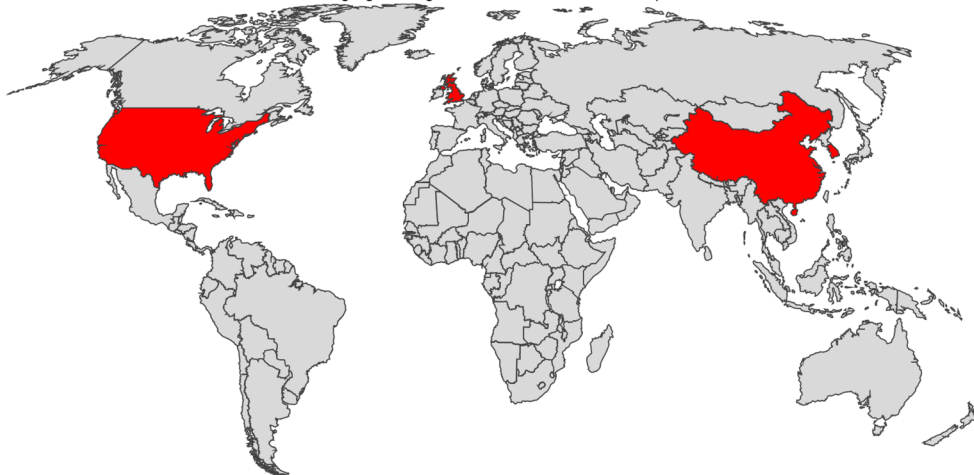
	Adults	Children
COVID+ Individuals	42,591	1,247
Median Age (years)	61	9.1



b



The countries highlighted in green indicate the location of the pediatric studies.



The countries highlighted in red indicate the location of the adult studies.

c

COVID-19 patients	2030
Confirmed deaths	66
MIS-C Diagnosis	485
Patients with renal/urinary manifestations	281
Patients requiring Kidney replacement therapy	39

◀ **Fig. 6** (a) Comparison of the adult vs. pediatric COVID-19 population. (b) World map of pediatric vs. adult COVID-19 studies. (c) COVID-19 clinical data from North American pediatric intensive care units (<https://www.covid19.myvps.org>)

Conclusion

Overall, AKI has shown to be a negative prognostic factor in adult patients with AKI and now also in the pediatric cohort with high incidence and mortality rates. Additionally, our findings do show a strong comparison in epidemiology between adult and pediatric COVID-19 patients; however, they need to be confirmed with additional data and studies as the direction of the relationships cannot be ascertained and still remain unclear in the literature. With the prevalence of cases worldwide, it is crucial for clinicians to be informed about the prevalence of AKI in both adult and pediatric populations.

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Author contribution RR conceptualized the study. RR, RC, IM, SS, and MF drafted the study protocol, conducted the literature search, study screening, selection and data extraction, and drafted the manuscript. All authors critically reviewed the manuscript to ensure intellectual content and approved the final manuscript.

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Declarations

Patient consent for publication Not required.

Conflict of interest The authors declare no competing interest.

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