International Journal of Research and Review
Vol. 9; Issue: 11; November 2022
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

COVID-19 Infection and Acute Kidney Injury in Paediatric Population: A Systematic Review and Meta-Analysis

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DOI: https://doi.org/10.52403/ijrr.20221102

ABSTRACT

Background: Acute Kidney Injury (AKI) posed a dreaded health complication in COVID-19 infection in paediatrics. In this review we systematically documented evidence on AKI incidence and associated death in COVID-19 infection among paediatric populations to aid healthcare workers towards appropriate clinical management.
Methods: Documentation on AKI incidence and associated death in COVID-19 infection worldwide in paediatrics in PubMed and medRxiv databases during December, 2019-June19, 2021 was included in this study. Guidelines laid by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) were followed which facilitated clarity and transparency in the reporting.
Result: 23 out of 1976 total articles were eligible with mean age of 8.6 years. Database of Abstract of Reviews of Effects (DARE) tool was used for quality assessment. Studies on AKI incidence (19), mortality (19) and AKI related mortality (10) respectively were included for meta-analysis. An estimated AKI incidence of 28.8%with overall death of 2.3% and AKI related death of 5.2% were reported. Overall pooled AKI incidence in the paediatric population was statistically significant.
Conclusion: Therefore, aggressive investigation of COVID-19 infection associated with AKI in paediatrics posed a necessity for efficient health-care management.

Keywords: Acute kidney injury; Box plot; COVID-19; Forest plot; Meta-analysis

INTRODUCTION

The coronavirus outbreak is a fast-emerging pandemic, empowering immense stress on community healthcare management globally. The etiologic agent identified as a novel coronavirus; SARS-CoV-2 caused acute respiratory illness described as Coronavirus Disease 2019 (COVID-19). In January 2020, COVID-19 was declared a global health emergency of international concern by the World Health Organization (WHO).(1) COVID-19 infection was reported in more than a 272.6 million people of all ages with a mortality of 5.33 million worldwide as on December 16, 2021 (John Hopkins University Coronavirus Tracker). Our knowledge about the pathophysiology, diagnosis, management, and post-infection complications of COVID-19 infection has developed substantially over the past two and half years however several

areas are yet to be explored to combat the evolving pandemic effectively.[2]

Coronaviruses (CoVs) (known as *Coronaviridae* and belonging to the order *Nidovirales*) are a group of highly diverse, enveloped, positive-sense, and single-stranded RNA viruses of zoonotic origin. These groups of viruses can be subdivided into four different classes: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*.[3] Some variants are HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1, which generally cause mild respiratory illnesses like the common cold.[4,5] Intricate studies were conducted to understand the infection strategy of these viruses. The SARS-CoV2 virus required an angiotensin-converting enzyme (ACE-2) to infect the host. ACE-2 was found to be expressed in various organs including the kidney, in addition to alveolar cells in the lungs, the latter being the primary site of injury by the virus as it reached the lungs after entry through the nose or mouth.[6, 7]Dipeptidyl peptidase 4 (DPP-4), a type II transmembrane ectopeptidase was found to act as the receptor for the MERS-CoV virus.[8] DPP-4 was found to be principally expressed in type I and II cells, alveolar macrophages, vascular endothelia, and pleural mesothelial and hence showed signs of lower respiratory tract-associated illness.[9] Moreover, DPP-4 similar to ACE-2 was also found to be expressed in different tissues including the renal tubular cells. Furthermore, in both SARS and MERS infections, viral RNA has been found in kidney tissue and urine.[10]

Patients infected by nCoV-19 were categorized into three types, mild, severe, and critical, according to the severity of the symptoms. Serious patients report dyspnea, respiratory frequency ≥ 30/minute, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, and/or lung infiltrates greater than 50% within 24 to 48 hours.[4]

Primarily thought to be immune to the deleterious effect of COVID-19, children were susceptible to the virus. Most of the cases of COVID-19 in children are mild diseases like other viral infections. Nonetheless, there is a high probability that it can be fatal in children with underlying chronic diseases of the heart, liver, and kidney, children suffering from malnutrition, and children with immune deficiency. The Centers for Disease Control and Prevention published a case definition for Multisystem Inflammatory Syndrome in Children (MIS-C) associated with recent COVID-19 infection in May 2020 along with a public health recommendation. Children showed symptoms resembling those of Kawasaki Disease including toxic shock syndrome, macrophage activation syndrome, secondary hemophagocytic lymphohistiocytosis, and multisystem organ involvement, including AKI.[11] An independent risk factor for mortality in patients with acute respiratory distress syndrome was the development of AKI irrespective of their age. High intrathoracic pressures in ventilated children can cause low cardiac output, resulting in inadequate renal perfusion. Subsequent gas exchange abnormalities that resulted in hypoxemia, hypercarbia, and systemic acidosis might affect renal vascular resistance, which might change renal perfusion pressures and cause AKI.[2] Moreover, studies found the deleterious effect of AKI on patient outcomes like mortality, length of stay (LOS) and duration of ventilation (PICU LOS and Length of Ventilation [LOV] were almost twice as long in patients with severe AKI compared to those with no AKI, which has a significant effect in the case of COVID-19 pandemic where ICU resources may be scarce.[12] However, recent emerging evidence shows that AKI is prevalent in COVID-19 patients and that

SARS-CoV-2 specifically invades the kidneys [13] and more than 20% of the deceased patients are affected by chronic kidney disease. [14] Since there exist little early data on the incidence of AKI in paediatrics with COVID-19 infection, the rates, outcomes, and clinical characteristics was not conclusively elucidated which results in difficulty in paediatric health management issues. Worldwide COVID-19 vaccination among adults and children between 12-18 years has effectively aided the present clinical management of the viral infection. However, the paediatric population below 12 years has remained vulnerable to COVID-19 disease severity.

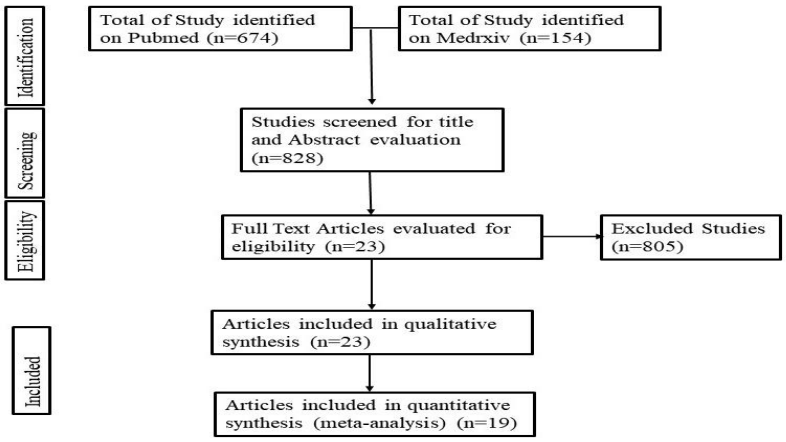
This systemic review and meta-analysis aimed to account for the important summary of published reports on AKI incidence, mortality, and mortality due to AKI in the course of COVID-19 infection in the paediatric population across the world.

METHODOLOGY

Review of literature

This study conducted a comprehensive search of scientific publications using the keywords "COVID-19", "Coronavirus", "SARS-CoV-2", "Kidney injury", "Paediatric", "MIS-C" in the 'Pubmed' and 'medRxiv' electronic database spanned from December 2019 to June 19, 2021. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses "PRISMA" checklist (Figure 1) used to compose the systematic review. [15] Inclusion criterion included different studies (original research articles on relevant experimental and observational research, case studies, and reports) in paediatric (age <18 years) populations on the incidence of COVID-19 with AKI and reported mortality as an outcome of interest. The data were retrieved from the studies relevant to zone and country, duration, the mean age of the patients, total population included, AKI incidence, MIS-C incidence and diagnosis associated with kidney involvement in COVID-19 infection. Publications that included systemic review and meta-analysis on COVID-19 in paediatrics with incidence of AKI and publications not in English language excluded from the study.

Figure 1. - PRISMA Flowchart for the different stages of the systematic review on acute kidney injury in COVID-19 infection



Quality Assessment

The quality assessment on the included publications was evaluated using the Database of Abstract of Reviews of Effects (DARE) tool.[16] The study quality had five questions: (i)were exclusion/inclusion criteria reported; (ii) was the search adequate; (iii) were the included studies synthesized; (iv) was the

quality of the included studies assessed and (v) are sufficient details about the individual included studies presented. Publications that met at least four out of five criteria were included for meta-analysis. Two reviewers with a third reviewer to settle in case of dispute performed the quality assessment process.

Statistical analysis

The statistical analysis was performed using Open Meta-Analyst software (for Windows 10 version; Brown University, Providence, USA). [17] Random effects models and the Dersimonian-Laird method used to examine the pooled estimate of the incidence of AKI, mortality and AKI associated mortality in COVID-19 infected paediatric populations. All outcomes evaluated at their 95 % confidence interval (CI). The outcome from each study along with the combined estimated outcomes with 95% confidence interval (CI) represented by Forest plots. The extent of statistical heterogeneity among different study groups was assessed by I^2 values, where I^2>75% indicated high statistical heterogeneity. The mean, median values with the interquartile ranges (IQR) were calculated. Funnel Plots were drawn using QI-Macros add-ins in Microsoft Excel 2016to graphically assess publication bias in each study. Box plots drawn using Microsoft Excel 2016 and were used to visualize the distribution of the data for each parameter (Student's T-test was applied to calculate the statistical significance. A P-value ≤ 0.05 used to consider statistically significant). The data obtained through independent-sample Student's T-test for AKI incidence and mortality used to infer the difference and a P-value ≤0.05 was used to consider the statistical significance.

RESULTS

Study details and selection criteria

The database search yielded 23 reports that included outcomes of interest in the COVID-19 infected paediatric population. (Figure 2). Out of the 23 studies, 3 were retrospective studies, 6 included case reports, 1 each of retrospective cohort, observational and prospective study and 1 cross-section analysis (Table 1). Most of the studies were reported from the USA (10) followed by UK (3), China (2), France (2), Italy (2), Chile (1), Luxembourg (1), Russia (1), Saudi Arabia (1) and India (1) (Figure 2). The mean age of the study population was 8.6 years. 19 out of the 23 studies reported sufficient data on the incidence of AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria in the COVID–19 infected patients.

Figure 2. - Reports on incidence of AKI from adult and paediatric patients in COVID-19 infection across the globe

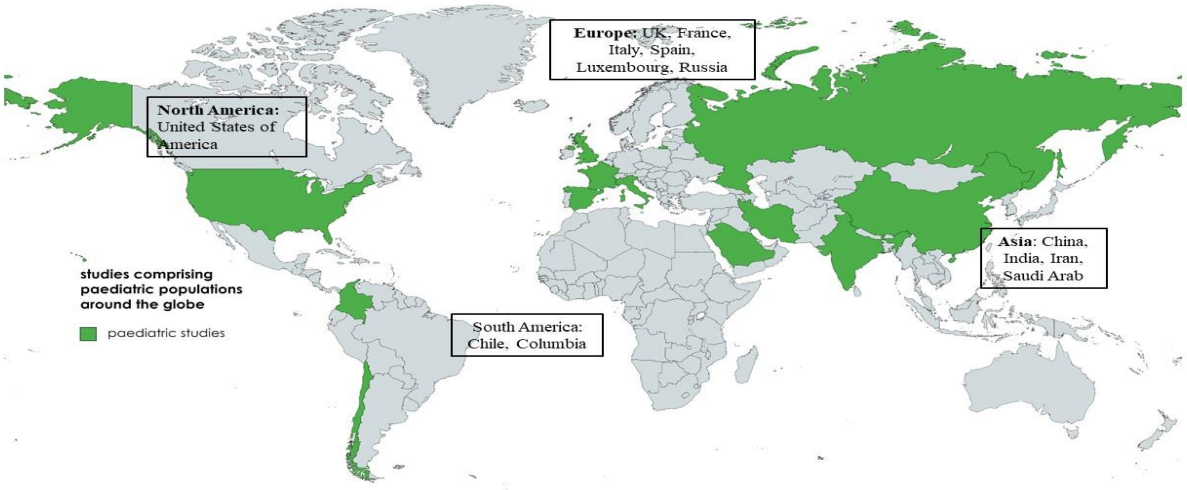


Table 1. Details on the pediatric population with COVID-19 infection

Article Name	Zone and Country	Time of Study	Type	Mean age (years)	Population	AKI reported and stages	MIS-C incidence	Diagnosis
González-Dambrauskas et al. (2020) [18]	Chile, Colombia, Italy, Spain, United States	Dec 2019 – April 23, 2020	Retrospective Multicenter Study	4.0	17	3 (18%)	NA	13 out 17 high CRP on admission
Dufort et al. (2020) [19]	New York, USA	March 1, 2020 - May 10, 2020	Multicenter Retrospective Study	0-20	99	10 (10%)	Y	Kawasaki's disease, toxic shock syndrome, or myocarditis
Lee et al. (2020) [20]	Boston, USA	March 17, 2020 – June 6, 2020	Retrospective Study	9.0	28	6 (21%)	Y	High CRP in 93%. complete or incomplete KD, and coronary abnormalities were found
Whittaker et al. (2020) [21]	England	March 23, 2020 - May 16, 2020	Uncontrolled Multicenter case series Study	9.0	45	11 (24%)	Y	myocardial dysfunction. High CRP, neutrophilia,and ferritin. Troponin concentrations 68%
Capone et al. (2020) [22]	New York, USA	April 17, 2020 - May 13, 2020	Retrospective study	8.6	33	23 (70%)	Y	72% developed myocardial dysfunction.Compete KD 64%, High CRP
Wang et al (2020) [23]	Wuhan, China	January 24, 2020 - March 20, 2020	Retrospective study	13 months, 10 months, 8 years	238	3 (1.3%)	NA	high CRP, IL-6, BUN and creatinine
Samies et al. (2020) [24]	Alabama, USA	May, 2020	Case Study	16	1	Not reported	NA	High BUN, creatinine, Aminotransferase and aspartate aminotransferase and creatine kinase
Qiu L et al. (2020) [25]	China	January 25, 2020 - March 16, 2020	Case Study	8 months	1	Not reported	NA	lymphocytes, white blood cells, CD3+, CD4+, CD8+ T cells and fibrinogen were below the normal range,
Niño-Taravilla et al. (2020) [26]	Chile	May 11, 2020 - May 28, 2020	Case Study	8	1	Not reported	Y	Multi-organ dysfunction with acute kidney failure, metabolic acidosis, hyponatremia, slight increase in creatinine, lactate and hypoalbuminemia.
Mamishi et al. (2020) [27]	Iran	March 7, 2020 - June 23, 2020	Retrospective study	7.0	45	13 (29%)	Y	Kawasaki-like disease (69%), while toxic shock-like and sepsis-like diseases11%
Grimaud M et al. (2020) [28]	France	April 15-27, 2020	Retrospective study	10 (2.9–15)	20	14 (70%)	NA	High CRP and procalcitonin
Oberweis et al. (2020) [29]	Luxembourg	NS	Case report	8	1	Not reported	NA	Rapid increase in CRP, IL-6, ferritin, C-reactive protein, leukopenia with

								lymphopenia thrombocytopenia, renal function impairment serum creatinine, hepatic cytolysis
Toubiana et al. (2020) [30]	Paris, France	April 27, 2020 - May 15, 2020	Prospective Study	7.9 (3.7-16.6)	21	11 (52%)	NA	Lymphopenia in 81%, transient kidney failure in 52 %
Shahbaznejad L et al. (2020) [31]	Sari, Iran	March 28,2020 - June 24, 2020	Case study	5.37 ± 3.9	10	3 (30%)	Y	High level of CRP, Lymphopenia, hypoalbuminemia
Godfred-Cato et al. (2020) [32]	District of Columbia and New York, USA	March 2020- July 2020	Retrospective study	8 (2 weeks to 20 years)	570	Distribution of these AKI incidences in class I (37.9%) and class II (16.6%) stages of MIS-C patients	Y	Shock, cardiac dysfunction, gastrointestinal symptoms, significantly elevated markers of inflammation and cardiac damage
Dionne et al. (2020) [33]	Boston, USA	March 1, 2020- May 30, 2020	Retrospective cohort study	9.7 (2.7–15.0)	25	2 (8%)	Y	Hypotension (44%) and acute renal failure (8%), elevated values for C-reactive protein,interleukin 6
Derespina et al. (2020) [34]	New York, USA	March 14, 2020 - May 2, 2020	Retrospective study	15 (1 month – 21 years)	70	9 (12.5%)	Y	Elevated CRP, creatinine.
Stewart et al. (2020) [35]	London, UK	Till March 25,2020	Retrospective study	0- 16 years	52	15 (29%)	Y	Higher creatinine in 46%, Effected with AKI
Bjornstad et al. (2020) [36]	United States, Western Europe, Eastern Europe/Russia	April 15, 2020 - May 20, 2020	Cross-sectional analysis	Age 1 month to 18 years; Median range 11	106	47 (44%) AKI stage-1, 47%, stage 2 – 23%, stage 3 – 30%	NA	High prevalence of AKI in critically ill children
Deep A et al. (2020) [12]	United Kingdom	March 14, 2020, to May 20, 2020	Observational study	11.0 (7-14)	116	48 (41.4%)	Y	27% patients diagnosed to develop severe AKI
Kari et al. (2021) [37]	Jeddah, Kingdom of Saudi Arabia	March 1, 2020 – Mid-July 2020	Retrospective multicentre study	54.6 (30.0 – 79.3) for AKI, 74.7 (61.1 -88.3) for non-AKI	89	19 (21%) AKI Stage 1: (58%), Stage 2: (31.5%), Stage 3: (10.5%)	NA	Baseline creatinine, estimated glomerular filtration rate (eGFR), highest creatinine.
Chopra et al. (2021)[38]	New Delhi, India	March 1, 2020 – November 30, 2020	Retrospective study	6 (1.04 – 10)	105	24 (22.8%) AKI Stage 1: (33.3%), Stage 2: (29.2%), and Stage 3:(37.5).	NA	Elevated AKI, fever (73.3%) vomiting (37.1%). Diarrhea (11.4%)
Basalely et al. (2021) [11]	New York, USA	March 9, 2020 – August 13, 2020	Retrospective multicentre study	8.2 (1.5 – 13.8)	97	8 (8.2%) AKI; AKI Stage I: (75%), Stage and 3: each (12.5%)	Y	Elevated AKI

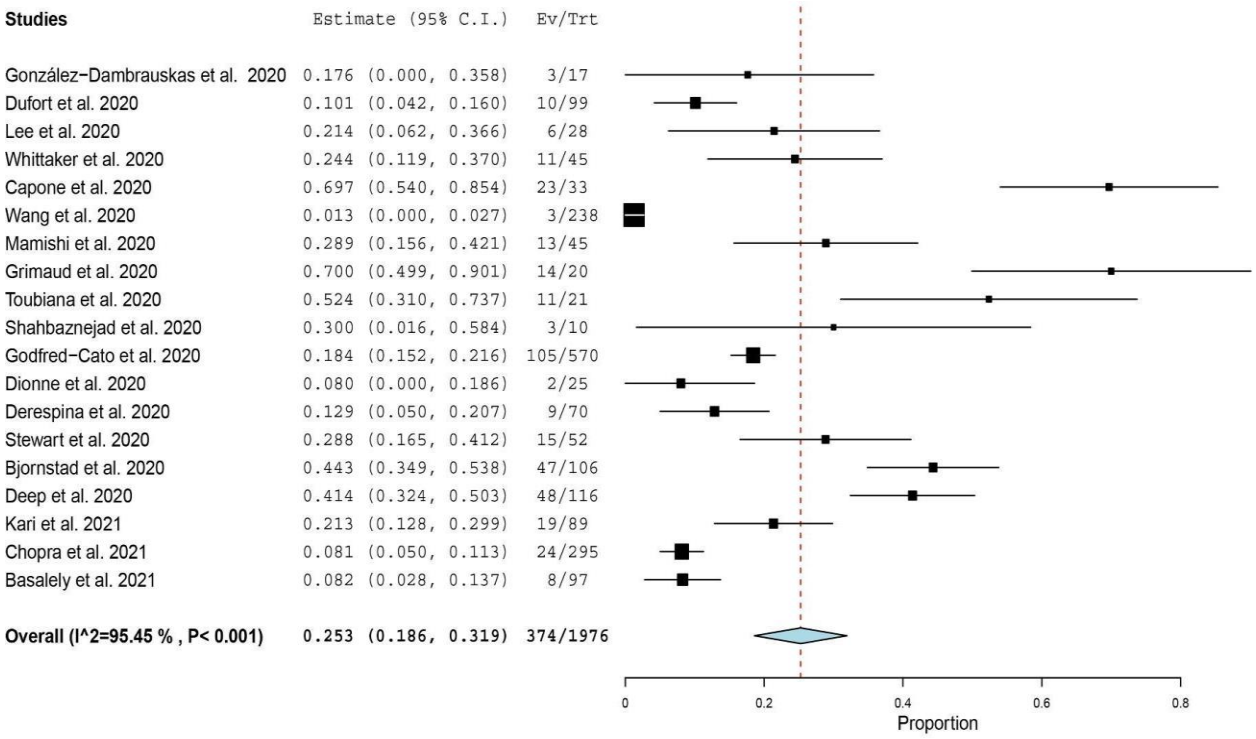
Data Analysis

The overall sample across the 19 different studies on paediatric population with AKI was 1976; however, the incidence estimated from the individual studies included a total sample size ranging from 10-570. Meta-analysis conducted on the 19 different studies demonstrated 25.3% (18.6-31.9%) [I^2 = 95.35%, P<0.001] pooled (95% CI) AKI incidence in the COVID-19 infected paediatric population (Figure 3A, 3B) with considerable heterogeneity.

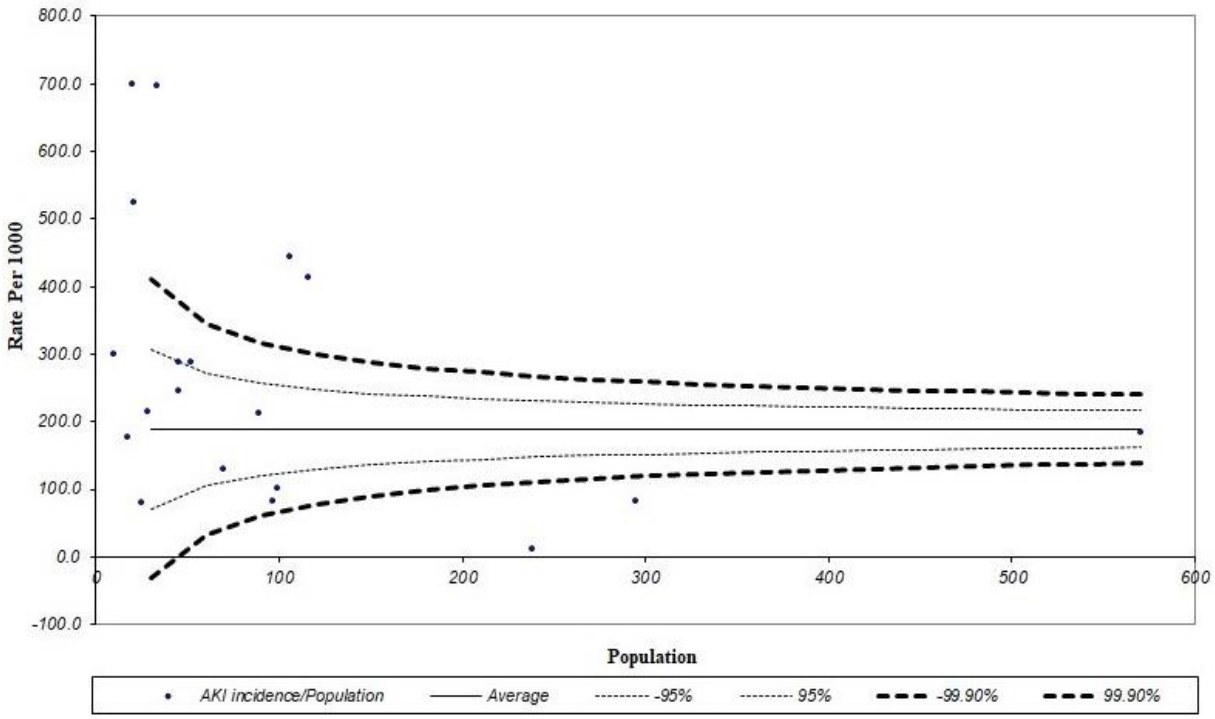
Our analysis revealed a very low overall mortality rate among the 19 studies analyzed. The estimated pooled mortality value (95% CI) of 2.3% (1.2 – 3.3%) [I^2=61.49, P< 0.001] was evident in an overall sample size of 1976 (ranging from 10-570) (Figure 3C, 3D) with substantial heterogeneity. Mortality due to AKI was reported in 10 out of 19 different studies with overall sample size n=215, however, the incidence from the individual studies included a total sample size ranging from 6-48. Our analysis on estimated mortality rate due to AKI showed a higher pooled mortality (95% CI) of 5.2% (1.4 – 9.0%) [I^2 =42.51%, P=0.074, n=10] in the overall sample size of 215 (ranging from 6 – 48) (Figure3E, 3F) with moderate heterogeneity.

Figure 3. - Forest Plot of the meta-analysis (A, C, E) and Funnel Plot (B, D, F) for AKI incidence, overall mortality, and AKI-related death respectively in COVID-19 infection in paediatrics across different studies. The lower diamond in the Forest Plot represents the pooled estimate. 'Ev' indicates the event sizes. 'Trt' indicates the total number of COVID-19 positive patients screened (A, C) and the total number ofCOVID-19 positive patients screened with AKI only (E) in this population

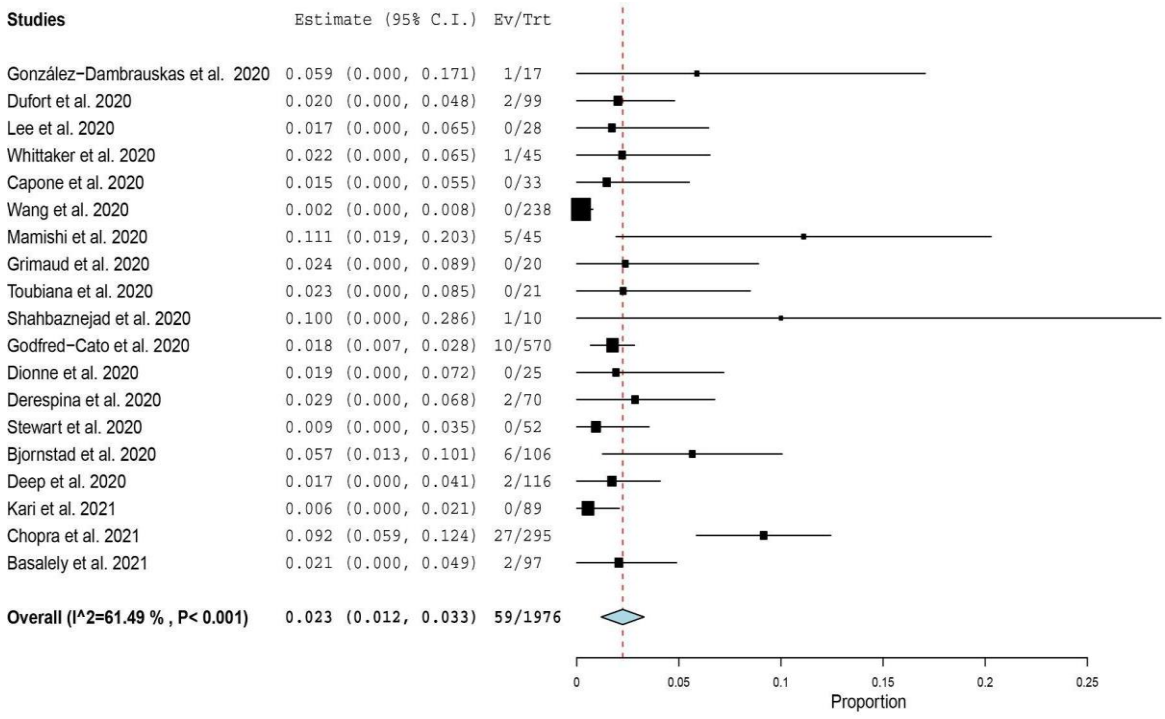
A



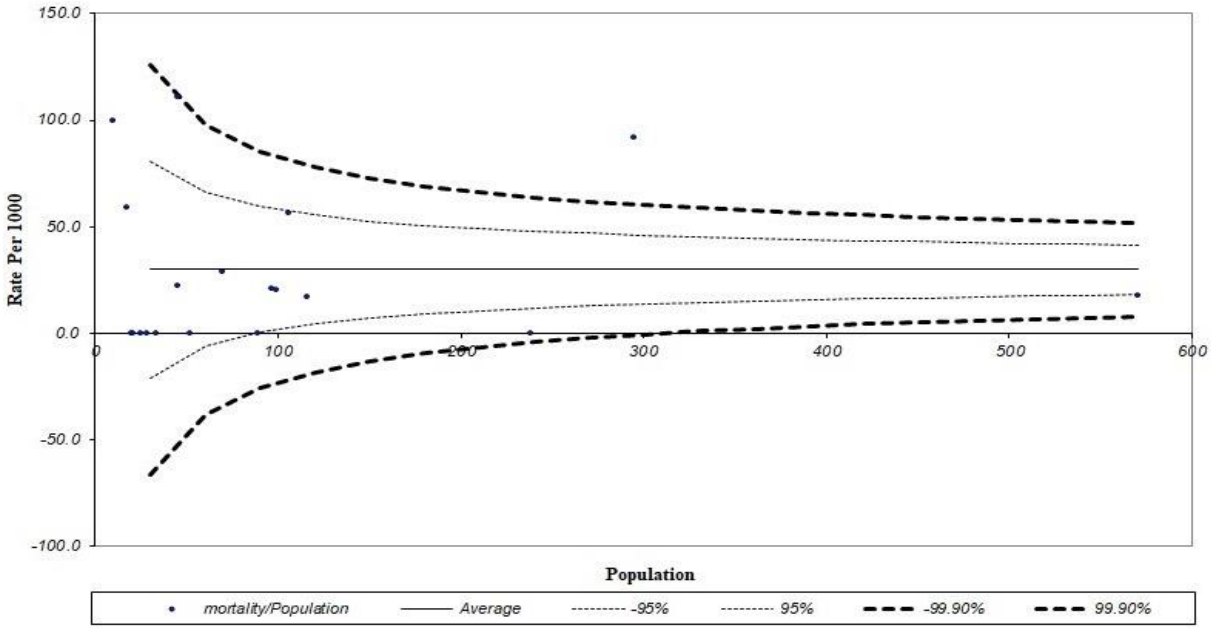
B


800.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
-100.0
Rate Per 1000
0
100
200
300
400
500
600
Population
AKI incidence/Population
Average
-95%
95%
-99.90%
99.90%

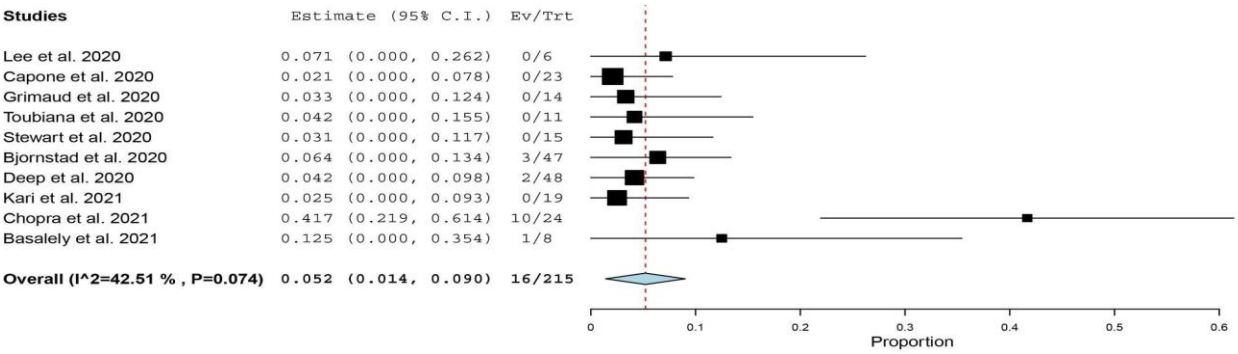
C


Studies
Estimate (95% C.I.)
Ev/Trt
González−Dambrauskas et al. 2020 0.059 (0.000, 0.171) 1/17
Dufort et al. 2020 0.020 (0.000, 0.048) 2/99
Lee et al. 2020 0.017 (0.000, 0.065) 0/28
Whittaker et al. 2020 0.022 (0.000, 0.065) 1/45
Capone et al. 2020 0.015 (0.000, 0.055) 0/33
Wang et al. 2020 0.002 (0.000, 0.008) 0/238
Mamishi et al. 2020 0.111 (0.019, 0.203) 5/45
Grimaud et al. 2020 0.024 (0.000, 0.089) 0/20
Toubiana et al. 2020 0.023 (0.000, 0.085) 0/21
Shahbaznejad et al. 2020 0.100 (0.000, 0.286) 1/10
Godfred−Cato et al. 2020 0.018 (0.007, 0.028) 10/570
Dionne et al. 2020 0.019 (0.000, 0.072) 0/25
Derespina et al. 2020 0.029 (0.000, 0.068) 2/70
Stewart et al. 2020 0.009 (0.000, 0.035) 0/52
Bjornstad et al. 2020 0.057 (0.013, 0.101) 6/106
Deep et al. 2020 0.017 (0.000, 0.041) 2/116
Kari et al. 2021 0.006 (0.000, 0.021) 0/89
Chopra et al. 2021 0.092 (0.059, 0.124) 27/295
Basalely et al. 2021 0.021 (0.000, 0.049) 2/97
Overall (I^2=61.49 % , P< 0.001) 0.023 (0.012, 0.033) 59/1976
0
0.05
0.1
0.15
0.2
0.25
Proportion

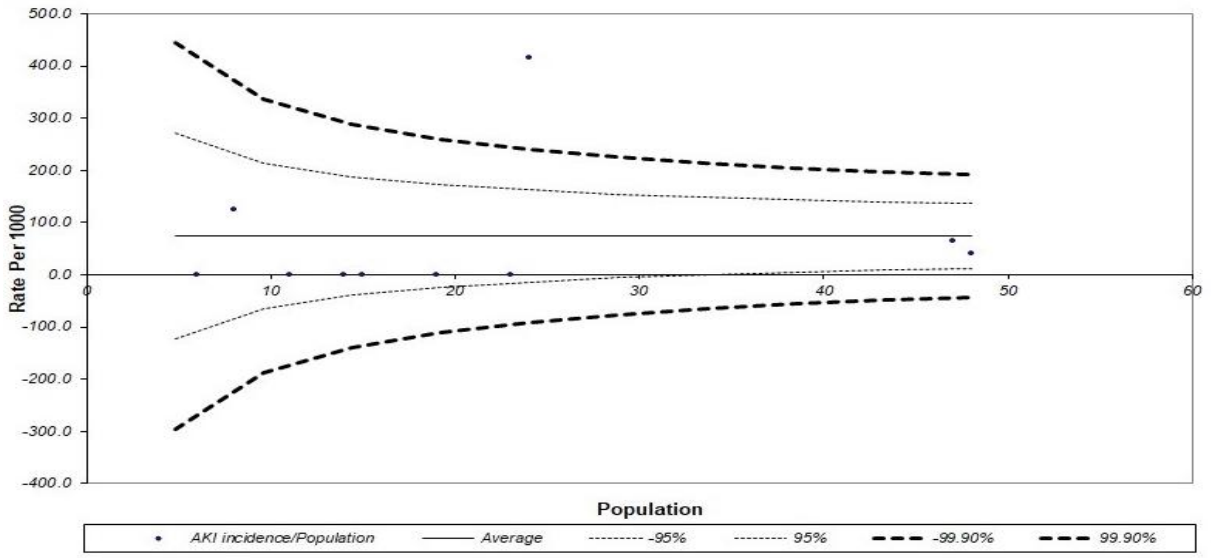
D


150.0
100.0
50.0
0.0
-50.0
-100.0
Rate Per 1000
0
100
200
300
400
500
600
Population
mortality/Population
Average
-95%
95%
-99.90%
99.90%

E


Studies
Estimate (95% C.I.)
Ev/Trt
Lee et al. 2020 0.071 (0.000, 0.262) 0/6
Capone et al. 2020 0.021 (0.000, 0.078) 0/23
Grimaud et al. 2020 0.033 (0.000, 0.124) 0/14
Toubiana et al. 2020 0.042 (0.000, 0.155) 0/11
Stewart et al. 2020 0.031 (0.000, 0.117) 0/15
Bjornstad et al. 2020 0.064 (0.000, 0.134) 3/47
Deep et al. 2020 0.042 (0.000, 0.098) 2/48
Kari et al. 2021 0.025 (0.000, 0.093) 0/19
Chopra et al. 2021 0.417 (0.219, 0.614) 10/24
Basalely et al. 2021 0.125 (0.000, 0.354) 1/8
Overall (I^2=42.51 % , P=0.074) 0.052 (0.014, 0.090) 16/215
0
0.1
0.2
0.3
0.4
0.5
0.6
Proportion

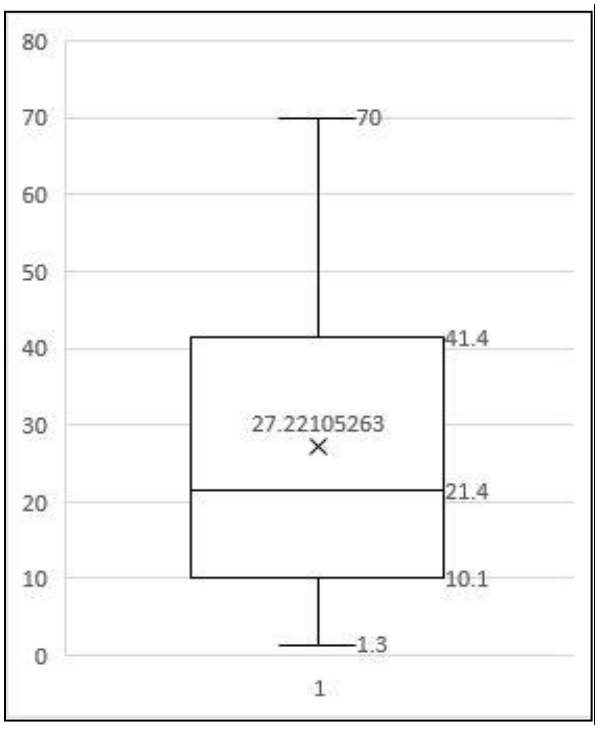
F


500.0
400.0
300.0
200.0
100.0
0.0
-100.0
-200.0
-300.0
-400.0
Rate Per 1000
0
10
20
30
40
50
60
Population
AKI incidence/Population
Average
-95%
95%
-99.90%
99.90%

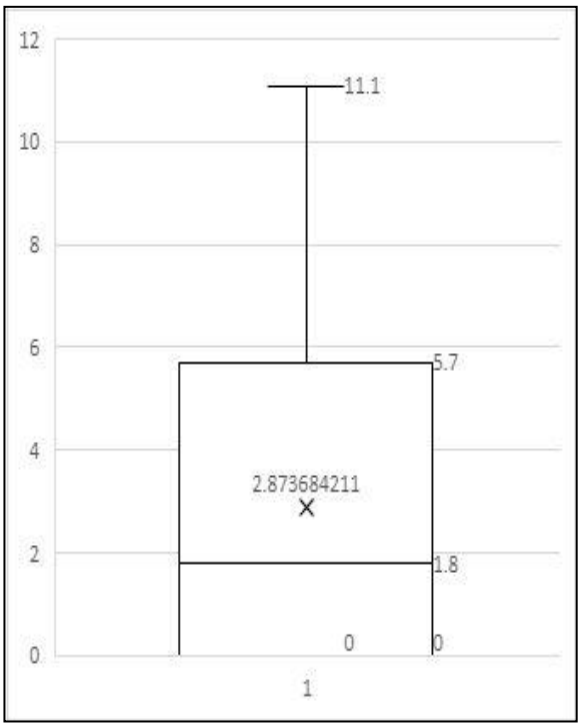
Box plots represented the median (IQR) AKI incidence estimate [21.4% (10.1 – 41.4%), P< 0.10], overall estimated death [1.8% (0 – 5.7%), 0.001<P] and estimated death due to AKI [0% (0 – 7.295%) 0.001<P] in the COVID-19 infected paediatric population (Figure 4A, 4B, 4C).

Figure 4.– Box plot distribution of AKI incidence, overall mortality, and AKI-related death in COVID-19 infection in the paediatrics (A, B, C) respectively from different studies. The circular dots represent the outliers.

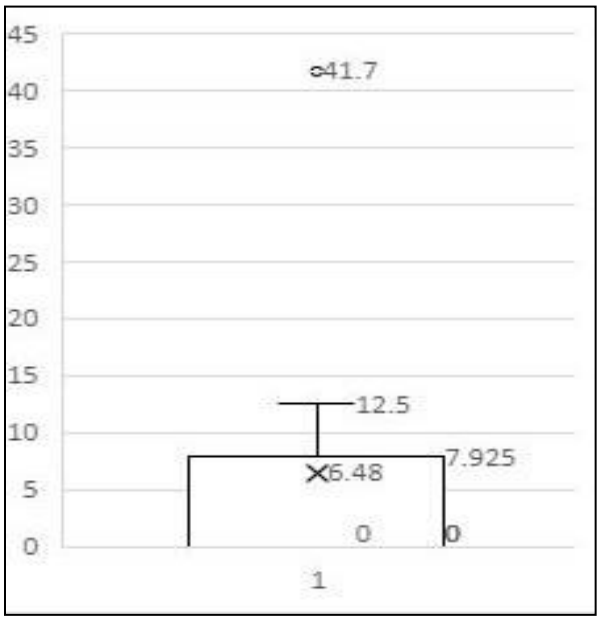
A



B



C



DISCUSSION

There were several reports on significant incidence of AKI associated with morbidity and mortality in adults with COVID-19 infection across the globe, which aided clinicians to formulate appropriate health-care guidelines. [(39)] Reports on AKI prevalence in paediatrics with COVID-19 with related morbidity and mortality were infrequent. In this systemic review and meta-analysis we accumulated the findings of relevant individual reports on AKI, mortality and mortality rates due to AKI in COVID-19 infection in the paediatric population and presented balanced important summary of findings with due consideration of any error in the evidence. More precise estimate of the effect size, which enhanced simplification of the results from the individual studies, presented.

A wide variance of incidence of AKI in critically ill COVID-19 infected paediatric patients was estimated; 70.0% (49.9 – 90.1%) in a population of 20 from a study in the France[(28)] to as low as 1.3% (0.0– 2.7%) in a population of 238 from a study in Wuhan, China. [(23)] Meta-analysis on reports from 14 different paediatric population (n=1247) by Raina et al.[(2)] revealed 30.51% (21.84 – 39.94%) pooled prevalence of AKI associated with COVID-19 infection which was higher compared to our study; 25.3% (18.6 – 31.9%) in the COVID-19 infected paediatric population (n=1976). Additionally, they reported a higher median (IQR) incidence of 26.6% (17.8–43.6%) among their paediatric patients associated with AKI, in comparison to the estimated incidence obtained from this study 21.4% (10.1 – 41.4%).

Among the paediatric population, AKI incidence and mortality rate revealed high statistical heterogeneity, although mortality estimated due to AKI retained a very low value. Therefore, AKI may complicate COVID-19 clinical management and framing of appropriate guidelines is necessary to address effective clinical management.

At present, COVID vaccination to eligible kids and teenagers is an absolute necessity. A vaccine that lowers COVID transmission in this age group might restrict transmission from kids and teens to older adults. Such a strategy will help to diminish hospital admission especially with COVID-19 infection and avoid complications in children with co-morbid conditions and will help to control the health-care management in resource limiting countries like India.

The main limitation in this study was the insufficient sample size among the paediatric population especially on mortality rate due to AKI. Moreover, as to date, there is paucity of literature on COVID-19 and AKI incidence from different parts of the world in the aforementioned population, which further limits the study globally. Nonetheless, in our meta-analysis for AKI mortality in COVID-19 paediatric populations, only studies with a sample size >5 was included to eliminate the outcome of studies with small sample sizes.

CONCLUSION

Our study provided important insights of AKI in paediatric population with COVID-19 which will aid clinicians in better preparedness towards health-care management.AKI incidence in COVID-19 infection was statistically significant which is alarming in view of this ongoing fourth wave COVID-19 pandemic era.

Acknowledgement: None

Conflict of Interests: All authors declare that there is no conflict of interest.

Funding sources: None.

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How to cite this article: Snehashis Koley, Ambar Bose, Sudeshna Mallik et.al. COVID-19 infection and acute kidney injury in paediatric population: a systematic review and meta-analysis. *International Journal of Research and Review*. 2022; 9(11): 7-20.
DOI: *https://doi.org/10.52403/ijrr.20221102*

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