Incidence of Acute Kidney Injury in Hospitalized Children: A Meta-analysis

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abstract

BACKGROUND AND OBJECTIVES: There is limited literature on the incidence of acute kidney injury (AKI) and associated mortality in hospitalized children. To systematically assess the worldwide incidence of AKI in hospitalized children to inform policymakers regarding appropriate health resource allocation.

METHODS: Three different databases were searched (PubMed, Embase, Web of Sciences) from March 2012 to January 2022 without language or geographical restrictions. We included cohort and cross-sectional studies that reported AKI incidence in hospitalized children. Eligible studies had at least 100 participants and used the standard Kidney Disease Improving Global Outcomes criteria to define AKI. Two authors extracted data on the study and patients' characteristics and outcomes (incidence and AKI-associated mortality) and performed the risk of bias assessment. We used a random-effects meta-analysis to generate pooled estimates.

RESULTS: We included 94 studies (202 694 participants) from 26 countries. The incidence of any AKI was 26% (95% confidence interval: 22–29), and that of moderate-severe AKI was 14% (11–16). The incidence of AKI was similar in high-income 27% (23–32), low-middle-income 25% (13–38), and low-income 24% (12–39) countries. Overall, AKI-associated mortality was observed in 11% (9–13) of the pediatric population. AKI-associated mortality rate was highest at 18% (11–25) and 22% (9–38) in low-income and low-middle-income countries, respectively.

CONCLUSIONS: AKI was observed in one-quarter of the hospitalized children and is associated with increased mortality risk. Low-income and low-middle-income countries had observed higher mortality rates compared with high-income countries despite a similar AKI burden.

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Dr Meena conceptualized and designed the study, performed literature search, data extraction and data analysis, and drafted the manuscript; Dr Mathew participated in data extraction and risk of bias assessment and critically reviewed the manuscript; Dr Kumar participated in conceptualization, literature search, data collection, risk of bias assessment, and critically reviewed the manuscript; Dr Chanchlani participated in study design and data analysis, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Acute kidney injury (AKI) is increasingly recognized in hospitalized children partly because of efforts to standardize the criteria for diagnosis and the introduction of a uniform Kidney Disease Improving Global Outcomes (KDIGO) classification in 2012.[1–3] A large multinational prospective study from pediatric intensive care units observed that AKI is quite common (26.9%) among children admitted to intensive care units.[4] AKI is strongly associated with an increased risk of short-term outcomes, such as prolonged hospital stay and in-hospital mortality.[3,4] In addition, it is also linked to increased health care utilization and adverse long-term consequences, such as hypertension, proteinuria, and chronic kidney disease in infants and children.[5–7]

The burden and etiologies of AKI are reported to vary across the globe.[8] Although AKI chiefly develops in the hospital setting in high-income countries (HIC), community-acquired AKI is more common in lower-middle-income countries (LMIC). Similarly, tropical infections, sepsis, and nephrotoxins are commonly attributed to AKI in LMIC; intervention or surgery-related AKI is common in HIC.[3,8]

There is a lack of systematically synthesized data on AKI burden and mortality in the pediatric population. A meta-analysis published in 2013 reported a worldwide incidence of pediatric AKI (33.7%) and a high AKI-associated mortality risk (13.8%).[9] However, this meta-analysis included studies with variable AKI definitions and was mostly limited to high-income countries; hence, it was not accurately representative of the overall incidence of AKI across the world in pediatric population. In the last decade, many studies have reported AKI incidence in children using uniform KDIGO criteria.[10] Moreover, a number of studies have been published from low and lower-middle-income countries.[11,12]

In this systematic review, we aim to provide the worldwide pooled estimates of incidence and mortality of pediatric AKI in hospitalized children from studies using uniform KDIGO 2012 criteria.

METHODS

Literature Search and Data Source

The protocol for this systematic review was registered on PROSPERO (CRD42021292618) on December 22, 2021. We adhered to preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines in reporting review findings.[13] Two authors (J.M. and J.K.) with expertise in health care data retrieval performed a literature search in 3 different electronic databases (PubMed, Embase, and Web of Sciences) for articles published between March 2012 to January 2022. We formulated an individual search strategy for each database using keywords and Medical Subject Headings terms related to acute kidney injury and the pediatric population (Supplemental Table 5). The search strategy was peer-reviewed by 2 authors using a Peer Review of Electronic Search Strategies checklist and revised accordingly.[14] We chose 2012 to start our literature search as KDIGO criteria for diagnosing and staging AKI were published in the same year and have been consistently used since then. Therefore, we aimed to include studies using only KDIGO criteria for reporting AKI incidence and mortality. During the literature search, we did not use any language restrictions. The electronic search was supplemented by manually screening the bibliography of relevant eligible studies.

Study Selection

As we aimed to provide pooled estimates of the worldwide incidence of AKI, we restricted ourselves to studies enrolling 100 or more participants considering that small studies might lead to effect size inflation and may not truly represent the pooled incidence of AKI. Prospective and retrospective cohort and cross-sectional studies reporting AKI incidence and in-hospital mortality in children (age >1 month to 18 years) were eligible for this review. We made some amendments to the protocol as reported in Supplemental Table 6. We excluded studies (1) evaluating neonates (age <1 month) or adults (age >18 years) exclusively; (2) using criteria other than KDIGO; (3) not clearly mentioning the criteria for diagnosis of AKI; (4) conference abstracts not providing sufficient information on diagnostic criteria and risk of bias assessment; (5) studies evaluating children with preexisting CKD and kidney transplant recipients. We also excluded studies defining AKI in children from the hospital records or other databases using the International Classification of Diseases, Ninth or Tenth Revision (ICD-9 or 10) codes and e-alerts to maintain a homogenous data set. Initially, 2 authors independently screened through the title and abstract of electronic records. Later, the same authors reassessed the full text of relevant articles for final inclusion in the systematic review. The conflict between the 2 authors was resolved through mutual discussion.

Data Extraction

After selecting studies, 2 authors independently retrieved data from the studies to a predesigned extraction form. During data extraction, any discrepancy between the 2 reviewers was resolved through discussion with a third

author. We retrieved the following data: first author's name, year of publication, country, study period, study design, clinical setting (such as ICU, cardiac surgery, etc), characteristics of participants (gender and age), sample size, number of children with AKI and severity of AKI, children requiring kidney replacement therapy, and in-hospital mortality rates. We broadly classify studies into multiple clinical settings as described in Appendix 1 in the Supplemental Information.

Risk of Bias Assessment

We used the modified Hoy et al tool to assess the risk of bias in included studies.[15] This tool consists of 9 items addressing the internal and external validity of the study. Each item is assigned a score of 0 or 1. Therefore, the overall score for a study can vary from 0 to 9. Based on the overall score, studies were considered to be at low (score 0–3), moderate (4–6), or high risk (7–9) (Supplemental Table 7).

Outcomes

Our primary outcome was to provide pooled incidence of AKI in hospitalized children. The secondary outcomes include pooled incidence of moderate-severe AKI (defined as stage 2 and above as per KDIGO criteria), AKI-associated in-hospital mortality, and the proportion of patients receiving dialysis.

Data Synthesis and Statistical Analysis

We used a random-effects model for meta-analysis to generate the pooled estimates of outcomes mentioned above. We also calculated pooled odds ratios (95% CI) for mortality in patients with AKI compared with those without AKI. To estimate the odds ratio of mortality, we choose only a subset of studies that provide data for AKI and non-AKI groups. Heterogeneity was assessed by inspecting forest plots and χ^2 statistics and quantified using I^2 (inconsistency). To explore heterogeneity, we performed subgroup analyses as per clinical setting geographical and subregional classification as per United Nations geoscheme,[16] economic groups of countries classified by World bank,[17] and the country's location (northern versus southern hemisphere).

Meta-regression was performed to assess the effects of gross domestic product (GDP) per capita (constant 2015 US$) in the year 2020 and % of GDP spent on health expenditure (the year 2018) on AKI incidence and its associated mortality rate separately. Publication bias was assessed using the Doi plot and LFK index. The Doi plot uses a normal quantile versus effect plot rather than a scatter plot of precision versus effect used in the conventional plot. Both the Doi plot and LFK index have been reported to be better than the funnel plot and Egger's regression test in assessing the small study effect.[18] Stata version 14.2 (College Station, Texas, United States) was used for statistical analysis.

RESULTS

Study Selection and Characteristics of the Included Studies

We identified a total of 10 906 potential citations from electronic databases. Finally, 94 studies were included in this systematic review after screening through 283 full-text articles (Fig 1). These studies (Supplemental Table 8) from 26 countries included 202 694 children. Out of 94 studies, 85 reported the primary outcome, ie, AKI incidence. The remaining 9 studies did not provide data on AKI incidence but reported AKI-associated mortality (1 of the secondary outcomes) and hence were eligible for this review.

A list of excluded full-text studies and the reason for exclusion is reported in Appendix 2 in Supplemental Information. Characteristics of the included studies are reported in Supplemental Table 8. All studies enrolled hospitalized children. In terms of the clinical setting, most studies reported AKI from intensive care units ($n = 29$), followed by nephrotoxins ($n = 14$), severe tropical infections ($n = 10$), and cardiac surgery ($n = 9$). Twenty-4 studies (26%) were prospective, and 19 were multicentric (20%). Most studies were from the geographical regions of the Americas ($n = 43$) and Asia ($n = 25$). Three studies originated from multiple continents.[3,4,19] Based on gross national income (GNI) per capita in 2020, most studies were from HIC ($n = 63$), followed by upper-middle-income countries (UMIC) ($n = 15$). Only a small number of studies were from lower-middle-income (LMIC) ($n = 10$) and low-income countries (LIC) ($n = 4$). Among the 94 studies, 41 (43.6%), 46 (48.9%), and 7 (7.4%) studies had a low, moderate, and high risk of bias, respectively (Supplemental Table 9).

Incidence of Acute Kidney Injury

Overall Incidence of AKI

Eighty-five studies (199 643 participants) reported AKI incidence using the KDIGO criteria. The pooled incidence of AKI was 26% (95% CI: 22–29, $P < .01$) (Table 1). Sixty-seven studies used only the serum creatinine-based KDIGO definition, and the pooled incidence of AKI was 24% (95% CI: 21–28). In comparison, AKI incidence was 31% (95% CI: 23–40) in 17 studies using urine output and serum creatinine-based KDIGO criteria. Overall, pooled incidence of various AKI stages in hospitalized children are shown in Fig 2. Among the 72 192 participants evaluated in 34 studies 2% (95% CI: 2–4) received dialysis.

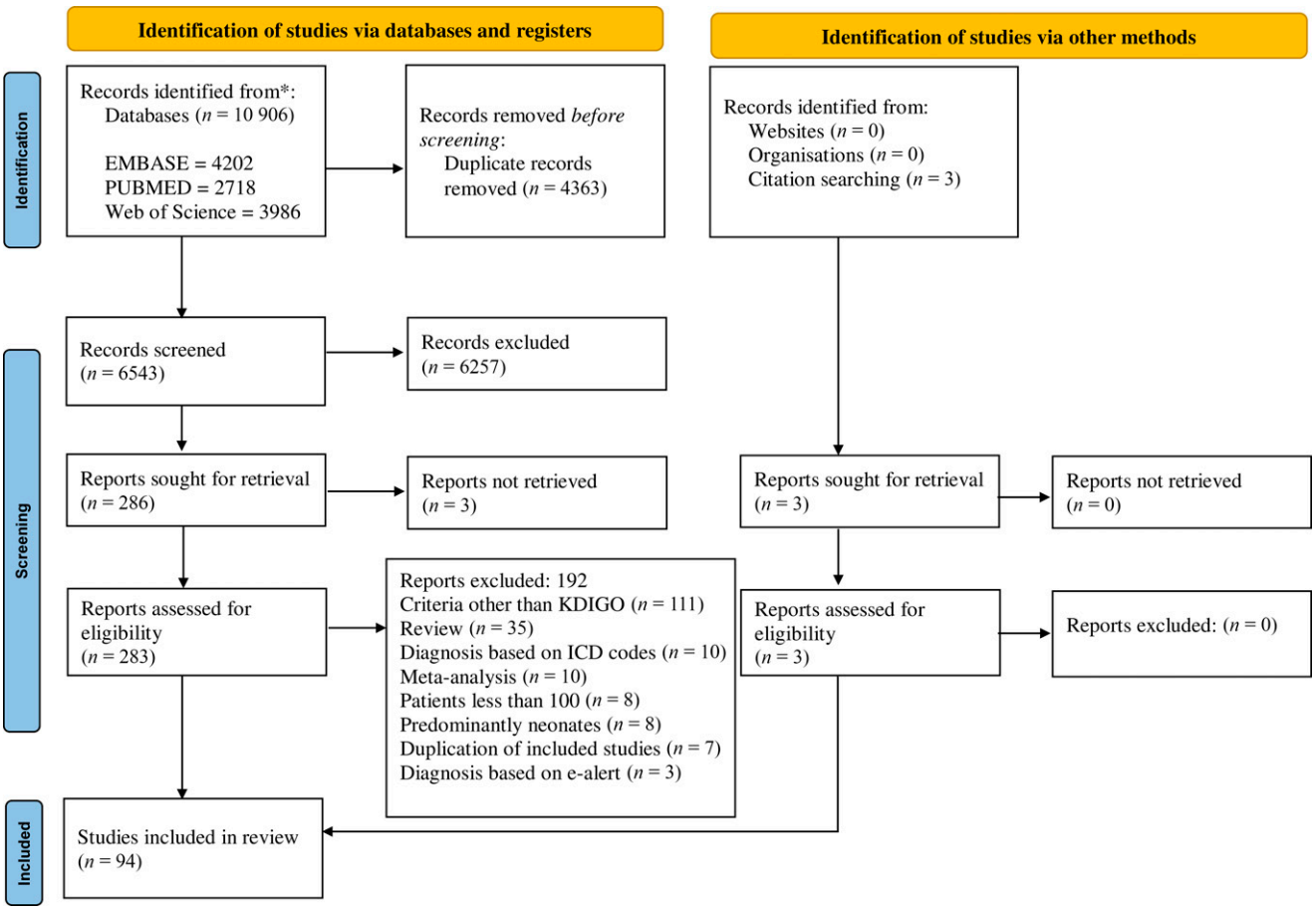


FIGURE 1
Preferred reporting items for systematic review and meta-analysis flow diagram for study selection.

We observed significant heterogeneity in the pooled estimates (Table 1). Considering that we pooled data from studies of variable sizes, diverse clinical settings, and severity of AKI, some heterogeneity was expected. To explore this heterogeneity, we performed subgroup and sensitivity analysis as reported in Table 1; a considerable proportion of heterogeneity remained unexplained. The pooled incidence of AKI was higher in studies with a low risk of bias (30%) compared with studies with a high risk of bias (23%), although this difference was not statistically significant ($P = .09$). The Doi plot showed asymmetry suggestive of a small study effect (Supplemental Fig 6). LKF index was also suggestive of a small study effect. The observed small study effect could be caused by the exclusion of 8 small sample size cohort studies ($n < 100$ participants) in this review (Appendix 2 in Supplemental Information).

AKI in Various Clinical Settings

There was a wide variation in the pooled incidence of AKI across various clinical settings (Table 1). Most studies (27 studies, 40 316 participants) were from intensive care settings. The pooled AKI incidence was 27% (95% CI: 22–33) among children admitted to the ICU, followed by 33% (95% CI: 20–47) among those with cardiac surgery (8 studies; 6905 participants). Thirteen studies (17–365 participants) reported data on AKI related to nephrotoxin exposure and had a pooled AKI incidence of 14% (95% CI: 11–19).

AKI Across Geographical and Economic Groups

We also assessed the variation in the pooled incidence of AKI across various geographical (Fig 3A) and economic groups of the countries (Fig 4A). Most studies were from the Americas (40 studies, 154 966 participants), and among them, the pooled incidence of AKI was 26% (95% CI: 21–31). In Asia, the pooled incidence of AKI was 24% (95% CI: 18–31) (Table 1). The AKI incidence was similar in the northern versus southern hemisphere (25% vs 26%, $P = .5$). Although there were a limited number of studies from LIC

TABLE 1 Incidence of Acute Kidney Injury and its Distribution Across Various Subgroups

Parameters	Studies (participants)	Pooled Incidence (%), (95% CI)	Heterogeneity (I^2), *P*	*P**
Primary outcome				
Any stage AKI	85 (199 643)	26 (22 to 29)	99%, <.001	—
AKI stages (as per severity)				
AKI stage 1	52 (140 824)	12 (10 to 14)	99%, <.001	
AKI stage 2	48 (139 632)	06 (05 to 08)	98%, <.001	
AKI stage 3	48 (139 632)	05 (04 to 07)	99%, <.001	
Moderate-Severe AKI[a]	55 (148 941)	14 (11 to 16)	99%, <.001	
AKI requiring Dialysis	34 (72 192)	02 (02 to 04)	98%, <.001	
Subgroup analysis- for all stages AKI				
Study design				
Prospective	22 (16 432)	27 (21 to 34)	98%, <.001	.6
Retrospective	63 (183 211)	25 (21 to 29)	99%, <.001	
Study sites (single versus multicentric)				
Single center	67 (155 303)	25 (21 to 29)	99%, <.001	.5
Multicentric	18 (44 340)	27 (22 to 33)	99%, <.001	
Risk of bias in studies				
Low risk	40 (118 064)	30 (25 to 35)	99%, <.001	.09
Moderate risk	38 (76 425)	22 (17 to 27)	99%, <.001	
High risk	7 (5154)	23 (12 to 35)	99%, <.001	
Clinical settings				
Intensive care units	27 (40 316)	27 (22 to 33)	99%, <.001	<.001
Hospitalized (mixed, unspecified)	07 (78 802)	15 (05 to 28)	99%, <.001	
Cardiac surgery	08 (69 05)	33 (20 to 47)	99%, <.001	
Infection	10 (58 57)	27 (18 to 36)	97%, <.001	
Nephrotoxins	13 (17 365)	14 (11 to 19)	96%, <.001	
Community-acquired	06 (33 955)	12 (05 to 20)	99%, <.001	
Diabetic Ketoacidosis	04 (3020)	52 (45 to 59)	92%, <.001	
Nonkidney solid organ transplant	05 (1135)	51 (41 to 61)	99%, <.001	
Malignancy	02 (11 696)	22 (21 to 22)	92.6%, <.001	
Nephrotic syndrome	02 (478)	24 (20 to 28)	99%, <.001	
Trauma	01 (114)	10 (05 to 16)	—	
Geographical regions				
Africa	10 (4224)	23 (14 to 34)	98%, <.001	.69
Americas	40 (154 966)	26 (21 to 31)	99%, <.001	
Asia	23 (22 885)	24 (18 to 31)	99%, <.001	
Europe	7 (3503)	33 (19 to 48)	98%, <.001	
Oceania	3 (9203)	18 (05 to 36)	92.6%, <0.001	
Country income classification (as per gross national income per capita)				
Low income	4 (3147)	24 (12 to 39)	98%, <.001	.5
Low-middle income	9 (1722)	25 (13 to 38)	97%, <.001	
Upper-middle income	14 (166 82)	20 (14 to 27)	98%, <.001	
High-income	57 (173 409)	27 (23 to 32)	99%, <.001	
Latitude location, with respect to the equator				
Northern Hemisphere	72 (180 581)	25 (21 to 29)	99%, <.001	.55
Southern Hemisphere	8 (11 465)	26 (15 to 40)	99%, <.001	
Both Hemispheres of North and South	5 (7597)	31 (21 to 42)	98%, <.001	

—, not applicable.

[a] Moderate-severe AKI is defined as KDIGO stages 2 and 3.

* For subgroup differences (<.05 is considered significant).

and LMIC, the pooled incidence of AKI was 24% (95% CI: 12–39) and 25% (95% CI: 13–38), respectively, which was similar to that in HIC 27% (95% CI: 23–32)]. The lowest incidence, 20% (95% CI: 14–27), was reported from UMIC, although it was not statistically significant (Fig 4A). Meta-regression analysis did not show any relationship between AKI incidence and countries' GDP or % of GDP spent as total health expenditure (Table 2).

Incidence of Moderate-Severe Acute Kidney Injury

Fifty-five studies (148 941 participants) reported data on moderate-severe AKI (KDIGO Stages ≥2). The pooled incidence of moderate-severe AKI was 14%

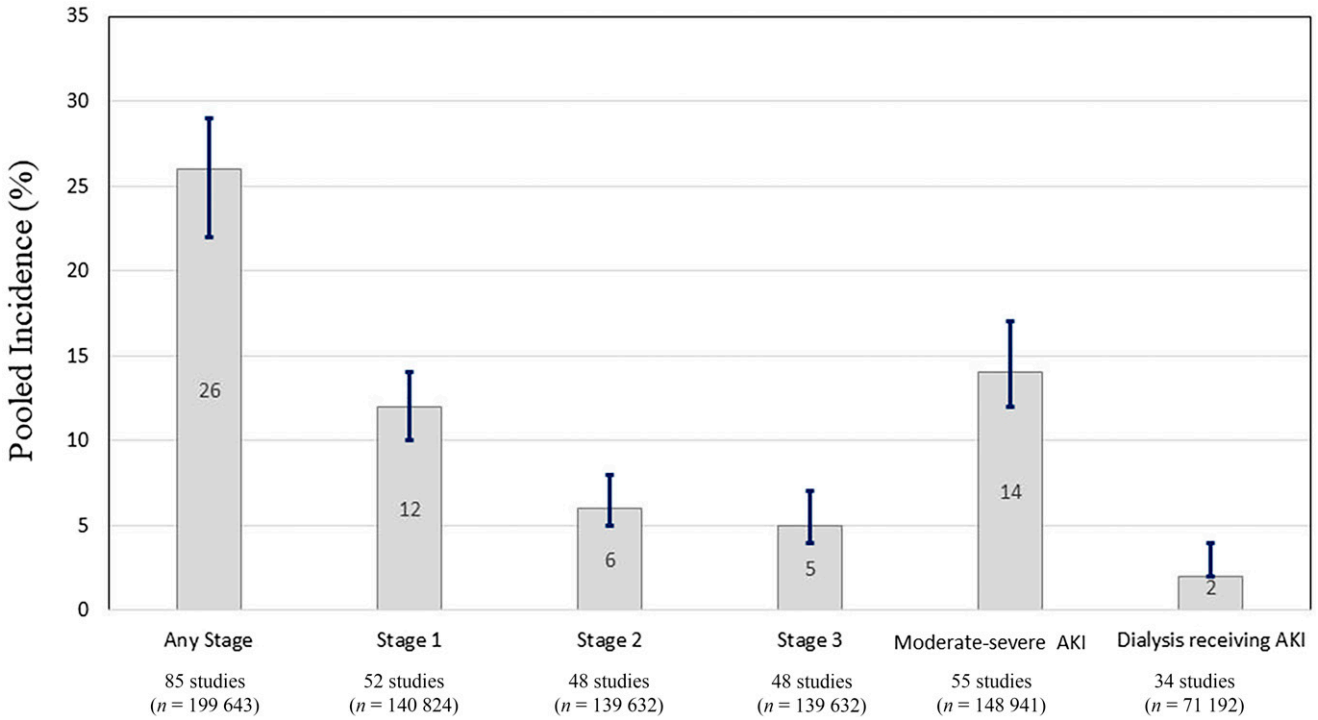


FIGURE 2

Pooled incidence of various stage of acute kidney injury in hospitalized children. Moderate-severe acute kidney injury indicates stages 2 and 3 as per KDIGO criteria; dialysis receiving acute kidney injury denotes proportion of children managed with dialysis out of all children assessed in included studies.

(95% CI: 11–16) (Table 3, Supplemental Fig 7). Among the children with any stage AKI, 11% (95% CI: 7–16) received dialysis (Supplemental Fig 8). We did not find a statistically significant difference in moderate-severe AKI between various subgroups, except for the clinical setting (Table 3). Variation in the incidence of moderate-severe AKI across various subgroups is reported in Table 3.

Acute Kidney Injury Associated Mortality

Overall Mortality

The pooled AKI-associated all-cause hospital mortality (60 studies, 161 877 participants) was 11% (95% CI: 9–13) (Table 4). The AKI-associated mortality rate based on KDIGO stages 1, 2, and 3 was 4% (2–7), 8% (4–12), and 20% (13–27), respectively, as depicted in Supplemental Fig 9. Pooled mortality in moderate-severe AKI (13 studies, 68 103 participants) was 15% (95% CI: 10–21). Among the children with AKI receiving dialysis (13 studies, 25 959 participants), the pooled mortality was 31% (95% CI:16–47) (Supplemental Fig 10). Forty-nine studies compared mortality in AKI and non-AKI groups. Children with AKI had 4.6 (95% CI: 3.7–5.8) higher odds of mortality than those without AKI (Fig 5). The odds of mortality in children with AKI increased with increasing AKI severity (Supplemental Fig 11).

Mortality Across Various Clinical Settings

We also assess the AKI-associated mortality rates across various clinical settings and geographical variations (Table 4). The highest mortality was observed in children admitted to the ICU (17%; 13–21), whereas the lowest was community-acquired AKI (5%; 2–9).

Mortality Across Geographical and Economic Groups

AKI-associated mortality was comparatively higher in Africa (15%, 95% CI: 9–21) and Asia (14%, 95% CI: 8–20) than Americas (10%, 95% CI: 6–14) and Europe (7%, 95% CI: 2–13), although difference across various continents did not reach statistical significance ($P = .15$) (Table 4). We observed significantly lower mortality in HIC at 7% (95% CI: 4 to 9) as compared with LIC at 18% (95% CI: 11–25) and LMIC at 22% (95% CI: 9–38) (Fig 4B, Table 4). The AKI-associated mortality rate in studies reported from the southern and northern hemispheres was 17% (95% CI: 10–25) and 10% (95% CI: 7–13), respectively. Geographical variations in AKI-associated mortality across various geographical regions are depicted in Fig 3B.

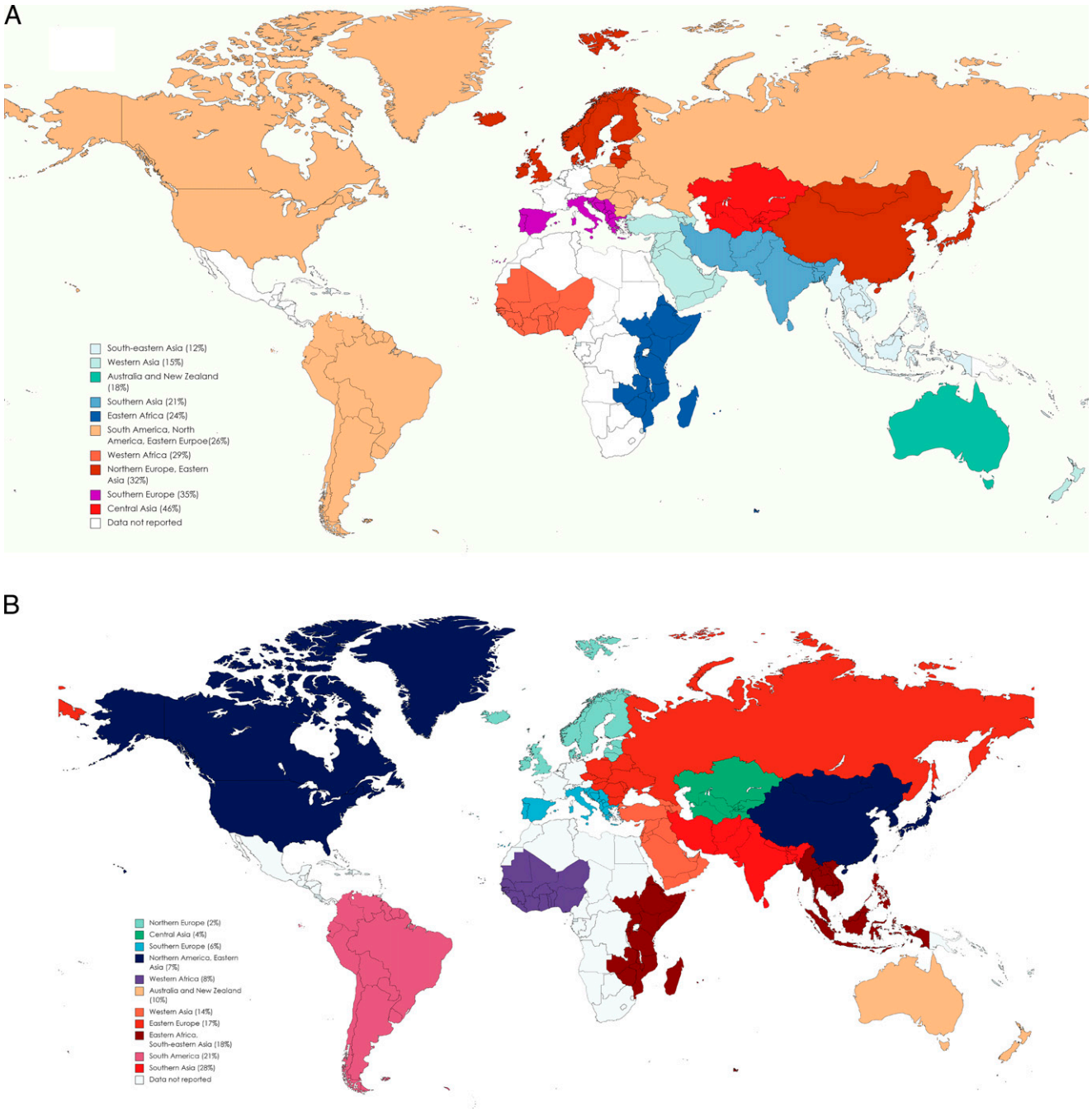
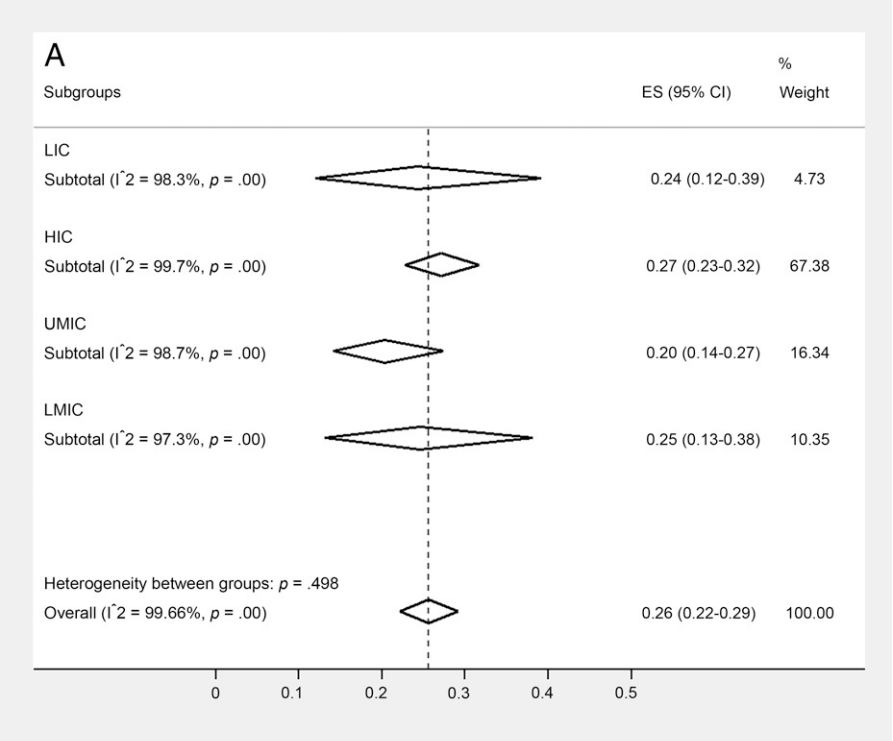


FIGURE 3
Geographical variation of (A) pooled incidence of acute kidney injury and (B) acute kidney injury-associated mortality.

We performed a meta-regression to assess the effect of GDP and its proportion spent on health (Table 2). We observed that a 10 000 United States Dollar increase in the GDP resulted in a 0.3% reduction in AKI-associated mortality. Similarly, with each 1% increase in GDP spent on total health expenditure, there was a 0.08% reduction in AKI-associated mortality.

DISCUSSION

In this systematic review of cohort studies reporting AKI as per KDIGO criteria, the worldwide incidence of AKI in hospitalized children was 26% (22 to 29). Among those with any AKI, 11% (7 to 16) of children received dialysis, and AKI-associated mortality was 11% (9 to 13). The odds of mortality were 4.6 folds higher in children with AKI than in those without AKI. As anticipated, there was an incremental association of the mortality risk



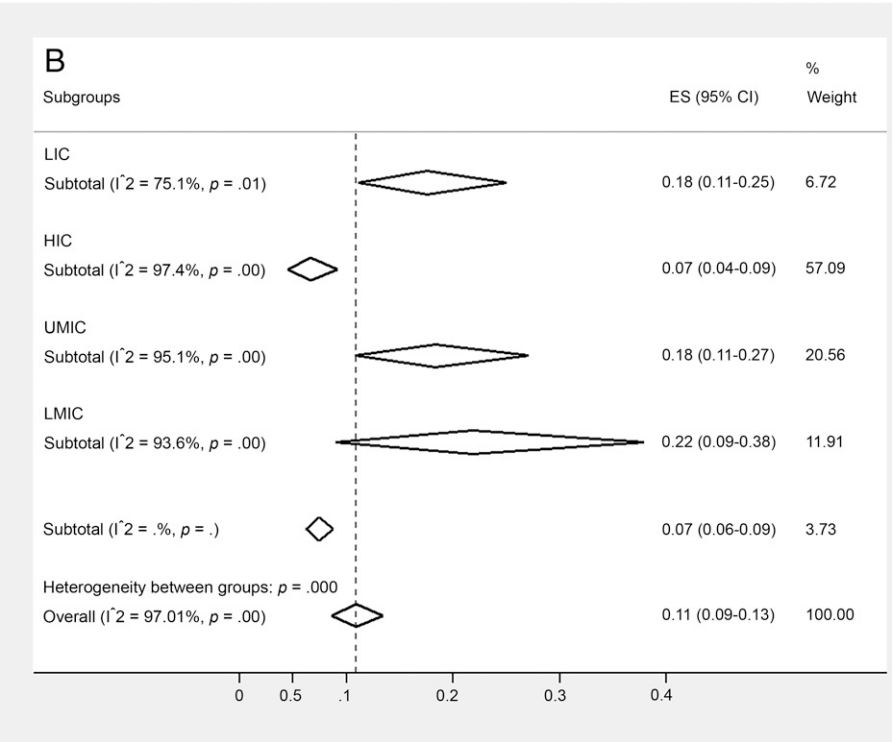


FIGURE 4

Variation in (A) incidence of acute kidney injury and (B) acute kidney injury-associated mortality based on the economic status of countries. HIC, high-income countries; LIC, low-income countries; LMIC, low-middle income countries; UMIC, upper-middle income countries.

TABLE 2 Association of Pooled AKI Incidence and Mortality With GDP and % of GDP Spent on Health Expenditure

Parameters	Change (%; 95% CI)	*P*
Incidence of AKI		
Gross national income per capita	1.0 (0.99 to 1.0)	.89
% GDP spent on total health expenditure (per 1% ↑)	1.0 (0.96 to 1.03)	.99
AKI associated mortality		
Gross domestic income per capita	0.99 (0.99 to 0.998)	<.001
% GDP spent on total health expenditure	0.92 (0.88 to 0.97)	.003

AKI, acute kidney injury; GDP, gross domestic product.

with AKI severity. There were no significant variations in the AKI incidence across various geographical regions, but the mortality was higher in Africa and Asia compared with Europe and the Americas. Similarly, the burden of AKI did not differ much, but mortality was much higher in LIC and LMIC comred with HIC.

To the best of our knowledge, this meta-analysis is the most extensive systematic evaluation of incidence of pediatric AKI using uniform KDIGO criteria. A previous meta-analysis of 24 studies (14 220 children) published before 2012 (using heterogenous criteria) reported an AKI incidence of 33.7% (95% CI: 26.9–41.3).[9] However, that metanalysis[9] did not include studies from LIC and LMIC countries in children; therefore, the estimates may not accurately represent a worldwide incidence. Another potential reason for lower AKI

TABLE 3 Pooled Incidence of Moderate-Severe Acute Kidney Injury

Subgroups	Studies (Participants)	Pooled incidence % (95% CI)	Heterogeneity I^2, *P*	*P**
Moderate-severe AKI[a]	55 (148 941)	14 (11 to 16)	99%, <.001	—
Subgroup analysis				
Study design				
Prospective	18 (15 200)	16 (12 to 21)	98%, <.001	.44
Retrospective	37 (133 741)	13 (10 to 16)	99%, <.001	
Study center				
Single center	42 (114 004)	14 (11 to 18)	99%, <.001	.48
Multicentric	14 (34 937)	13 (10 to 16)	98%, <.001	
Risk of bias				
Low	29 (98 821)	14 (11 to 18)	99%, <.001	.72
Moderate	21 (45 926)	14 (10 to 18)	99%, <.001	
High	05 (4194)	11 (04 to 23)	99%, <.001	
Clinical settings				
PICU	21 (28 431)	17 (13 to 22)	99%, <.001	<.001
Hospitalized, mixed setting, unspecified	04 (64 348)	07 (01 to 19)	99%, <.001	
Cardiac surgery	06 (6250)	17 (08 to 30)	99%, <.001	
Infection	06 (2882)	13 (06 to 23)	97%, <.001	
Nephrotoxins	08 (16 054)	08 (05 to 11)	96%, <.001	
Community-acquired	04 (18 158)	04 (03 to 05)	99%, <.001	
Diabetic ketoacidosis	03 (2719)	27 (19 to 37)	97.8%, <.001	
Nonkidney solid organ transplantation	01 (156)	24 (18 to 32)	Not applicable	
Malignancy	01 (9828)	09 (08 to 09)	Not applicable	
Nephrotic syndrome	01 (115)	19 (13 to 27)	Not applicable	
Continent				
Africa	04 (2889)	17 (08 to 29)	98%, <.001	.21
America	28 (120 252)	13 (10 to 17)	99%, <.001	
Asia	14 (17 392)	14 (10 to 18)	99%, <.001	
Europe	06 (3396)	14 (06 to 26)	98%, <.001	
Oceania	02 (150)	09 (06 to 15)	97.8%, <.001	
Country groups as per income				
Low income	03 (2645)	12 (06 to 19)	97.8%, <.001	.15
Low-middle income	06 (1141)	16 (07 to 28)	95%, <.001	
Upper-middle income	09 (15 774)	15 (09 to 21)	99%, <.001	
High-income	38 (124 698)	13 (10 to 17)	99%, <.001	
Latitude location (with respect to the equator)				
Northern Hemisphere	45 (139 434)	13 (11 to 16)	99%, <.001	.96
Southern Hemisphere	7 (2412)	16 (06 to 30)	99%, <.001	
Both Hemispheres of North and South	4 (7095)	14 (11 to 18)	88%, <.001	

—, not applicable.

[a]Moderate-severe AKI is defined as KDIGO stages 2 and 3.

*For subgroup differences (<.05 is considered significant).

TABLE 4 Acute Kidney Injury Associated Mortality

Subgroups	Studies (participants)	Pooled incidence (%), (95% CI)	Heterogeneity I^2, *P*	*P**
Mortality across various AKI stages				
Any stage AKI	60 (161 877)	11 (09 to 13)	97%, <.001	Not applicable
AKI stage 1	12 (67 947)	04 (02 to 07)	92%, <.001	
AKI stage 2	12 (67 733)	08 (04 to 12)	84%, <.001	
AKI stage 3	12 (67 733)	20 (13 to 27)	90%, <.001	
Moderate-severe AKI[a]	13(68 103)	15 (10 to 21)	93%, <.001	
Received dialysis	13 (25 959)	31 (16 to 47)	97%, <.001	
Subgroup analysis- for AKI-associated mortality				
Clinical settings				
Intensive care units	21 (32 365)	17 (13 to 21)	94%, <.001	<.001
Hospitalized (mixed, unspecified)	7 (66 626)	03(02 to 05)	96%, <.001	
Cardiac surgery	8 (6905)	07 (03 to 12)	88%, <.001	
Infection	6 (5287)	16 (09 to 24)	90%, <.001	
Nephrotoxins	6 (31 617)	09 (05 to 14)	76%, <.001	
Community-acquired	5 (31 617)	05 (02 to 09)	62%, .05	
Nonkidney solid organ transplantation	2 (273)	07 (02 to 12)	87%, <.001	
Nephrotic syndrome	2 (478)	01 (00 to 03)	97%, <.001	
Trauma	1 (114)	36 (15 to 65)	Not applicable	
Malignancy	1 (9828)	05 (04 to 07)	Not applicable	
Geographical regions				
Africa	8 (3954)	15 (09 to 21)	79%, <.001	.15
Americas	23 (124 370)	10 (06 to 14)	98%, <.001	
Asia	18 (15 818)	14 (08 to 20)	95%, <.001	
Europe	4 (4815)	07 (02 to 13)	97%, <.001	
Oceania	2 (9053)	10 (08 to 12)	89%, <.001	
Country income classification (as per gross national income per capita)				
Low income	4 (3147)	18 (11 to 25)	99%, <.001	<.001
Low-middle income	8 (1588)	22 (09 to 38)	98%, <.001	
Upper-middle income	13 (15 095)	18 (11 to 27)	99%, <.001	
High-income	33 (138 359)	07 (04 to 09)	99%, <.001	
Latitude location (with respect to the equator)				
Northern Hemisphere	47 (143 960)	10 (07 to 13)	97, <.001	.20
Southern Hemisphere	7 (11 315)	17 (10 to 25)	93, <.001	
Both Hemispheres of North and South	6 (7951)	13 (07 to 19)	92, <.001	

CI, confidence intervals.

[a]Moderate-severe AKI is defined as KDIGO stage 2 and 3.

*for subgroup differences (<.05 is considered significant).

incidence in our study may be the inclusion of more studies (including 13 from LIC and LMIC) with uniform diagnostic criteria. While assessing the variation in AKI incidence, we observed that it was slightly higher in Europe than in Africa and Asia, which may reflect increased recognition of AKI because of better availability of diagnostic resources and increased physician awareness in developed countries.

The pooled mortality rate (11%) in children with AKI was slightly lower than in the previous meta-analysis (13.8%).[9] This may be because of better access to healthcare and improved diagnostics in the past several years, leading to an overall reduction in mortality. Similar to the previous reports,[2,9,20,21] we observed an incremental relationship between AKI severity and mortality. The highest proportion of deaths (31%) was in children receiving dialysis for AKI; similar findings were also reported previously.[22] When we compared various clinical settings, not surprisingly, the highest mortality rates (17%) were seen in the ICU setting, followed by tropical infection-associated AKI (16%). We also demonstrated higher mortality in Africa and Asia compared with the Americas and Europe, despite the similar AKI burden in hospitalized children. We showed that AKI-associated mortality is higher in LIC and LMIC than in HIC. This variation in AKI-associated mortality has also been highlighted in the 0by25 global snapshot study.[3]

We observed a significant reduction in AKI-associated mortality with an increase in GDP of the countries. Even with a slightly lower AKI burden in LIC and LMIC, higher mortality is likely caused by lack of awareness, delayed recognition and diagnosis of AKI, late hospital presentation, and limited dialysis

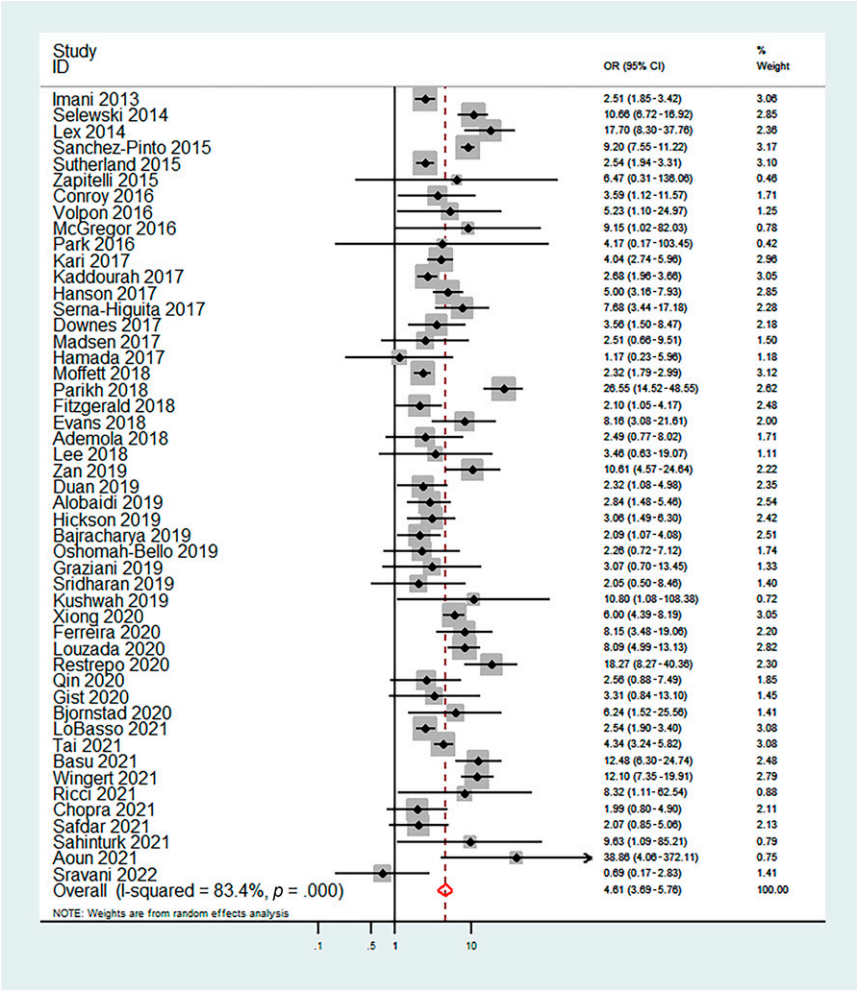


FIGURE 5

Forest plot showing a comparison of acute kidney injury-associated mortality between children with or without acute kidney injury. The red diamond represents pooled estimate with 95% CI. The red dotted vertical line corresponds to pooled odds ratio. AKI, acute kidney injury.

resources. In the meta-regression analysis, an increase in the expenditure on infrastructure was associated with a reduction in AKI-associated mortality, highlighting the much-needed raise in the allocated health care budget. Finally, we observed slightly higher mortality from the south of the equator, where the AKI is chiefly caused by diarrhea, dehydration, and tropical infections.[23]

This systematic review focused on synthesizing the evidence on the worldwide epidemiology of pediatric AKI among hospitalized children using the KDIGO criteria. Although we have assessed the geographical variation and followed a robust methodology, several limitations exist. First, the studies included in this review were done in hospital settings only, so the pooled estimates represent worldwide incidence of AKI in hospitalized children rather than the true global burden. Second, despite rigorous efforts to identify duplicate reports, the possibility of data duplication remains between large multicentric and small single-center studies. Third, we observed significant heterogeneity in pooled estimates for all outcomes. Although we performed various subgroup analyses and meta-regression, the heterogeneity largely remains unexplained. Fourth, we did not standardize AKI rates to at-risk periods. Fifth, we used the latest world bank classification for various economic groups of countries and the GDP. As the study data originates over 2 decades (2003 to 2021), these assessments may not accurately represent the relationship between AKI burden and mortality with current GDP.

Notwithstanding these limitations, we believe that the evidence generated from this meta-analysis carries implications for policymakers, researchers, and clinicians. Higher mortality rates in LMIC and LIC compared with HIC, albeit with similar AKI burden, warrant special attention to reducing preventable AKI-associated deaths to meet the goals of the 0by25 initiative. Disproportionately fewer studies from LIC and LMIC indicate a lack of awareness and poor resource availability for early recognition and diagnosis of AKI. Therefore, a better infrastructure and more research is needed in these countries for the prevention and early treatment of AKI to save more lives. Increasing healthcare expenditure in LIC and LMIC may help lower AKI-associated mortality, as demonstrated in this meta-analysis. Increased funding can be used for creating awareness programs among primary care physicians regarding AKI and its complications, establishing and sustaining acute dialysis facilities and training nursing staff to performing peritoneal and/or hemodialysis, which would improve the care among children with AKI. Similarly, more financial support will allow development of basic laboratory support that would facilitate early recognition of AKI, which is currently lacking in some parts of the world. Saving Young Lives is an excellent example of such

initiative, which has helped in significantly improving the care of children with AKI in resource limited settings in Africa and South-East Asia.[24,25]

CONCLUSIONS

AKI affects a considerable proportion of hospitalized children and significantly increases short-term mortality risk. The severity of AKI confers an incremental risk of death; hence early recognition is paramount. Variation in epidemiology suggests that achieving the goal of reducing AKI-associated deaths needs tremendous political and scientific efforts with a specific focus on resource-limited countries.

ABBREVIATIONS

AKI: acute kidney injury
GDP: gross domestic product
HIC: high-income countries
KDIGO: Kidney Disease Improving Global Outcomes
LIC: low-income countries
LMIC: lower-middle-income countries
UMIC: upper-middle-income countries

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