Acute Kidney Injury in Neonates: A Meta-Analysis

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abstract

BACKGROUND AND OBJECTIVE: There is a paucity of pooled synthesized data on the epidemiology of neonatal acute kidney injury (AKI). Our objective with this study is to systematically assess the worldwide incidence of AKI in neonates.

METHODS: We searched 3 electronic databases (Embase, PubMed, Web of Sciences) from January 2004 to December 2022 without language restrictions. We included cohort and cross-sectional studies that reported the incidence of AKI or associated mortality in neonates. Eligible studies had at least 10 participants and used standard criteria (Acute Kidney Injury Network/Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE)/ Kidney Disease Improving Global Outcomes) to define AKI. Two authors independently retrieved data on demographic characteristics, clinical setting, and outcomes (incidence and AKI-associated mortality) using a semi-structured proforma and assessed the risk of bias. We used a random-effects meta-analysis to calculate pooled estimates with 95% confidence intervals.

RESULTS: We included 201 studies (98 228 participants) from 45 countries. The incidence of any stage AKI was 30% (95% confidence interval 28–32), and that of severe AKI was 15% (14–16). Overall, AKI-associated mortality was 30% (27–33). The odds of mortality were higher (odds ratio 3.4; 2.9–4.0) in neonates with AKI compared with those without AKI. We found that perinatal asphyxia, sepsis, patent ductus arteriosus, necrotizing enterocolitis, and nephrotoxic medications were significant risk factors for AKI. Significant heterogeneity in the pooled estimates was a limitation of this study.

CONCLUSIONS: AKI was observed in one-third of the neonates and was associated with increased risk of mortality. The incidence of AKI was almost similar in neonates with perinatal asphyxia and sepsis, but mortality was higher in the former group.

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Dr Meena conceptualized and designed the study, performed the literature search, data extraction, and data analysis, and drafted the manuscript; Dr Kumar participated in conceptualization, literature search, data collection, risk of bias assessment, and critically reviewed the manuscript; Drs Kocharlakota, Gupta, Mittal, and Kumar participated in data extraction and risk of bias assessment and critically reviewed the manuscript; Drs Sinha and Hari participated in data analysis and critically reviewed the manuscript; Dr Bagga supervised the conduct of this systematic review and revised the initial draft; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Prospective studies have revealed that acute kidney injury (AKI) is common in children[1,2] and is associated with an increased risk of mortality and adverse outcomes.[2–4] The understanding of the epidemiology of AKI in children has improved chiefly because of the standardization of diagnostic criteria.[5–7] Similar to the multicenter AWARE study in critically ill children, the AWAKEN study reported the epidemiology of AKI in sick neonates requiring intravenous fluids for at least 48 hours.[1,8] The latter study revealed that AKI was common in neonates across all gestational ages and was associated with increased mortality and prolonged hospitalization. Similar findings were reported in another large cohort of extremely premature infants.[9] With improved survival of neonates with extreme prematurity and perinatal asphyxia, the burden and long-term sequelae of AKI are likely to increase.[10,11]

Defining AKI in neonates has been challenging because of several factors, including difficulty in accurately monitoring urine output and determining the baseline serum creatinine.[12,13] Similarly, the frequency of monitoring of serum creatinine might also affect the incidence of AKI. Most guidelines suggest that the Kidney Disease Improving Global Outcomes (KDIGO) criteria can be used to define and stage neonates with AKI.[10,12,14]

The incidence and mortality of AKI in children varies in different clinical settings and across geographical regions.[2] However, for neonatal AKI, there is a lack of systematically synthesized data across gestational age, clinical settings, and geographic regions. A recent meta-analysis revealed that AKI affected 25% of neonates and increased the risk of mortality by 7-fold.[15] However, this meta-analysis was limited to preterm infants and did not provide insight into the overall epidemiology of AKI in neonates. The authors of several studies with large sample sizes,[9,16–19] including those from low-middle-income countries, have reported the etiology and outcomes of AKI in newborn infants.

To improve our understanding of the incidence, risk factors, and outcomes of neonatal AKI, we systematically reviewed worldwide data on its epidemiology to examine whether differences exist across geographical regions and clinical scenarios.

METHODS

Literature Search and Data Source

The protocol for this systematic review was registered on PROSPERO (CRD42020180651). We adhered to Meta-analysis of Observational Studies in Epidemiology guidelines[20] and used Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting.[21] The literature search, study selection, data extraction, and quality assessment of the studies were performed in duplicate by 2 authors (JM, JK) with expertise in health care data retrieval. Any discrepancy between the 2 authors was resolved through discussion with the third author (AB). We formulated an individual search strategy for each database using keywords and (Medical Subject Headings) MeSH terms related to AKI and the neonatal population (Supplemental Table 4). The search strategy was peer-reviewed by the 2 authors using a Peer Review of Electronic Search Strategies checklist and revised accordingly.[22] We conducted a literature search in 3 different electronic databases (PubMed, Embase, and Web of Science) for articles published between January 2004 and December 2022. We chose 2004 as the start year because the first standardized criteria for diagnosis and staging of AKI were published in that year.[5] We did not use any language or geographic restrictions during the literature search. The electronic search was supplemented by a hand search of the bibliography of relevant articles and reviews.

Study Selection

We aimed to provide pooled estimates of the global burden of AKI restricted to studies reporting 10 or more neonates. Studies meeting all the following inclusion criteria were considered suitable for this review: (1) population: neonates (<28 days or 44 weeks postmenstrual age), (2) disease: AKI due to any etiology reported as per KDIGO/pRIFLE/Acute Kidney Injury Network (AKIN) or similar classifications, (3) study design: prospective, retrospective cohort, and cross-sectional studies, and (4) reporting data on AKI incidence and/or in-hospital mortality. We excluded studies (1) evaluating beyond the neonatal period with no separate data for neonates, (2) not clearly defining the criteria for the diagnosis of AKI, (3) with conference abstracts not providing sufficient information on diagnostic criteria, and (4) evaluating neonates with congenital anomalies of kidney and urinary tract. We also excluded studies defining AKI using *International Classification of Diseases, Ninth or Tenth Revision* codes.

Data Extraction

Two authors independently extracted data from the studies to a predesigned semi-structured extraction form. Retrieved data included year of publication, country, geographic region, study design, setting and period, participant characteristics (gestational age, birth weight, sex, etiology), number of neonates with AKI, stage of AKI, risk factors, length of hospital stay and in-hospital all-cause mortality.

Risk of Bias Assessment

We used the modified Hoy et al tool to assess the risk of bias in the studies.[23] This tool consists of 9 items addressing the internal and external validity of the study, with each item being assigned a score of 0 or 1. On the basis of the overall score, studies were classified as having low (score 0–3), moderate (4–6), or high risk (7–9) of bias (Supplemental Table 5).

Outcomes

The primary outcome was to provide the pooled incidence of AKI (any stage) in neonates. Secondary outcomes include pooled incidence of severe AKI (stage 2–3 AKI), AKI-associated in-hospital mortality, and risk factors for AKI in neonates.

Data Synthesis and Statistical Analysis

We used a random-effects model for meta-analysis to account for inherent heterogeneity in the study population and the underlying etiology of AKI. We calculated the pooled proportion (along with 95% confidence intervals [CI]) of various AKI stages. We also calculated pooled odds ratios (95% CI) for all-cause mortality in neonates with AKI compared with those without AKI. To estimate the odds of mortality, we chose only those studies that reported mortality data for AKI and non-AKI groups. Heterogeneity was assessed by inspecting forest plots and χ-square statistics and quantified using I^2. I^2 value represents the percentage of total variability in pooled estimates due to true variation (clinical, methodological, and statistical) between studies rather than sampling error. I^2 values of 75% to 100%, 50% to 90%, and 30% to 60% were interpreted as considerable, substantial, and moderate heterogeneity, respectively. To explore heterogeneity, we performed subgroup analyses based on clinical settings, geographical and subregional classification, and economic groups.[24] Countries were divided into low- and low-middle income (LLMIC), upper-middle income (UMIC), and high-income (HIC) based on their gross national income per capita for the year 2020.[24]

Meta-regression was performed to assess the effects of gross domestic product (GDP) per capita and the percentage of GDP spent on health expenditure (for the year 2020) on the incidence of AKI and AKI-associated mortality. Publication bias was assessed using a funnel plot and Egger's linear regression analysis.[25] Stata version 14.2 (College Station, Texas, USA) was used for statistical analysis.

RESULTS: SELECTION AND BASELINE CHARACTERISTICS OF INCLUDED STUDIES

The selection process of studies is shown in Fig 1. A literature search through the 3 electronic databases retrieved a total of 6990 records. After deduplication, we screened through the titles and abstracts of 4532 citations and selected 428 potentially eligible articles. Finally, 201 studies were selected for this systematic review after full-text screening. Details of these studies are described in Supplementary Table 6. The primary outcome of the incidence of AKI was reported in 189 studies; the remaining 13 studies revealed other outcomes. The authors of these 201 studies from 45 countries assessed 98 228 neonates. Seventy-seven (38.3%) and 63 (31.3%) studies were reported from America and Asia, respectively. Based on gross national income per capita in 2020, studies predominantly originated from HIC (54.2%) and UMIC (26.9%), with few studies from LLMIC (18.4%). Most studies were from the United States (33%), India (11%), and Turkey (9%); 84 studies (42%) were prospective. Neonatal AKI was defined by using KDIGO, pRIFLE, and AKIN or equivalent criteria in 143 (71%), 26 (13%), and 32 (16%) articles, respectively. The authors of 37 (18%) and 84 (42%) studies assessed term and preterm infants, respectively, whereas the authors of 80 (40%) studies evaluated both term and preterm babies. Among the 201 studies, 150 (75%), 44 (21.8%), and 7 (3.2%) studies had a low, moderate, and unclear risk of bias, respectively (Supplementary Table 6).

INCIDENCE OF ANY AKI

Overall Incidence of Any AKI

The authors of 189 (97 118 neonates) reported the incidence of AKI. The pooled incidence of AKI was 30% (95% CI 28 to 32, $I^2 = 99\%$, $P < .001$; Table 1). The incidence of AKI was 30% (28 to 32), 28% (22 to 33), and 33% (26 to 40) in studies using KDIGO, pRIFLE, and AKIN criteria, respectively. The incidence of stages 1, 2, and 3 of AKI was 18% (17 to 20), 7% (6 to 8), and 7% (6 to 7), respectively (Fig 2). We performed sensitivity and subgroup analyses to explore the heterogeneity observed in the pooled incidence of AKI. The pooled incidence of AKI was almost similar in retrospective studies (32%) compared with prospective studies (28%; $P = .12$). No significant difference was observed in pooled estimates in studies with low, moderate, and unclear risk of bias (Table 1). The funnel plot showed asymmetry, suggesting a small study effect (Supplementary Fig 5). Eggers linear regression analysis also suggested a small study effect (coefficient −0.94; 95% CI −1.11 to −0.77; $P < .001$).

Any AKI in Various Clinical Settings

There was a wide variation in the incidence of AKI across various clinical settings (Table 1). The incidence of AKI in neonates with perinatal asphyxia was 34% (28 to 40), whereas in neonates who underwent cardiac surgery, it was 45% (38 to 52). The authors of 17 studies assessed AKI in neonates receiving nephrotoxic medications with a pooled incidence of 18% (14 to 23). The incidence of AKI in neonates with sepsis, necrotizing enterocolitis, and patent ductus arteriosus was 30% (14 to 47), 31% (1 to 61), and 32% (13 to 51), respectively (Table 1).

Any AKI Across Geographical and Economic Groups

Variations in the incidence of AKI in neonates across various geographical and economic groups of the countries are reported in Table 1 and Fig 3A. The pooled incidence of

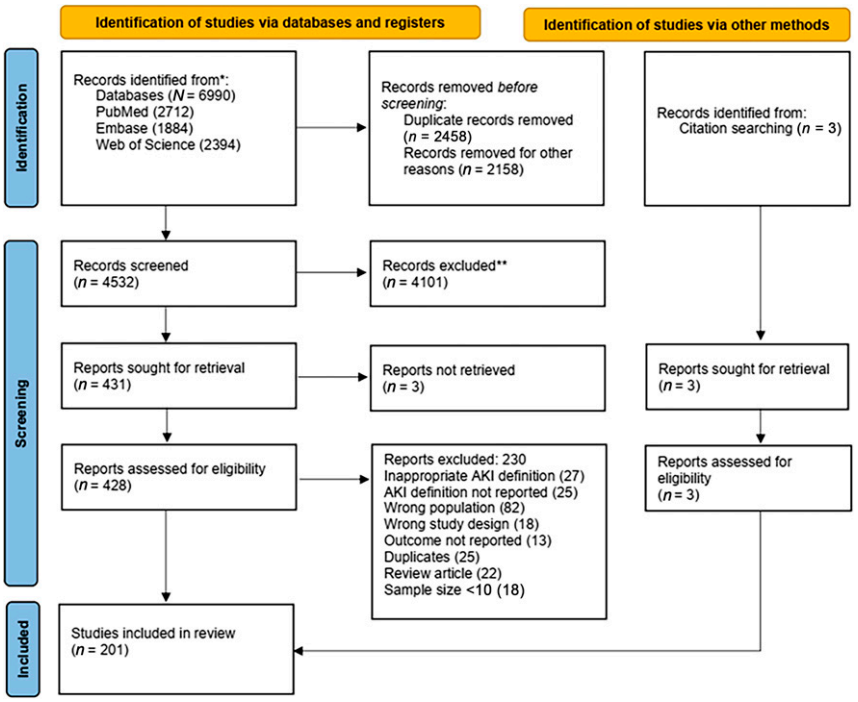

FIGURE 1
Preferred reporting items for systematic review and meta-analysis flow diagram for selection of studies.

AKI was 31% (27 to 35), 32% (28 to 36), and 37% (28 to 46) in America, Asia, and Africa, respectively. Although there were a limited number of studies from LLMIC, the pooled incidence of AKI was 32% (27 to 37), which was not different from UMIC 27% (23 to 31) and HIC 31% (29 to 34).

INCIDENCE OF SEVERE AKI

Severe AKI (stages 2 and 3) was reported in 99 studies evaluating 51 911 neonates. The incidence of severe AKI was 15% (95% CI 14 to 16, I^2 = 98%, $P < .001$; Supplementary Table 7). The incidence of severe AKI using KDIGO, pRIFLE, and AKIN criteria was 15% (13 to 16), 15% (9 to 21), and 18% (13 to 24), respectively. We did not find significant differences in pooled estimates of severe AKI as per study design and risk of bias among the studies (Supplementary Table 7).

Severe AKI in Various Clinical Settings

Variation in the burden of severe AKI as per clinical setting is reported in Supplemental Table 7. The incidence of severe AKI in neonates with perinatal asphyxia was 18% (95% CI 12 to 24), and in those who underwent cardiac surgery, it was 21% (16 to 27). Term infants (37%) had a slightly higher incidence than preterm infants (27%; $P = .01$).

Severe AKI Across Geographical and Economic Groups

Variation in the epidemiology of severe AKI across geographical and economic groups of countries is described in Supplementary Table 7. The incidence of severe AKI was higher in Africa and Asia compared with Europe and America. We did not observe a significant difference in the incidence of severe AKI as per the economic groups of the countries.

AKI ASSOCIATED MORTALITY

Overall Mortality (Any AKI and Various Stages)

The incidence of AKI-associated mortality (105 studies, 45 708 neonates) was 30% (95% CI 27 to 33, I^2 = 95%, $P < .001$; Table 2). Mortality was higher in stage 3 AKI (46%; 32 to 61) as compared with stage 2 (28%; 19 to 37) and stage 1 (20%; 14 to 26; Fig 2). Pooled mortality was 36% (26 to 45) in neonates with severe AKI (Table 2). The overall odds of mortality were 3.4 (2.9 to 4.0) times in neonates with AKI compared with those who did not have AKI (Fig 3). The highest mortality odds were observed with AKI stage 3 (odds ratio 6.7; 4.8 to 9.2), compared with no AKI.

Mortality Across Various Clinical Settings

We observed higher AKI-associated mortality in term infants (40% [28 to 52]), compared with preterm infants (34% [29 to 40]; Table 2). The highest AKI-associated mortality was observed in neonates with perinatal asphyxia (35%; 16 to 54; Table 2).

Mortality Across Geographical and Economic Groups

There was wide variation in mortality across various geographical regions. AKI-associated mortality was higher in

TABLE 1 Incidence of AKI and Its Distribution Across Various Subgroups

Parameters	Studies (Participants)	Pooled Incidence % (95% CI)	Heterogeneity[a] (I^2), *P*	*P*[b]
Primary outcome				
Any stage AKI	189 (97 118)	30 (28 to 32)	99, <.001	Not applicable
Stage 1	99 (52 170)	18 (17 to 20)	98, <.001	
Stage 2	95 (50 538)	7 (6 to 8)	97, <.001	
Stage 3	90 (49 142)	7 (6 to 7)	96, <.001	
Severe AKI[c]	99 (51 911)	15 (14 to 16)	98, <.001	
Definition of AKI				
KDIGO	136 (87 788)	30 (28 to 32)	99, <.001	.51
RIFLE	23 (4245)	28 (22 to 33)	97, <.001	
AKIN	30 (5085)	33 (26 to 40)	97, <.001	
Subgroup analysis				
Gestational age				
Term	36 (5411)	37 (30 to 42)	99, <.001	.01
Preterm	81 (51 404)	27 (24 to 30)	98, <.001	
Mixed	72 (40 303)	31 (27 to 34)	99, <.001	
Clinical Settings				
Perinatal asphyxia	28 (3396)	34 (28 to 40)	95, <.001	<.001
Sepsis	5 (985)	30 (14 to 47)	98, <.001	
Necrotizing enterocolitis	3 (26 062)	31 (01 to 61)	—	
Patent ductus arteriosus	10 (1689)	32 (13 to 51)	99, <.001	
Nephrotoxic medications	17 (12 385)	18 (14 to 23)	98, <.001	
Cardiac surgery	27 (5997)	45 (38 to 52)	97, <.001	
Mixed	95 (46 406)	27 (24 to 30)	99, <.001	
Geographical regions				
Africa	14 (1490)	37 (28 to 46)	99, <.001	<.001
Americas	75 (33 383)	31 (27 to 35)	98, <.001	
Asia	57 (16 913)	32 (28 to 36)	93, <.001	
Australia	1 (359)	4 (2 to 6)	—	
Europe	41 (42 951)	25 (22 to 28)	99, <.001	
Economic classification[a]				
Low- and lower-middle-income	32 (8606)	32 (27 to 37)	97, <.001	.30
Upper-middle-income	48 (14 434)	27 (23 to 31)	98, <.001	
High-income	108 (72 056)	31 (29 to 34)	99, <.001	
Study design				
Prospective	82 (48 212)	28 (25 to 31)	99, <.001	.12
Retrospective	107 (48 906)	32 (29 to 35)	99, <.001	
Risk of bias in studies				
Low risk	143 (88 491)	30 (28 to 32)	99, <.001	.95
Moderate risk	40 (8005)	30 (24 to 36)	98, <.001	
Unclear risk	6 (622)	28 (17 to 40)	91, <.001	

RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease. —, not applicable.
[a] Based on countries' gross national income per capita. Heterogeneity (I^2) value represents the percentage of total variability in pooled estimates due to true variation in-between studies rather than sampling.
[b] For subgroup differences ($P < .1$ is considered significant).
[c] Severe AKI is defined as stages 2 and 3.

Africa (45%, 31 to 60) compared with America (27%, 22 to 33) and Europe (32%, 26 to 39) (Table 2). We observed similar AKI-associated mortality in LLMIC at 32% (24 to 40), UMIC at 32% (26 to 38), and HIC at 28% (24 to 32) (Table 2). A graphical representation of the odds of AKI-associated mortality among neonates with AKI (vs neonates without AKI) according to the geographical classification and economic groups of countries is depicted in Fig 4.

RISK FACTORS FOR AKI IN NEONATES

Major risk factors for AKI included perinatal asphyxia (odds ratio 3.3; 1.4 to 7.7) and patent ductus arteriosus (odds ratio 2.4; 1.8 to 3.1) (Table 3). Other factors associated with an increased risk of AKI were sepsis, exposure to nephrotoxic medications, and necrotizing enterocolitis (Table 3).

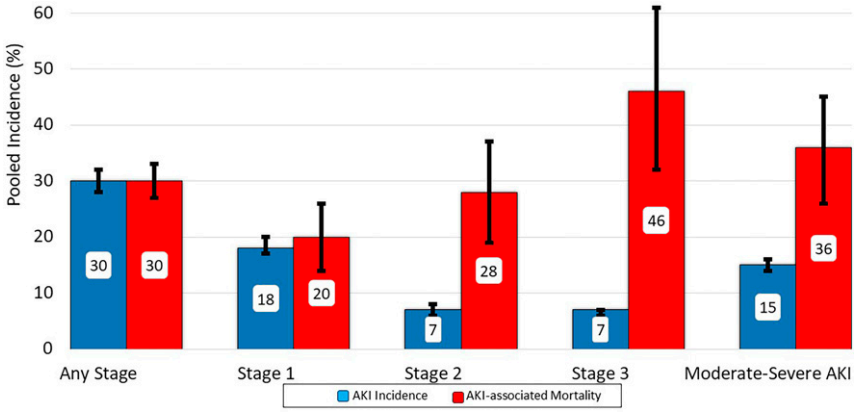

FIGURE 2
Pooled incidence and associated mortality (95% CI) of AKI in neonates. Severe AKI indicates stages 2 and 3 as per AKIN/KDIGO/pRIFLE criteria.

META-REGRESSION

Meta-regression analysis did not reveal any relationship between the incidence of AKI and GDP or the percentage of GDP spent as total health expenditure (Supplementary Table 8). Similarly, no significant association was observed between AKI-associated mortality and these economic parameters (Supplementary Table 8).

DISCUSSION

In this study, we examined the hypothesis that incidence of neonatal AKI varies across various geographical regions and clinical settings. Meta-analysis of studies published since 2004 showed that the worldwide incidence of AKI in neonates was 30% (28 to 32). Almost half (15%) of these neonates had severe AKI. Mortality was observed in every third neonate who suffered AKI during the hospital stay. The odds of mortality was 3.4 times higher in neonates with AKI compared with those who did not develop AKI. There was an incremental relationship between the severity of AKI and the odds of mortality. Although AKI incidence was highest in neonates who underwent cardiac surgery, mortality was higher in neonates with perinatal asphyxia. The highest incidence of AKI and AKI-associated mortality was observed in studies reported from African countries, although this was based on limited studies and might not accurately represent data from entire continent. We did not find significant differences in the incidence and mortality of AKI among LLMIC, UMIC, and HIC.

Findings from this systematic review indicate that neonatal AKI (30%) is as common as that observed in older hospitalized children (~26%).[1,2,8] As reported previously in multicentric studies, the incidence of AKI in critically ill neonates in Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) (29.9%)[8] and

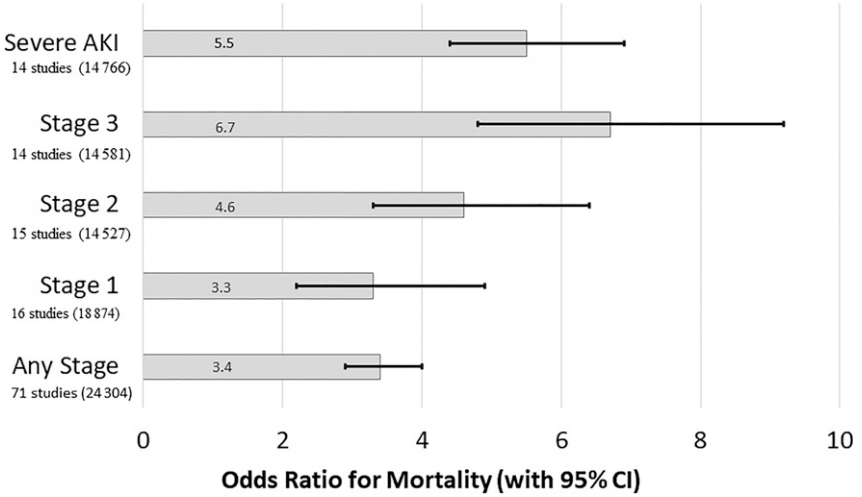

FIGURE 3
Mortality in neonates with or without AKI. Severe AKI indicates stages 2 and 3 as per AKIN/KDIGO/pRIFLE criteria.

TABLE 2 AKI Associated Mortality in Neonates and Its Distribution Across Various Subgroups

Parameters	Studies (Participants)	Pooled Incidence % (95% CI)	Heterogeneity[a] (I^2), *P*	*P*[b]
Primary outcome				
Any stage AKI	105 (45 708)	30 (27 to 33)	95, <.001	Not applicable
Stage 1	15 (18 874)	20 (14 to 26)	92, <.001	
Stage 2	13 (14 527)	28 (19 to 37)	79, <.001	
Stage 3	14 (14 581)	46 (32 to 61)	90, <.001	
Severe AKI[c]	16 (14 766)	36 (26 to 45)	90, <.001	
Definition of AKI				
KDIGO	73 (40 021)	30 (27 to 34)	95, <.001	.36
RIFLE	14 (2058)	34 (25 to 43)	84, <.001	
AKIN	18 (3629)	25 (16 to 34)	93, <.001	
Subgroup analysis				
Gestational age				
Term	18 (2592)	40 (28 to 52)	95, <.001	<.001
Preterm	40 (10 661)	34 (29 to 40)	92, <.001	
Mixed	47 (32 455)	22 (19 to 25)	93, <.001	
Clinical Settings				
Asphyxia	12 (1115)	35 (16 to 54)	97, <.001	<.001
Sepsis	2 (448)	14 (06 to 21)	—	
Patent ductus arteriosus	1 (298)	28 (16 to 45)	—	
Drugs	2 (419)	12 (05 to 18)	—	
Cardiac surgery	13 (4502)	21 (12 to 31)	96, <.001	
Mixed	74 (38 876)	31 (28 to 34)	93, <.001	
Geographical regions				
Africa	9 (1447)	45 (31 to 60)	92, <.001	<.001
Americas	35 (15 735)	27 (22 to 33)	95, <.001	
Asia	37 (11 512)	27 (22 to 33)	94, <.001	
Australia	1 (2022)	69 (42 to 87)	—	
Europe	22 (14 633)	32 (26 to 39)	92, <.001	
Economic classification[a]				
Low- to low-middle-income	26 (7029)	32 (24 to 40)	96, <.001	<.001
Upper-middle-income	27 (9393)	32 (26 to 38)	89, <.001	
High-income	51 (27 264)	28 (24 to 32)	95, <.001	
Study design				
Prospective	42 (17 139)	28 (23 to 33)	95, <.001	.39
Retrospective	63 (28 569)	31 (27 to 35)	93, <.001	
Risk of bias in studies				
Low risk	84 (41 717)	30 (27 to 34)	95, <.001	.24
Moderate risk	16 (3400)	28 (20 to 37)	94, <.001	
Unclear risk	4 (517)	33 (20 to 46)	70, <.001	

RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease. —, not applicable.

[a] Based on countries' gross national income per capita. Heterogeneity (I^2) value represents the percentage of total variability in pooled estimates due to true variation in-between studies rather than sampling.

[b] For subgroup differences ($P < .1$ is considered significant).

[c] Severe AKI is defined as stages 2 and 3.

older children in the AWARE (26.9%) study[1] is barely different. The authors of a previous meta-analysis of 50 studies (10 744 preterm neonates) in neonates reported a pooled incidence of AKI 25% (20 to 30).[15] Because the meta-analysis included only preterm infants and the literature search was restricted to the English language, these estimates may not represent the true global burden of neonatal AKI. In the present review, the incidence of AKI in preterm neonates was almost similar (27%) to the previous meta-analysis (25%).[15] Similar to the AWAKEN study, we observed a higher incidence of AKI in term neonates than in preterm babies. These findings might be because perinatal asphyxia is the major cause of AKI in term neonates, and serum creatinine is monitored more frequently in this specific cohort.

AKI-associated mortality was significantly higher in neonates (30%) compared with older children (11%), although an incremental trend of mortality with severity

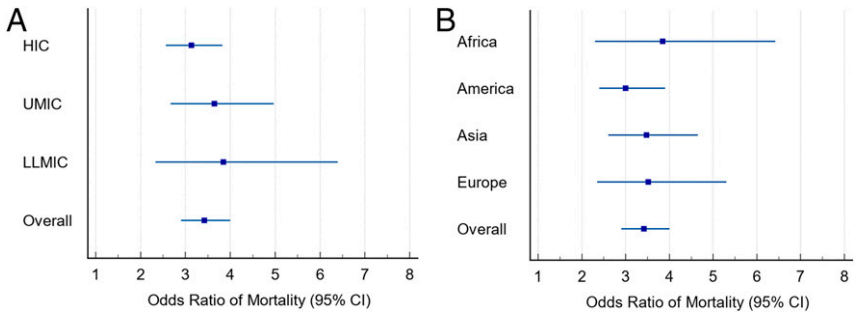

FIGURE 4

Variation in odds of mortality between neonates with or without AKI (A) as per geographical classification and (B) economic groups of countries. Data in some geographical areas is based on a limited number of studies and, hence, may not be a true representation of population estimates.

of AKI is observed in both age groups.[2] The etiological profile of neonatal AKI (perinatal asphyxia, patent ductus arteriosus, necrotizing enterocolitis, congenital cyanotic heart disease) differs from the older children and tends to have multisystemic involvement. Neonates therefore show a more complicated clinical course and are at a higher risk of mortality. Another factor that may contribute to higher mortality in neonates is the pattern of serum creatinine monitoring. Serum creatinine and urine output monitoring are performed for most hospitalized older children but are performed only in critically ill neonates, who have a higher risk of mortality.

Global variation in AKI incidence and associated mortality revealed higher rates in Africa compared with Asia and the Americas, which mirrors the burden of perinatal asphyxia and all-cause neonatal mortality. Infants born in Africa are at higher risk for prematurity, perinatal asphyxia, and sepsis (the leading cause of AKI) and have poor access to health care facilities. These findings highlight the need for improvement in health care infrastructure, accessibility, and training of health personnel.

Our findings suggest that the presence of perinatal asphyxia, sepsis, necrotizing enterocolitis, patent ductus arteriosus, and exposure to nephrotoxic medications significantly increases the risk of developing AKI. Similar risk factors for neonatal AKI have been reported previously.[10,15] Neonates with patent ductus arteriosus have a unique case scenario because if it is left untreated, compromised blood flow can lead to AKI. Treatment with nonsteroidal anti-inflammatory agents (such as ibuprofen) also increases the risk of neonatal AKI.[10] Perinatal asphyxia and congenital cardiac disease significantly contribute to AKI in term neonates. Studies have revealed an incremental relationship between the severity of perinatal asphyxia and incidence of AKI.[26,27]

With this systematic review, we focused on synthesizing the evidence on the worldwide epidemiology of neonatal AKI using studies published after the first attempt to standardize the definition of AKI in 2004. Although we have assessed the worldwide variation and followed a robust methodology, several limitations exist. First, despite rigorous efforts to identify duplicate reports, the possibility of data duplication exists between large multicenter and small single-center studies. Second, we observed significant heterogeneity in pooled estimates for all outcomes. Although we performed various subgroup analyses and meta-regression, the heterogeneity remains unexplained. Neonatal units have different practices for monitoring blood levels of creatinine and urine output, which might explain the heterogeneity between the studies.[8,10] Third, we did not standardize AKI rates to at-risk periods. Fourth, subgroup classification in different clinical settings was not uniform, and many of these conditions may coexist in a neonate. Finally, we used the latest World Bank classification for economic group of countries and for the GDP. Because the study covers data over 2 decades (2004 to 2022), these assessments might not accurately represent the relationship

TABLE 3 Risk Factors for AKI in Neonates

Parameters	Studies (Participants)	Pooled Odds Ratio (95% CI)	Heterogeneity (I^2); *P*
Sepsis	28 (18 413)	1.76 (1.41 to 2.2)	80, <.001
Perinatal asphyxia	14 (3026)	3.26 (1.38 to 7.72)	93, <.001
Nephrotoxic medications	12 (3503)	1.26 (0.87 to 1.81)	71, <.001
Patent ductus arteriosus	16 (6599)	2.38 (1.83 to 3.1)	59, .002
Necrotizing enterocolitis	16 (32 666)	1.8 (1.23 to 2.63)	85, <.001

between AKI burden and mortality to current GDP and health expenditure.

CONCLUSIONS

Findings from this meta-analysis have implications for policymakers, researchers, and clinicians. AKI affects almost a third of hospitalized neonates. One-third of neonates who develop AKI die during the hospital stay, with an incremental risk of mortality with increasing severity of AKI. Despite not dissimilar incidence, AKI-associated mortality was higher in perinatal asphyxia compared with sepsis and even those undergoing cardiac surgery. Disproportionately fewer studies from LLMIC indicate a lack of awareness and limited health infrastructure for timely recognition of neonatal AKI. Our findings suggest higher AKI-associated mortality in Africa compared with Europe and America. International collaborations are needed to acquire more data, especially from LLMIC to better understand the global burden and its implications. This will help us in the prevention and early treatment of AKI and reduce infant mortality. Further studies are also required to examine the long-term outcomes of neonatal AKI, especially including hypertension and progression to chronic kidney disease.

ABBREVIATIONS

AKI: acute kidney injury
AKIN: Acute Kidney Injury Network
CI: confidence interval
GDP: gross domestic product
HIC: high-income countries
KDIGO: Kidney Disease Improving Global Outcomes
LLMIC: low- and lower-middle-income countries
pRIFLE: Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease
UMIC: upper-middle-income countries

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