Risk Factors for Acute Kidney Injury in Critically Ill Neonates: A Systematic Review and Meta-Analysis

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Background and Objective: Acute kidney injury (AKI) is recognized as an independent risk factor for mortality and long-term poor prognosis in neonates. The objective of the study was to identify the risk factors for AKI in critically ill neonates to provide an important basis for follow-up research studies and early prevention.

Methods: The PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, WanFang Med, SinoMed, and VIP Data were searched for studies of risk factors in critically ill neonates. Studies published from the initiation of the database to November 19, 2020, were included. The quality of studies was assessed by the Newcastle-Ottawa Scale and the Agency for Healthcare Research and Quality (AHRQ) checklist. The meta-analysis was conducted with Stata 15 and drafted according to the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Results: Seventeen studies (five cohort studies, ten case-control studies, and two cross-sectional studies) were included in meta-analysis, with 1,627 cases in the case group and 5,220 cases in the control group. The incidence of AKI fluctuated from 8.4 to 63.3%. Fifteen risk factors were included, nine of which were significantly associated with an increased risk of AKI in critically ill neonates: gestational age [standardized mean difference (SMD) = −0.31, 95%CI = (−0.51, −0.12), P = 0.002], birthweight [SMD = −0.37, 95%CI = (−0.67, −0.07), P = 0.015], 1-min Apgar score [SMD = −0.61, 95%CI = (−0.78, −0.43), P = 0.000], 5-min Apgar score [SMD = −0.71, 95%CI = (−1.00, −0.41), P = 0.000], congenital heart disease (CHD) (odds ratio (OR) = 2.94, 95%CI = (2.08, 4.15), P = 0.000), hyperbilirubinemia [OR = 2.26, 95%CI = (1.40, 3.65), P = 0.001], necrotizing enterocolitis (NEC) [OR = 6.32, 95%CI = (2.98, 13.42), P = 0.000], sepsis [OR = 2.21, 95%CI = (1.25, 3.89), P = 0.006], and mechanical ventilation [OR = 2.37, 95%CI = (1.50, 3.75), P = 0.000]. Six of them were not significantly associated with AKI in critically ill neonates: age [SMD = −0.25, 95%CI = (−0.54, 0.04), P = 0.095], male sex [OR = 1.10, 95%CI = (0.97, 1.24), P = 0.147], prematurity [OR = 0.90, 95%CI(0.52, 1.56),
INTRODUCTION

Acute kidney injury (AKI) is characterized by an abrupt decrease in kidney function, which is significantly associated with increased mortality in neonates (1, 2). Due to a number of features of neonatal renal physiology including tubular immaturity and low renal blood flow, the incidence of neonatal AKI has been reported to be high (3). This increased risk for AKI makes early identification of potential risk factors for AKI in neonates important so that they can benefit from potential preventive strategies. Many studies on the risk factors of AKI in critically ill neonates were published, but there are differences between their results (2, 4–6). Though several studies have clarified some risk factors, there is a lack of meta-analysis evaluating these risk factors associated with the occurrence of AKI in critically ill neonates (3, 7–9).

This study was designed to perform a meta-analysis to identify risk factors associated with AKI in critically ill neonates. It may be helpful for the prediction of AKI in critically ill neonates.

METHODS

This meta-analysis was reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (10). The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42020188032). This meta-analysis was conducted on the neonates admitted to the neonatal intensive care unit. Risk factors to be investigated included gestational age, birthweight, 1-min Apgar score, 5-min Apgar score, congenital heart disease (CHD), hyperbilirubinemia, necrotizing enterocolitis (NEC), mechanical ventilation, age, male sex, prematurity, Cesarean section, prenatal hemorrhage, sepsis, and vancomycin. We included cohort studies, case-control studies, and cross-sectional studies that investigated AKI as an outcome.

Data Sources and Searches

We conducted an electronic search of PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, WanFang Med, VIP Data, and SinoMed with the keywords including “neonates,” “acute kidney injury,” “risk factors,” and “risk.” Retrieval time was from inception to November 19, 2020. Search terms and Boolean operators included in the search strategies of PubMed and Embase are presented in online Supplementary Material 1.

Study Selection

Study selection was independently conducted by QH and SJL, with any discrepancies resolved by MW. Inclusion criteria were as follows: (1) Patients are neonates admitted to the neonatal intensive care unit; (2) the risk factors for AKI in neonates are reported; and (3) the definition of AKI is clear, such as Kidney Disease: Improving Global Outcomes (KDIGO) definition, Acute Kidney Injury Network (AKIN) definition, or arbitrary definition (1, 11, 12). Exclusion criteria were as follows: (1) reviews, case reports, nonclinical studies, and the studies inconsistent with the purpose of evaluation; (2) full data cannot be provided; (3) repetitive reports; and (4) non-English or non-Chinese literature studies.

Data Collection and Extraction

Data were independently extracted by QH and S-JL, with any discrepancies resolved by MW. Data collected included the characteristics of the studies, the demographic characteristics of the patients, accompanying diseases, and therapeutic measures. When full data cannot be obtained from the study, we tried to contact the corresponding author to obtain all the data.

Quality Assessment

Quality assessment was independently conducted by QH and S-JL, with any discrepancies resolved by MW. The quality of cohort and case-control studies was assessed using the Newcastle-Ottawa Scale (NOS), which was widely used in the quality assessment of case-control and cohort studies (13, 14). The NOS conducts a comprehensive evaluation from three aspects of the study: selection, comparability, and outcome (cohort studies) or exposure (case-control studies). A study can be awarded a maximum of one point for each numbered item within the selection and exposure categories. A maximum of two points can be given for comparability. The quality of the study was assessed as follows: low quality = 0–3; moderate quality = 4–6; and high quality = 7–9 (15). The quality of cross-sectional studies was assessed by the 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ), which included the definition of information source, inclusion and exclusion criteria, time period and continuity for identifying patients, blinding of personnel, assessments for quality assurance, confounding and missing data, and response rates and completeness of patients. An item would
be scored “0” if it was answered “UNCLEAR” or “NO”; for the answer of “YES,” the item would get a score of “1.” Quality of the study was assessed as follows: low quality = 0–3; moderate quality = 4–7; and high quality = 8–11 (16, 17).

**Statistical Analysis**

Effect sizes have been reported in odds ratio (OR) for dichotomous data and standardized mean difference (SMD) for continuous outcomes. Raw data of continuous variables were converted into mean and standardized difference (SD) wherever possible (18). Pooled effect estimates were reported with 95% CIs. Heterogeneity was tested using the $I^2$ test, with $I^2 > 50\%$, or $p$-value $< 0.1$ was considered significant. If there was significant heterogeneity, a random-effects model was used or else a fixed-effects model. Statistical significance was defined as a two-tailed $p$-value $< 0.05$. Sensitivity analyses were conducted on each risk factor by removing each individual study from the overall analysis. Subgroup analyses were performed on the risk factors with significant heterogeneity, which were based on the definition of AKI (KDIGO or non-KDIGO) and research method (cohort or non-cohort study) (1). Publication bias was estimated via Egger’s test, and a $p > 0.05$ was considered non-significant publication bias. If there was publication bias, the non-parametric clipping was used to evaluate the impact of publication bias on the results. All statistical analyses were performed using Stata 15.0 software (19).

**RESULTS**

**Characteristics of Included Studies**

Initial screening identified 2,629 publications (Figure 1). Finally, only 17 studies satisfied our inclusion criteria and were involved in the meta-analysis (2, 4–6, 12, 20–31), including five cohort studies, ten case-control studies, and two cross-sectional studies (Table 1). Of these, nine studies employed the KDIGO definition or the KDIGO definition modified for neonates (mKDIGO), six studies employed arbitrary definitions, and two studies employed the AKIN definition. The 17 studies included in qualitative
### TABLE 1 | Basic characteristics of included studies.

| References            | Country    | AKI (n) | Non-AKI (n) | Incidence rate (%) | Definition of AKI | Research method |
|------------------------|------------|---------|-------------|--------------------|-------------------|-----------------|
| Fonseca et al. (12)    | Mexico     | 47      | 53          | 47.0               | arbitrary         | case-control    |
| Türker et al. (22)     | Turkey     | 78      | 475         | 14.1               | arbitrary         | case-control    |
| Bolat et al. (23)      | Turkey     | 168     | 1,824       | 8.4                | arbitrary         | case-control    |
| El-Badawy et al. (27)  | Egypt      | 41      | 59          | 41                 | arbitrary         | cohort          |
| Kriplani et al. (28)   | America    | 28      | 52          | 35                 | mKDIGO            | case-control    |
| Zhang et al. (29)      | China      | 75      | 140         | 34.8               | KDIGO             | case-control    |
| Bansal et al. (4)      | India      | 74      | 100         | -                  | arbitrary         | case-control    |
| Jetton et al. (2)      | multicenter| 605     | 1,417       | 29.9               | mKDIGO            | cohort          |
| Ghobrial et al. (24)   | Egypt      | 30      | 60          | -                  | arbitrary         | case-control    |
| Shalaby et al. (5)     | Saudi Arabia| 120 | 94          | 56.1               | mKDIGO            | cohort          |
| Gong et al. (21)       | China      | 35      | 101         | 25.7               | AKIN              | cohort          |
| Liu et al. (25)        | China      | 32      | 212         | 13.1               | AKIN              | case-control    |
| Lei et al. (26)        | China      | 76      | 44          | 63.3               | mKDIGO            | case-control    |
| Mazaheri et al. (30)   | Iran       | 20      | 186         | 9.7                | mKDIGO            | cross-sectional |
| Mwamanenge et al. (6)  | Tanzania   | 119     | 259         | 31.5               | KDIGO             | cross-sectional |
| Hamsa et al. (20)      | India      | 49      | 114         | 30.0               | mKDIGO            | cohort          |
| El-sadek et al. (31)   | multicenter| 30      | 30          | -                  | mKDIGO            | case-control    |

AKI, acute kidney injury; KDIGO, kidney disease: improving global outcomes definition; mKDIGO, kidney disease: improving global outcomes definition modified for neonates; AKIN, acute kidney injury network definition.

### TABLE 2 | Newcastle-Ottawa Scale (cohort) for five studies included in this meta-analysis.

| Item | I | II | III | IV | V |
|------|---|----|-----|----|---|
| Representativeness of the exposed cohort | a) truly representative of the average ___(describe) in the community#; | 1 | 1 | 1 | 1 |
| | b) somewhat representative of the average ___ in the community#; | | | | |
| | c) selected group of users, e.g., nurses, volunteers; | | | | |
| | d) no description of the derivation of the cohort | | | | |
| Selection of the nonexposed cohort | a) drawn from the same community as the exposed cohort#; | 0 | 0 | 0 | 0 |
| | b) drawn from a different source; | | | | |
| | c) no description of the derivation of the nonexposed cohort | | | | |
| Ascertaining of exposure | a) secure record (e.g., surgical records)#; | 1 | 1 | 1 | 1 |
| | b) structured interview#; | | | | |
| | c) written self-report; | | | | |
| | d) no description | | | | |
| Demonstration that outcome of interest was not present at start of study | a) yes#; | 1 | 1 | 1 | 1 |
| | b) no | | | | |
| Comparability of cohorts on the basis of the design or analysis | a) study controls for ___ (select the most important factor)#; | 1 | 1 | 1 | 1 |
| | b) study controls for any additional factor# (These criteria could be modified to indicate specific control for a second important factor.) | | | | |
| Assessment of outcome | a) independent blind assessment#; | 1 | 1 | 1 | 1 |
| | b) record linkage# | | | | |
| | c) self-report; | | | | |
| | d) no description | | | | |
| Was follow-up long enough for outcomes to occur | a) yes (select an adequate follow-up period for outcome of interest)#; | 1 | 1 | 1 | 1 |
| | b) no | | | | |
| Adequacy of follow-up of cohorts | a) complete follow-up - all subjects accounted for#; | 1 | 1 | 1 | 1 |
| | b) subjects lost to follow-up unlikely to introduce bias - small number lost - > ___ % | | | | |
| | c) follow-up rate < ___% (select an adequate %) and no description of those lost; | | | | |
| | d) no statement | | | | |

Score: 7 7 7 7 7

*Studies: I = (2); II = (5); III = (20); IV = (21); V = (27). #One point.*
TABLE 3 | Newcastle-Ottawa Scale (case-control) for ten studies included in this meta-analysis.

| Item                                    | I    | II   | III  | IV   | V    | VI   | VII  | VIII | IX   | X   |
|-----------------------------------------|------|------|------|------|------|------|------|------|------|-----|
| Was the case definition adequate       | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   |
| Representativeness of the cases         | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   |
| Selection of controls                   | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0   |
| Definition of controls                  | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   |
| Comparability                           | 0    | 1    | 1    | 0    | 1    | 1    | 1    | 1    | 1    | 2   |
| Ascertainment of exposure               | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   |
| Same method of ascertainment for cases and controls | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   |
| Non-Response rate                       | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1    | 1   |
| Total score                             | 6    | 7    | 7    | 6    | 7    | 7    | 7    | 7    | 7    | 8   |

Notes: Studies: I = (12); II = (22); III = (23); IV = (4); V = (24); VI = (25); VII = (26); VIII = (28); IX = (29); and X = (31).

TABLE 4 | Agency for healthcare research and quality (AHRQ) checklist (cross-sectional) for 2 studies included in this meta-analysis.

| Item                                    | I    | II   |
|-----------------------------------------|------|------|
| 1) Define the source of information (survey, record review) | 1    | 1    |
| 2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications. | 1    | 1    |
| 3) Indicate time period used for identifying patients. | 1    | 1    |
| 4) Indicate whether or not subjects were consecutive if not population-based. | 1    | 1    |
| 5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants. | 1    | 1    |
| 6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements). | 0    | 1    |
| 7) Explain any patient exclusions from analysis. | 1    | 1    |
| 8) Describe how confounding was assessed and/or controlled. | 0    | 1    |
| 9) If applicable, explain how missing data were handled in the analysis. | 0    | 0    |
| 10) Summarize patient response rates and completeness of data collection. | 0    | 0    |
| 11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained. | 0    | 1    |
| Total score                             | 6    | 9    |

Notes: Studies: I = (30); II = (6).

Analysis contributed to 1,627 cases and 5,220 controls. The incidence of neonatal AKI fluctuates between 8.4 and 63.3%.

Quality Assessment
Based on the NOS quality assessment and AHRQ checklist, 14 studies were classified as high quality and three studies as moderate quality (Tables 2–4). The comparability scores of the two medium-quality case-control studies are both zero. In the cohort and case-control studies, the controls were not community based.

Results of Meta-Analysis
The analyses of risk factors are shown in Table 5. The heterogeneities of age, gestational age, birthweight, Cesarean section, 1-min Apgar score, 5-min Apgar score, prematurity, sepsis, and mechanical ventilation were significant, which, in
### TABLE 5 | Results of meta-analysis.

| Risk factors                  | Number of studies | Net change (95% CI) | P     | Heterogeneity | Analysis model | Egger’s test |
|-------------------------------|-------------------|---------------------|-------|---------------|----------------|--------------|
| Age                           | 5                 | −0.25 (−0.54, 0.04)# | 0.095 | 61.3          | Random         | P = 0.341    |
| Male sex                      | 15                | 1.10 (0.97, 1.24)*   | 0.147 | 18.2          | Fixed          | P = 0.393    |
| Gestational age               | 10                | −0.31 (−0.51, −0.12)# | 0.002 | 67.8          | Random         | P = 0.511    |
| Prematurity                   | 6                 | 0.90 (0.52, 1.56)*   | 0.716 | 76.4          | Random         | P = 0.923    |
| Birthweight                   | 8                 | −0.37 (−0.67, −0.07)# | 0.015 | 84.1          | Random         | P = 0.800    |
| Cesarean section              | 3                 | 1.52 (0.76, 3.01)*   | 0.234 | 74.5          | Random         | P = 0.020    |
| Apgar 1                       | 10                | −0.61 (−0.78, −0.43)# | 0.000 | 66.2          | Random         | P = 0.020    |
| Apgar 5                       | 10                | −0.71 (−1.00, −0.41)# | 0.000 | 91.3          | Random         | P = 0.140    |
| Antepartum hemorrhage         | 2                 | 1.41 (0.86, 2.33)*   | 0.171 | 0.0           | Fixed          | P = 0.003    |
| Sepsis                        | 11                | 2.21 (1.25, 3.89)*   | 0.006 | 89.5          | Random         | P = 0.426    |
| Congenital heart disease      | 6                 | 2.94 (2.08, 4.15)*   | 0.000 | 0.0           | Fixed          | P = 0.975    |
| Hyperbilirubinemia            | 2                 | 2.26 (1.40, 3.65)*   | 0.001 | 0.0           | Fixed          | P = 0.975    |
| Necrotizing enterocolitis     | 4                 | 6.32 (2.98, 13.42)*  | 0.000 | 0.0           | Fixed          | P = 0.385    |
| Mechanical ventilation        | 8                 | 2.37 (1.50, 3.75)*   | 0.000 | 66.5          | Random         | P = 0.392    |
| Vancomycin                    | 2                 | 1.16 (0.71, 1.89)*   | 0.555 | 0.0           | Fixed          |              |

* Odds ratio (OR) and 95% CI; # standardized mean difference (SMD) and 95% CI.

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### FIGURE 2 | Pooled standardized mean difference (SMD) for gestational age from random-effects meta-analysis.

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Apgar score [SMD = −0.71, 95%CI = (−1.00, −0.41), P = 0.000]. As compared to the non-AKI group, the AKI group had higher incidences of comorbidities such as CHD [OR = 2.94, 95% CI = (2.08, 4.15), P = 0.000], hyperbilirubinemia [OR = 2.26, 95%CI = (1.40, 3.65), P = 0.001], NEC [OR = 6.32, 95%CI = (2.98, 13.42), P = 0.000], and sepsis [OR = 2.21, 95%CI = (1.25, 3.89), P = 0.006]. Compared to the non-AKI group, the AKI group was more likely to use mechanical ventilation [OR = 2.37, 95%CI = (1.50, 3.75), P = 0.000]. Age [SMD = −0.25, 95%CI = (−0.54, 0.04), P = 0.095], male sex [OR = 1.10, 95%CI = (0.97, 1.24), P = 0.147], prematurity [OR = 0.90, 95%CI = (0.52, 1.56), P = 0.716], Cesarean section [OR = 1.52, 95%CI = (0.77, 3.01), P = 0.234], prenatal hemorrhage [OR = 1.41, 95% CI = (0.86, 2.33), P = 0.171], and vancomycin [OR = 1.16, 95% CI = (0.71, 1.89), P = 0.555] were not significantly associated with AKI in critically ill neonates.

**Sensitivity and Subgroup Analyses**

The sensitivity analyses for each risk factor showed that no individual study significantly altered the results. The results for birthweight and sepsis were shown in Figure 3. Subgroup analyses based on the research method showed that both cohort and non-cohort studies had similar results except for sepsis (Table 6). Because the studies included in the age and Cesarean section were all non-cohort studies, subgroup analyses based on the research method were not conducted. Subgroup analyses based on the definition of AKI revealed that both studies of KDIGO definition and non-KDIGO definition had similar results except for age, birthweight, and sepsis (Table 7). Because the studies included in the Cesarean section were all non-KDIGO defined, subgroup analysis based on the definition of AKI was not conducted.

**Publication Bias**

Assessment of publication bias using Egger’s tests showed that there was no potential publication bias among the included trials in the study except for 1-min Apgar score and sepsis (Table 5). However, the results were stable after non-parametric clipping for 1-min Apgar score and sepsis.

**DISCUSSION**

This study revealed that early gestational age and low birthweight were significantly associated with an increased risk of AKI in critically ill neonates. This finding is consistent with the review published by Perico et al. (9). This may be attributed to the fact that the earlier the gestational age and (or) lower the birthweight, the lower the number of nephrons and their maturity (32, 33), which leads to an increased susceptibility toward kidney injury (34). However, we found a significant association of AKI with lower gestational age but not with preterm birth gestation (<37 weeks) (35). It is possible that AKI is associated with a lower gestational age cutoff and should be evaluated.

In this study, we observed that CHD may increase the risk of AKI in neonates by nearly three times, which may be due to the decreased renal perfusion induced by unstable hemodynamics (36). We were able to show that hyperbilirubinemia was significantly associated with an increased risk of AKI in critically ill neonates. Possible pathophysiological mechanisms are as follows: (1) Circulatory disturbance caused by liver dysfunction and portal hypertension can lead to renal hypoperfusion; (2) an afferent arterial vasoconstriction caused by inadequate effective circulatory volume and renin–angiotensin–aldosterone activation; and (3) the formation of intratubular bile casts and the direct bilirubin tubular toxicity (37). In agreement with the findings of Nilsen et al., our findings indicated that the risk of AKI in neonates with NEC increased approximately by six times. This may be attributed to the fact that a significant inflammatory cascade caused by NEC can lead to microcirculatory disturbance, resulting in progressive afferent arteriolar constriction and increased pressure within the renal tubules, in turn, producing a sustained loss of filtration (38).

In agreement with the findings of van den et al. regarding AKI in critically ill neonates (39), mechanical ventilation was a risk factor. The study by Koyner et al. elaborated on the possible mechanisms, which all ultimately lead to AKI by...
TABLE 6 | Subgroup analyses based on the research method.

| Risk factors         | Research methods          | Number of trials | Net change (95% CI) | P     | Heterogeneity |
|----------------------|---------------------------|------------------|---------------------|-------|---------------|
|                      |                           |                  |                     |       | I² (%) | P      |
| Gestational age      | Cohort study              | 3                | −0.46 (−0.89, −0.04)# | 0.032 | 76.7  | 0.014  |
|                      | Non-cohort study          | 7                | −0.24 (−0.44, −0.04)# | 0.017 | 55.3  | 0.037  |
| prematurity           | Cohort study              | 2                | 0.62 (0.20, 1.88)*   | 0.394 | 76.9  | 0.038  |
|                      | Non-cohort study          | 4                | 1.08 (0.57, 2.06)*   | 0.818 | 77.7  | 0.004  |
| Birthweight          | Cohort study              | 3                | −0.43 (−0.96, 0.10)# | 0.115 | 85.3  | 0.001  |
|                      | Non-cohort study          | 5                | −0.34 (−0.72, 0.05)# | 0.090 | 85.0  | 0.000  |
| Apgar 1              | Cohort study              | 3                | −0.64 (−1.00, −0.28)# | 0.001 | 83.8  | 0.002  |
|                      | Non-cohort study          | 7                | −0.60 (−0.82 −0.38)# | 0.000 | 48.9  | 0.068  |
| Apgar 5              | Cohort study              | 3                | −0.54 (−0.97, −0.12)# | 0.013 | 88.3  | 0.000  |
|                      | Non-cohort study          | 7                | −0.80 (−1.02, −0.58)# | 0.000 | 58.10 | 0.026  |
| Sepsis               | Cohort study              | 4                | 1.73 (0.76, 3.96)*   | 0.191 | 88.7  | 0.000  |
|                      | Non-cohort study          | 7                | 2.58 (1.09, 6.13)*   | 0.032 | 88.60 | 0.000  |
| Mechanical ventilation| Cohort study              | 3                | 2.38 (1.21, 4.66)*   | 0.012 | 56.30 | 0.101  |
|                      | Non-cohort study          | 5                | 2.36 (1.19, 4.68)*   | 0.014 | 74.50 | 0.003  |

OR and 95% CI; SMD and 95% CI.
Non-cohort study = case-control study or cross-sectional study.

TABLE 7 | Subgroup analyses based on the definition of AKI.

| Risk factors         | Diagnostic criteria | Number of trials | Net change (95% CI) | P     | Heterogeneity |
|----------------------|---------------------|------------------|---------------------|-------|---------------|
|                      |                     |                  |                     |       | I² (%) | P      |
| Age                  | KDIGO               | 3                | −0.42 (−0.75, −0.09)# | 0.014 | 49.6  | 0.137  |
|                      | Non-KDIGO           | 2                | −0.002 (−0.29, −0.28)# | 0.987 | 0.0   | 0.896  |
| Gestational age      | KDIGO               | 4                | −0.41 (−0.89, 0.08)# | 0.098 | 87.5  | 0.000  |
|                      | Non-KDIGO           | 6                | −0.26 (−0.41, −0.12)# | 0.000 | 0.0   | 0.863  |
| prematurity           | KDIGO               | 2                | 0.56 (0.25, 1.26)*   | 0.160 | 71.6  | 0.060  |
|                      | Non-KDIGO           | 4                | 1.18 (0.59, 2.36)*   | 0.650 | 75.8  | 0.006  |
| Birthweight          | KDIGO               | 4                | −0.48 (−1.04, 0.12)# | 0.122 | 91.3  | 0.000  |
|                      | Non-KDIGO           | 4                | −0.28 (−0.55, −0.01)# | 0.042 | 59.8  | 0.058  |
| Apgar 1              | KDIGO               | 6                | −0.55 (−0.77, −0.33)# | 0.000 | 70.2  | 0.005  |
|                      | Non-KDIGO           | 4                | −0.72 (−0.95, −0.49)# | 0.000 | 13.7  | 0.324  |
| Apgar 5              | KDIGO               | 5                | −0.54 (−0.86, −0.23)# | 0.001 | 81.7  | 0.000  |
|                      | Non-KDIGO           | 5                | −0.91 (−1.10, −0.71)# | 0.000 | 36.4  | 0.178  |
| Sepsis               | KDIGO               | 8                | 1.88 (0.99, 3.58)*   | 0.055 | 89.8  | 0.000  |
|                      | Non-KDIGO           | 3                | 3.32 (1.78, 6.20)*   | 0.000 | 43.8  | 0.169  |
| Mechanical ventilation| KDIGO               | 2                | 2.65 (1.36, 5.19)*   | 0.004 | 0.0   | 0.013  |
|                      | Non-KDIGO           | 6                | 2.26 (1.30, 3.98)*   | 0.004 | 75.8  | 0.001  |

OR and 95% CI; SMD and 95% CI.
AKI, acute kidney injury; Non-KDIGO, arbitrary or acute kidney injury network definition; KDIGO, kidney disease: improving global outcomes or kidney disease: improving global outcomes definition modified for neonates.

decreasing renal perfusion. The specific mechanisms are as follows: (1) The increase in intrathoracic pressure caused by mechanical ventilation can reduce cardiac output by compressing the mediastinal structures and pulmonary vasculature to increase the right ventricular afterload and to decrease the venous return to the heart. (2) Mechanical ventilation can alter a variety of neurohormonal systems including sympathetic outflow, the renin–angiotensin axis, nonosmotic vasopressin release, and atrial natriuretic peptide production. (3) The increased intrathoracic pressure caused by mechanical ventilation has been shown that it may directly correlate with a decrease in renal perfusion and glomerular filtration rate (40).

Constance et al. (41) in their propensity-matched cohort study, observed that combined use of vancomycin in addition to gentamicin did not increase the risk of AKI in neonates. This is similar to our result. However, some studies believe that the use of
vancomycin can significantly increase the risk of AKI in children and adults, especially when combined with other nephrotoxic drugs and (or) diuretics. Due to the inclusion of fewer studies and the lack of analysis of different doses and treatment courses of vancomycin, the result of this study needs larger sample studies to confirm.

Subgroup analysis based on the research method showed that sepsis was significantly associated with AKI in the non-cohort studies while not significant in the cohort studies. So research method was one of the sources of heterogeneities. The possible explanation is that different types of studies have different strengths of evidence. According to A Manual for Evidence-based Practice, the exposure data of the cohort studies are collected before the outcome, so the data are reliable and the evidence of causality is good. Case-control studies are easily affected by confounding factors, while it is difficult for cross-sectional studies to determine the order of “exposure” and “outcome.” Therefore, the strength of evidence in case-control studies is inferior to cohort studies, which in cross-sectional studies is even more inferior.

Subgroup analyses based on the definition of AKI showed that age, birthweight, and sepsis had different results between KDIGO-defined and non-KDIGO-defined studies. Meanwhile, some of the heterogeneities have declined after subgroup analyses. So the definition of AKI was one of the sources of meta-analysis. Nowadays, the diagnosis of neonatal AKI has not been unified. There are five definitions that describe the state of neonatal AKI in our meta-analysis: (1) arbitrary definition mainly based on absolute serum creatinine (SCr) ≥ 1.5 mg/dl (4, 23, 24, 27), (2) arbitrary definition based on absolute SCr > 1 mg/dl and > 1.3 mg/dl (for ≥ 33 weeks and < 33 weeks, respectively) after 48 h of life (12, 22), (3) AKIN definition based on absolute SCr ≥ 0.3 mg/dl or SCr ≥ 1.5 times baseline within 48 h or urine volume < 0.5 ml/kg/h for 6 h (11, 21, 25), (4) KDIGO definition based on absolute SCr > 0.3 mg/dl within 48 h or SCr > 1.5 times baseline, which is known or presumed within 7 days, or urine volume < 0.5 ml/kg/h for 6 h (1, 6, 29), and (5) modified KDIGO definition changes the baseline to previous trough value in SCr (2, 5, 20, 26, 28, 30, 31, 45). As we can see, the arbitrary definitions are mainly dependent on an absolute increase in SCr for at least 1 mg/dl, whose critical value is higher than that of AKIN and KDIGO. These definitions do not account for the significance in a percentage increase in SCr and a percentage decrease in urine output. Meanwhile, it is not difficult to find that on the basis of AKIN, KDIGO extended the time to 7 days for percentage increase in SCr. Since the baseline level of SCr changes constantly during the first week of birth, the modified KDIGO definition seems to be more suitable for the diagnosis of neonatal AKI. As mentioned above, the KDIGO definitions are more sensitive than AKIN and arbitrary definitions, which may be the reason why the definition of AKI became a source of heterogeneity.

Therefore, subgroup analyses indicated that the results of age, birthweight, and sepsis were not robust. It is necessary to carry out cohort studies to analyze the relationship between risk factors and different stages of AKI in critically ill neonates.

**LIMITATIONS**

First, this analysis was based on cross-sectional, cohort, and case-control studies, whose controls were not community based, so well-designed multicentric cohort studies are needed to explore the above risk factors that are relied on as causal factors associated with AKI in critically ill neonates. Second, some of the risk factors studied, such as antepartum hemorrhage, hyperbilirubinemia, and vancomycin, were assessed in only two publications, which prevented more robust meta-analyses of these factors. Third, birth asphyxia was not included in this analysis for only one study that provided corresponding data. Fourth, among the 17 included studies, only 10 studies excluded congenital anomalies of the kidney and urinary tract (2, 5, 6, 22, 24, 26, 28–31), and 2 studies excluded lethal chromosomal anomaly (2, 5), which may bring some bias to the results. Finally, the studies included have a large time span, and different clinical factors, such as different treatment methods, may bring some bias.

**CONCLUSIONS**

In this study, we found the incidence of AKI fluctuates from 8.4 to 63.3%. Gestational age, birthweight, 1-min Apgar score, 5-min Apgar score, CHD, hyperbilirubinemia, NEC, sepsis, and mechanical ventilation were risk factors for AKI in critically ill neonates. Well-designed studies with a considerable number of critically ill neonates are necessary to determine the possible link between these nine risk factors and AKI.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

**AUTHOR CONTRIBUTIONS**

QH, S-JL, and MW contributed to the study concept and design, article selection and quality assessment, data analysis and interpretation, and manuscript writing. Q-LC, HC, and QL contributed to the study concept and design, and manuscript writing. All authors contributed to the article and approved the submitted version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.666507/full#supplementary-material
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