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RESEARCH

Risk factors for acute kidney injury in very-low birth weight newborns: a systematic review with meta-analysis

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Abstract

This study aims to analyze the main risk factors for acute kidney injury in the subgroup of very-low birth weight newborns, using the diagnosing criteria of the *Kidney Disease Improving Global Outcomes* (KDIGO) or the *Acute Kidney Injury Network* (AKIN). A systematic review of the literature was performed on the EMBASE® and PubMed® platforms. Studies that evaluated the risk factors for developing AKI in VLBW newborns were included. For the meta-analysis, we only included the risk factors that were associated with AKI in the univariate analysis of at least two studies. After an initial screening, abstract readings, and full-text readings, 10 articles were included in the systematic review and 9 in the meta-analysis. The incidence of AKI varied from 11.6 to 55.8%. All the studies have performed multivariate analysis, and the risk factors that appeared most were PDA and hemodynamic instability (use of inotropes or hypotension), sepsis, and invasive mechanical ventilation. After the meta-analysis, only cesarian delivery did not show an increased risk of AKI, all the other variables remained as important risk factors. Moreover, in our meta-analysis, we found a pooled increased risk of death in newborns with AKI almost 7 times.

Conclusion: AKI in VLBW has several risk factors and must be seen as a multifactorial disease. The most common risk factors were PDA, hemodynamic instability, sepsis, and invasive mechanical ventilation.

What is known:
• *Acute kidney injury is associated with worst outcomes in all ages. It´s prevention can help diminish mortality.*
What is new:
• *A synthesis of the main risk factors associated with AKI in very low birth weight newborns.*

Keywords Acute kidney injury · Infant, premature · Infant, very low birth weight · Risk factors · Systematic review

Introduction

Acute kidney injury (AKI) is very common in newborns and is related to poor outcomes such as prolonged invasive mechanical ventilation (IMV), length of stay, and mortality, independently of the criteria used for diagnosing [1–5]. Currently, the most accepted criterion for AKI is based on the elevation of the serum creatinine, using the modified KDIGO criteria [1, 6]. In 2021, in response to the 22nd Acute Disease Quality Initiative conference, Harer et al. proposed to stratify the newborns according to the risk of developing AKI, to improve neonatal care [3].

Recently, a systematic review with meta-analysis of studies with premature newborns showed an overall incidence of AKI of 25% with an increased odds ratio for death in this group (OR 7.13) [7] .

However, diagnosing AKI in very low birth weight newborns is not easy. First, as it relies on blood sampling the newborns, trying to identify AKI may lead to an increased risk of anemia in this group (< 1500 g) [8]. Moreover, monitoring the urine output (UO) is feasible, as there is no consensus on the cutoff for oliguria in this population [9] .

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In addition, there is still not enough data to support the use of urinary biomarkers for the identification of AKI in VLBW newborns, as the studies are small and very heterogeneous [10, 11].

It is very important to have a standardized protocol for identifying patients with AKI, as pediatricians and neonatologists are not familiar with the current definitions of AKI [12] and therefore, it can be misdiagnosed. So, knowing the risk factors for developing AKI can help reduce unnecessary blood sampling and optimize the identification of this condition in the population of VLBW newborns.

The purpose of this study is to perform a Systematic Review of the literature to identify the main risk factors for AKI in the subgroup of VLBW newborns, using the diagnosing criteria of the *Kidney Disease Improving Global Outcomes* (KDIGO) or the *Acute Kidney Injury Network* (AKIN) [6, 13].

Methods

A systematic review of the literature was conducted on the databases PubMed® and EMBASE®, according to the *PRISMA* (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendation [14]. The following search strategies were performed: "acute kidney injury" AND "risk factors" AND ("very low birth weigh" OR "extremely low birth weight"). Only articles written in English, Spanish, Portuguese, or French were included for full reading. Articles published from conception until February 15th, 2024, were included.

We included only original articles (randomized clinical studies, cohort studies, case-control studies) that evaluated the risk factors for developing AKI in VLBW newborns. Moreover, we only included articles that adopted the KDIGO or AKIN criteria for diagnosing AKI [6, 13].

The following types of studies were excluded from this systematic review: all types of reviews, letters to editors, case reports, case series, meeting abstracts, and comments. For the meta-analysis, we also excluded preprints, as they were not yet peer-reviewed.

Other exclusion criteria were evaluation of risk factors for AKI in newborns weighing more than 1500 g, analysis of subgroups of VLBW (e.g., Persistent ductus arteriosus, sepsis) without analysis of the full cohort, and those which didn't mention the diagnosing criteria for AKI.

Two different investigators (L.H.A.M and V.L.J.K) screened the articles for inclusion in the systematic review. Any discordances were discussed between both researchers and, if any disagreement remained, a third investigator (W.B.C) would give the final decision. The same investigators (L.H.A.M and V.L.J.K) performed independently the extraction of the relevant information from the articles and evaluated the risk of bias using the Newcastle-Ottawa Scale (NOS) [15]. The articles were defined as of good quality if they had 8 or more "stars" using NOS.

For the meta-analysis, we only included the risk factors that were associated with AKI in the univariate analysis of at least two studies. The data analysis was made with the available information extracted from the studies, if the information could not be extracted, the study was excluded from the analysis. For continuous variables, we included in the meta-analysis only those reported as mean with the following standard deviation. If the data was reported as a median and interquartile range, we calculated the standard deviation only if the authors reported the variable as normally distributed, otherwise, this calculus could not be made, and the article was not included in the analysis. The results were expressed as mean difference with its 95% confidence interval. For dichotomous variables, the results were expressed as odds ratio with the following confidence interval of 95%. We defined a $p < 0.05$ as relevant to the present study.

To evaluate the heterogeneity between the studies, we calculated the I^2 statistics and the Q-test. For an $I^2 > 50\%$ or a $p < 0.1$ in the Q-test, we used a random-effect model. For those risk factors without high heterogeneity (i.e., $I^2 < 50\%$ or $P > 0.1$), we used a fixed-effect model. We also evaluated the publication bias for the studies by funnel plots.

All statistical analyses were performed using the IBM SPSS Statistics (v29.0) software for Windows.

Results

After an initial screening, 76 articles were retrieved, of those, 14 were duplicated and 62 articles were included for title/abstract reading. In the end, 13 articles were elected for full reading, of which 3 were excluded because have used definitions different from KDIGO or AKIN. The remaining 10 articles were included in the systematic review. As 1 article included was available only as a preprint, we excluded it from the meta-analysis to avoid any bias (Fig. 1).

The main characteristics of the studies are summarized in Table 1. Only 1 study was a case-control study, all the other studies were retrospective cohort analyses. Of those, 5 studies were performed in North America [9, 16–19], 1 study in South America [20], 1 in Europe [21], and 3 in Asia [22–24]. All the studies were defined as "good quality" using the NOS.

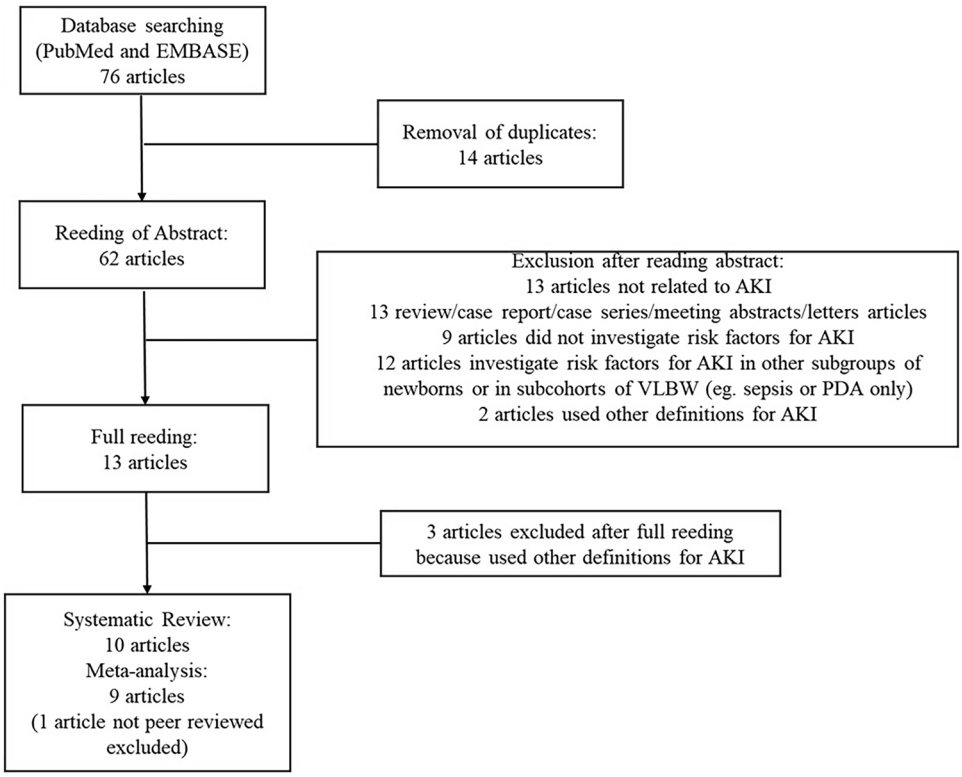

Fig. 1 Flow diagram of the literature search strategy and study selection

AKI definition

All the studies used the increase of creatinine from the basal level to define AKI with or without the measurement of urine output. Most of the studies (6 of the total) didn´t use the urine output to define AKI.

Incidence of AKI

The incidence of AKI in VLBW newborns varied from 11.6 to 55.8% between the studies [22, 24].

Risk factors

For the risk factors identified at univariate analysis, we only described in Table 1 those that have appeared more than once or those that remained as risk factors after a multivariate analysis. Gestational age (GA) and birth weight (BW) were the most relevant risk factors in the univariate analysis. Both were inversely proportional with the risk of AKI, with the most immature and with lower birth weight at greater risk. Invasive mechanical ventilation appeared in a study as an outcome of AKI instead of a risk factor [20]. However, the association of both remained.

All the studies have performed multivariate analysis to diminish the bias related to confounding factors. After the adjustment for potential confounders, the risk factors that appeared most were PDA and hemodynamic instability (use of inotropes or hypotension) [17–20, 22, 23] followed by sepsis [16, 19, 20, 23] and IMV [17, 19, 21, 22]. GA, however, remained an independent risk factor in only 3 studies [17, 18, 25] and BW in only 1 study [18]. Other important variables associated with AKI found in the studies after multivariate analysis were NEC (2 studies), lower Apgar at 1 and 5 min (both 1 study), exposure to non-steroidal anti-inflammatory drug (NSAID – 1 study), Furosemide (1 study), Vancomycin (1 study), higher CRIB II and use of pos-natal steroids (PNS).

Meta-analysis

For meta-analysis, we excluded one study (Coleman et al. 2023) [19] as it was not yet peer-reviewed and fully published.

We analyzed the variables that were relevant in at least two studies. Unfortunately, we could not extract enough data to perform a meta-analysis of Apgar scores as the distribution was non-parametric, and, therefore, the standard deviations could not be calculated. In the study by Malla et al. [24], the stratification into gestational ages made it impossible to

Table 1 Summarized characteristics of the included articles in the systematic review

Author (year)	Country	Type	Inclusion criteria	Nº of patients	*N* groups	Risk factors (univariate analysis)	Risk factors (multivariate analysis)	NOS/quality
Arcinue et al. (2015)	USA	Case-control	Cases: BW < 750 g w/ AKI Controls: BW < 750 g w/o AKI	*N* = 211	AKI (case) = 109 No Aki (controls) = 102	(3), (7), (8), (9), (10), (11), (13)	(7), (13)	S 4 C 2 O 3 Good quality
Mian et al. (2015)	USA	Retrospective cohort	< 32 weeks GA AND BW < 1500 g	*N* = 266	AKI = 70 newborns No AKI = 196 newborns	(1), (2), (3), (4), (5), (6), (11), (15)	(1), (3), (6), (11)	S 3 C 2 O 3 Good quality
Daga et al. (2017)	USA	Retrospective cohort	BW < 1500 g	*N* = 115	AKI = 24 newborns No AKI = 91 newborns	(1), (2), (3), (5), (6), (7), (11), (12), (16), CRIB II	CRIB II	S 3 C 2 O 3 Good quality
Srinivasan et al. (2017)	USA	Retrospective cohort	BW < 1500 g AND ≥ 23 weeks GA	*N* = 457	AKI = 89 newborns No AKI = 368 newborns	(1), (2), (3), (4), (5), (7), (8), (10)	(1), (2), (3), (4), (5), (10)	S 3 C 2 O 3 Good quality
Malla et al. (2017)	UAE	Retrospective cohort	BW < 1500 g	*N* = 293	AKI = 34 newborns No AKI = 259 newborns	(1), (2), (6), (7), (8), (9), (10), (11), (13), (15)	(9)	S 4 C 2 O 3 Good quality
Lee et al. (2017)	Taiwan	Retrospective cohort	BW < 1000 g	*N* = 276	AKI = 154 newborns No AKI = 122 newborns	(1), (2), (3), (4), (5), (6), (8), (11), (12)	(1), (3), (6), (11)	S 3 C 2 O 3 Good quality
Moraes et al. (2022)	Brazil	Retrospective cohort	BW < 1500 g	*N* = 155	AKI = 61 newborns No AKI = 94 newborns	(1), (2), (3), (6), (7), (9), (10), (11), (16)	(6), (7), (9)	S 3 C 2 O 3 Good quality
Lazarovits et al. (2023)	Israel	Retrospective cohort	BW < 1500 g	*N* = 152	AKI = 32 newborns No AKI = 120 newborns	(1), (2), (3), (5), (6), (7), (9), (16)	(3), (6), (7)	S 3 C 2 O 3 Good quality
Burgmaier et al. (2023)	Germany	Retrospective cohort	BW < 1500 g AND ≥ 22 weeks GA	*N* = 128	AKI = 25 newborns No AKI = 103 newborns	(1), (2), (3), (4), (6), (9), (10), (11), (14), (15)	(11), (15)	S 4 C 2 O 3 Good quality
Coleman et al. (2023)[a] (preprint)	USA	Retrospective cohort	BW < 1500 g	*N* = 567	AKI = 130 newborns No AKI = 347 newborns	(1), (3), (4), (5), (6), (7), (9) (11), PNS.	PNS, (3), (6), (7), (11)	S 3 C 2 O 3 Good quality

Numbers: (1) Gestational age, (2) Birth weight, (3) PDA, (4) APGAR 1', (5) APGAR 5', (6) Inotropes/Vasopressors/Hypotension, (7) Sepsis, (8) IVH, (9) Necrotizing enterocolitis, (10) Vancomycin, (11) Invasive mechanical ventilation, (12) Cesarian delivery, (13) Furosemide, (14) Cephalosporin, (15) Non-steroidal anti-inflammatory drug, (16) Respiratory distress syndrome

PNS post-natal steroid, *CRIB II* Clinical Risk Index for Babies II

[a]Not included in the meta-analysis as it was not yet peer reviewed

extract the overall mean and standard deviation of the continuous variables. For all the other common variables, we could extract enough information from at least two studies.

After analysis of heterogeneity, gestational age, NSAID, PDA, culture-proven sepsis, NEC and cesarian delivery had an $I^2 > 50\%$. For those variables, we used the random-effect model.

Table 2 summarizes the meta-analysis of the dichotomous variables. Only in the analysis of NSAID, all the studies have been included, with a pooled number of patients of 2053. On the other hand, only two studies had information on the use of cephalosporin as a risk factor for AKI, with a pooled number of newborns of 339. The results are expressed as

Table 2 Results of the meta-analysis for dichotomous variables

Risk factor	Number of studies (*n*)	Pooled number of patients (*N*)	Heterogeneity test			Pooled OR (95% CI)	Pooled *p*-value	Statistical method
			Q	*p*	I^2			
NSAID	9	2053	41.5	< 0.001	78%	3.86 (1.76–5.61)	< 0.001	Random
PDA	8	1925	24.9	< 0.001	73%	4.04 (2.58–6.33)	< 0.001	Random
Vasoactive drugs	7	1385	9	0.17	33%	7.06 (5.28–9.44)	< 0.001	Fixed
BSI	6	1544	17.6	0.003	73%	2.70 (1.57–4.67)	< 0.001	Random
IVH	6	1480	5	0.413	1%	2.56 (1.93–3.39)	< 0.001	Fixed
NEC	6	1215	34.2	< 0.001	85%	4.35 (1.5–12.6)	0.01	Random
Vancomycin	5	1244	7.5	0.112	47%	4.93 (3.49–6.96)	< 0.001	Fixed
Cesarian delivery	5	1050	15.7	0.003	82%	0.73 (0.33–1.63)	0.44	Random
RDS	4	550	1.3	0.727	0%	3.2 (1.93–5.3)	< 0.001	Fixed
IMV	3	519	0.42	0.812	0%	6.31 (4.08–9.76)	< 0.001	Fixed
Furosemide	3	961	3.2	0.198	38%	8.69 (5.21–14.48)	< 0.001	Fixed
Cephalosporin	2	339	0.7	0.398	0%	2.58 (1.49–4.5)	< 0.001	Fixed

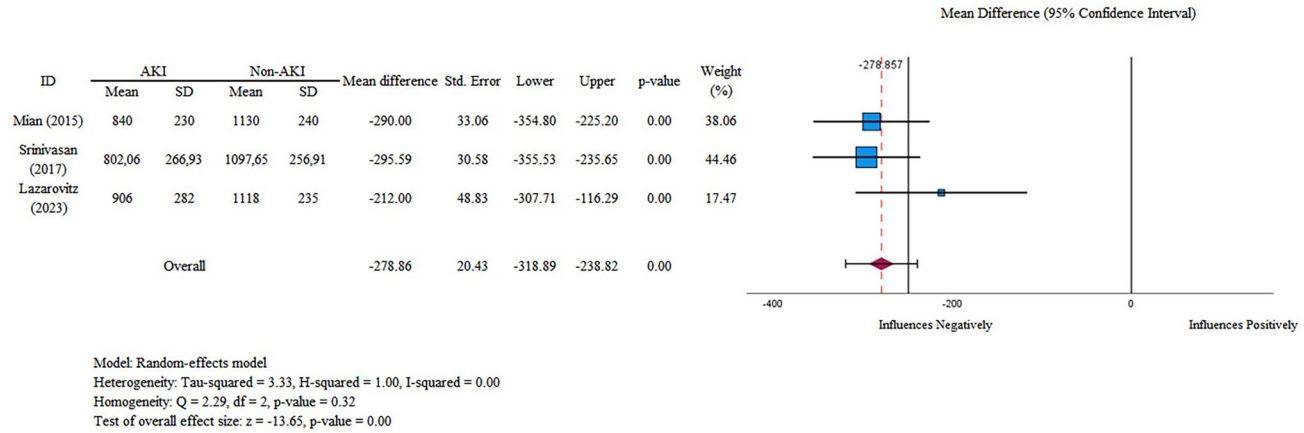

Fig. 2 Forest-plot of the meta-analysis for the birth weight

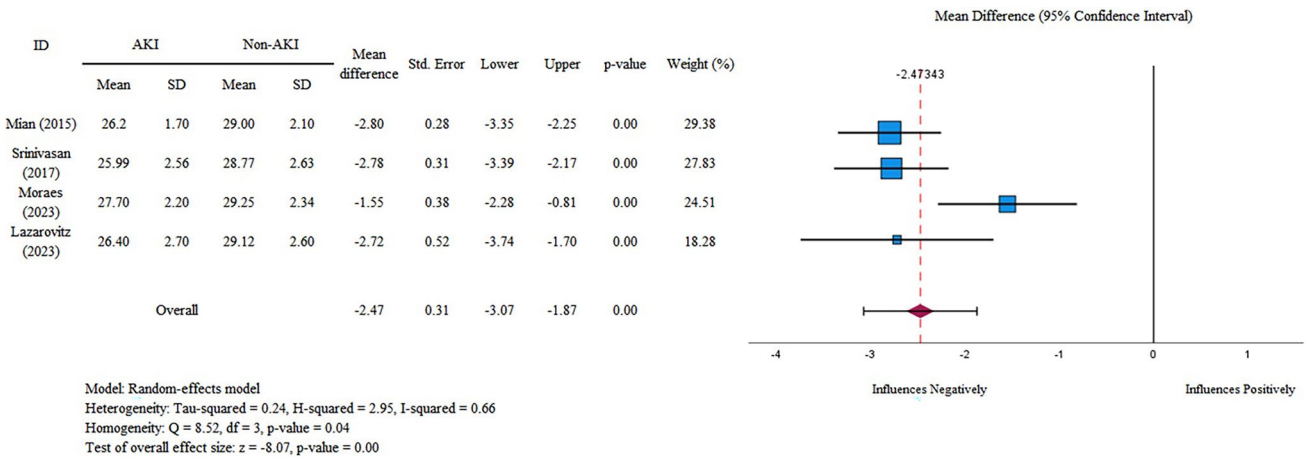

Fig. 3 Forest-plot of the meta-analysis for the gestational age

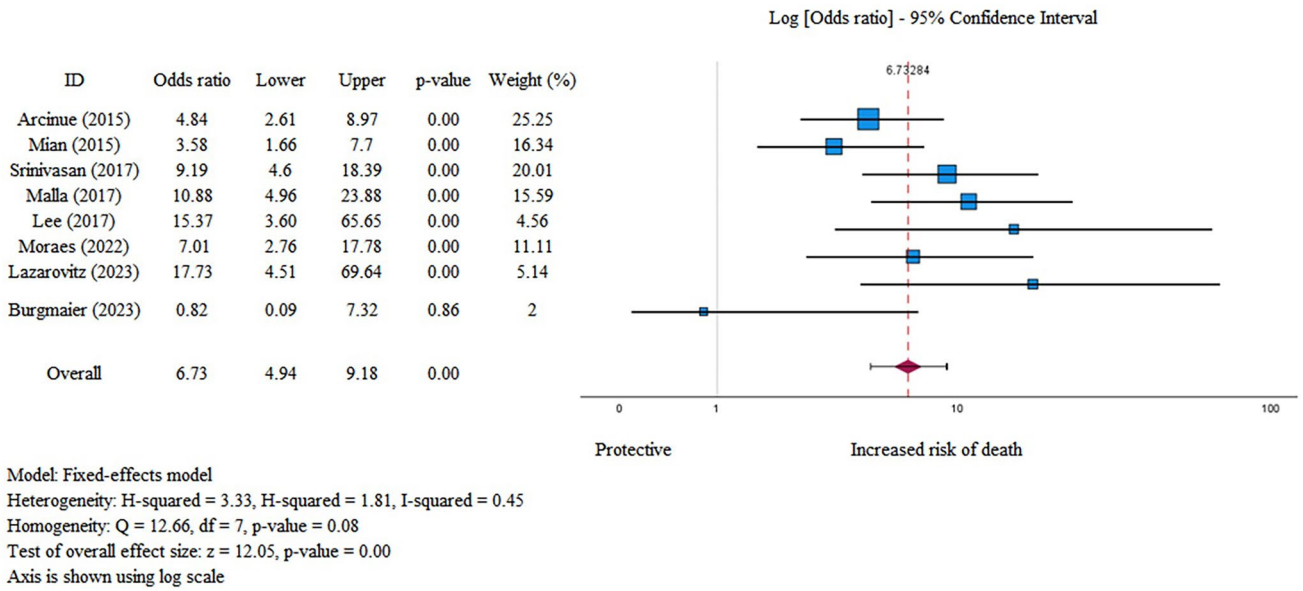

Fig. 4 Forest plot for the outcome death

odds ratio. All the analyzed variables, apart from cesarian delivery, remained relevant as risk factors for AKI.

Figures 2 and 3 show the forest plot of the continuous variables of birth weight and gestational age. The results are expressed as mean-difference and show that the lower the gestational age and the birth weight, the higher the risk of developing AKI.

To analyze the impact of AKI in this population, we also performed a meta-analysis for the outcome of death, comparing the newborns with and without AKI (Fig. 4). As expected, the results showed an increased risk of death (pooled OR 6.73, CI 95% 4.94–9.18).

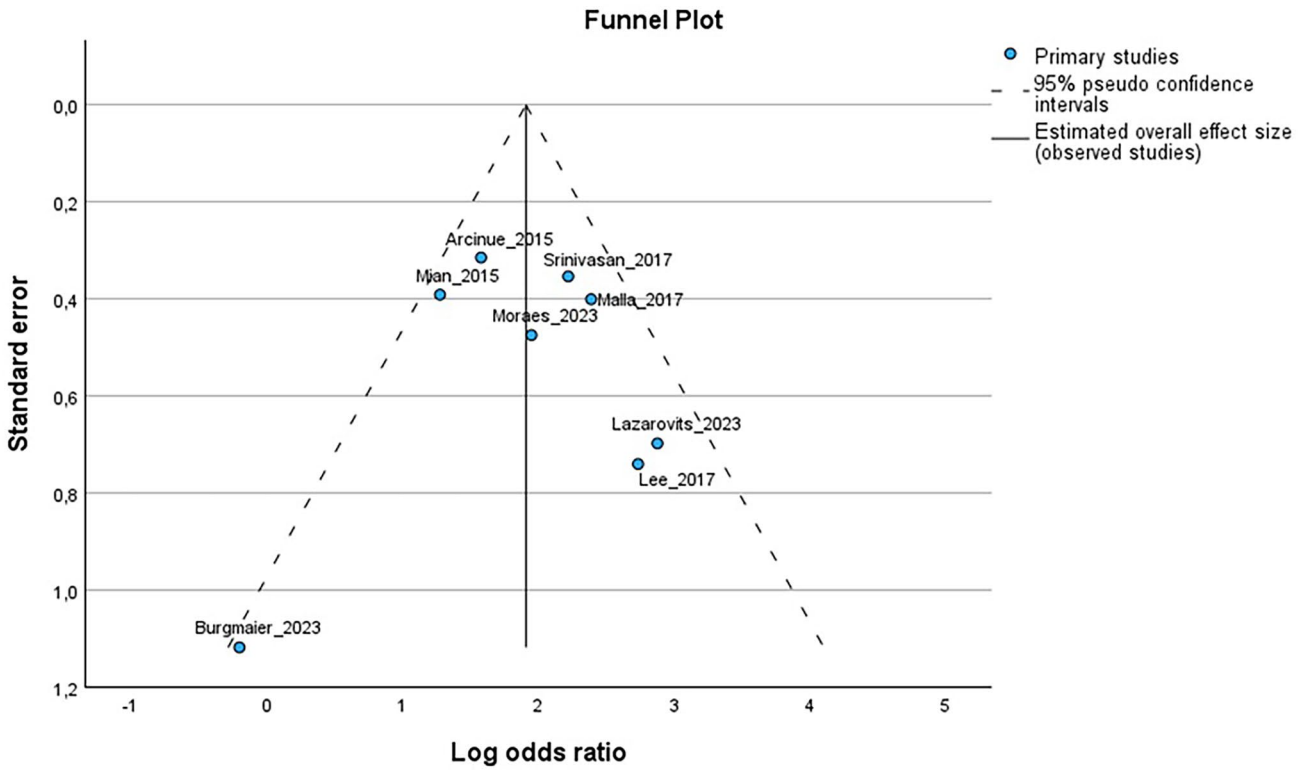

Fig. 5 Funnel-plot for the outcome death

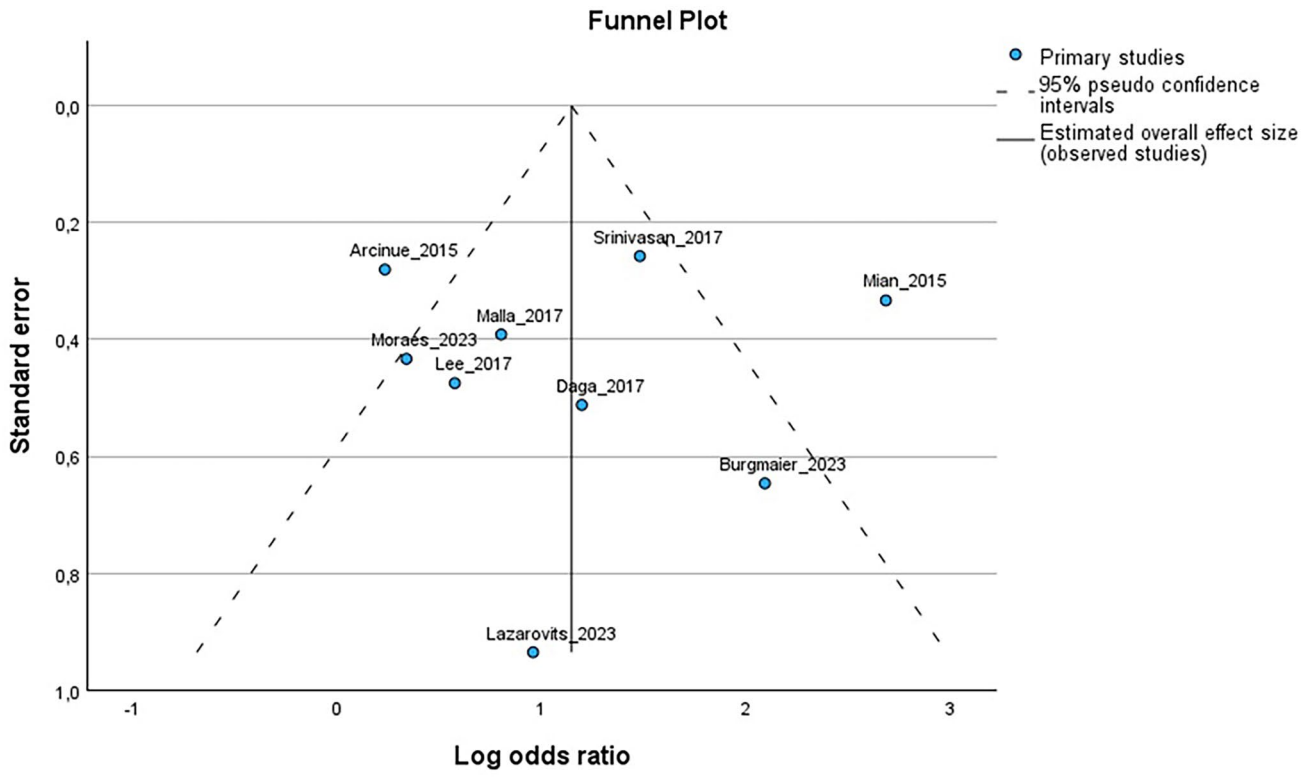

Fig. 6 Funnel-plot for the risk factor NSAID

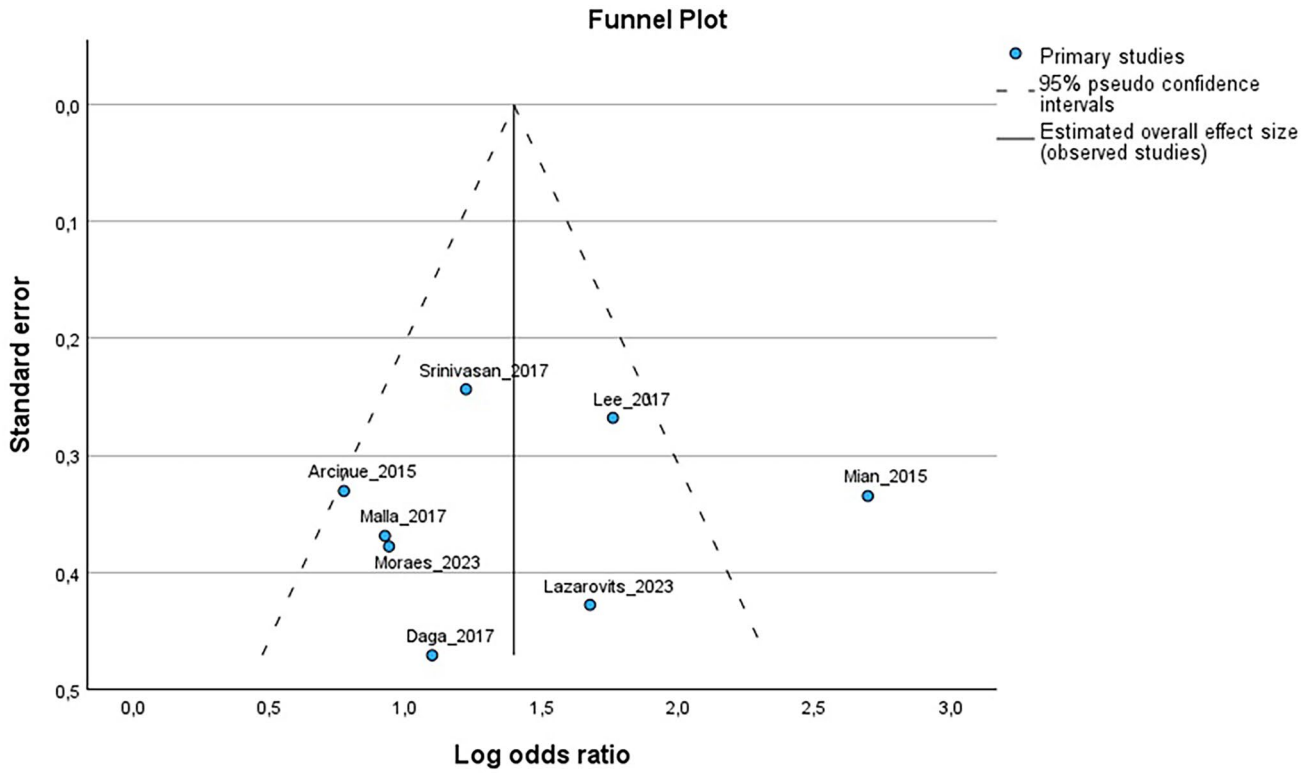

Fig. 7 Funnel-plot for the risk factor PDA

We also performed the analysis of funnel plots for the variables presented in more than 8 studies and for death (Figs. 5, 6, and 7).

Discussion

This is the first study that has analyzed the risk factors for developing AKI in the subgroup of VLBW infants with a systematic method. It is very important to understand the risk factors for developing AKI as the gold-standard criteria for diagnosing AKI uses the measurement of creatinine and blood sampling this subgroup of newborns can lead to anemia with the necessity of blood transfusions [8].

In our systematic review, we could find a wide range in the incidence of AKI. This might be caused by the fact that some authors didn't use the urine output to define AKI. Recently, a study found that a urine output lower than 2 ml/kg/h is associated with poor outcomes, suggesting that this is a reasonable cut-off for oliguria [26].

The most common risk factors, after multivariate analysis, were PDA, hemodynamic instability, sepsis, and invasive mechanical ventilation. The result of our meta-analysis shows that infants with PDA have odds of developing AKI four times higher than those without PDA. For hemodynamic instability 7 times higher, for sepsis almost 3 times higher, and for invasive mechanical ventilation 6 times higher.

Invasive mechanical ventilation appears to be both a risk factor and an outcome related to AKI, as shown in the studies. The IMV can be a cause of AKI by augmenting the central venous pressure with an increase in the renal venous pressure. Consequently, a diminished perfusion of the kidneys could lead to an increased risk of AKI [21]. On the other hand, IMV can be an outcome of AKI. AKI can lead to a fluid overload, which is associated with the increased necessity of mechanical ventilation, as shown in a previous systematic review by Matsushita et al. [27].

In addition, we found that after controlling for confounding factors, birth weight and gestational age disappeared as a relevant risk factor in most of the studies. This relies on the fact that both are risk factors for developing other conditions such as NEC, sepsis, PDA, and hemodynamic instability, as well as the necessity of invasive mechanical ventilation. In our meta-analysis, we found that the lower the gestational age and the birth weight the higher the risk of AKI.

The only variable analyzed that after the meta-analysis was not related to AKI was cesarian delivery. In the univariate analysis, both Lee et al. and Daga et al. observed that C-section was a risk factor for developing AKI. However, after multivariate analysis, it did not remain a risk factor in both studies [9, 22]. Even though, as described in the methodology of our study, we still analyzed this risk factor as it appeared in at least two studies as a risk factor.

After analyzing the data from this study, we can conclude that newborns with the presented conditions are at higher risk of developing AKI, justifying serial blood sampling for identification of AKI, and preventing the use of nephrotoxic medications in this population. Not taking blood sampling is not reasonable, as AKI is associated with a higher risk of poor outcomes [2–4]. In our study, the pooled risk of death is almost 7 times higher in infants who present with AKI.

Additionally, recent studies have shown that preterm newborns may benefit from continuous kidney replacement therapy. The new technologies such as the CARPEDIEM® can diminish the fluid overload, improve oxygenation, and diminish the lactate in newborns with multi-organ failure and AKI. Therefore, monitoring the fluid balance and the serum creatinine can help to improve the outcomes of these populations [28, 29].

Our study has several limitations. First, we could not extract data on gestational age and birth weight from most of the studies as both were described as having a non-parametric distribution. Secondly, the included studies didn't analyze the same variables as risk factors and, therefore, we could not perform a regression with the available data to identify the main risk factors with the removal of potential confounders.

To conclude, AKI in VLBW has several risk factors and must be seen as a multifactorial disease. More studies with noninvasive techniques to identify AKI are awaited. Until then, it is reasonable to reserve the blood sampling for the patients at higher risk of developing AKI.

In our systematic review, we could find a wide range in the incidence of AKI. The most common risk factors were PDA, hemodynamic instability, sepsis, and invasive mechanical ventilation.

Authors' contributions All authors contributed to the study conception and design. L.H.A.M. and V.L.J.K. were responsible for reviewing the articles, for data collection and analyzes. Prof. W.B.C. was responsible for advising in case of disagreement between the other authors during the selection of articles and data extraction. All the authors contributed to the preparation and review of the manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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