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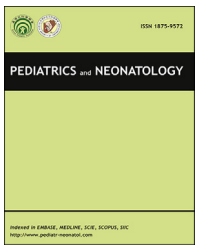

ORIGINAL ARTICLE

Diagnosis and Risk Factors of Acute Kidney Injury in Very Low Birth Weight Infants

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Key Words
acute kidney injury;
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very low birth weight infants

Background: Acute kidney injury (AKI) is common in critically ill premature infants. There is a lack of consensus on the diagnostic definition of AKI in very low birth weight (VLBW) infants. The primary aim of this study was to determine the incidence and risk factors for AKI in VLBW infants using the AKI network (AKIN) and pRIFLE (pediatric Risk, Injury, Failure, Loss, End-Stage) criteria and to evaluate whether Clinical Risk Index for Babies (CRIB II) score is a predictor of AKI. The secondary objective was to determine the extent of agreement between the AKIN and pRIFLE criteria in the diagnosis of AKI in VLBW infants.
Methods: This was a retrospective chart review of 115 VLBW (< 1500 g) infants born in an academic center with a Level 3B neonatal intensive care unit. Multiple congenital anomalies, transfer to other centers, or death within the first 2 weeks were the exclusion criteria. Relevant data were collected and analyzed in the first 2 weeks postnatally.
Results: AKI incidence, according to AKIN and pRIFLE criteria, was 20.1% and 22.6%, respectively. As per the interrater reliability analysis, there was a fair agreement between the two criteria (kappa = 0.217). AKI was nonoliguric. The length of stay was significantly longer in the AKI group. Prenatal nonsteroidal anti-inflammatory drug exposure, lower gestational age, lower birth weight, respiratory distress syndrome, mechanical ventilation, patent ductus arteriosus, hypotension, late onset sepsis, and higher CRIB II scores were significantly associated with AKI. Our regression analysis found CRIB II scores to be an independent risk factor for AKI (odds ratio = 1.621; 95% confidence interval, 1.230–2.167; $p = 0.001$).
Conclusion: The determination of AKI using the pRIFLE and AKIN criteria yielded different results. pRIFLE appears to be more sensitive in VLBW infants. A high CRIB II score was recorded for AKI. Future studies are necessary to develop a uniform definition and identify the risk factors to improve the outcomes in this population.

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1. Introduction

Acute kidney injury (AKI) has replaced acute renal failure as a term used for the sudden decline in kidney function. AKI has been shown to be an independent risk factor for morbidity and mortality in neonates.[1,2] However, there is a lack of consensus as to which AKI diagnostic definition should be used in very low birth weight (VLBW) infants. In 2004, the Acute Dialysis Quality Initiative group proposed the RIFLE (Risk, Injury, Failure, Loss, End-Stage) criteria for AKI diagnosis.[3] These criteria have been modified to pediatric RIFLE (pRIFLE) for use in children[4] and the AKI network (AKIN) criteria. The AKIN definition of AKI includes patients who experience a 0.3-mg/dL increase in serum creatinine within a 48-hour period.[5] More recently, neonatal RIFLE (nRIFLE) was proposed with a new cutoff value for oliguria defined as UO $<$ 1.5 mL/kg/h in neonates.[6]

The incidence and risk factors for neonatal AKI in VLBW infants vary depending on the hospital and population studied.[1,7] This may be attributable to the varied pattern of care delivered at different neonatal intensive care units (NICUs) and the differences in birth weight (BW) of preterm infants. To overcome this and allow for comparison, several neonatal illness severity scores have been developed to predict mortality and morbidity in preterm infants. The Clinical Risk Index for Babies (CRIB) II[8] is a validated 5-item scoring system used worldwide to determine the illness severity in addition to predicting morbidity and mortality[9,10] in preterm infants $<$ 32 weeks. CRIB II is determined within 1 hour, and the 5-item components include BW, gestational age (GA), body temperature, base excess, and the sex of the infant. Scores range from 0 to 27 and are inversely related to outcomes. Limited data exist on the incidence and risk factors for AKI in VLBW infants when compared to other patient populations,[11] and the utility of CRIB II scores as a predictor of AKI in VLBW infants has not been extensively studied.

Despite multiple modifications for each unique population, there is no unifying AKI diagnostic definition. Although AKIN and pRIFLE have been compared in pediatric intensive care unit patients,[12] there have been no studies comparing these criteria in VLBW infants. The primary aim of the study was to determine the incidence and risk factors for AKI in VLBW infants using the AKIN and pRIFLE criteria, and evaluate whether CRIB II score is a predictor of AKI. The secondary objective was to determine the extent of agreement between the AKIN and pRIFLE criteria in the diagnosis of AKI in VLBW infants.

2. Methods

2.1. Study population

We retrospectively reviewed all VLBW infants admitted to a level 3B NICU of an academic center serving an inner city population. All infants who were born between January 2012 and December 2013 and whose BW was $\leq$ 1500 g were included in the study. Patients born with any major congenital anomalies involving the kidneys were excluded. We also excluded infants who died within the first few days of life, those who had an insufficient number of serum creatinine values prior to death or transfer to another center as well, as periviable infants who were not resuscitated and provided with only comfort care. The Institutional Review Board at the center approved the study protocol and waived the need for consent.

2.2. Data collection

Data were collected from the electronic medical records of all patients. The data included maternal and infant demographics, GA, BW, APGAR (Appearance, Pulse, Grimace, Activity, Respiration) scores, admission temperature and base excess, medications, laboratory results, respiratory support, and morbidities. Illness severity on admission was assessed using the updated CRIB II score.[8] AKI was classified using all three definitions: pRIFLE, AKIN, and nRIFLE (Table 1). For each definition, the creatinine criterion and/or urine output criterion was used. An AKI diagnosis was made only after the first 48 hours of life, which avoided calling the expected low urine output during the first 2 days of life of an infant as AKI. Additionally, because neonatal serum creatinine may reflect maternal creatinine in the first 2 days of life, serum creatinine measurements were recorded only after the first 48 hours of life. For patients with multiple episodes of AKI, the highest stage reached for any episode was used for the analysis. Serum creatinine was measured using an alkaline picrate (Jaffe) method traceable to isotope dilution mass spectrometry. As the pRIFLE criterion uses the estimated glomerular filtration rate (eGFR) in its definition (Table 1), we used the modified Schwartz and Work[13] method to best calculate the eGFR, which has been used in prior studies for pediatric patients aged between 0 years and 18 years.[4,14–16]

2.3. Definitions

Respiratory distress syndrome was defined as respiratory distress accompanied by hypoxemia, Fio_2 requirement $>$ 35%, and ground glass appearance on chest X-ray. Small for gestational age was defined as BW $<$ 10^{th} percentile for the GA. Presumed early-onset clinical sepsis was defined as the onset of signs of sepsis within the first 72 hours of life without a positive blood or cerebrospinal fluid culture and receipt of antibiotics for at least 5 days.[17] Late-onset sepsis was defined as occurring after 72 hours of life.[18]

2.4. Statistical analysis

All statistical analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). Medians for continuous variables were compared using with Mann–Whitney *U* test because the assumptions of normality could not always be satisfied. Proportions for categorical variables were compared using Pearson's Chi-square or Fisher's exact tests as appropriate. Continuous variables with normal distribution were compared using means and Student *t* test. Odds ratios and 95% confidence intervals were calculated to determine the odds of developing AKI among infants with or without it. Because of the high possibility of multicollinearity, forward stepwise binary logistic regression was performed to determine the variables that were considered to be independent risk factors for AKI within the first 2 weeks

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Table 1 Staged diagnostic criteria for AKI.

AKIN			pRifle			nRifle		
Stage	Serum creatinine	Urine output	Class	eGFR	Urine output	Class	eGFR	Urine output
1	Increased by >0.3 mg/dL or increased by 150–200%	<0.5 mL/kg/h × 6 h	Risk	Decreased by 25%	<0.5 mL/kg/h × 6 h	Risk	Decreased by 25%	<1.5 mL/kg/h × 24 h
			Injury	Decreased by 50%	<0.5 mL/kg/h × 12 h	Injury	Decreased by 50%	<1.0 mL/kg/h × 24 h
2	Increased by >200–300%	<0.5 mL/kg/h × 12 h	Failure	Decreased by 75%	<0.3 mL/kg/h × 24 h or anuria × 12 h	Failure	Decreased by 75%	<0.7 mL/kg/h × 24 h or anuria × 12 h
3	Increased by >300% or >4.0 mg/dL with acute rise of 0.5 mg/dL	<0.3 mL/kg/h × 24 h or anuria × 12 h	Loss ESRD	Failure >4 wk Failure >3 mo		Loss ESRD	Failure >4 wk Failure >3mo	

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; eGFR = estimated GFR; ESRD = end-stage renal disease; nRIFLE = neonatal RIFLE (Risk, Injury, Failure, Loss, End-Stage); pRIFLE = pediatric RIFLE.

of life using covariates that were significantly associated with the development of AKI in univariate analysis. A two-sided significance level of 0.05 was set for all tests.

3. Results

A total of 165 patients (weighing < 1500 g) were admitted to the NICU during the study period. Forty-two infants died within the first 4 days of life. Most of these infants were periviable and were only provided comfort, whereas the remainder had an insufficient number of serum creatinine measurements for the diagnosis of or otherwise of AKI. Other exclusions involved eight infants transferred to outside hospitals within the first 8 days of life. Thus, a total of 115 patients were included in the final AKI analysis (see Figure 1).

3.1. Demographics/patient characteristics

The median maternal age was 26.0 years [interquartile range (IQR), 22.0–31.0]. The median GA and BW were 29.0 weeks (IQR, 27.0–30.0) and 1100 g (IQR, 790–1330), respectively. Fifty-six percent of the population was male, and 64% (74/115) of the population was African American. Hispanics accounted for 22% (25/115), Caucasians 4.3% (5/115), and others 9.6% (11/115).

3.2. AKI incidence

Twenty-four patients (20.1%) developed AKI using the AKIN criteria. Twenty-six patients (22.6%) developed AKI using the pRIFLE criteria. All patients who had AKI based on the AKIN criteria also had the same diagnosis using the pRIFLE criteria. Two infants with AKI based on the pRIFLE criteria had changes only in eGFR over a 1-week period. None of the patients included in this study had the F, L, and E stages of pRIFLE or stage 3 of the AKIN criteria. Sixty-two percent of the patients who were diagnosed to have AKI using the AKIN criteria had their first episode in the 1st week of life. As per the interrater reliability analysis, there was a fair agreement between these two criteria (kappa = 0.217). All infants diagnosed with AKI were nonoliguric (UO > 1.5 mL/kg/h). The incidence rate of AKI using nRIFLE definition was 22.6%, which is exactly the same rate as that diagnosed by pRIFLE, because both of these definitions entail the same eGFR criteria for AKI diagnosis (Table 1). None of the patients met nRIFLE's new oliguria criteria (UO < 1.5 mL/kg/h) as proposed by Bezerra et al.[6]

3.3. Risk factors

Maternal, perinatal, and infant factors were compared between infants, with and without AKI (diagnosed by AKIN criteria). Out of the maternal factors listed in Table 2, prenatal NSAID (nonsteroidal anti-inflammatory drug) exposure and cesarean delivery were significantly higher in patients who developed AKI. Greater illness severity as assessed using the CRIB II score was significantly higher in the AKI group as compared to the non-AKI group (13.5 vs. 7, p <0.001). Additionally, infants with AKI were more likely to be of lower GA, have lower BW, be intubated at birth, and become mechanically ventilated in addition to being exposed to prenatal NSAIDs. Furthermore, infants who developed AKI were more likely to have respiratory distress syndrome, have a patent ductus arteriosus, require vasopressor support for hypotension, as well as develop late-onset sepsis. Maternal hypertensive disorders, exposure to prenatal steroids, chorioamnionitis, and maternal substance abuse were similar between the AKI and non-AKI groups (p > 0.05). Among the infant factors (Table 3), APGAR scores, umbilical artery catheterization, early-onset sepsis, and intraventricular hemorrhage were similar between the AKI and non-AKI groups.

Variables included in the forward stepwise binary logistic regression analysis with an entry and removal probability cutoff of 0.05 and 0.1, respectively, were GA, BW, CRIB II score, late onset sepsis, 5-minute APGAR score, hemodynamically significant PDA, vasopressor support, intubation at birth, and mechanical ventilation. CRIB II score was the strongest and the only independent predictor of AKI in this cohort of VLBW infants (odds ratio = 1.621; 95% confidence interval, 1.230–2.167; p = 0.001).

Mortality analysis was not performed because none of the patients included in this study died within the first 2 weeks of life. However, length of stay was noted to be significantly higher in patients with AKI (68 days vs. 34 days; p = 0.02).

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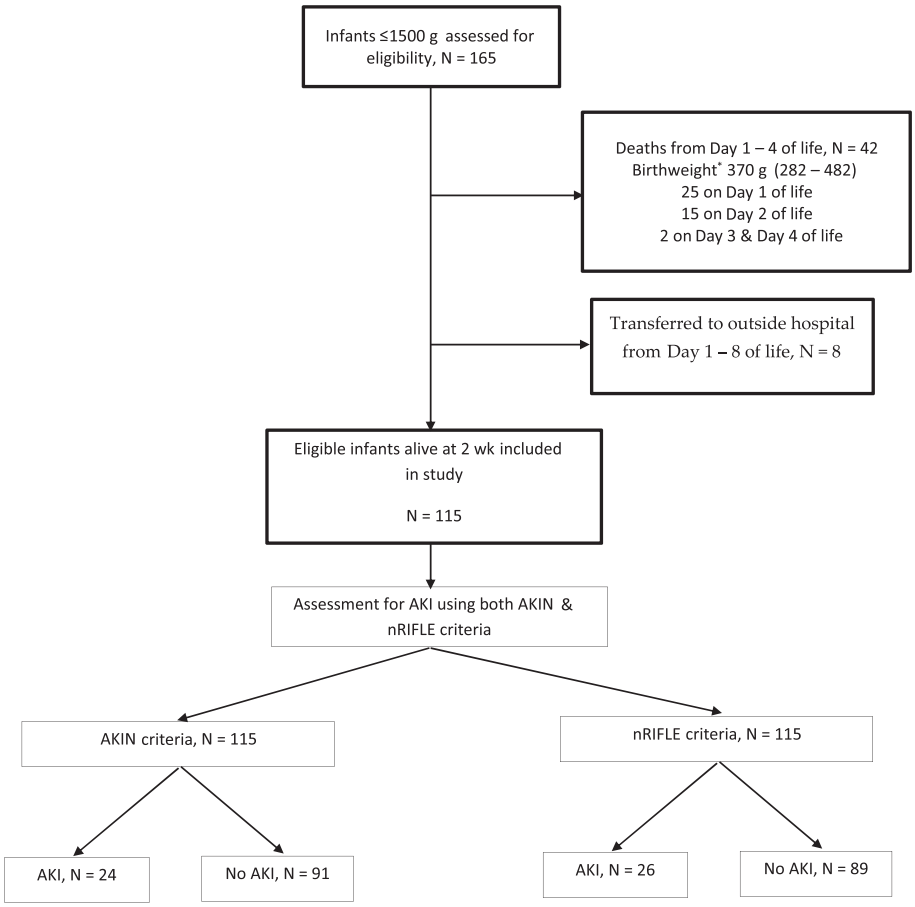

Figure 1 Patient flow and eligibility diagram. * Median (interquartile range).

4. Discussion

This primary aim of this study was to determine the incidence and risk factors for AKI in VLBW infants using the AKIN and pRIFLE criteria, and evaluate whether CRIB II score is a predictor of AKI. The secondary objective was to determine the extent of agreement between the AKIN and pRIFLE criteria in the diagnosis of AKI in VLBW infants. We found that AKI was associated with lower GA, lower BW, higher CRIB II scores, need for mechanical ventilation, vasopressor support for hypotension, hemodynamically significant PDA requiring medical, or surgical treatment along with late-onset sepsis. These risk factors suggest that the lightest, more premature, and sickest VLBW infants within the cohort developed AKI. Our study found that a higher CRIB II score on admission is an independent and strong predictor of AKI in VLBW infants. In this population of preterm VLBW infants, the components of the CRIB II scores that are modifiable include body temperature and base excess. Thus, the association between higher CRIB II scores and AKI[19] and other unfavorable outcomes[10] could potentially be ameliorated using proper and effective neonatal

Table 2 Comparison of maternal and perinatal characteristics of infants with and without acute kidney injury.

Variables	All patients (N = 115) n (%)	AKI		OR (95% CI)
		Yes (N = 24) n (%)	No (N = 91) n (%)	
Chorioamnionitis	36 (32)	8 (33)	28 (31)	1.089 (0.417–2.843)
Prolonged rupture of membranes	36 (32)	6 (25)	30 (35)	0.611 (0.219–1.704 0)
Prenatal NSAID exposure	20 (18)	8 (33)	12 (14)	3.083 (1.084–8.768)
Prenatal steroids	95 (86)	20 (83)	75 (87)	0.733 (0.211–2.550)
Maternal substance abuse	22 (20)	4 (17)	18 (20)	0.778 (0.236–2.562)
Pregnancy-induced hypertension/preeclampsia	32 (28)	7 (29)	25 (27)	1.071 (0.396–2.892)
Clinically identifiable intrapartum event*	43 (41)	12 (55)	31 (37)	2.052 (0.794–5.300)
Cesarean delivery	68 (61)	20 (87)	48 (55)	5.556 (1.539–20.061)

AKI = acute kidney injury; CI = confidential interval; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.
* Includes placenta previa, placental abruption, cord prolapse, uterine rupture.

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Table 3 Comparison of the characteristics and clinical course of infants with and without acute kidney injury.

Variables	All patients ($N = 115$) *n* (%)* or median (IQR)	AKI		OR (95% CI) or *p*
		Yes ($N = 24$) *n* (%)* or median (IQR)	No ($N = 91$) *n* (%)* or median (IQR)	
Gestational age (wk)	29 (27–30)	25 (24–27)	29 (27–30)	<0.001
Birth weight (g)	1100 (790–1330)	700 (605–960)	1170 (920–1380)	<0.001
CRIB II score	7.0 (5.0–11.0)	13.5 (8.0–15.0)	7.0 (4.0–9.0)	<0.001
APGAR scores (1 min)	5 (3–7)	5 (3–6)	5 (3–7)	0.34
APGAR scores (5 min)	8 (6–9)	7 (6–8)	8 (7–9)	0.046
SGA	12 (10)	4 (17)	8 (9)	2.132 (0.581–7.822)
Positive pressure ventilation at birth	94 (83)	22 (92)	72 (80)	2.750 (0.591–12.788)
Intubation	69 (61)	19 (79)	50 (56)	2.964 (1.016–8.645)
Mechanical ventilation	66 (59)	21 (88)	45 (51)	6.689 (1.860–24.055)
Respiratory distress syndrome	88 (77)	23 (96)	65 (71)	9.200 (1.181–71.688)
Patent ductus arteriosus	43 (37)	14 (58)	29 (32)	2.945 (1.169–7.420)
Patent ductus arteriosus treatment†	23 (20)	9 (38)	14 (16)	2.443 (0.670–8.901)
Vasopressor support	20 (18)	8 (33)	12 (13)	3.250 (1.144–9.231)
Early onset sepsis	80 (75)	21 (88)	59 (68)	3.201 (0.880–11.667)
Late onset sepsis	44 (38)	19 (79)	25 (27)	12.540 (3.883–40.499)
Umbilical artery catheter	81 (71)	17 (71)	64 (71)	0.99 (0.366–2.655)
Intraventricular hemorrhage	25 (22)	5 (21)	20 (22)	0.984 (0.310–2.815)
Length of stay (d), $\mu \pm \sigma$	44 ± 25	68 ± 14	34 ± 19	0.02

APGAR = Appearance, Pulse, Grimace, Activity, Respiration; CI = Confidence interval; CRIB = Clinical Risk Index for Babies; IQR = interquartile range; OR = odds ratio; SGA = small for gestational age.

* Percentages rounded off to the nearest whole number.

† Includes treatment with indomethacin or ibuprofen.

resuscitation and the maintenance of normothermia in the immediate postdelivery period. Our results are consistent with the recent studies by Weintraub et al[19] and Carmody et al[20] in VLBW infants.

The results of our study reveal that one in five VLBW infants developed AKI within the first 2 weeks. This is similar to the rate of 18% reported by Koralkar et al[1] but substantially lower than the 30–40% reported in other studies.[19,20] This can be explained by the wide variation in the AKI diagnostic definitions. Although there was no mortality data in this study, AKI was associated with increased length of stay, as reported previously. Our study also shows that most neonatal AKI were mild and classified as either stage 1 of AKIN or R and I stages of pRIFLE.

We found that the incidence rates of AKI based on the pRIFLE and AKIN definitions were different, and this is similar to the findings of two other studies,[15,21] which compared pRIFLE and AKIN among pediatric inpatients. They found pRIFLE to be more sensitive because it identified more stage 1 AKI events. In this study, pRIFLE identified more patients with AKI because of the changes in eGFR over a 1-week period and was found to be more sensitive in diagnosing AKI. Going forward, it would be interesting to determine whether one criterion is superior to the other based on the differences in outcomes seen with AKI being diagnosed with one criterion versus the other. However, given the small sample size of this study and the lack of long-term follow-up of these patients, we were unable to study this difference in outcomes. Each definition has its advantages. AKIN definition does not require the measurement of the infant's length or eGFR calculation, whereas pRIFLE does. Meanwhile, pRIFLE tracks creatinine changes over a 1-week period as opposed to 48 hours as per the AKIN criteria. Because of the differences in the incidence of AKI reported based on different definitions applied and lack of uniformity, it is difficult to compare studies from an epidemiological standpoint. This highlights the need to adopt a single and universal diagnostic definition in VLBW infants, which has the capability to predict both short-to-medium and long-term outcomes such as bronchopulmonary dysplasia, retinopathy of prematurity, and chronic kidney disease.

Our study evaluated the urine output of each patient. However, none of the patients who developed AKI had oliguria. This result is consistent with the fact that AKI in newborns is generally nonoliguric.[22] However, a recent study concluded that a higher cutoff for oliguria (UO < 1.5 mL/Kg/24 h) was associated with higher mortality, mechanical ventilation duration, and the length of hospital stay.[6] Thus, a new urine output criterion (UO < 1.5 mL/kg/24 h) was incorporated into pRIFLE, which was later referred to as neonatal RIFLE[23] (see Table 1). Our study also evaluated AKI based on nRIFLE's urine output criteria and found that none of the patients met this proposed criterion.

Recent studies have largely focused on specific subgroups such as neonates with congenital diaphragmatic hernia[24] or congenital heart disease,[25] thereby making it difficult to determine the risk for the broader population of VLBW infants.

Our study has several limitations. First, because of the retrospective nature of the study and its reliance on already existing serum creatinine values, we were unable to assess the potential confounders in the diagnosis of AKI. VLBW infants have unique and distinct physiologies, making the interpretation of serum creatinine and the measurement of urine output difficult. Serum creatinine may also reflect maternal values and fluctuate during the 1st week of

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life. In neonates, serum creatinine usually does not increase until 25–50% of the kidney function has been lost.[26] Second, newer AKI definitions such as Kidney Diseases Improving Global Outcomes[24] and Neonatal AKI criteria[26] were not evaluated in this study. Third, our laboratory uses an alkaline picrate (Jaffe) method to measure creatinine. This technique is subject to interference from albumin, immunoglobulins, unconjugated bilirubin, and hemoglobins (both A and F),[25] and it may overestimate serum creatinine by 0.2 mg/dL in VLBW infants.[27] Fourth, we did not look into novel biomarkers, which have been shown to predict AKI in this population.[28]

In summary, in this single-center retrospective review of VLBW infants, AKI was common (20–22%). AKI was more likely in those who had a CRIB II score of $>$ 10. AKI in VLBW infants was nonoliguric and associated with a longer length of stay. AKIN and pRIFLE diagnostic definitions resulted in different AKI incidence in our study. Thus, our findings support the need for a uniform AKI diagnostic definition tailored for unique, challenging, and developmentally immature VLBW infant populations. Further prospective studies are needed to develop a better AKI diagnostic tool that includes novel biomarkers in conjunction with serum creatinine and urine output.

Conflicts of interest

The authors declare no conflict of interest.

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