Clinical profile of acute kidney injury in neonatal sepsis and perinatal asphyxia using nRIFLE and modified KDIGO criteria

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Received - 09 October 2019 Initial Review - 16 October 2019 Accepted - 20 November 2019

ABSTRACT

Background: Newborn babies with sepsis and perinatal asphyxia form a high-risk group for developing neonatal acute kidney injury (nAKI). The diagnosis and staging of nAKI is challenging and has several limitations. **Objective:** The objectives of this study were to estimate the hospital-based incidence of nAKI in septic and asphyxiated neonates, describe their clinical profile and outcome, and compare the two classifications – neonatal risk, injury, failure, loss, and end-stage renal disease (nRIFLE) and neonatal modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria for their agreement. **Materials and Methods:** Consecutive neonates who fulfilled the diagnosis of sepsis or perinatal asphyxia were included in this prospective cohort study. Urine output was monitored 6 hourly by diaper weight and serum creatinine every 48 h or earlier if required. The clinical profile and outcome of neonates who developed AKI were studied, and AKI was staged using both nRIFLE and KDIGO criteria. Chi-square test was used to test the association of risk factors with AKI, Pearson's Chi-square and Kappa statistics were used to compare the two staging criteria. **Results:** Of 90 neonates enrolled, the incidence of AKI in sepsis was 145/1000 neonates and perinatal asphyxia was 464/1000 neonates. AKI was maximally observed in the early preterm neonates (45.4%) and very low birth weight neonates (36.36%). Oliguria was present in a majority of the neonates with nAKI but varied according to the classification system used. nAKI was significantly associated with high mortality (54.2%) ($p<0.01$) which increased with decreasing gestation and birth weight and increasing severity of nAKI. On comparing KDIGO and nRIFLE criteria, there was a poor agreement between the two. **Conclusion:** AKI is a common occurrence in septic and asphyxiated neonates and portends poor outcomes. Although studies have evaluated nRIFLE and KDIGO individually, larger studies comparing the two criteria are required to improve early diagnosis and accurate staging of neonatal AKI.

Key words: *Kidney Disease: Improving Global Outcomes, Neonatal acute kidney injury, Neonatal risk, injury, failure, loss, and end-stage renal disease, Neonatal sepsis, Perinatal asphyxia*

Critically ill babies are a high-risk group susceptible to neonatal acute kidney injury (nAKI) which has emerged as an independent risk factor for morbidity and mortality. The kidneys of the newborn are highly susceptible to nAKI due to the interplay between several vasoactive agents and hormones, leading to a low glomerular filtration rate (GFR), high renal vascular resistance, high plasma renin activity, and decreased intercortical perfusion. The incidence of nAKI in developing countries has been reported in the range from 10.8% to 41% in newborns admitted to the neonatal unit [1,2].

There are a number of challenges in the diagnosis and staging of nAKI. Measurement of urine output (UO) in neonates is difficult, and moreover, non-oliguric renal failure is a common entity in this age group making oliguria difficult to interpret [3,4]. Serum creatinine (SCr) measurements immediately after birth are influenced by maternal creatinine levels. With time, maturational renal changes impose a barrier to creatinine [5]. The proposed diagnostic classification systems for nAKI are mostly based on functional abnormalities in SCr and UO. The neonatal risk, injury, failure, loss, and end-stage kidney disease (nRIFLE) criteria proposed UO as a parameter to stage nAKI [6]. In 2013, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines workgroup published a definition that combined aspects of both SCr and UO to provide a single tool for use in both research and clinical practice [7].

In India, perinatal asphyxia and neonatal sepsis contribute to 53.0% and 10.6% of neonatal deaths, respectively [8]. Both sepsis and asphyxia compromise renal perfusion, and consequently, these neonates are at a higher risk of developing nAKI [9-12]. This study aims to estimate the hospital-based incidence of nAKI in septic and asphyxiated neonates, describe their clinical profile

and outcome, and compare the two classifications – nRIFLE and neonatal modified KDIGO for their agreement.

MATERIALS AND METHODS

This was a prospective cohort study conducted in a tertiary care neonatal intensive care unit (NICU) over 14 months. Assuming a prevalence of AKI in sepsis and asphyxia of 40% from the previous studies, a sample size of 90 was arrived at. A total of 90 consecutive neonates (inborn and outborn) admitted to the NICU fulfilling the diagnosis of sepsis or perinatal asphyxia during the first 28 days of life were included in the study. Neonates in whom UO measurement was unsuccessful, neonates with a congenital abnormality of the kidney or urinary tract, undergoing surgery and those who had both perinatal asphyxia and sepsis were excluded from the study. The Institutional Ethics Committee approval was sought and informed consent taken from the parents before enrolling the neonate.

A neonate was diagnosed with sepsis if two of five parameters of the sepsis screen were positive (septic screen comprises total leukocyte count <5000, low absolute neutrophil count as per Manroe's chart for term and Mouzinho's chart for very low birth weight (VLBW) infants, immature/total neutrophil ratio >0.2, C-reactive protein >1 mg/dL, and micro-erythrocyte sedimentation rate >15 mm in the 1st h) or if a positive blood culture was obtained, in a clinically suspected case [13]. Perinatal asphyxia was diagnosed if the Apgar score was <6 at 5 min of life and/or the umbilical arterial blood pH at birth was <7.0 [14].

Enrolled neonates were screened for nAKI on day 3 of life or at admission, whichever was later. Clinical profile of all enrolled neonates was noted. UO was measured daily using diaper weights and condom catheter bag/neonatal uro-bag when applicable as per NICU protocol, and calculations were made 6 hourly. The dry diaper weight was deducted from the total weight of each wet diaper to arrive at the weight of urine in grams, which was numerically equal to the volume. In case, stool and urine were found to be mixed in the diaper, a constant value of 15 g was subtracted from the total diaper weight to correct for the stool weight. Catheterization was not done to obviate the risk of introducing infection.

SCr measurement, using modified Jaffe's kinetic method, was performed on the day of recruitment and once every 48 h until 7 days of recruitment. In neonates with established nAKI, the interim values of creatinine were recorded during therapy, hospital stay, and at discharge. If the baby's clinical condition was improving and the first and second creatinine measurements were normal, the third was deferred. To interpret SCr at recruitment and at discharge, a reference table was used [15]. Staging was done using both nRIFLE and modified KDIGO classifications, as shown in Tables 1 and 2. The KDIGO SCr criterion was used as the standard against which the other two criteria were compared.

Once nAKI was diagnosed, the neonates were managed according to the standard protocol. Babies were followed up during hospital stay for UO, clinical status, and therapeutic interventions. The clinical outcome in terms of recovery and discharge, discharge against medical advice (DAMA), or death was documented.

The number of neonates developing nAKI per 1000 septic and asphyxiated neonates was computed to calculate the incidence rate. The clinical and demographic details of neonates developing nAKI were reported using number and percentages. The Chi-square test was used to test the association of various risk factors with nAKI. To evaluate the agreement between the two mentioned criteria to stage nAKI, Pearson Chi-square and Kappa statistics were undertaken, and $p<0.05$ was considered statistically significant. All analyses were done using SPSS version 20 software.

RESULTS

Of the 90 neonates, 62 were diagnosed with sepsis and 28 were diagnosed with perinatal asphyxia. The demographic data are summarized in Table 3.

A total of 22 neonates developed nAKI (13 in sepsis and 9 in perinatal asphyxia) during the course of the study with a hospital-based incidence in neonatal sepsis and perinatal asphyxia being 145 and 464/1000 neonates, respectively, making an overall incidence in the study group as 244/1000 neonates. Oliguria was documented using both KDIGO (59.1%) and nRIFLE (81.8%) criteria.

As SCr has been the most widely used marker in most studies to stage nAKI, KDIGO SCr criteria were used as the standard of comparison for nRIFLE and KDIGO UO criteria. According

Table 1: Neonatal RIFLE staging criteria [6]

Parameter	SCr criteria	UO criteria
Risk	?	UO <1.5 mL/kg/h for 24 h
Injury	?	UO <1.0 mL/kg/h for 24 h
Failure	?	UO <0.7 mL/kg/h for 24 h or anuric for 12 h
Loss	Persistent failure >4 weeks	
End stage	Persistent failure >3 months	

Question mark is intended to mean uncertain thresholds. GFR: Glomerular filtration rate, eCCl: Estimated creatinine clearance, UO: Urine output, SCr: Serum creatinine

Table 2: Neonatal modified Kidney Disease: Improving Global Outcomes staging criteria [7]

Stage	SCr	Urine output
0	No change in SCr or increase <0.3 mg/dL	≥0.5 mL/kg/h
1	SCr increase ≥0.3 mg/dL within 48 h OR SCr increase ≥1.5–1.9×reference SCr[a] within 7 days	<0.5 mL/kg/h for 6–12 h
2	SCr increase ≥2–2.9×reference SCr[a]	<0.5 mL/kg/h for ≥12 h
3	SCr increase ≥3 × reference SCr[a] OR SCr ≥2.5 mg/dL OR Receipt of dialysis	<0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

[a]Baseline defined as the lowest previous. SCr value. SCr: Serum creatinine

to KDIGO SCr, most of the neonates belonged Stage I AKI (77.8%) followed by Stage II. When nRIFLE was employed, the majority (45.4%) was found to be in Stage II followed by Stage I while KDIGO UO classified majority as having no AKI (40.9%) followed by Stage I AKI (Fig. 1).

Stage I AKI constituted a major proportion of neonates irrespective of gestational age with term, late preterm, early preterm, and extreme preterm babies having 83.30%, 80.00%, 70.00%, and 100% Stage I AKI. Overall, the mortality in neonates with Stage I AKI was 41.18%, whereas in Stage II and Stage III AKI, the mortality was 100%.

In terms of the clinical outcome of neonates with nAKI, in-hospital mortality rate in septicemic neonates with nAKI was 44.4% and 61.5% for asphyxiated babies. Further, the mortalities in nAKI affected neonates with Stage I, Stage II, and Stage III hypoxic-ischemic encephalopathy (HIE) were 0, 50.0%, and 75.0%, respectively. The overall mortality was 54.6% in nAKI in contrast to 22.1% in neonates without nAKI. Stage-wise AKI mortality was reflective of an increasing mortality with worsening stage of AKI with 41% mortality in Stage I and 100% in Stages II and III AKI. The clinical recovery was observed in 40.91% who were eventually discharged, while 4.54% went DAMA. We observed that the nRIFLE and KDIGO classification systems used to stage nAKI had poor agreement, as described in Table 4.

Table 3: Demographic details of the study population (n=90)

Parameter	Category	Sepsis, n (%)	Perinatal asphyxia, n (%)
Sex	Male	42 (67.74)	14 (50.00)
	Female	20 (32.26)	14 (50.00)
Birth weight	≥2500 g	9 (14.52)	6 (21.43)
	≥1500–<2500 g	25 (40.32)	9 (32.14)
	≥1000–<1500 g	24 (38.71)	8 (28.57)
	<1000 g	4 (6.45)	5 (17.86)
Gestational age	<28 weeks	0 (0.00)	2 (7.14)
	28–34 weeks	33 (53.22)	12 (42.86)
	34–37 weeks	9 (14.52)	4 (14.28)
	≥37 weeks	20 (32.36)	10 (35.71)

DISCUSSION

The hospital-based incidence of nAKI in our study was 14.52% in sepsis and 46.43% in perinatal asphyxia. nAKI in neonatal sepsis was studied by Mathur *et al*., Salah *et al.*, and Jagrawal *et al.* and they reported incidence ranging from 26% to 32% [12,16,17]. The higher incidence seen in these studies could be due to the different criteria for the diagnosis of AKI in terms of higher cutoff value of SCr. The incidence of nAKI in perinatal asphyxia in our study was similar to the incidence reported by other studies in India and the West, ranging from 38% to 64% [9,18,19].

The wide range of incidence may be explained by the difference in the criteria used to define AKI – while Selewski *et al.* studied 96 newborns undergoing therapeutic hypothermia using the neonatal modified KDIGO criteria reporting an nAKI incidence of 38%, and Kaur *et al.* studied 36 neonates using the AKIN criteria and reported a 41.7% incidence [9,18]. Gopal in their study of 50 asphyxiated neonates used oliguria as the marker to diagnose AKI and did not use SCr, which could explain the higher incidence of 64% that they found [19].

The male preponderance in nAKI found in our study was in agreement with Mortazavi *et al.* who reported a male:female ratio of 2:1 in their retrospective study of 6042 hospitalized newborns and by Salah *et al.* who studied nAKI in 250 septicemic babies [16,20]. However, this could be due to the higher proportion of males in the sample.

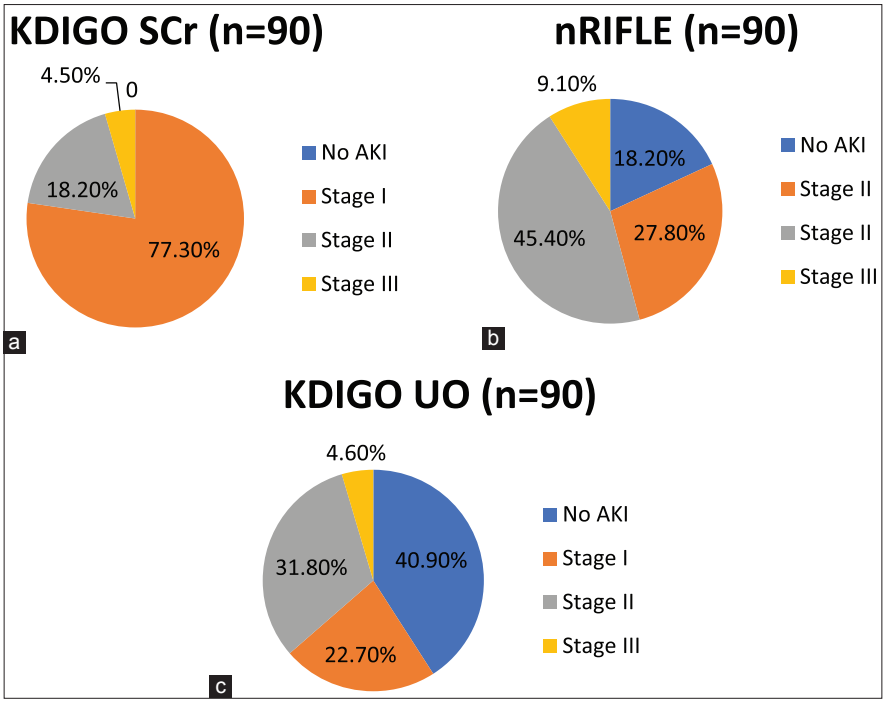

Figure 1: (a-c) Neonatal acute kidney injury based on different classification criteria (n=90)

Table 4: Comparison between nRIFLE and modified KDIGO classifications

Comparison between criteria	p value	Kappa
KDIGO UO and nRIFLE UO	0.038	0.060
KDIGO UO and KDIGO creatinine	0.001	NA
nRIFLE UO and KDIGO creatinine	0.043	NA

nRIFLE: Neonatal risk, injury, failure, loss, and end-stage renal disease, KDIGO: Kidney Disease: Improving Global Outcomes. UO: Urine output

Table 5: nAKI mortality based on gestational age and birth weight (n=22)

Gestational age	nAKI mortality (%)	Birth weight	nAKI mortality (%)
<28 weeks	100	<1000 g	100.0
28–34 weeks	80.0	1000–1499 g	62.5
34–37 weeks	20.0	1500–2500 g	50.0
≥37 weeks	33.3	≥2500 g	25.0

nAKI: Neonatal acute kidney injury

Oliguria has been defined differently by different nAKI staging systems in use. In our study, with nRIFLE, 81.8% of neonates were oliguric, whereas 59.1% were found to be oliguric by modified KDIGO. The stark contrast in these values could be due to the high UO cutoff considered by the nRIFLE criteria (UO <1.5 mL/kg/h for 24 h). Most other studies define oliguria as UO <1 mL/kg/h (34) or UO <0.5 mL/kg/h but do not specify the duration to label a baby as oliguric [21]. Recent studies show that neonates have non-oliguric renal failure, making the traditional definition of oliguria an insensitive marker of AKI [22]. Hence, a higher cutoff may be required to detect oliguria in the neonatal population.

The majority of our AKI neonates belonged to Stage I when considered under KDIGO SCr criteria (77.8%), while according to KDIGO UO and nRIFLE, majority were in Stage II. Most other studies which have used the modified KDIGO criteria have been done on the subset of only VLBW infants or did not stage nAKI [23,24]. Koralkar *et al.*, in their study, found a greater proportion of Stage III AKI, possibly because premature infants had lower GFR predisposing them to a higher degree of injury [24]. Other studies which looked at asphyxiated or septicemic neonates used criteria only to diagnose the presence of nAKI and did not stage it according to severity [9,12]. It is possible that modified KDIGO SCr criteria with its lower cutoffs pick up milder degrees of nAKI which reflects our finding of the majority being in Stage I as per KDIGO SCr.

The incidence of AKI in term and preterm neonates was comparable at 20.0% and 26.7%, respectively, though the severity increases with decreasing gestational age. These findings are in contrast to the findings of Mathur *et al.* and Mortazavi *et al.* who reported that preterm was less frequently accompanied by AKI than full-term neonates [12,20]. A study by Askenazi *et al.* also estimated AKI incidence in sick near-term/term infants to be similar to other neonatal cohorts [25]. In our study, the incidence of AKI in VLBW neonates was 25.00% and severity increased with decreasing birth weight. Studies done by Koralkar *et al.*, Rhone *et al.*, and Carmody *et al.* showed an AKI incidence between 18.0% and 39.8% [24,26,27].

In our study, the mortality rate was 44.4% in septicemic neonates with nAKI and 61.5% in asphyxiated neonates. The overall mortality in those with nAKI was significantly higher than those without nAKI. Recent studies have shown nAKI mortality in sepsis and asphyxia to be 56.5–72.2% and 7.6–71.4%, respectively [9,12,16,17,19,28]. Furthermore, the mortality rates in our study increased with decreasing gestational age and birth weight as shown in Table 5, and increasing stage of nAKI. The higher risk of mortality in VLBW infants has been explored by many studies [24,27]. However, the high rate of mortality in premature infants in our study could reflect the lesser renal reserve they have and lower GFR at birth. This was in accordance to the study done by Stojanovic *et al.* [29]. Askenazi *et al.* also found that a much higher proportion of Stage III nAKI was found in children who died (19.1%) as compared to those who survived (6.3%) [25].

Although studies have employed nRIFLE or modified KDIGO criteria separately to stage nAKI, none have compared them in a single study. While nRIFLE entirely omits SCr and uses only UO as a tool to stage nAKI, modified KDIGO uses a combination of the two. The poor agreement between the KDIGO SCr, KDIGO UO, and nRIFLE UO could indicate that substituting one for the other is not feasible. KDIGO and, less frequently, nRIFLE have been employed by different studies but have not been compared for their feasibility, for which larger studies are required.

Our study was limited by a small sample size and larger multicenter studies are required to establish their individual use in the neonatal population. In addition, inherent inaccuracies may exist in UO measurement by diaper weight, which was the method used in our study.

CONCLUSION

AKI in neonates is common in neonates with both sepsis and perinatal asphyxia. Staging nAKI may be challenging, but early diagnosis is essential, especially in small and/or premature neonates as it is associated with significant mortality in these babies. Oliguria may still be a useful indicator of nAKI and considering higher cutoffs as per the nRIFLE criteria may help pick up milder stages.

REFERENCES

1. Youssef D, Abd-Elrahman H, Shehab MM, Abd-Elrheem M. Incidence of acute kidney injury in the neonatal intensive care unit. Saudi J Kidney Dis Transpl 2015;26:67-72.
2. El-Badawy AA, Makar S, Abdel-Razek AR, Abd Elaziz D. Incidence and risk factors of acute kidney injury among the critically ill neonates. Saudi J Kidney Dis Transpl 2015;26:549-55.
3. Bezerra CT, Vaz Cunha LC, Libório AB. Defining reduced urine output in neonatal ICU: Importance for mortality and acute kidney injury classification. Nephrol Dial Transplant 2013;28:901-9.
4. Karlowicz MG, Adelman RD. Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol 1995;9:718-22.
5. Guignard JP, Drukker A. Why do newborn infants have a high plasma

creatinine? Pediatrics 1999;103:e49.
6. Ricci Z, Ronco C. Neonatal RIFLE. Nephrology Dial Transplant 2013;28:2211-4.
7. Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr 2012;24:191-6.
8. NNPD Network. Report of the National Neonatal Perinatal Database 2002-03. New Delhi: NNPD Nodal Center at Department of Pediatrics, WHO Collaborating Centre Newborn Training and Research, All India Institute of Medical Sciences; 2006. p. 10-37.
9. Kaur S, Jain S, Saha A, Chawla D, Parmar VR, Basu S, *et al*. Evaluation of glomerular and tubular renal function in neonates with birth asphyxia. Ann Trop Paediatr 2011;31:129-34.
10. Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of renal functions in asphyxiated newborns. J Trop Pediatr 2005;51:295-9.
11. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian Pediatr 2005;42:928-34.
12. Mathur NB, Agarwal HS, Maria A. Acute renal failure in neonatal sepsis. Indian J Pediatr 2006;73:499-502.
13. Singh M. Care of the Newborn. 8th ed., Vol. 16. New Delhi: Sagar Publications; 2010. p. 292.
14. Hansen AR, Soul JS. Perinatal asphyxia and hypoxic-ischemic encephalopathy. In: Cloherty JP, Eichenwald EC, Martin CR, Stark AR, editors. Manual of Neonatal Care. 8th ed. Ch. 55. New York: Lippincott, Williams and Wilkins; 2017. p. 790-811.
15. Samuels JA, Munoz H, Swinford RD. Neonatal kidney conditions. In: Cloherty JP, Eichenwald EC, Martin CR, Stark AR, editors. Manual of Neonatal Care. 8th ed. Ch. 28. New York: Lippincott, Williams and Wilkins; 2017. p. 377.
16. Salah MH, Hamdi N, Algayar A, Khashab AE, Marashli M, Amin W. Effect of septicaemia on renal performance in the neonate. Med J Cairo Univ 2010;78:361-7.
17. Jagrawal G, Arora V, Gunawat M, Malik P. Acute renal failure in neonatal septicemia. Int J Biomed Res 2016;7:260-4.
18. Selewski DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. J Pediatr 2013;162:725-90.
19. Gopal G. Acute kidney injury (AKI) in perinatal asphyxia. Indian J Pharm Biol Res 2014;2:60-5.
20. Mortazavi F, Hosseinpour Sakha S, Nejati N. Acute kidney failure in neonatal period. Iran J Kidney Dis 2009;3:136-40.
21. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: What do we know? What do we need to learn? Pediatr Nephrol 2009;24:265-74.
22. Viswanathan S, Manyam B, Azhibekov T, Mhanna MJ. Risk factors associated with acute kidney injury in extremely low birth weight (ELBW) infants. Pediatr Nephrol 2012;27:303-11.
23. Askenazi DJ, Griffin R, McGwin G, Carlo W, Ambalavanan N. Acute kidney injury is independently associated with mortality in very low birthweight infants: A matched case-control analysis. Pediatr Nephrol 2009;24:991-7.
24. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. Pediatr Res 2011;69:354-8.
25. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. Pediatr Nephrol 2013;28:661-6.
26. Rhone ET, Carmody JB, Swanson JR, Charlton JR. Nephrotoxic medication exposure in very low birth weight infants. J Matern Fetal Neonatal Med 2014;27:1485-90.
27. Carmody JB, Swanson JR, Rhone ET, Charlton JR. Recognition and reporting of AKI in very low birth weight infants. Clin J Am Soc Nephrol 2014;9:2036-43.
28. Alaro D, Bashir A, Musoke R, Wanaiana L. Prevalence and outcomes of acute kidney injury in term neonates with perinatal asphyxia. Afr Health Sci 2014;14:682-8.
29. Stojanović V, Barišić N, Milanović B, Doronjski A. Acute kidney injury in preterm infants admitted to a neonatal intensive care unit. Pediatr Nephrol 2014;29:2213-20.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Subramanian S, Malik S, Wade PA. Clinical profile of acute kidney injury in neonatal sepsis and perinatal asphyxia using nRIFLE and modified KDIGO criteria. Indian J Child Health. 2019; 6(11):609-613.

Doi: 10.32677/IJCH.2019.v06.i11.009