Original Article

Renal Function Status after 6 Months in Term Sick Newborns with Acute Kidney Injury

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Abstract

Background: Assumption that resolution of acute kidney injury (AKI) is followed by complete renal recovery has been challenged by recent studies in adults and children. However, data in term newborns are scarce. This study was done to observe deranged renal parameters and hence risk factor for chronic kidney disease at 6 months of age in term newborns who develop AKI due to various causes. **Methods:** This was a descriptive cohort study in term newborns developing AKI (nRIFLE). Sixty-one babies completed the study for final analysis. After 6 months of follow-up, clinical and laboratory renal parameters were studied. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. **Results:** The median gestational age of cohort was 38 weeks, and the mean birth weight and length were 2.8 ± 0.45 kg and 48.3 ± 2.25 cm, respectively. Sepsis was the most common etiological factor in 54% cases of AKI followed by birth asphyxia (34%). The median age and serum creatinine at diagnosis of AKI were 4 days and 2.7 mg/dL, respectively. Nearly 77% of cases (n = 47) were oliguric and the median value of fractional excretionof sodium was 0.87 (0.688–1.335). One (1.64%) neonate was in risk stage, 8 (13.11%) in injury, and 52 (85.246%) in failure stage. At 6 months of follow-up, 41% (n = 25) had decreased serum bicarbonate values. Four out of 61 patients (6.56%) had reduced estimated glomerular filtration rate, while 15 (24.59%) had hyperfiltration. Overall, 63.93% (n = 39) of the cases had one or more renal parameters deranged at 6 months. **Conclusion:** A large proportion of term newborns with AKI continue to have deranged renal parameters, therefore they need careful monitoring for long duration.

Keywords: *Acute kidney injury, long-term outcome, term newborn*

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Introduction

Burden of neonatal acute kidney injury (AKI) varies with the study cohort and criteria used. Defining AKI in newborn period is challenging because of the presence of maternal creatinine, varying degrees of creatinine reabsorption in the proximal tubules, overall lower glomerular filtration rate (GFR), and maturational differences[1] ts incidence range from 15.6% to 71%.[2,3] Following acute insult, recovery depends on severity, duration, etiology, as well as mechanism of injury.[4-7] Studies in adults show persisting abnormal renal functions in the form of hypertension, abnormal urinalysis, suboptimal GFR, proteinuria, and even end-stage renal disease (ESRD) in patients with AKI after follow-up of 6 months to 10 years.[4,5] There is paucity of similar data inchildren, less so in newborns.[8,9] With better health-care facilities, now the prime focus of management has shifted from mortality to long-term morbidity. This study was done to observe the renal function and risk of chronic kidney disease (CKD) at 6 months of age in term newborns developing AKI.

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Methods

This was an descriptive cohort study done at a tertiary care centre in northern India from November 2017 to April 2019 over a period of 18 months. Initial 9 months were taken as the enrollment period followed by 6 months of follow-up and subsequently 3 months for data analysis. Newborns with gestational age more than or equal to 37 completed weeks and birth weight more than or equal to 2000 g developing AKI were included. Babies with known congenital renal or heart disease, postoperative cases, mothers on known nephrotoxic drugs, or not willing to take part in study were excluded from the study. As there was no previous study of follow-up done exclusively in term babies with AKI, taking reference of study by Mammen *et al*.,[9] a value of 10% as incidence of CKD in patients with AKI, using the formula, $z^2 \times p \times (1 - p)/e^2$, where P = incidence of CKD in patients with AKI, Z = confidence level at 95% (1.96–2) e = accepted error kept as 5% and assuming a loss of 20% due to follow-up, the initial sample size planned was 172 but due to fixed time frame, a minimum number of fifty newborns developing AKI with 6-month follow-up were. During this period, 609 neonates were admitted, out of which 306 were excluded due to various reasons (preterm, low birth weight, congenital kidney disease, post operative cases, etc). Out of 303 eligible, 79 developed AKI (defined with nRIFLE criteria)[10] and were eligible. Twelve cases were further excluded and out of 67 babies finally 61 cases completed the followup of 6 months [Figure 1]. Informed written consent from the parents/guardian was taken. The study was approved by the institutional review board. Serum creatinine (S. Cr) measured after 48 h of birth was taken as baseline and subsequently measured serially. Urine output was measured by diaper weight and monitored. All serum and urine biochemical measurements were done using automated clinical chemistry analyzer ADVIA 2400 (Siemens). Fractional excretionof sodium (FENa) was calculated to differentiate between prerenal (FENa <2.5) and intrinsic renal failure (FENa >2.5).[11] Ultrasound kidney ureter bladder (US KUB) was done using Phillips iU22 model Amsterdam, Netherlands for baseline size of kidneys to rule out any structural kidney disease. All the neonates were managed as per standard protocol and after discharge were followed up at 14 weeks (12–16 weeks), time coinciding with third routine immunization) for length, weight, and blood pressure (BP), and at 6 months for clinical (BP, length, weight), biochemical (blood urea, S. Cr, urinary spot protein creatinine ratio, venous blood gas) parameters, and US KUB. Normal renal function at 6 months was defined as normal BP (<90th centile), normal spot urinary protein/urinary creatinine ratio (Up/Uc) <0.5 mg/mg,[11] normal routine microscopic urine analysis, no metabolic acidosis (pH >7.32 and bicarbonate between 24 and 28 mmHg) and normal estimated GFR (eGFR) for age calculated by Schwartz formula using reference S. Cr values appropriate for the age[6,12] and normal US KUB. The primary outcome was any abnormal renal parameters including hypertension, increased Up/Uc >0.5, eGFR less than the normal value for the age (<90 ml/min/1.73 m^2), hyperfiltration (eGFR >150 ml/min/1.73 m^2), abnormal urine analysis, abnormal US KUB or decreased bicarbonate levels, etc., and were defined as risk factors for developing CKD. For statistical analysis, categorical variables were presented in number and percentage (%) and continuous variables as mean ± standard deviation and median (interquartile range [IQR]). Normality of data was tested by Kolmogorov–Smirnov test and nonparametric tests were used where required. Quantitative variables were compared using ANOVA or Kruskal–Wallis test between more than two groups, whereas qualitative variables were correlated using Chi-square test. A $P < 0.05$ was considered statistically significant. The data waswere entered in MS EXCEL spreadsheet, and analysis was done using Statistical Package for Social Sciences (SPSS) IBM statistics, New York, USA version 21.0.

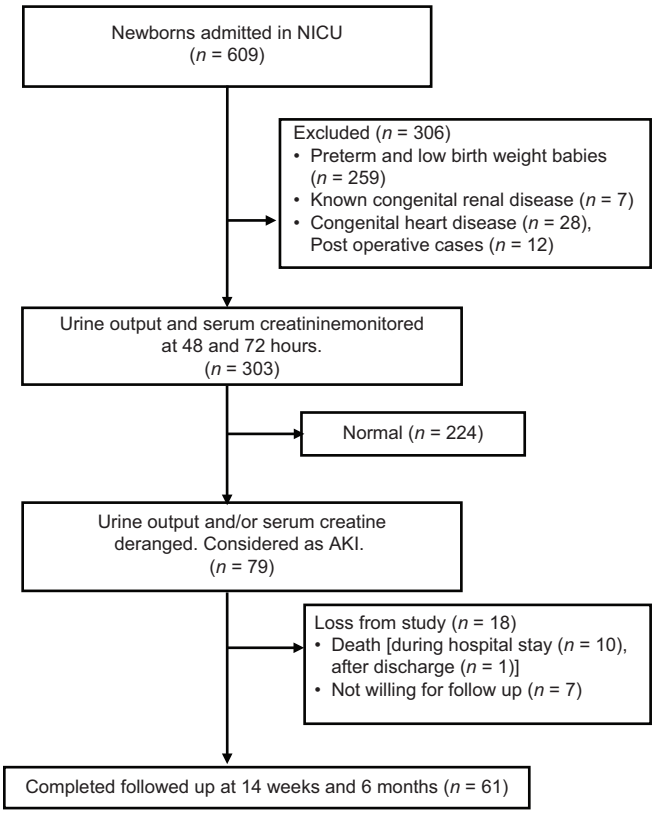

Figure 1: Diagram showing flow of the study

Results

The median gestational age of the patients was 38 (IQR 37.857–39.321) weeks, the median birth weight was

2.8 (IQR 2.4–3.1) kg, and the median length at birth was 48 cm (IQR 47–50). The minimum APGAR at 5 min was 1 and the maximum was 9 with the median of 7 (2–8). The minimum APGAR score at 5 min was 1 with mean value of 5.56 ± 2.83. There was slight female predominance of 52.46% (32/61). The demographic details of study population is shown in Table 1.

Sepsis was the most common etiological risk factor for developing AKI, accounting for 54% (33) cases of AKI followed by birth asphyxia 34% (21) [Figure 2].

The mean age of diagnosis of AKI in the neonates was 5.2 ± 3.36 days ranging from 2 to 19 days. The mean S. Cr at diagnosis was 3.05 ± 0.9 mg/dL, whereas the mean systolic BP and diastolic BP were 83.23 ± 5.32 mmHg and 48.8 ± 6.35 mmHg, respectively.

Among 61 cases, 77% (n = 47) were oliguric with a mean urine output of 0.32 ± 0.32 ml/kg/h.

The median value of FENa was with

The mean age of developing AKI in neonates with BA was early 3.71 ± 0.72 days compared to sepsis (5.61 ± 3.48 days) and nephrotoxic drugs (12.67 ± 5.13 days) (P = 0.012). In addition, 57% (12/21) of these neonates were oliguric compared to 97% (32/33) in sepsis group, and the difference was statistically significant (P = 0.0004).

According to nRIFLE criteria, 1 (1.64%) neonate was in risk stage, 8 (13.11%) in injury, and 52 (85.246%) in failure stage [Figure 3].

At 14-week follow-up, 97% (59/61, except one in sepsis and one in BA group) cases had appropriate length and 98% (60/61 except one in BA group) had appropriate weight for age. BP was normal (below 90th centile) in all [Table 2].

At 6 months of follow-up length, weight and BP were normal and appropriate for age among all study patients and difference was statistically insignificant when divided in groups as per AKI staging [Table 3].

The mean pH at 6-month follow-up in the study patients was 7.39 ± 0.03, while the mean bicarbonate level was 23.33 ± 2.64 mmol/L. Nearly 41% (n = 25) of the patients had decreased serum bicarbonate values (HCO_3 <24 mmol/L). Almost 48% (n = 10) of the neonates with BA, 36% (n = 12) cases in sepsis group, 67% (n = 2) in nephrotoxic drug group and 25% (n = 1) with combined risk factors had low serum bicarbonate. The mean Up/Uc ratio was (0.19 ± 0.07) in normal reference range in all patients.

When compared among various stages of AKI, laboratory parameters did not vary significantly except for Up/Uc ratio, but overall the values were in normal reference range [Table 4].

The urine analysis for protein, sugar, RBC, epithelial cells, and USKUB was also normal in all the study patients.

Table 1: Demographic profile of the study population

	Median	Minimum-maximum	Inter quartile range
Birth weight (kg)	2.8	2.08-3.8	2.400-3.100
Birth length (cm)	48	43-53	47-50
Gestational age (weeks)	38.43	37.14-41.29	37.857-39.321
Apgar at 5 min	7	1-9	2-8

Table 2: Clinical parameters of the study patients at 14-week follow-up

	Mean±SD
Length (cm)	61.06±2.68
Weight (kg)	6.01±0.59
SBP (mmHg)	94.38±4.2
DBP (mmHg)	49.62±4.74

SD – Standard deviation; SBP – Systolic blood pressure; DBP – Diastolic blood pressure

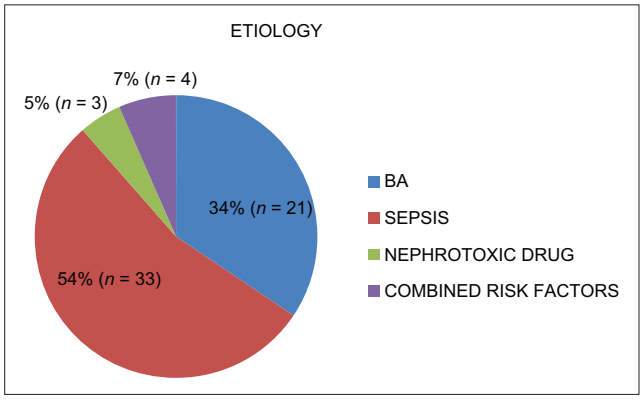

Figure 2: Pie chart showing distribution of cases as per etiology of acute kidney injury

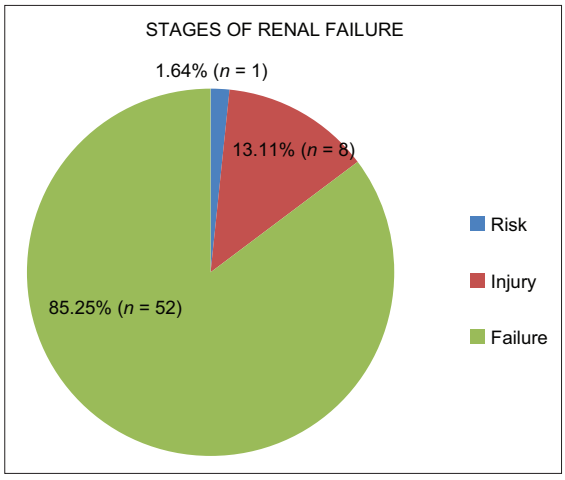

Figure 3: Pie chart showing the distribution of cases as per acute kidney injury staging

The mean S Cr at 6 months was 0.22 ± 0.08 mg/dL and median eGFR of the study population at 6 months was 133.25 (94.3–176.8) ml/min/1.73 m^2 however difference among subgroups was statistically not significant. Four out of 61 subjects (6.56%) had reduced eGFR, while 15 (24.59%) cases had hyperfiltration but difference among groups was not significant (P = 0.97) [Table 5].

Overall, 63.93% (n = 39) of the cases had one or more renal parameters deranged at 6 months of evaluation. 62% (13/21) of neonates with birth asphyxia, 51.5% (17/33) with sepsis, 67% (2/3) with nephrotoxic drugs and 25% (1/4) with combined risk factors had one or more altered parameter. However, among group comparison this was not statistically significant.

Table 3: Clinical parameters at 6 months of follow-up based on acute kidney injury staging

	Risk	Injury	Failure	*P*
Length (cm)				
n	1	8	52	0.841
Mean±SD	66±0	67.5±3.25	67.58±2.57	
Weight (kg)				
n	1	8	52	0.302
Mean±SD	6.9±0	7.76±0.98	7.37±0.74	
SBP (mmHg)				
n	1	8	52	0.900
Mean±SD	96±0	94.38±3.66	94.19±3.79	
DBP (mm Hg)				
n	1	8	52	0.510
Mean±SD	53±0	50.75±3.96	49.25±4.61	

SD – Standard deviationl; SBP – Systolic blood pressure; DBP – Diastolic blood pressure

Table 4: Laboratory parameters at 6 months based of acute kidney injury staging

	Risk	Injury	Failure	*P*
eGFR (ml/min/1.73 m^2)				
n	1	8	52	0.450
Mean±SD	270.6±0	144.43±58.84	152.23±72.94	
HCO3 (mmol/L)				
n	1	8	52	0.833
Mean±SD	22.2±0	24.3±2.03	23.2±2.73	
VBG (pH)				
n	1	8	52	0.985
Mean±SD	7.39±0	7.39±0.03	7.39±0.03	
Up/Uc ratio				
n	1	8	52	0.016
Mean±SD	0.08±0	0.14±0.06	0.2±0.07	

SD – Standard deviationl; Up/Uc – Urinary protein creatinine ratio; VBG – Venous blood gas; eGFR – Estimated glomerular filtration rate

Discussion

This was a descriptive cohort study in term neonates developing AKI after admission. Main objective was to see renal outcome in these babies at 6 months. Previous studies included AKI cases from records and followed them subsequently. As prematurity and low/very low birth weight are known risk factors for kidney dysfunction due to reduced nephron mass and immature tubular function and impaired nephrogenesis,[13,14] they were excluded. In this study sepsis was biggest contributor (54.1%) for AKI followed by BA (34.4%). These are well-established causes for AKI in neonatal period with sepsis accounting upto 78% cases and BA in 38%–42% cases in various studies.[15-17] The mean age of developing AKI was 5.2 ± 3.36 days with incidence of 26% (79 of 303). The incidence of neonatal AKI varies from 8% to 24% depending on age, weight, criteria used, and the underlying risk factor.[18] In a recent multi-centric retrospective cohort (AWAKEN) study, overall 21% (449 of 2110) experienced AKI, but on subgroup analysis in term babies (≥36 weeks), the incidence was 27% (n = 247) similar to our study, mean age of diagnosis in their study was 2.8 ± 1.8 days, however it included AKI in all gestational ages.[19]

In the present study, the median value of FENa was 0.87 (<2.5), suggesting prerenal AKI in all. Prerenal AKI represents a functional change with rise in S. Cr and decreased urine output without actual kidney damage and is generally due to decreased renal blood flow and hypoperfusion secondary to hypovolemia. This is the most frequent cause of neonatal AKI in around 85%.[20,21] In present study majority of cases (77.1%) were oliguric with median urine output of 0.3 ml/kg/h in contrast to general observation that neonatal AKI is nonoliguric.[21] This could be because majority of the neonates had pre renal AKI (due to sepsis and third space loss of fluids). This was further supported by subgroup analysis which showed sepsis group to have higher proportion of

Table 5: Comparison of estimated glomerular filtration rate at 6 months based on etiology

eGFR	Etiology				Total	*P*
	BA (%)	Sepsis (%)	Nephrotoxic drugs (%)	Combined factors (%)		
Normal	15 (71.43)	22 (66.67)	2 (66.67)	3 (75.00)	42 (68.85)	0.973
Reduced	2 (9.52)	2 (6.06)	0 (0.00)	0 (0.00)	4 (6.56)	
Hyperfiltration	4 (19.05)	9 (27.27)	1 (33.33)	1 (25.00)	15 (24.59)	
Total	21 (100)	33 (100)	3 (100)	4 (100)	61 (100)	

eGFR – Estimated glomerular filtration rate

oliguric cases, i.e., 97% (32 of 33) compared to 57% in birth asphyxia ($P = 0.0007$).

According to nRIFLE criteria used in this study, majority of the neonates (85.2%) were in failure stage. The reason for this may be inclusion of decreased urine output independently as criteria for AKI leading to over diagnosis of severe staging. As most previous studies have taken increase in S Cr to diagnose AKI. In recent trial AKI was defined by nKDIGO with reported incidence of AKI to be 15% out of which 48.2% (216 of 449) cases in Stage I, 23.3% (105 of 449) in Stage II and 28.5% (128 of 449) were in Stage III.[19] Utility of categorizing AKI in various stages is still not robust as there is more emphasis on rise in S Cr from baseline.

At 6-month follow-up, length, weight, and BP were in normal range in all the neonates with no significant difference among different stages of AKI [Table 3]. 41% (25) of the patients had reduced levels of serum bicarbonate with highest numbers 47.6% (10 of 21) in BA group although among etiological subgroups, it was not statistically significant ($P = 0.59$). Low serum bicarbonate could be due to excess renal loss of bicarbonate and indicator of continued tubular dysfunction. Not much data is available on bicarbonate levels during follow up in previous studies. When laboratory parameters were compared in different stages of AKI, there was no significant difference except in urine protein to creatinine ratio with significant proteinuria in failure stage ($P = 0.016$) [Table 4]. The median eGFR was 133.25 ml/min/1.73 m^2 with 6.56% (4) having reduced eGFR while 24.59% (15) had hyperfiltration. More babies in BA group had low eGFR 47% (10 out of 21) than sepsis 39% (13 out of 33) group though difference was not significant ($P = 0.40$). Overall, significant number of cases that is 63.93% (39 of 61) had one or more parameters deranged at six months follow-up.

The traditional belief that AKI is followed by complete renal recovery has been challenged in recent years.[4,5,9,13,22] Studies in adults show that risk of progression to CKD after AKI is as high as 31%.[4,5] In pediatric population, Askenazi *et al*. followed 29 patients of acute renal failure with median age of 6.7 years for duration of 3–5 years showed that 31% of study subjects had microalbuniuria, 14% had reduced GFR and 20% had hypertension. Overall, 59% of the patients had at least one sign of residual renal injury.[22] In another study by Mammen *et al*. in 126 patients of 0–18 years with AKI (23.8% were neonates) followed for duration of 1–3 years observed that 12.5% patients had persistent proteinuria (either microalbuminuria or overt proteinuria), 3.2% had hypertension, 10.3% of them developed CKD (defined as the presence of albuminuria/proteinuria and/or GFR <60 ml/min/1.73 m^2), while 46.8% were at risk of developing CKD (GFR 60–90 ml/min/1.73 m^2 and/or hyperfiltration and/or hypertension).[9] In neonatal age group, there are reports of long term renal dysfunction in preterm and low birth weight babies with AKI,[13,14] others have studied newborns with risk factors like renal vein thrombosis, post cardiac surgery, ECMO etc.[23-25] In term good weight babies, data are sparse with few studies reporting long term sequelae in 19%–40%.[8,9] Most studies were retrospective cohort including babies from records and had small sample size (5–16 in number), however follow-up period was robust ranging from 1 month to as long as 19 years. Polito *et al*. studied six full term neonates with AKI in a retrospective cohort study followed up from 6.5 to 19 years of age and revealed ESRD in one patient (17%), proteinuria in 66% patients, hypertension in 17% renal atrophy on ultrasonography in 50% of the patients. Nearly 66.7% of the study patients developed abnormal renal functions in the long run.[8] The pathophysiology for progression to CKD is hypothesized that inflammation after AKI leads to interstitial inflammatory cell infiltrations which further exacerbate injury and promote ongoing fibrosis. In addition, loss of nephrons during acute insult to the kidney leads to a compensatory glomerular hypertrophy and hyperfiltration in the remaining nephrons, which in turn trigger tubulointerstitial fibrosis, arteriosclerosis, and eventual glomerulosclerosis.[26-28] The strength of this study is prospective cohort of term babies which were followed from diagnosis of AKI till 6 months and an effort toward finding answer as to late consequences of AKI in term good weight newborns. On the other hand, small sample size and relatively short duration of follow-up are main limitations, as many long-term effects like proteinuria, fibrosis and scarring may take long to develop.[29]

Conclusion

A large proportion of term newborns with AKI continue to have deranged renal parameters therefore need careful monitoring for long duration.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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