Original Article

DOI: 10.7860/JCDR/2023/63089.18370

Incidence of Acute Renal Failure in Preterm Babies in a Tertiary Care Centre from Southern India: A Cross-sectional Study

Neonatology Section

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ABSTRACT

Introduction: Preterm babies are a vulnerable population group who are more susceptible to multiple end-organ damage due to an immature immune system and incomplete organogenesis/organ function. There is scanty data on preterm Acute Kidney Injury (AKI) in India.

Aim: To investigate the incidence of acute renal failure and the risk factors predisposing preterm babies to renal failure in an inborn at a tertiary care centre in Southern India. Additionally, we aimed to evaluate the usefulness of a biomarker, Neutrophil Gelatinase Associated Lipocalin (NGAL), as both a marker of renal function and a predictor of AKI in preterm babies.

Materials and Methods: A cross-sectional study was conducted in the Neonatal Intensive Care Unit (NICU) at Christian Medical College, Vellore, Tamil Nadu, India, between May 2014 and August 2014. The study included babies born <33 weeks of gestation, while those with abnormal antenatal renal scans, major systemic congenital anomalies, and chromosomal anomalies were excluded. Demographic details and clinical features were noted. Weekly monitoring included urine output, assessment of clinical deterioration, details of interventions, unexpected events, and the use of nephrotoxic drugs. Blood samples for serum creatinine and urine samples for NGAL were collected once a week starting from 72 hours of age. The data was statistically analysed using Statistical Package for the Social Sciences (SPSS) software, version 16.0. Descriptive statistics were reported using mean±SD for continuous variables. Repeated measures Analysis of Variance (ANOVA) and Chi-square test/Fisher's-exact test were used for categorical variables. Risk factor analysis was done using log binomial to estimate the Relative Risks (RR), considering values greater than 1 as significant.

Results: During the study period, a total of 4823 live births were recorded. Among them, 80 babies had a gestational age <33 weeks (10.14%). One baby was not recruited as the parents did not provide consent, leaving a total of 79 babies included in the study. Five babies did not complete the study (three died and two were discharged against medical advice). The incidence of AKI in babies <32±6 weeks in this study was 10 out of 79 (12.6%). It was higher in babies <28 weeks, with 4 out of 10 (40%) affected, and all 10 babies (100%) weighed less than 1500 gm at birth. Risk factors for AKI included oliguria, Patent Ductus Arteriosus (PDA), nephrotoxic drugs, low APGAR score, mechanical ventilation, Continuous Positive Airway Pressure (CPAP), and abnormal antenatal scans. Urine NGAL was estimated in 30 babies, and it was found that NGAL levels were high in week 1 or rose by week 2 in those with AKI, while creatinine levels increased in week 2 or 3. NGAL was inversely proportional to gestational age and birth weight. Both NGAL rise and creatinine levels were observed in babies with AKI associated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), umbilical lines, and asphyxia.

Conclusion: The incidence of AKI was found to be 10%. Although NGAL levels were noted to rise earlier than creatinine levels in those with AKI, a definitive cutoff value for NGAL to define AKI could not be calculated. Due to the small study population, the sensitivity and specificity of NGAL could not be determined.

Keywords: Acute kidney injury, Biomarkers, Creatinine, Neonatal nephrology, Neutrophil gelatinase associated lipocalin, Urine output

INTRODUCTION

Preterm babies are susceptible to multiple end-organ damage due to an immature immune system and incomplete organogenesis/organ function [1]. Assessing renal function in newborn babies can be challenging [2]. There is a knowledge gap in identifying neonatal AKI as a significant morbidity and its repercussions on long-term renal function in the Indian scenario [3].

Serum creatinine, the standard measure of renal function, is not a sensitive marker for kidney injury, particularly in neonates. There is a dearth of prospective data regarding the incidence of renal failure in preterm babies in India [4]. Creatinine levels in the first 24-72 hours reflect maternal creatinine and take upto 14 days to reflect neonatal renal function; and hence cannot be relied upon [5,6]. Since existing studies have used creatinine as a marker for AKI [7,8], the present study used an absolute creatinine value of >1.3 mg/dL or a 50% rise from the baseline to define AKI [9,10].

Various biomarkers have been used to assess renal function. Among the known biomarkers, NGAL is one that has been extensively studied and found to be a more sensitive marker of AKI [11,12]. Similar to Troponin, a marker of myocardial injury, there is a need for markers that accurately predict early loss of renal function to prevent irreversible kidney injury [13,14].

Therefore, the aim of this study was to determine the incidence and risk factors of acute renal failure in preterm babies and to investigate whether NGAL levels can be used as an early marker of kidney injury in preterm babies. Urine NGAL levels were tested weekly for four weeks. Due to financial constraints, NGAL testing was performed for only 30 babies.

MATERIALS AND METHODS

A cross-sectional study was conducted at Christian Medical College, Vellore, Tamil Nadu, India, involving the Departments of Neonatology and Paediatric Nephrology subdivision during the period from

May 2014 to August 2014. Institutional research board clearance was obtained prior to starting the study, and the approval number is FG/8588/12/2013.

Inclusion criteria: Babies born at <33 weeks of gestational age who were admitted to the neonatal ICU. The reason for this was that these babies typically require a longer hospital stay, making it feasible to perform weekly creatinine and NGAL tests.

Exclusion criteria: Babies with abnormal antenatal renal scans, major systemic congenital anomalies, and chromosomal anomalies were excluded from the study. All babies who met the inclusion criteria and did not have any of the exclusion criteria were recruited after obtaining informed consent from the parents.

Sample size: Previous studies have shown varying incidences of renal failure in neonates. Based on two studies [8,9], the sample size was calculated assuming an incidence of renal failure in the population of 10%, with a precision of 6% and a 95% confidence interval. The calculated sample size was 96.

Formula

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where,

p: Expected proportion

d: Absolute precision

1-α/2: Desired Confidence level

Procedure

The details, including demographic information, maternal history (both antenatal and perinatal), intrapartum and neonatal history, the entire clinical course in the hospital with complications that may predispose to acute kidney injury, routine investigations, and procedures, were recorded in a standardised proforma.

Parameters included antenatal risk factors in the mother, like gestational diabetes, gestational hypertension, Urinary Tract Infection (UTI), and chorioamnionitis. Neonatal details analysed included birth weight, gestational age, APGAR score, presence of, invasive lines, any invasive procedures performed, course in the hospital (like mechanical ventilation, CPAP), use of nephrotoxic drugs (like Ibuprofen, aminoglycosides), and co-morbidities in the baby (like asphyxia, sepsis, necrotising enterocolitis). The final condition of the neonate at discharge and feeding details were also noted.

During the hospital stay, in addition to the weekly monitoring of clinical status, urine output, and any clinical deterioration, details of interventions (such as long lines, ventilation), any life-threatening events, and the use of nephrotoxic drugs were recorded.

Serum creatinine was collected after 72 hours of life and then weekly thereafter. An increase in serum creatinine to more than 1.3 mg/dL or more than a 50% rise compared to the previous value was used to define AKI [9,10].

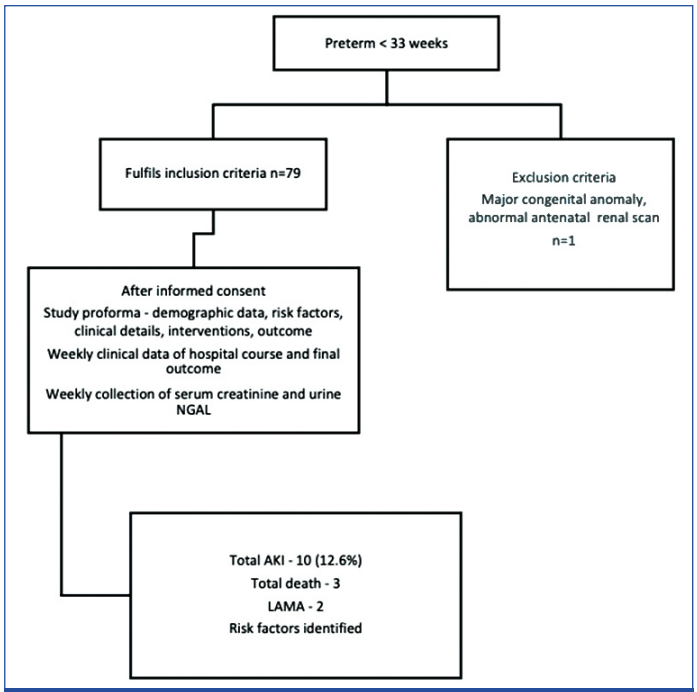
Urine for NGAL was collected and stored in all babies at 72 hours of life and then weekly thereafter. Due to cost restraints, NGAL testing was performed for only 30 babies as part of this study to assess its usefulness in detecting AKI in this population. Babies who were discharged before four weeks were followed-up on an outpatient basis, and serum creatinine and urine NGAL were collected during these visits. Babies who left against medical advice prior to four weeks were considered as case dropouts.

STATISTICAL ANALYSIS

The data were statistically analysed using SPSS software version 16.0. Descriptive statistics were reported using Mean±SD for continuous variables. ANOVA analysis was performed for parameters measured at various time points (such as Creatinine and NGAL values). Categorical variables were assessed using the Chi-square or Fisher's exact test. Incidence was reported using n and %. Risk factor analysis was conducted using Log binomial to estimate the RR. Survival analysis was done to assess the outcome of renal failure.

RESULTS

There were a total of 4,823 live births during this period. Of these, 789 were preterm deliveries (<37 weeks) (16.36%). Among them, 80 were preterm deliveries <33 weeks of gestation (10.14%). There were 79 babies who met the study criteria and were recruited. One baby was excluded due to a renal anomaly identified in the antenatal scan. Out of these, three died-one within three days of life and two as late neonatal deaths (3.7%), and two left against medical advice (2.5%). These five babies could not complete the evaluation. The remaining 93.6% were discharged alive and well. Flow diagram for the study in [Table/Fig-1].



[Table/Fig-1]: Flow diagram.

Among the recruited babies, there were 12 babies (15.2%) between 27 to 28 weeks, 26 (32.9%) between 29 to 30 weeks, and 41 (51.9%) between 31 to 33 weeks. In terms of birth weight, 45 babies (56.1%) weighed between 1001 to 1500 gm, 25 babies (31.6%) weighed between 1501 and 2000 gm, 8 babies (10.1%) weighed less than 1000 gm, and 1 baby (1.2%) weighed more than 2000 gm. There were 45 males (57%) and 34 females (43%). The male-to-female ratio was 1.3:1 [Table/Fig-2]. Out of the total 79 babies, 69 babies had antenatal scans done. Normal scans were noted in 45 babies (65.2%), while 12 babies (17.3%) had abnormal scans. There were 10 sets of twins and one set of triplets. Abnormal scans included abnormal Doppler and Intrauterine Growth Restriction (IUGR), and one baby had foetal ascites.

The most common morbidity seen in the mothers was pregnancy-induced hypertension (PIH) in 31 cases (39.2%), followed by preterm Pre-labour Rupture of Membranes (PPROM) in 18 cases (22%). Other risk factors included Gestational Diabetes Mellitus (GDM) (GDM) in 11 cases (13.9%), urinary tract infection (UTI) in 2 cases (2.5%), and chorioamnionitis in 5 cases (6.3%) [Table/Fig-2].

Respiratory distress was the most common symptom {n=52 (65.8%)} followed by poor perfusion {n=9 (11.3%)}. Other symptoms included abdominal distension {n=6 (7.5%)}, apnoea {n=5 (6.3%)},

Parameters	N (%)
Gestational age (weeks)	
<28	12 (15.2)
29 to 30	26 (32.9)
30 to 33	41 (51.9)
Birth weight (in gm)	
<1000	8 (10.1)
1001 to 1500	45 (56.1)
1501 to 2000	25 (31.6)
>2000	1 (1.2)
Gender	
Male	45 (57)
Female	34 (43)
Mode of delivery	
Lower Segment Caesarean Section (LSCS)	47 (59.5)
Normal	25 (39.7)
Breech/instrumental	7 (8.8)
Maternal antenatal risk factors	
Pregnancy induced hypertension	31 (39.2)
Preterm premature rupture of the membranes	18 (22.7)
Gestational diabetes mellitus	11 (13.9)
Chorioamnionitis	5 (6.3)
Urinary tract infection	2 (2.5)
Peripartum period	
Resuscitation at birth	17 (21.5)
Intubation	15 (18.9)
Symptomatic at birth	55 (69.6)
Symptoms (N=55)	
Respiratory distress	52 (65.8)
Poor perfusion	9 (11.3)
Abdominal distension	6 (7.5)
Apnoea	5 (6.3)
Temperature instability	4 (5.0)
Shock	2 (2.5)
Oliguria	2 (2.5)
Anuria	1 (1.2)
Seizure	2 (2.5)
Hypoglycaemia	1 (1.2)
Morbidity during hospital stay	
Hyaline membrane disease	33 (41.7)
Sepsis	24 (30.3)
Necrotising enterocolitis	10 (12.6)
Patent ductus arteriosus	9 (11.3)
Depressed at birth	5 (6.3)
Intraventricular haemorrhage	1 (1.2)
Intervention	
i.v. fluids	79 (100)
Nasogastric feeds	79 (100)
Umbilical venous line	64 (81)
Umbilical arterial line	29 (45.5)
Continuous positive airway pressure	36 (36.7)
Mechanical ventilation	9 (11.3)
Percutaneous central line	3 (3.7)
Inotropes	17 (21.5)
Drugs	
Aminoglycosides	61 (77.21)
Ibuprofen	4 (5.0)
Indomethacin	3 (3.7)
Inotropes	17 (21.51)

[Table/Fig-2]: Showing various parameters (n=79).

temperature instability {n=4 (5%)}, seizures {n=2 (2.5%)}, hypoglycaemia {n=1 (1.2%)} and decreased urine output {n=2 (2.5%)}. Hyaline membrane disease was the commonest associated morbidity seen {n=33 (41.7%)} followed by sepsis {n=24 (30.3%)}, which affected one-third of the cases. Other co-morbid conditions included Necrotising Enterocolitis (NEC) {n=10 (12.6%)}, PDA {n=6 (7.5%)} and intraventricular haemorrhage {n=1 (1.2%)} were other co-morbid conditions. There were five babies who were depressed at birth (6.3%) [Table/Fig-2].

The incidence of AKI in preterm <33 weeks of gestational age was found to be 12.6%. There was a higher incidence in babies born at 28 weeks or less (4/10- 40%). There were three (30%) babies at 32 weeks and one baby (10%) each at 29, 30, and 31 weeks of gestation. All babies with AKI weighed <1500 gm at birth. The mean value of weekly creatinine values decreased from 0.73 to 0.35 mg/dL from week one to week four [Table/Fig-3]. In the first week, 15 babies (19.2%) had creatinine levels more than 0.9 mg/dL but by week four this had decreased to only one (2.2%).

Creatinine (mg/dL)	Min.	Max.	Mean±Std. Dev.
Week-1 (N=79)	0.33	1.31	0.73±0.21
Week-2 (N=77)	0.29	1.22	0.58±0.2
Week-3 (N=76)	0.1	1.65	0.44±0.21
Week-4 (N=74)	0.13	1.19	0.35±0.19

[Table/Fig-3]: Creatinine trend over four weeks.

Certain high-risk conditions where renal injury was expected were looked at. These included babies with asphyxia, NSAID use, inotropes, umbilical lines, mechanical ventilation, and CPAP [Table/Fig-4]. Creatinine values were almost similar in the IMV and CPAP groups except in week three when the difference was statistically significant (p-value <0.05). Similarly, there was a significant increase in creatinine in week three among babies exposed to NSAIDs. The values of creatinine showed no statistical difference in the asphyxiated and non-asphyxiated group.

Creatinine in asphyxiated babies				
Creatinine (mg/dL)	**Asphyxia (N=6)**	**Normal (N=73)**	**M±SD**	**p-value**
Week-1	0.75	0.73	0.778±0.15	0.75
Week-2	0.53	0.59	0.488±0.09	0.12
Week-3	0.43	0.44	0.856±0.06	0.69
Week-4	0.33	0.35	0.856±0.06	0.69
Creatinine and NSAID drugs				
Creatinine (mg/dL)	**NSAID drugs (n=7)**	**No NSAID drugs (n=72)**	**M±SD**	**p-value**
Week-1	O.72	0.73	0.884±0.12	0.83
Week-2	0.69	0.57	0.149±0.19	0.11
Week-3	**0.61**	**0.42**	**0.048±0.15**	**0.002**
Week-4	0.34	0.49	0.102±0.32	0.24
Creatinine trend in IMV and CPAP groups				
Creatinine (mg/dL)	**IMV (n=9) {95% CI)**	**CPAP (n=36)**	**Non ventilation (n=34)**	**p-value (Bonferroni test post hoc analysis)**
Week-1	0.8 (0.006-1.4)	0.7 (0.65-0.89)	0.7 (0.55-0.74)	0.401
Week-2	0.6 (0.07 to -0.24)	0.6 (0.45-0.6)	0.6 (0.43-0.64)	0.944
Week-3	**0.7 (-4.1-6.6)**	**0.4 (0.03-0.33)**	**0.4 (0.03-0.3)**	**0.03***
Week-4	0.3 (-1.16-0.52)	0.4 (0.24-0.63)	0.3 (0.24-0.35)	0.573

Creatinine and umbilical lines			
Creatinine (mg/dL)	**UA+UV lines (N=29)**	**No lines (N=50)**	**p-value (t-test with Levene's test for equality of variance)**
Week-1	0.78 (-0.15 to 0.13)	0.71 (-0.14 to 0.12)	0.884
Week-2	0.6 (-0.18 to 0.07)	0.56 (-0.16 to 0.05)	0.149
Week-3	**0.51 (-0.35 to 0.03)**	**0.41 (-0.43 to 0.11)**	**0.048***
Week-4	0.39 (-0.32 to 0.03)	0.33 (-0.32 to 0.03)	0.102

Creatinine and umbilical lines				
Creatinine (mg/dL)	**Inotropes (N=17)**	**No inotropes (N=62)**	**p-value (ANOVA test)**	**95% Confidence interval**
Week-1	0.8241	0.7126	0.53	-0.001 to 0.22
Week-2	0.6264	0.5714	0.388	-0.07 to 0.18
Week-3	**0.6429**	**0.4177**	**0.008**	**0.06 to 0.39***
Week-4	0.3425	0.3581	0.879	-0.22 to 0.19

[Table/Fig-4]: Creatinine trend in babies with asphyxia, NSAIDS, inotropes, umbilical lines, mechanical ventilation, CPAP.

In the weekly assessment of risk factors and complications, the risk factors identified for AKI were anuria oliguria, PDA, nephrotoxic drugs, low Apgar, mechanical ventilation, CPAP, and abnormal antenatal scan. This was based on a relative risk value of more than 1 [Table/Fig-5].

Factors	AKI	No AKI	Relative risk	95% Confidence interval
Gestational hypertension	3	28	0.664	0.185 to 2.375
Abnormal scan	3	13	1.625	0.457 to 5.772
Apgar < 6	2	6	2.188	0.558 to 8.574
Asphyxia	0	8	-	
Oliguria	2	0	9.652	4.995 to 18.547
Hyaline membrane disease	3	30	0.597	0.167 to 2.141
Patent ductus arteriosus	4	5	5.185	1.800 to 14.933
Ibuprofen/Indomethacin	3	4	4.408	1.456 to 13.346
Aminoglycosides	10	51	1.352	1.176 to 1.556
Inotropes	2	15	1.097	0.256 to 4.693
Mechanical ventilation	2	7	1.944	0.487 to 7.770
CPAP	5	31	1.194	0.375 to 3.802
Death/DAMA	1	4	1.622	0.253 to 10.387

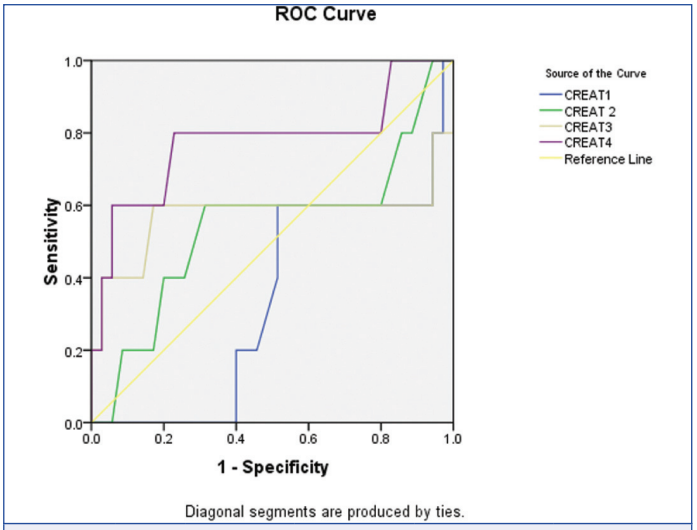
[Table/Fig-5]: Relative risk of various factors in AKI.

Urine NGAL was collected for 79 babies, of which only 30 were processed due to cost restraints. [Table/Fig-6] shows NGAL trend over four weeks. Of the ten babies with AKI, only four had NGAL processed as well. There are no absolute known values for NGAL to say if it is elevated. It was found that these babies had NGAL values >200 (ng/mL) in week one. One baby who had intraventricular haemorrhage and hydrocephalus continued to have elevated NGAL.

NGAL (ng/mL)	Mean±Std. Dev.
Week-1	260.51±264.09
Week-2	184.66±228.12
Week-3	83.68±93.91
Week-4	36.33±35.19

[Table/Fig-6]: NGAL trend over four weeks.

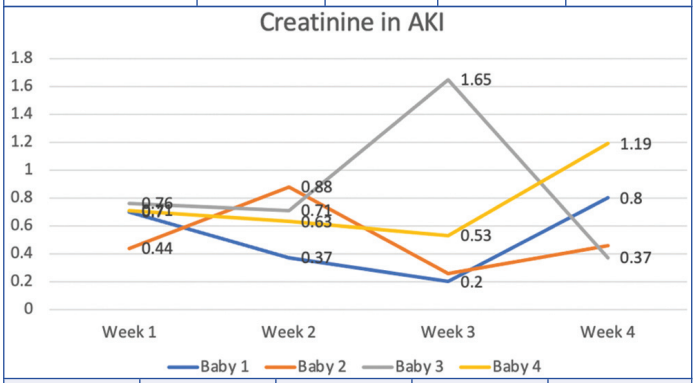
The ROC curve plotted for creatinine showed very low sensitivity and specificity [Table/Fig-7]. NGAL could not be plotted due to the very small sample size. There were four babies who had AKI in whom NGAL was also processed. In these babies, it was found that NGAL was high in week one or rose in week two, while creatinine levels rose only in week three [Table/Fig-8].



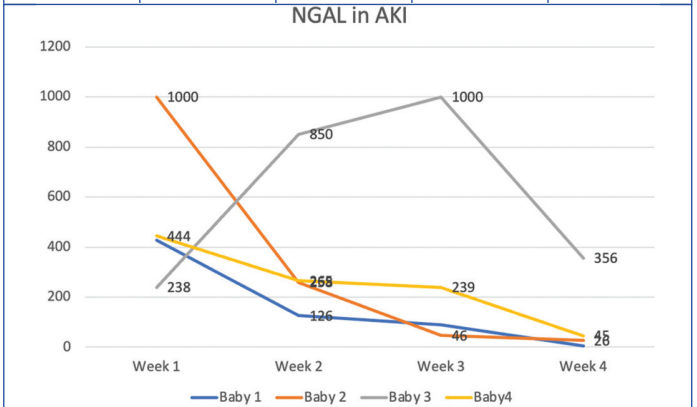
Area under the curve					
Test result variable (s)	**Area**	**Std. Error[a]**	**Asymptotic Sig.[b]**	**Asymptotic 95% Confidence interval**	
				Lower bound	**Upper bound**
CREAT-1	0.337	0.122	0.244	0.097	0.577
CREAT-2	0.543	0.162	0.759	0.226	0.860
CREAT-3	0.574	0.202	0.595	0.178	0.970
CREAT-4	0.777	0.140	0.047	0.502	1.052

[Table/Fig-7]: ROC for creatinine.

Creatinine (mg/mL)	Week-1	Week-2	Week-3	Week-4
Baby-1	0.7	0.37	0.2	0.8
Baby-2	0.44	0.88	0.26	0.46
Baby-3	0.76	0.71	1.65	0.37
Baby-4	0.71	0.63	0.53	1.19



NGAL	Week-1	Week-2	Week-3	Week-4
Baby-1	427.5	126	90.1	6.4
Baby-2	>1000	258.9	46.2	26.7
Baby-3	238	850	>1000	356
Baby-4	444.3	265	239	45.58



[Table/Fig-8]: Creatinine and NGAL in babies with AKI.
NGAL in babies with AKI

DISCUSSION

The incidence of AKI in preterm babies reportedly ranges between 3.4-24% [7]. There is a real need to define AKI in neonates, as reported by Zappitelli M et al., in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) neonatal AKI workshop [15]. Since available studies have used creatinine as a marker for renal function [16-21], this study used an absolute value of creatinine >1.3 or an increase of 50% from the previous value to define AKI, based on a study by Cataldi L et al., and AKIN criteria [9,10]. The incidence in the present study was found to be 12.6%. Various studies have shown a wide range of incidence of neonatal AKI, and most of them are retrospective studies. Like in a 25 year retrospective study by Vachvanichsanong P et al., from Thailand showed an incidence of AKI ranging from 6.4% to as high as 30% in a multicentric international collaborative study called the Assessment of Worldwide AKI Epidemiology in Neonates (AWAKEN) study by Jetton JG et al., [22,23]. The TINKER (The Indian PCRRT-ICONIC Neonatal Kidney Educational Registry) study, a large multicentric prospective study, showed an AKI incidence of 30% in neonates. In their study, significant risk factors included cardiac disease, usage of inotropes, severe peripartum events, requirement of respiratory support in the NICU, necrotising enterocolitis, any grade of intraventricular haemorrhage, evidence of fluid overload during the first 12 hours in the NICU, and requirement of resuscitation in the delivery room [24]. Results from the present study identified risk factors such as oliguria, PDA, nephrotoxic drugs, low APGAR, mechanical ventilation, CPAP, and abnormal antenatal scan (based on a relative risk value of more than 1).

In the present study, the population included extreme, very, and moderate preterm babies. AKI was more common in more preterm babies, as observed in the AWAKEN study by Jetton JG et al., which is an international multicentric retrospective study [25]. Although the number was small, nephrotoxic drugs like Indomethacin and Ibuprofen were associated with the development of AKI in the present study. Similar incidences of PDA (40%) were found in studies by Cataldi L et al., and Stojanović V et al., [9,16]. Cataldi L et al., also found that Ibuprofen was one of the factors predisposing to AKI [9]. In the present study, the creatinine levels normalised in babies exposed to nephrotoxic drugs, similar to the findings of the present study. The use of NSAIDs and other nephrotoxic drugs can be challenging for neonatologists in cases of babies with evidence of renal injury [26]. However, in the present study, the renal dysfunction caused by nephrotoxic drugs was transient, and creatinine levels normalised by week 4.

NGAL was measured in 30 babies, and the mean value of NGAL showed a decreasing trend from week 1 to 4. Studies have looked at babies with post-cardiac bypass and perinatal asphyxia and have found elevated levels of NGAL [27,28]. However, NGAL was found to be sensitive but with low specificity in determining AKI in prospective pilot studies [29]. In the present study, serial monitoring of urine NGAL was done in four babies with AKI. In these babies, a rise in urine NGAL was seen at week two, whereas a rise in creatinine was seen in week three. This suggests the possibility of urine NGAL being useful for the early determination of AKI in neonates.

Long-term follow-up of this cohort is ongoing, as based on renal morbidity observed in the FANCY study by Harer MW et al. The FANCY study found a higher incidence of renal dysfunction in Very Low Birth Weight (VLBW) babies on follow-up at five years [30]. Creatinine values normalised by week four among the survivors of AKI, but the long-term renal outcome needs to be evaluated. A prospective study with a large population size is needed to determine the incidence of AKI in neonates, as most studies are based on retrospective data.

Limitation(s)

This study specifically focused on preterm babies, and the sample size was small. Due to financial constraints, NGAL could not be processed for all babies. It is important to establish normal levels of urinary NGAL in different gestational age, and a larger study is needed to determine its usefulness as a biomarker for early diagnosis of AKI.

CONCLUSION(S)

This study found that the incidence of AKI in preterm babies <33 weeks of gestational age was 12.6%. The incidence was higher in babies born at 28 weeks or less and weighing <1500 gm. Risk factors for AKI included oliguria, PDA, nephrotoxic drugs, low APGAR, mechanical ventilation, CPAP, and abnormal antenatal scan. Serial weekly measurements of NGAL showed a decreasing trend. In the small number of babies with AKI who had both creatinine and NGAL measurements, NGAL levels showed a rise in week 2, while creatinine levels increased in week 3.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 13, 2023
- Manual Googling: May 19, 2023
- iThenticate Software: Jun 17, 2023 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Feb 07, 2023**
Date of Peer Review: **Apr 28, 2023**
Date of Acceptance: **Jun 21, 2023**
Date of Publishing: **Aug 01, 2023**