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Factors associated with acute kidney injury in neonates admitted in a tertiary-care setting of a developing country: A cross-sectional study.

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ABSTRACT… Objective: To assess the prevalence, risk factors and outcome of acute kidney injury (AKI) in neonates admitted in a neonatal intensive care unit (NICU) of developing country. **Study Design:** Cross-sectional study. **Setting:** Neonatal Intensive Care Unit at Sheikh Saeed Memorial Campus (SSMC) of Indus Hospital and Health Network (IHHN), Karachi, Pakistan. **Period:** April 2022 to September 2022. **Material & Methods:** Four hundred and seventy-one newborns hospitalized to the NICU were analyzed. Demographic details along with maternal and neonatal history, vitals, and clinical signs of newborns were noted. All at-risk newborns had their urine output assessed. Serum creatinine levels were assessed to classify AKI into stages using modified KDIGO criteria. **Results:** Out of 471 participants, 256 (54.4%) neonates were male. The prevalence of AKI was noted in 42 (8.9%) neonates. Based on the modified KDIGO stages, 26 (61.9%), 7 (16.6%), 7 (16.6%), and 2 (4.7%) neonates met the requirements for AKI stages 0, 1, 2, and 3, respectively. In comparison to newborns with normal renal function, newborns with AKI had significantly higher serum creatinine levels ($p<0.001$), lower urine output ($p=<0.001$), and lower creatinine clearance rates ($p=0.001$). Multivariate analysis showed that sepsis enhanced the risk of acquiring AKI (OR: 60.50, 95% CI: 26.03-169.88). Neonates in distress, and on ventilator had a higher risk of having AKI (OR: 13.88, 95% CI: 1.26-152.91) and (OR: 20.77, 95% CI: 1.1-390.49) respectively. **Conclusion:** The prevalence of AKI among neonates admitted in NICU was 8.9%. Fetal distress, sepsis and mechanical ventilation were significantly associated with AKI.

Key words: Acute Kidney Injury, Neonate, NICU, Newborns, Sepsis, Serum Creatinine.

INTRODUCTION

Failure of kidneys to maintain their normal functions (removal of nitrogenous wastes, fluids and electrolytes balance) is termed acute kidney injury (AKI).[1] A more traditional definition of AKI is Serum creatinine (sCr) elevation exceeding 1.5 mg/dL (132 micromol/L).[2] Neonatal kidneys are more vulnerable to injury or failure because of their inherently immature functions, congenital deformities, antenatal and maternal risk factors, hemodynamic and oxygenation instabilities.[3] AKI in neonatal population is reported to be 8-24% worldwide.[4] A multicenter study from china reported an incidence of 0.32% & 25.1% in a study from India.[5] Both term & preterm sick neonates frequently develop AKI, without pre-existing renal disease.[6]

Commonly encountered risk factors for AKI in Newborns are sepsis & birth asphyxia, however, other causes may include, dehydration, respiratory distress syndrome, bleeding & nephrotoxic drugs. Neonates of mothers exposed to "non-steroidal anti-inflammatory drugs (NSAIDs)" in perinatal period are also at risk of developing AKI.[7] Non-oliguric renal failure is a prevalent condition in newborns, however, oliguria (urine output <0.5 ml/kg/hour) is considered an insensitive biomarker for AKI. Recent studies have shown most promising early noninvasive biomarkers for AKI, including urinary interleukin-18 (IL-18), serum cystatin C (cysC), serum and urinary neutrophil gelatinase-associated lipocalin (N-GAL), Kidney Molecule-1 (KIM-1), however the best indicator for AKI continues to be serum

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creatinine (sCr).[8,9] Some researchers have also shown that theophylline resulted in almost 60% reduction in the incidence of AKI in neonates with birth asphyxia.[10]

Most commonly used criteria like AKIN and p-RIFLE are usually followed in in-patient setting using assessment of declining renal function, done with serial serum creatinine and urine output measurements, although these are slightly delayed in their presentation and kidney injury is already under progression before their noticeable interpretation.[11] "Kidney Diseases Improving Global Outcome (KDIGO)" developed feasible criteria to diagnose AKI in at-risk neonates for early identification, as it includes not only serum creatinine level but also helps to assess other parameters like urine output and change in creatinine level from baseline.[12] As there is paucity of data from Pakistan for neonatal AKI and it is one of the major morbidities which influences short-term and long-term outcome, so we wanted to determine the prevalence, risk factors and outcome of AKI in neonates admitted in a NICU of a developing country.

MATERIAL & METHODS

This cross-sectional study was carried out at NICU of Sheikh Saeed Memorial Campus (SSMC) of Indus Hospital and Health Network (IHHN), Karachi, Pakistan from April 2022 to September 2022 after the Ethics committee approval (Approval number: IRB_ IHHN_2022_02_002, Dated: 30/03/2022). All neonates born at the SSMC campus of the IHHN between the study period and requiring ICU admissions were analyzed. The exclusion criteria were neonates born with congenital malformations involving more than one system or newborns with congenital heart diseases. Out-patient babies who were admitted to NICU due to any reasons or re-admission of newborns due to any reason were also exclusion criteria.

Before data collection, informed consent was taken from parents or care givers. Data was collected on a special proforma. The data collected from the neonates include demographic, clinical and laboratory investigations details like gender, gestation, mode of delivery, weight at birth, age at presentation, maternal and neonatal risk factors, baseline and highest creatinine level, urine output and further progression of disease. A modified KDIGO criterion was used to define AKI and its stages. Neonates with serum creatinine of >1.0-1.5mg/dl and UOP of < 1 ml/kg/hour were considered stage 0, serum creatinine of > 1.5-1.9mg/dl and UOP < 1-0.5ml/kg/hour were considered stage 1, serum creatinine of > 2-2.5mg/dl and UOP < 0.5-0.3ml/kg/hour were considered stage 2 and serum creatinine of > 2.5mg/dl and UOP < 0.3ml/kg/hour were considered stage 3.

"Statistical Package for Social Sciences (SPSS)", version 26 (IBM, Armonk, NY, USA) software was used for statistical analysis. For quantitative variables (age, urine output and serum creatinine), we used mean, standard deviation, or median (interquartile range, or IQR), and for categorical variables (gender, birth weight, gestational age, AKI and risk factors status), we used numbers and percentages. Shapiro-Wilk test was applied to evaluate the normality of quantitative variables. Chi-square test/Fisher exact test were used to determine the relationship among various parameters and AKI. Additionally, the univariate and multivariable logistic regression methods were applied to evaluate unadjusted and adjusted odds ratios (ORs). All variables significant at univariate analysis ($p<0.25$) were used to make a final model using multivariable binary logistic regression through Backward LR variable selection. Confidence level was taken at 95% and a p-value less than or equal to 0.05 was regarded statistically significant.

RESULTS

In a total of 471 neonates, 256 (54.4%) were male and 215 (45.6%) female. The prevalence of AKI noted in 42 (8.9%). There were 26 (62.0%) neonates who had stage 0 AKI while 7 (16.6%), 7 (16.6%), and 2 (4.7%) neonates had AKI stage 1, 2, and 3, respectively. In terms of risk factors, 34 (81.0%) neonates (34/42) with AKI had sepsis, 14.3% of patients were infants of diabetic mother (IDM), 16.7 were on ventilator support, 16.7% were in fetal distress and 12.3% of neonates

were the babies of mothers who had pregnancy-induced hypertension (PIH) as shown in Figure-1.

Neonates having AKI had significantly higher serum creatinine levels (p=<0.001), lower urine output (p=<0.001), and lower creatinine clearance rates (p=0.001). AKI risk was also greater in newborns with low birth weight and premature delivery. The median gestational age and birth weight of infants with AKI were 36.85 (32.5-37.8) weeks and 2.26 (1.77-2.8) kg, respectively. In 42 neonates who had AKI, 23 (54.8%) had LBW. Furthermore, neonates with sepsis, fetal distress, IDM, PIH, or requiring ventilator support were more likely to develop AKI as shown in Table-I.

When neonates with AKI were divided into groups based on the degree of impaired renal function (modified neonatal KDIGO stages 0 to 3), our finding discovered that 57% of term neonates with AKI fall in stage I, three late-preterm neonates fall in stage II, and 2 neonates with low birth weight fall in stage III (Table-II).

Backward LR logistic regression analysis was applied to evaluate all parameters associated with newborn AKI development. We discovered that Sepsis enhanced the risk of acquiring AKI (OR: 60.50, 95% CI: 26.03-169.88). Neonates in distress and on a ventilator had an increased chance of having AKI (OR: 13.88, 95% CI: 1.26-152.91) (OR: 20.77, 95% CI: 1.1-390.49) as shown in Table-III.

DISCUSSION

Despite the latest developments in neonatology, AKI-related mortality and morbidity continue to be a serious issue. This study gave a descriptive summary of AKI in newborns hospitalized to our NICU. In our study the prevalence of AKI was 8.9 percent. Based on the literature, the prevalence of AKI in neonates ranges between 2.5-82%.[5,13,14] Our results showed that LBW infants made up 54.8% of the AKI cases. Up to 75% of VLBW newborns have been shown to have AKI.[15] In contrast to our results, Bolat F et el discovered that the prevalence of AKI in VLBW neonates was 34%.[16]

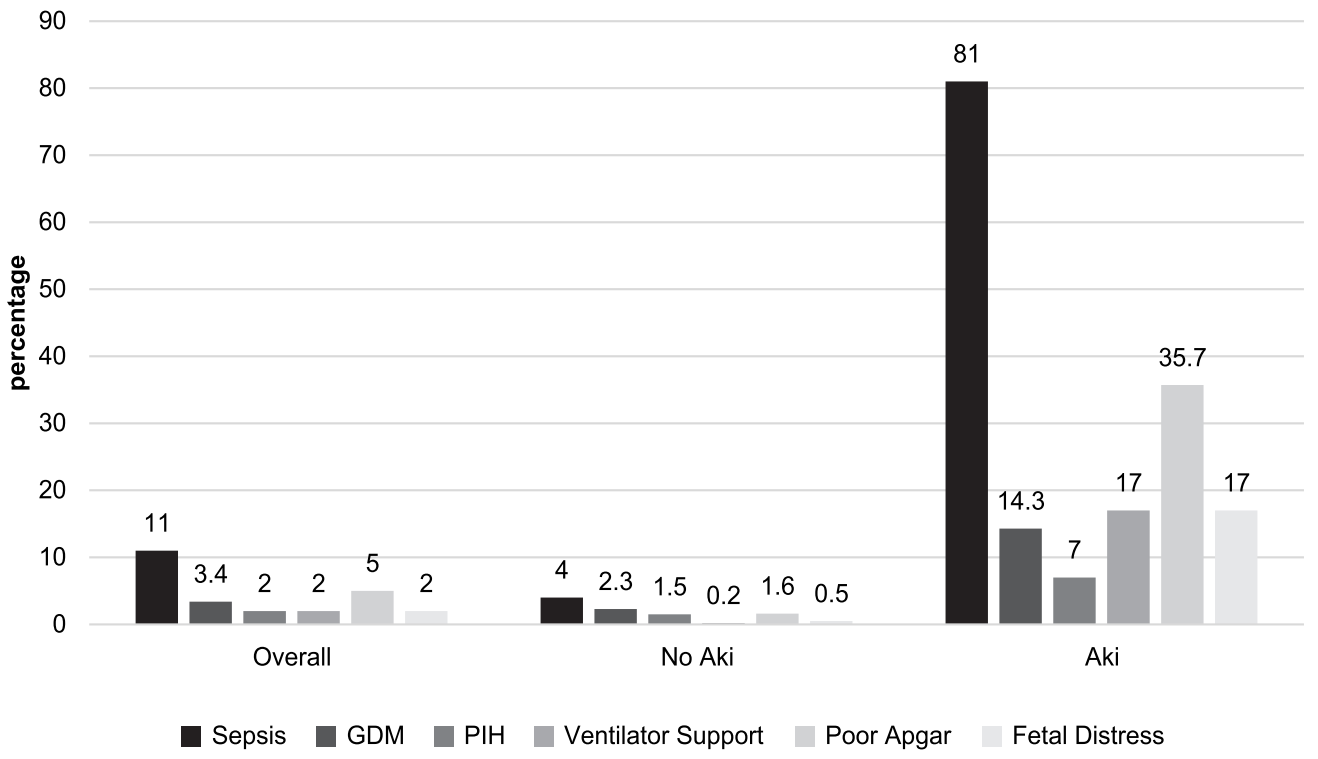

Figure-1. Distribution risk factors between acute kidney injury (AKI) status

Variables	Total (%)	Normal Renal Function (%)	Acute Kidney Injury (%)	P-Value
Gender				
Female	215 (45.6%)	198 (46.2%)	17 (40.5%)	0.481
Male	256 (54.4)	231 (53.8%)	25 (59.5%)	
Serum Creatinine mg/dl				
Median (IQR)	0.33 (0.25-0.43)	0.33 (0.25-.043)	1.95 (1.83-2.11)	*<0.001
Urine Output ml/kg/hr				
Median (IQR)	3.1 (2.2-3.8)	3.1 (2.4-3.9)	0.9 (0.62-1.57)	*<0.001
Creatinine Clearance ml/min				
Median (IQR)	61.32 (46.8-79.42)	61.32 (48-81)	9.26 (8.35-10.21)	*<0.001
Birth Weight in Kg				
Median (IQR)	2.7 (2.4-3.0)	2.7 (2.4-3.0)	2.26 (1.77-2.8)	*0.001
Gestational age				
Median (IQR)	37.50 (37-38.50)	37.5 (37-38.5)	36.85 (32.5-37.8)	
Gestational age category				
Term	359 (76.2%)	341 (79.5)	18 (42.9)	
Late Preterm	93 (19.7)	82 (19.1)	11 (26.2)	
Moderate Preterm	6 (1.3)	2 (0.5)	4 (9.5)	
Very Preterm	11 (2.3)	4 (0.9)	7 (16.7)	*<0.001
Extremly Preterm	2 (0.4)	-	2 (4.8%)	
Birth Weight Catogry				
Normal birth weight	340 (72.2%)	323 (75.3%)	17 (40.5%)	
Low birth Weight	127 (27.0%)	104 (24.2%)	23 (54.8%)	
Very low birth weight	3 (0.6%)	2 (0.5%)	1 (2.4%)	*<0.001
Extremely low birth weight	1 (0.2%)	-	1 (2.4%)	
Sepsis				
Yes	52 (11.0%)	18 (4.2%)	34 (81.0%)	*<0.001
No	419 (89.0%)	411 (95.8%)	8 (19.0%)	
GDM				
Yes	16 (3.4%)	10 (2.3%)	6 (14.3%)	*0.001
No	455 (96.6%)	419 (97.7%)	36 (85.7%)	
PIH				
Yes	9 (1.9%)	7 (1.5%)	3 (7.1%)	*0.038
No	423 (98.6%)	448 (98.5%)	39 (92.9%)	
Ventilator support				
Yes	8 (1.7%)	1 (0.2%)	7 (16.7%)	*<0.001
No	463 (98.3%)	428 (99.8%)	35 (83.3%)	
Poor Apgar Score				
Yes	22 (4.7%)	7 (1.6%)	15 (35.7%)	*<0.001
No	423 (98.6%)	422 (98.4%)	27 (64.3%)	
Fetal Distress				
Yes	9 (1.9%)	2 (0.5%)	7 (16.7%)	*<0.001
No	462 (98.1%)	427 (99.5%)	35 (83.3%)	

Table-I. Demographic character of study participants (n=471)

Variables	Non AKI (%)	AKI Stage 0 (%)	AKI Stage I (%)	AKI Stage II (%)	AKI Stage III (%)
Gestational Age Category					
Term	351 (77.1%)	10 (38.5%)	4 (57.1%)	2 (28.6%)	2 (100%)
Late Preterm	89 (19.6%)	7 (26.9%)	1 (14.3%)	3 (42.9%)	-
Moderate Preterm	5 (1.1%)	3 (11.5%)	-	1 (14.3%)	-
Very Preterm	8 (1.8%)	4 (15.4%)	2 (28.6%)	1 (14.3%)	-
Extremely Preterm	2 (0.4%)	2 (7.7%)	-	-	-
Birth Weight Category					
Normal birth weight	323 (75.3%)	12 (46.2%)	2 (28.6%)	3 (42.9%)	-
Low birth Weight	104 (24.2%)	13 (50.0%)	4 (57.1%)	4 (57.1%)	2 (100%)
Very low birth weight	2 (0.5%)	-	1 (14.3%)	-	-
Extremely low birth weight	-	1 (3.8%)	-	-	-

Table-II. Gestational age category and birth weight category distribution with AKI stages (n=471)

Variables	Groups	Unadjusted OR (95% CI)	P-Value	Adjusted OR (95% CI)	P-Value
Sepsis	No	Ref		Ref	
	Yes	97(39.32 – 239.5)	*<0.001	66.5(26.03-169.88)	*<0.001
GDM	No	Ref		-	
	Yes	6.98(2.4 – 20.3)	*<0.001	-	-
PIH	No	Ref		Ref	
	Yes	5.4(1.3-22.5)	0.02	-	-
Ventilator support	No	Ref		Ref	
	Yes	85.6(10.2-715.5)	*<0.001	20.7(1.1-390.4)	0.043
Fetal Distress	No	Ref		Ref	
	Yes	42.7(8.5 – 213)	*<0.001	13.88 (1.26-152.91)	0.032
Poor Apgar score	No	Ref		Ref	
	Yes	33.5(12.6 – 89.0)	*<0.001	-	-

Table-III. Univariate and multivariable association of risk factors and AKI status
CI: Confidence interval, Ref: Reference category, OR: Odds ratio, *Significant at p<0.05

Lee et al also discovered AKI in 56% of VLBW infants, which was linked to a poor prognosis.[17] According to our findings, term neonates accounted for 42.9% of the AKI cases. In agreement to our result, the AWAKEN cohort study found that babies with a later gestational age were similarly at risk of AKI. They discovered that the incidence of AKI varied by gestational age groups, along the higher rates in the younger (48%; 22 weeks to less than 29 weeks) and oldest (37%; more than 36 weeks) newborns.[18] A study investigated newborns with a gestational about a 34 weeks or greater and found that AKI was related with a higher birth weight as well as being male. This contrasts with our finding that gender had no effect on the prevalence of AKI.[19]

Mechanical ventilation can save the lives of people suffering from acute respiratory failure. Mechnical ventilation after birth was observed to be related with AKI development in this study. Mechanical ventilation might accelerate the onset of AKI, according to evidence. AKI is triggered by a number of factors rather than just one.[20] One probable explanation is that hypercapnia or hypoxemia reduces renal circulation, which may impact vascular dynamics by activating or inactivating vasoactive molecules such nitric oxide, angiotensin II, endothelin, and bradykinin. An additional theory is that barotrauma causes an inflammatory reaction in the lungs that results in the release of inflammatory mediators and the escalation of an inflammatory response throughout the body.[21] On multivariate analysis, newborns with sepsis and fetal distress had a considerably higher risk of developing AKI. These

findings are in agreement with the previous studies.[16]

Our study has several limitations. First, our study is cross-sectional and single-center, which limits the generalizability of the results. Second, the outcome of AKI patients is not analyzed, and outcomes over time and impaired renal function in discharged patients were not evaluated since their families were unable to be contacted , despite the fact that such an analysis is interesting and must be studied in future researches.

CONCLUSION

In conclusion, in spite of advancements in neonatal intensive care units, this study shows that AKI remains a significant concern. Fetal distress, sepsis and mechanical ventilation were the major risk factors for AKI. Timely management in babies with fetal distress, infection, or respiratory distress can reduce the onset of AKI, lowering the morbidity and mortality.

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2	Faraz Ahmed	Critical review and revisins.	
3	Sher Wali Khan	Data analysis and Intepretation.	
4	Syed Rehan Ali	Conception and drafting of artilce.	