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Incidence of Early Onset Neonatal Acute Kidney Injury in the NICU of Benha University hospital

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Abstract

Background: Neonatal Acute Kidney Injury (AKI) is a critical concern in neonatal intensive care units (NICUs), impacting morbidity and mortality. Early identification of AKI and its risk factors is crucial for improved neonatal care. **This study aimed to** identify the incidence, predisposing factors, clinical features of AKI in neonates admitted in NICU. **Methods:** A total of 200 neonates out of 570 cases attending the outpatient clinic were enrolled in the study. Clinical information, maternal medical history, examination findings, laboratory parameters, and medication exposures were collected and analyzed. The KDIGO workgroup definition was adapted to define neonatal AKI. **Results**: Among neonates, 45.0% developed AKI. Gender and gestational age showed no significant differences between AKI and non-AKI groups. Birth weight below 1000g was associated with AKI ($p = 0.03$). Neonates with AKI were more likely to receive aminoglycosides and vancomycin ($p < 0.001$), exhibit oliguric urine output ($p < 0.001$), and have hypertensive blood pressure levels ($p < 0.001$). Higher CRP levels ($p = 0.002$), total leukocyte count (TLC) ($p = 0.002$), and hemoglobin levels ($p = 0.04$) were observed in the AKI group. Additionally, sodium and potassium imbalances ($p < 0.001$) and metabolic acidosis ($p < 0.001$) were prevalent in AKI cases. **Conclusion:** This study showed the effect of birth weight, medication exposure, and clinical markers on AKI development. Elevated C-reactive protein levels and blood parameter imbalances serve as important risk indicators.

Keywords: Neonatal acute kidney injury, NICU, risk factors; clinical features, electrolyte imbalances.

Introduction

AKI is defined as a sudden decline in GFR resulting in the buildup of nitrogenous wastes and disruption of fluid, electrolyte, and acid-base balance (1).

Acute kidney injury (AKI) is frequently observed in neonates treated in Neonatal Intensive Care Units (NICUs). It is a multifaceted condition characterized by abrupt renal function reduction due to various underlying conditions. Clinically, its presentation ranges from slight kidney impairment to complete renal failure necessitating renal replacement therapy. The occurrence of AKI in neonates within NICUs varies from 2.4% to 56%, with associated mortality rates ranging from 33% to 78% (2, 3).

The causes of neonatal acute kidney injury encompass pre-renal, renal, and post-renal factors. Pre-renal azotemia, resulting from insufficient renal perfusion, accounts for over 80% of cases and is typically reversible with prompt treatment. Intrinsic renal injury can arise from parenchymal kidney damage. Post-renal injury arises from urinary tract obstruction leading to improper urine elimination (4).

Neonatal AKI contributes to heightened morbidity and mortality, along with an increased long-term risk of chronic kidney disease (CKD). Early identification of AKI through risk factor assessment may facilitate timely intervention and improved outcomes (1, 5).

The classification of neonatal AKI adheres to the KDIGO concept, incorporating urine output, duration, and serum creatinine changes. Severity of AKI is determined by considering all three factors collectively (6).

The purpose of this study was to identify the incidence, predisposing factors, clinical features of AKI in neonates admitted in NICU.

Patients and methods

Among cases attending the outpatient clinic, 200 cases of neonates out of 570 cases were enrolled in this study as they fulfilled the inclusion criteria. The data were collected from April 2022 to February 2023.

Inclusion criteria were preterm neonates (less than 37 weeks) need NICU & monitoring for at least 72 hours.

Exclusion Criteria were neonates with structural anomalies of the urinary tract (e.g., posterior urethral valve, hypoplastic kidneys…etc.) and neonates referred with insufficient data.

Written informed consent from the parents (guardians) of the neonates included in this study. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University.

All patients were subjected to the followings:

1) **Full history taking including:** A) Sex, post-natal age, gestational age, and birth weight. B) Maternal medical condition and maternal drugs administrated during pregnancy.

2) **Clinical examination of neonates:** a) Assessment of gestational age through analysis of maternal dates and Ballard scores. b) Assessment of Apgar score at 1 and 5 minutes. c) Assessment of reflexes like (suckling and Moro). d) Assessment of vital signs (respiratory rate, heart rate, blood pressure). e) Complete general examination including cardiac, chest, abdomen, CNS lying stress on chest condition, oral feeding, gastric aspirate, convulsion, jaundice, cyanosis, oliguria, polyurea, bleeding tendency, signs of septic shock. f) Urine collected using collecting bags every 8 hours and urine output calculated daily.

Investigation: Laboratory: All laboratory records of AKI cases reviewed include the following: Complete blood count, measurement of blood gases and serum blood urea, creatinine, electrolytes (Na-K-Ca).

Imaging: Abdominopelvic ultrasound searching for any abnormal size, shape, echogenicity of the kidneys and to exclude congenital anomalies of genitourinary tract.

Data Entry Points:

Daily information regarding weight, blood pressure, fluid intake (parenteral+ enteral), total fluid output (urine and others), use of nephrotoxic drugs, and laboratory parameters such as, blood creatinine, urea, sodium, markers of sepsis (blood cultures, urine cultures, and other cultures) were recorded.

Above mentioned variables were documented daily during the first week and thereafter first value of the week was noted.

We identified significant cardiac disease as hemodynamically significant patent ductus arteriosus (PDA), persistent pulmonary hypertension of the newborn (PPHN), cardiogenic shock and other congenital cardiac disease.

Discharge Data: The information about disposition status of the infant either discharged home before 120 days or still in the NICU at ≥120 days or transferred to another facility or NICU not in liaison with the national collaboration or history of death before completing 120 days were noted.

Definition of AKI: We defined AKI as an increase in serum creatinine of 0·3 mg/dl or more (≥26·5 μmol/L) or 50% or more from the previous lowest value, or a urinary output of <1 ml/kg/h on postnatal days 2–7, according to the KDIGO workgroup AKI definition modified for neonates **(7, 8)**.

Outcomes: The outcome of death was assessed over the time period of birth to 30 postnatal days or discharge from the hospital. Data were collected from admission until discharge from the neonatal ICU, death, or 120 days after birth. Duration of hospitalization was defined for neonates who died in the hospital by the number of days in the neonatal ICU (9).

Risk Factors for AKI: Data on congenital anomalies were extracted from kidney ultrasound reports and dichotomized into mild-to-moderate and severe congenital kidney anomalies.

Nephrotoxic medications were categorized as such in accordance with published studies (10, 11). Other medication exposures relevant to the neonatal ICU included methylxanthines, vasopressors, and diuretics. Medication exposure was categorized as being given before the AKI event. We assessed institutional factors including the median number of serum creatinine measurements and the type of assay. Frequency and methodology for laboratory monitoring were center-dependent. No adjustment was made for the type of creatinine assay because the AKI definition is on the basis of a change from baseline.

Statistical analysis

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by unpaired student t-test. Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analyzed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test when appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results

The gender distribution in the AKI group showed that 55.4% were males and 44.6% were females. In the Non-AKI group, 65.1% were males and 34.9% were females. There was no statically significant difference between the AKI and Non-AKI groups regarding the gender ($p = 0.2$). Among neonates with AKI, 29.7% were born before 32 weeks of gestation, while 70.3% were born at or after 32 weeks. In the Non-AKI group, 42.9% were born before 32 weeks and 57.1% were born at or after 32 weeks. There was no statically significant difference between the

AKI and Non-AKI groups regarding the gestational age (p = 0.07). Regarding the neonatal weight: Among neonates with AKI, 64.9% had a birth weight less than 1000g, and 35.1% had a birth weight of 1000g or more. In the Non-AKI group, 78.6% had a birth weight of 1000g or more, and 21.4% had a birth weight less than 1000g. The birth weight was statically significant between the AKI and Non-AKI groups (p = 0.03). **Table 1**

Neonates with AKI were more likely to have been administered aminoglycosides, vancomycin, and a combination of both drugs during their NICU stay compared to those without AKI. **Figure 1**

Neonates with AKI were more likely to exhibit oliguric urine output and hypertensive blood pressure levels than non-AKI neonates (P-value < 0.001). **Figure 2**

Among neonates with AKI, 13.5% had Apgar scores below 6, while 86.5% had scores of 6 or higher. In the Non-AKI group, 5.6% of neonates had Apgar scores below 6, and 94.4% had scores of 6 or higher with no significant difference between both studied groups (P-value =0.07). Among neonates with AKI, 77.0% required O_2 support, while 23.0% did not. In the Non-AKI group, 69.0% of neonates needed O_2 support, and 31.0% did not. The need of O_2 support was statistically insignificant between the studied groups (P-value =0.2).

diagnosis, maternal diseases and mode of delivery were shown in **Table 2**.

Laboratory findings were illustrated in **Table 3**.

Regarding the sodium levels, the AKI group showed 1.4% with levels below 135 and 75.7% with normal levels; in contrast, the non-AKI group had 26.2% with levels below 135 and 69.8% with normal levels, revealing a highly significant difference (p < 0.001). Regarding the potassium levels, 23.0% of neonates with AKI had levels above 5.5 and 56.8% had normal levels, whereas in the non-AKI group, 4.0% had levels above 5.5 and 95.6% had normal levels, showing a highly significant difference (p < 0.001). In terms of ABG values, the AKI group presented a higher prevalence of metabolic acidosis (MA) compared to respiratory acidosis (RA); conversely, the non-AKI group had lower MA prevalence and a significant proportion with normal ABG values, with a highly significant difference between the studied groups (p < 0.001). **Figure 3**

In terms of gender distribution, AKI Stage 1 was in 56.3% males and 43.8% females, while Stage 2 and 3 had an equal split of 50.0% for both genders. Regarding gestational age, 31.3% of AKI Stage 1 neonates were born before 32 weeks, whereas 68.8% were born at or after 32 weeks. For Stage 2 and 3 AKI cases, 20.0% were born before 32 weeks and 80.0% were born at or after 32 weeks. In terms of weight, 68.8% of AKI Stage 1 neonates had birth weights of 1000g or more, contrasting with 31.3% with weights less than 1000g. In Stage 2 and 3 AKI cases, 40.0% had birth weights of 1000g or more, and 60.0% had weights less than 1000g. The comparison of gender, gestational age and weight was insignificantly different between different stages of AKI.

There were no significant differences in drug usage patterns, including aminoglycosides, vancomycin, and both, between different stages of AKI. **Table 4**

Comparing AKI stage groups revealed significant differences in urine output and blood pressure. Specifically, AKI Stage 1 displayed a higher proportion of non-oliguric urine output (70.3%) compared to oliguric output (29.7%), while Stage 2 and 3 AKI cases predominantly exhibited oliguric output (80.0%). Hypertensive blood pressure was more prevalent in AKI Stage 2 and 3 (90.0%) compared to Stage 1 (34.4%), with the latter showing a greater occurrence of normal blood pressure (65.6%). Although Apgar scores and the need for O_2 support did not significantly differ between stages. **Figure 4**

There were no significant differences in diagnosis, maternal diseases and mode of delivery between different stages of AKI.

Hemoglobin (Hg) levels were significantly higher in Stage 2 and 3 of AKI compared to Stage 1 (P-value= 0.03). There were no significant differences in CRP, TLC and PLT between different stages of AKI. **Table 5**

There were no significant differences in Sodium, Potassium and ABG between different stages of AKI. **Table 6**

Table (1) Comparison between study groups regarding to the sex, gestational age and weight

Gender				Gestational age		Weight	
Males		**Females**		**≥32wks**	**<32wks**	**≥1000gm**	**<1000gm**
No.	%	No.	%	No. %	No. %	No. %	No. %

AKI	41	55.4%	33	44.6%	22	29.7%	52	70.3%	48	64.9%	26	35.1%
Non-AKI	82	65.1%	44	34.9%	54	42.9%	72	57.1%	99	78.6%	27	21.4%
X^2	1.8				3.4				4.5			
p-value	0.2				0.07				0.03*			

Table (2) Comparison between study groups regarding diagnosis, maternal diseases and mode of delivery

	Diagnosis				Maternal diseases				Mode of delivery			
	No RDS		RDS		Yes		No		CS		NVD	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
AKI	22	29.7%	52	70.3%	24	32.4%	50	67.6%	59	79.7%	15	20.3%
Non AKI	58	46.0%	68	54.0%	42	33.3%	84	66.7%	102	81.0%	24	19.0%
X^2	5.2				0.1				0.1			
p-value	0.02*				0.9				0.9			

Table (3) Comparison between study groups regarding Laboratory findings

	CRP			TLC			HB			PLT			
	≥10	<10		≥9000		<9000		≥11	<11		≥150000		<150000	
	No. (%)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
AKI	33 (44.6%)	41	55.4 %	60	81.1 %	14	18.9 %	4	5.4 %	70	94.6 %	21	28.4 %	53	71.6 %
Non-AKI	30 (23.8%)	96	76.2 %	76	60.3 %	50	39.7 %	1	0.8 %	12 5	99.2 %	33	26.2 %	93	73.8 %
X^2	9.3			9.2				4.1				0.1			
p-value	0.002*			0.002*				0.04*				0.7			

Table (4) Comparison between AKI stages groups regarding drug taking during NICU admission

	on aminoglycosides				on Vancomycine				on both			
	Yes		No		Yes		No		Yes		No	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Stage 1	63	98.4%	1	1.6%	17	26.6%	47	73.4%	17	26.6%	47	73.4%
Stage 2 and 3	10	100.0%	0	0.0%	2	20.0%	8	80.0%	2	20.0%	8	80.0%
X^2	0.1				0.2				0.2			
p-value	0.9				0.7				0.7			

Table (5) Comparison between AKI stages groups regarding laboratory findings

	CRP				TLC				PLT			
	≥10		<10		≥9000		<9000		≥150000		<150000	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Stage 1	28	43.8%	36	56.3%	51	79.7%	13	20.3%	17	26.6%	47	73.4%
Stage 2 and 3	5	50.0%	5	50.0%	9	90.0%	1	10.0%	4	40.0%	6	60.0%
X^2	0.1				0.6				0.8			
p-value	0.7				0.7				0.4			
	HB											
	≥11						<11					
	No.				%		No.		%			
Stage 1	2				3.1%		62		96.9%			
Stage 2 and 3	2				20.0%		8		80.0%			
X^2	4.8											
p-value	0.03*											

Table (6) Comparison between AKI stages groups regarding electrolytes and ABG

	Sodium						Potassium			
	<135		Normal		>145		Normal		>5.5	
	No.	%	No.	%	No.	%	No.	%	No.	%
Stage 1	1	1.6%	47	73.4%	16	25.0%	16	25.0%	35	54.7%
Stage 2 and 3	0	0.0%	9	90.0%	1	10.0%	7	70.0%	3	30.0%
X^2	1.3						0.8			
p-value	0.5						0.4			
	ABG									
	RA		MA		MA		Normal			
	No.	%	No.	%	No.	%	No.	%		
Stage 1	7	10.9%	5	7.8%	31	48.4%	21	32.8%		
Stage 2 and 3	1	10.0%	2	20.0%	6	60.0%	1	10.0%		
X^2	3.1									
p-value	0.4									

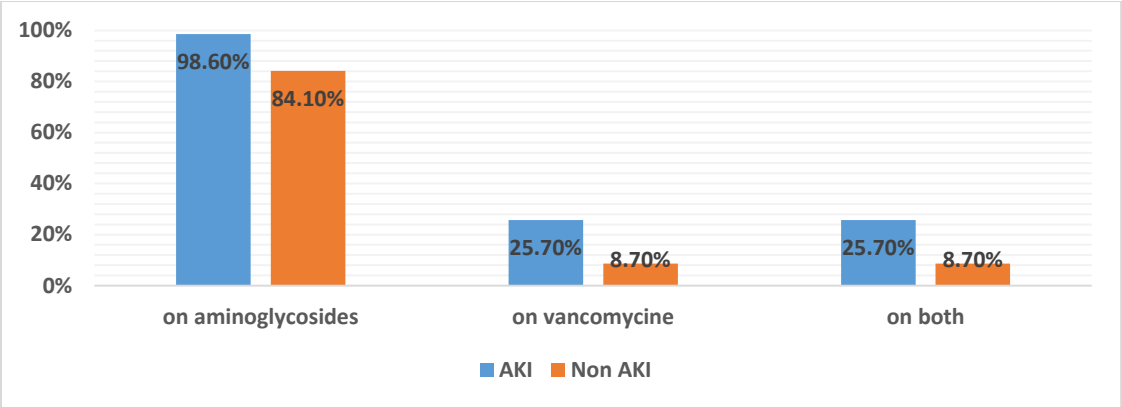

Fig. (1) study groups regarding drug history during NICU admission

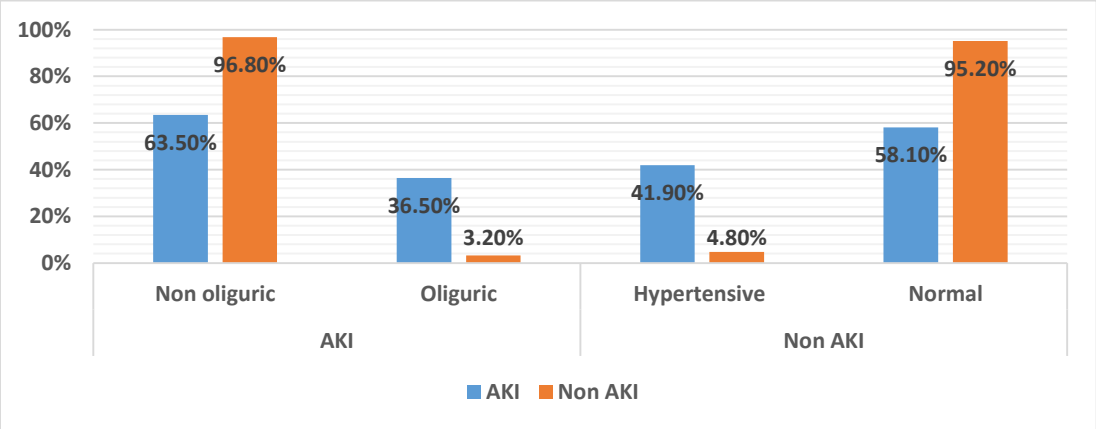

Fig. (2) study groups regarding urine output and blood pressure

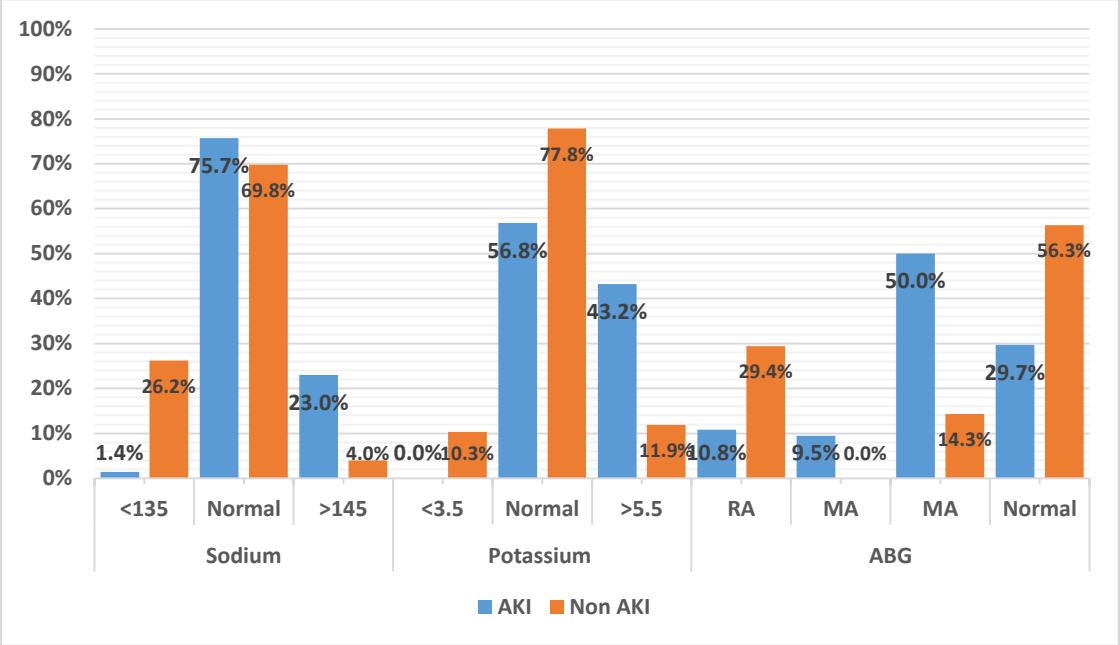

Fig. (3) study groups regarding electrolytes and ABG

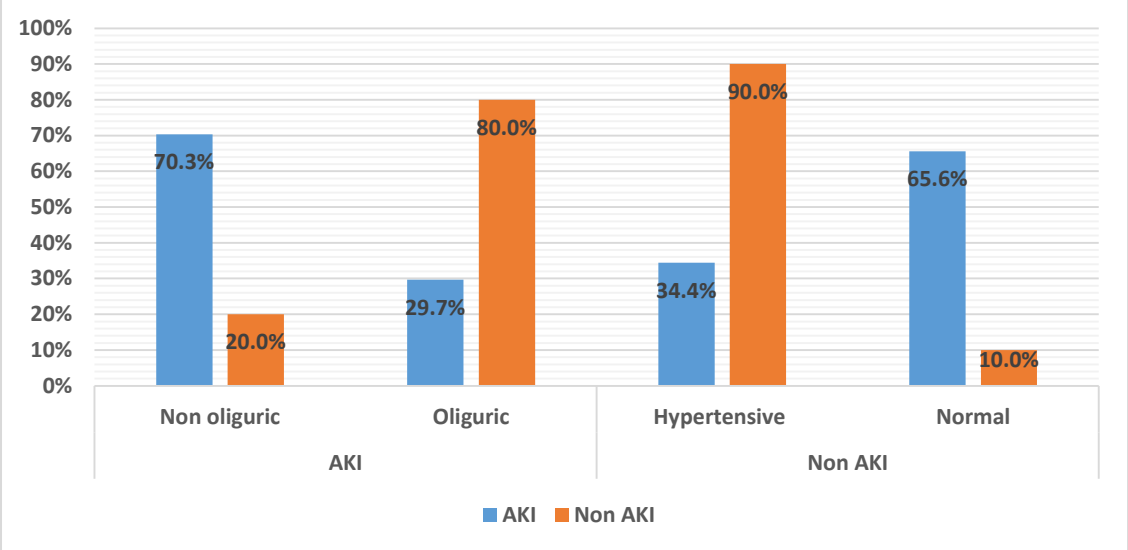

Fig. (4) AKI stages groups regarding urine output and blood pressure

Discussion

In the present study regarding the gender distribution, GA and birth weight. In agreement with the current study, a retrospective study revealed that the distribution of gender indicated a greater prevalence of males among neonates with AKI across all gestational age cohorts, with the highest percentage observed in the group of neonates with a gestational age of ≥36 weeks (62%) (10).

We observed a higher incidence of AKI in our NICU population than that in previous reports. In the multicenter, multinational, observational AWAKEN cohort study, AKI was found in 30% of the studied. However, the reported incidence of AKI varies according to the definition used (12).

A higher incidence was reported among sicker neonates and among those with risk factors for AKI (e.g., birth weight < 1500 g, perinatal asphyxia, or low Apgar scores), those treated with extracorporeal membrane oxygenation, and those requiring cardiac surgery (13-15).

Reported that AKI defined according to the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease) criteria occurs in 20% of NICU-admitted infants, whereas estimated that AKI defined in terms of the SCr cutoff (1.5 mg/dL) occurs in 8–24% of critically ill neonates (16).

Also, a study reported a lower AKI incidence of 18% among VLBW infants. However, they emphasized a substantial mortality risk associated with AKI, even after accounting for demographic factors and underlying health conditions (17).

Within the subgroup of neonates born at a gestational age of ≥32 weeks, the percentage of neonates with a birth weight of <1000g was higher in the AKI group (29.7%) compared to the non-AKI group (21.4%) (P-value = 0.03).

Confirming our finding, noted that infants in the AKI group had significantly lower gestational age and birth weight compared to those in the non-AKI group (6).

In contrast, a study found that the gestational age ranged from 22 to 28 weeks, 29 to 35 weeks, and ≥36 weeks. Birth weights varied across these groups, with the lowest in the 22–28-week cohort (797±198g) and the highest in the ≥36 week cohort (3213±618g) (10). They may be due to who had analyzed the entire spectrum of birth weights across different gestational age categories.

Neonates with AKI were more likely to exhibit oliguric urine output and hypertensive blood pressure levels than non-AKI neonates (P-value < 0.001).

Another study demonstrated a greater prevalence of AKI diagnosis based on urine output among neonates with AKI (10).

Regarding Apgar score. Parallel to our results, a study found that both Apgar scores at 1 and 5 minutes were significantly lower in the AKI group, indicating potential challenges in early health assessments for these neonates (6).

In addition, a study observed that the median Apgar score at 1 minute after birth was 6, with an IQR of 3 to 8. The median Apgar score at 5 minutes after birth was 8, with an IQR of 6 to 9 (10).

Regarding the mode of delivery: In the AKI group, 79.7% of neonates were delivered by Cesarean section (CS), while 20.3% were delivered by normal vaginal delivery (NVD). In the non-AKI group, 81.0% were delivered by CS, and 19.0% were delivered by NVD. The mode of delivery was insignificantly different between both studied groups (p = 0.9).

In the same line with our findings, declared that neonates delivered through scheduled cesarean sections have lower odds of early AKI. Similarly, neonates delivered through scheduled vaginal delivery also exhibit reduced odds of early AKI, but this association was not statistically significant (10).

Compatibly, a study reported that in Stage I AKI, there were 3 cases, with 66.7% undergoing vaginal delivery and 33.3% undergoing LSCS (Lower Segment Cesarean Section). Similarly, for Stage II AKI, out of 13 cases, 69.2% had vaginal delivery and 23.1% had LSCS. In the largest group, Stage III AKI, with 134 cases, 54.5% had vaginal delivery and 41.8% had LSCS. Overall, among a total of 150 cases, 56.0% had vaginal delivery and 40.0% had LSCS. Overall, they found that the mode of delivery was insignificantly different between both studied groups (18)

Among neonates with AKI regarding Hb levels. A study to determine if the minimum Hb levels measured during the first postnatal week of life were independently associated with early and or late neonatal AKI and severe AKI. Minimum Hb in the first postnatal week was significantly lower in neonates with AKI after the first postnatal week (late AKI). After controlling for multiple potential confounders, compared to neonates with a minimum Hb ≥17.0 g/dL, both those with minimum Hb ≤12.6 and 12.7-14.8 g/dL had an adjusted increased odds of late AKI and, respectively. The ability of minimum Hb to predict late AKI was moderate (c-statistic 0.68, 95% CI 0.64-0.72) with a sensitivity of 65.9%, a specificity of 69.7%, and a PPV of 20.8% (19).

A study presented a detailed analysis of baseline characteristics among infants admitted to the NICU, they categorized them according to KDIGO stage. The distribution of male infants across different KDIGO stages did not show a significant difference, suggesting gender parity in the assessed groups. There is a progressive decrease in gestational age and birth weight as KDIGO stages advance. Infants in higher KDIGO stages tend to have lower gestational age and birth weight. Both Apgar scores at 1 and 5 minutes declined as KDIGO stages increase. The p-values indicate statistical significance, suggesting potential associations between AKI severity and Apgar scores (6).

In another study, early AKI was identified in 449 (21%) of the 2110 enrolled neonates, representing 11% of the entire neonatal ICU population (449 of 4273), assuming that all non-enrolled infants did not have AKI. Of the 449 with AKI, 216 had stage 1 (48%), 105 had stage 2 (23%), and 128 had stage 3 (29%) (10).

Only few studies have assessed oliguria as a measure of neonatal AKI. Demonstrated that despite the assessment of UOP being important in AKI diagnosis, fewer patients are diagnosed with AKI based on UOP criteria alone, as UOP may be a restrictive tool in diagnosing AKI in the neonatal population. This could be explained by poor tubular function in premature infants, as well as higher rates of

nephrotoxic medications, which are known to cause non-oliguric AKI (15).

There is a contrast with the findings of regarding the association between Hb levels and different stages of AKI. In our study, we observed that Hb levels were significantly higher in Stage 2 and 3 of AKI compared to Stage 1, as indicated by a P-value of 0.03. This contrasts with the findings from where they reported that mean minimum Hb levels were not significantly lower in AKI Stage I and Stage II/III compared to those without AKI in various subgroups. Additionally, they found that mean maximum Hb levels were not significantly lower in the AKI group in most cases. This discrepancy in the relationship between Hb levels and AKI stages suggests differing observations between the two studies (19).

Conclusion

In conclusion, this study demonstrates that birth weight, medication exposure, laboratory parameters, and clinical indicators such as blood pressure and metabolic acidosis were found to be associated with the development of AKI. Our findings reveal the significance of birth weight and medication exposure, particularly aminoglycosides and vancomycin, in the development of AKI. Moreover, altered clinical markers such as elevated C-reactive protein levels and perturbations in blood parameters provide valuable indicators for identifying at-risk neonates.

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Author contribution

Authors contributed equally in the study**.**

Conflicts of interest

No conflicts of interest

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