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Neonatal acute kidney injury in Beni-Suef university hospital: incidence, associated risk factors and outcome

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Abstract

This research was done to examine infant acute kidney damage in the Neonatal intensive care unit at Beni-Suef University Hospital, including its incidence, associated risk factors, and outcome. This study included neonates admitted from August 2020 to August 2021. We excluded neonates discharged or died within less than 72 hours after birth, patients with urinary tract abnormalities, congenital kidney disorders, chromosomal anomalies, and congenital heart abnormality requiring surgical repair within 7 days of life. Criteria established by kidney disease: Improving Global Outcomes (KDIGO) were used to define Acute kidney injury. Newborns with and without AKI were monitored until discharge or death. Relative risk (RR) with 95% confidence intervals were reported based on adjusted risk studies (95 percent CI). The incidence of AKI was 22.9%. Neonates with AKI had a lower birth weight and a lower gestational age ($p < 0.001$). Prematurity, Respiratory distress syndrome, shock, sepsis, infection with Klebsiella, Hypoxic Ischemic Encephalopathy, Necrotizing Enterocolitis, inotropes, and respiratory support were significantly associated with the development of AKI. In our study, AKI prolonged the duration of hospital admission significantly. In our research, 77 (75.5%) of 102 AKI patients died, and 25 (24.5%) survived despite 57 (56%) patients with AKI improved, 32 (31%) patients deteriorated, and 13 (13%) patients had stationary course till death. The mortality rate among AKI patients was 75.5%, and among non-AKI patients was 26.8%. AKI incidence was 22.9%, associated with an increased mortality risk, and had a higher incidence among smaller and sicker infants.

Keywords: Duration of hospital admission; Mortality; NICU.

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1. Introduction

Formerly known as Acute Renal Failure (ARF), acute kidney injury (AKI) is characterized by a rapid and often reversible rise in nitrogen waste products such as blood urea nitrogen (BUN) and serum creatinine levels (SCr), which may last anywhere from a few hours to a few weeks. To meet this criterion, the amount by which SCr increases over a "baseline" steady state SCr level must be determined. Newborns do not have a steady-state baseline SCr since, medically speaking, SCr levels should fall after birth. Up to 72 hours after delivery, serum creatinine indicates maternal renal function [1]. Neonates that are ill enough to be admitted to a NICU often have acute kidney injury [2,3]. Neonates are more vulnerable to hypo-perfusion and have critical vascular resistance, higher plasma renin activity, and lower proximal tubular sodium reabsorption, all of which enhance the risk of AKI [2]. Necrotizing enterocolitis (NEC), sepsis, hypoxemia, and hemodynamically significant patent ductus arteriosus (PDA) are all diseases that are common in premature newborns and are known to increase the risk of AKI [3]. Additional risk factors for AKI were maternal use of non-steroidal anti-inflammatory medications and neonatal therapy with ibuprofen [4]. In the first few days of life, the neonatal kidneys work tirelessly to regulate the enormous water load from breastfeeding and to decrease the extracellular fluid concentration with urine output (UOP) up to 10 ml/kg/hr. In the context of low GFR and high UOP, the kidneys switch to the polyuric phase of AKI-like tubular reabsorption to control urine flow [5]. From the previous importance of acute kidney disease in neonates, our research was conducted to examine newborn acute kidney damage in the NICU at Beni-Suef University Hospital, including its incidence, associated risk factors, and outcome.

2. Methods

After receiving clearance from the Faculty of Medicine Research Ethics Board, Beni-Suef University Hospital's newborn critical care unit researchers performed a prospective study over 12 months (from August 2020 to August 2021). All neonates admitted to NICU during this period were included in the study. Written informed consent was obtained from the parents. Of the consecutive infants admitted to our NICU over 12 months from August 2020 to August 2021, 445 patients were screened. Patients were excluded if they had congenital heart disease requiring surgical repair within 7 days of life, patients with chromosomal anomalies, patients with hereditary kidney and urinary tract abnormalities, and patients discharged or died within less than 72 hours after birth. All patients admitted at our NICU were subjected to recording their gender, birth weight, gestational age, mode of delivery, consanguinity, presence of conditions including asphyxia (Apgar score less than 4), meconium aspiration, respiratory distress syndrome, sepsis, transient tachypnea of the newborn (TTN), congenital heart disease (CHD), congenital pneumonia, shock and treatments used including mechanical ventilation, antibiotics including aminoglycosides, use of other nephrotoxic drugs and use of inotropes, necrotizing enterocolitis (NEC), intracranial hemorrhage, duration of hospital admission, and mortality. In addition, vital signs, anthropometric measurements and urine output were calculated every 8 hours reported. We used weighted diapers for patients without a urinary catheter to calculate UOP. Moreover, complete Blood pictures, C reactive protein (CRP), serum urea and Creatinine measurements, arterial blood gases, blood, urine, and sputum cultures, and serial measurements of Na, K. Serum creatinine levels were monitored throughout the trial. Concerning the Kidney Disease Improving Global Outcomes (KDIGO) workgroup criteria, AKI was defined as a rise in serum creatinine of 0.3 mg/dL or more (26.5 mol/L) or 50% or more from the previous lowest value, or a urine output of less than 1 mL/kg per hour on postnatal days 3-7 [6] modified for neonates, as used in previous neonatal studies [7,8]. We applied the KDIGO classification system [3] for all neonates on the 3rd day, the 7th day of admission, and one day before discharge or death.

2.1. Statistical methods

Mean, standard deviation and median were used to statistically characterize quantitative data. In contrast, frequencies and relative frequencies were used to represent qualitative data. Two groups' numerical data were compared using the independent T-test. The chi-square test was used for category information. Pearson correlation was used to analyze the degree of similarity between two quantitative measures. Statistical significance was assumed when the p-value was less than 0.05.

3. Results and Discussion

In our study population, AKI was defined using the neonatal KDIGO criteria, with additional support from the UOP and SCr criteria. Because of continual nephrogenesis after birth, the average glomerular filtration rate (GFR) range shifts somewhat daily; thus, using SCr alone has several limitations like these [9]. The incidence of AKI among neonates admitted to our NICU and enrolled in our study was 22.9%. This incidence is consistent with values reported in studies [10] and [11]. Prevalence rates of 20% and 18% among infants with Acute Kidney Injury were observed in these studies. There have been reports of greater rates in other research. Examples include the 56% incidence of infant AKI in the prospective cohort research by [12]. Similarly, [13] found that 56% of newborns had AKI; 30% of these infants were diagnosed with stage II AKI, 17% with stage II, and 9% with stage III AKI. In contrast, the prevalence found by [14] was just 11.6%, making our finding greater. Depending on the criteria for diagnosis, AKI may have a wide range of reported frequencies [9]. While [15] estimated that AKI occurs in 8-24% of critically sick newborns using the SCr threshold (1.5 mg/dL), [16] observed that AKI occurs in 20% of NICU-admitted babies using the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease) criteria. In our study, we observed a significant negative relation between gestational age, birth weight, and incidence of acute kidney damage. Although low birth weight (LBW) is thought to increase the risk of newborn acute kidney injury (AKI), its incidence and impact on AKI are poorly understood. While we found that LBW was a significant predictor of newborn AKI in the univariate study, we could not replicate this result in the multivariate analysis. Compared to infants who did not have neonatal AKI, those who did had a lower birth weight, which increased the chance of mortality [12]. In our study, prematurity, RDS, shock, sepsis, UTI, infection with Klebsiella, NEC, HIE, and the need for inotropes and respiratory support were significantly associated with the development of AKI. Birth APGAR score, respiratory rate, heart rate, body temperature, mean arterial pressure and capillary refill time were also shown to be significantly different between AKI and non-AKI patients (Table 1). An elevated risk of newborn AKI was connected to prenatal depression, and the Clinical Risk Index for Babies (CRIB II) score of [12]. However, ventilation support, patent ductus arteriosus, a younger gestational age, and the use of inotropic agents were all shown to independently increase the risk of newborn acute kidney injury (AKI), as reported by [13, 17] mentioned that newborn AKI may be caused by several factors, including low body temperature, infection, premature birth, and respiratory distress. Factors like being severely ill or using epinephrine, which may cause a decrease in fractional renal blood flow, may increase the risk of kidney damage. Regarding neonatal sepsis, it could be sssociated with hypotension secondary to massive inflammatory response and redistribution of renal blood flow away from renal medulla to renal cortex with relative renal meulla hypoxia and direct tubular injury. out of 102 cases of AKI in our study, there was 92 (90.2%) cases with neonatal sepsis compared to other studies that found sepsis has been consistently reported as a risk factor for the development of AKI in neonates, noted in up to 78% of AKI cases [2,26]. We observed that there was a significant difference between non AKI and AKI patients regarding immature neutrophils, I/T ratio, hemoglobin level, platelets, CRP values and Hco3 level denoting that anemia, bandemia, thrombocytopenia, high CRP values and metabolic acidosis are highly associated with AKI. Sepsis markers include anemia, bandemia, thrombocytopenia, hypoperfussion with metabolic acidosis so all these markers were highly associated with development of AKI (Table 2).

Table 1: Comparison between AKI and NON-AKI patients as regards clinical and laboratory data at admission (AKI cases =102, Non-AKI cases=343)

Variable	Non-AKI (no=343)	AKI (no=102)	P-value
Gestational age (week)	36.12± 3.57	34.01± 3.53	<0.001
Weight	2.51± 0.63	2.01± 0.71	<0.001
Length	46.33± 3.99	43.16± 4.82±	<0.001
APGAR at birth	7± 1	5± 2	<0.001
RR	65.75± 12.11	70.09± 12.54	0.002
HR	136.67± 15.63	142.39± 22.60	0.004
Temperature	37.06± 0.52	36.83± 0.61	<0.001
Capillary refilling (seconds)	2.06± 0.87	3.02± 1.15	<0.001
Systolic BP	68.11± 9.99	58.44± 14.03	<0.001
Diastolic BP	38.40± 6.48	31.79± 10.17	<0.001
Mean BP	53.25± 7.72	45.12± 11.74	<0.001
UOP	3.54± 1.16	3.25± 1.89	0.064
Duration of admission	8.04± 5.64	10.19± 7.28	0.002
I/T	10.28±8.52	15.10±10.47	<0.001
Hgb	13.44± 2.75	11.56± 4.50	<0.001
Plt	248.38± 120.89	174.16± 135.25	<0.001
CRP	32.89± 39.54	55.69± 47.28	<0.001
s. Creatinine	0.65± 0.23	1.06± 0.76	<0.001
Blood urea	33.17± 17.92	63.93± 57.92	<0.001
Sodium	136.69± 11.686	140.44± 8.365	0.003
Hco3	16.82± 3.50	13.94± 4.78	<0.001

RR: respiratory rate, HR: heart rate, BP: blood pressure, I/T: immature to total neutrophilic ratio, UOP: urine output, Hgb: heamoglobin, Plt: platelates, CRP: C reactive protein

Table 2: Comparison between AKI and NON-AKI patients as regards risk factors for AKI (AKI cases =102, Non-AKI cases=343)

Variable	Non-AKI (no=343)	AKI (no=102)	P.value
Prematurity	20% (69)	51.0% (52)	<0.001
RDS	20.4% (70)	52.0% (53)	<0.001
Shock	8.8% (30)	43.1% (44)	<0.001
Sepsis	53.9% (185)	90.2% (92)	<0.001
NEC	1.5% (5)	8.8% (9)	<0.001
HIE	4.7% (16)	12.7% (13)	0.01
MV	60.9% (209)	88.2% (90)	<0.001
Nephrotoxic drugs	64.6% (221)	82.4% (84)	0.001

RDS: respiratory distress syndrome, NEC: necrotizing enterocolitis, HIE: hypoxic-ischemic encephalopathy, MV: Mechanical ventilator

Table 3: Timing of development of AKI and Stage classification according to the KDIGO system

Day of admission	Number of cases of AKI and Stage classification		
	Total	Stage	Frequency
3rd day	97	1	48
		2	32
		3	17
4th day	1	1	1
		2	0
		3	0
5th day	1	1	0
		2	1
		3	0
6th day	1	1	1
		2	0
		3	0
7th day	2	1	2
		2	0
		3	0
Total	102		

Table 4: Correlations between AKI and continuous variables using linear regression test

		Pearson coefficient	P-value
Variable	Gestational age (week)	-0.283-	<0.001*
	Age at admission	-0.032-	0.328
	Weight	-0.405-	<0.001*
	Temperature	-0.309-	<0.001*
	RR	0.170	0.008
	HR	0.179	0.006
	Capillary refilling (seconds)	0.490	<0.001*
	APGAR at birth	-0.324-	<0.001*
	Mean Blood Pressure	-0.434-	<0.001*
	TLC	0.035	0.311
	I/T	0.22	<0.001
	Hgb	-0.388-	<0.001*
	CRP	0.264	<0.001*
	Baseline Creatinine	0.476	<0.001*
	Duration of admission	0.123	0.041
	RR: respiratory rate, HR: heart rate, TLC: total leukocytic count, I/T: immature to total neutrophilic ratio, UOP: urine output, Hgb: heamoglobin, CRP: C reactive protein		

Table 5: Predictors and risk factors of AKI the study group using binary regression test

	Odds ratio	95% CI	p-value
prematurity	4.2531	2.6549 to 6.8134	<0.001
RDS	2.2666	1.1368 to 4.5189	0.02
Pneumonia	1.0950	0.5567 to 2.1541	0.776
Shock	2.2165	1.1726 to 4.1896	0.016
Sepsis	2.3261	1.0173 to 5.3184	0.043
NEC	1.7894	0.5425 to 5.9022	0.346
HIE	7.781	2.1368 to 7.5189	0.005
Positive urine culture	4.897	1. 261 to 4.916	0.027
Infection with Klebsiella	9.738	2.6 456 to 4.567	0.002
Nephrotoxic drugs	1.1490	0.5455 to 2.4205	0.770
Inotropes	3.0345	1.5265 to 6.0322	0.002
Respiratory support	4.0414	2.0509 to 7.9640	<0.001
RDS: respiratory distress syndrome, NEC: necrotizing enterocolitis, HIE: hypoxic-ischemic encephalopathy			

Table 6: The association between Nephrotoxic antibiotics and AKI using binary regression test

	Odds ratio	95% CI	P
Amikacin	0.4824	0.1947 to 1.1950	0.115
Ciprofloxacin	3.5841	1.6725 to 7.6805	0.001
Levofloxacin	3.1531	1.6919 to 5.8766	0.001
Polymyxin	2.0219	1.8809 to 4.6408	0.036
Vancomycin	1.5599	0.7249 to 3.3563	0.255

Also, Neonatal general illness is strongly correlated with respiratory assistance, and high mean airway pressure is known to reduce preload and, consequently, kidney perfusion. We also found that HIE was strongly associated with the development of AKI ((OR 7.781(95% CI 2.1368 to 7.5189)). Other research has shown a link between AKI and worsening hypoxia ischemic encephalopathy [18,19]. In our study, there wasn't a significant difference between AKI cases and non-AKI regarding UOP. However, as shown by [12], despite the importance of UOP evaluation in AKI diagnosis, fewer individuals are identified with AKI based on UOP criteria alone, suggesting that UOP may be a restricted tool in detecting AKI in the newborn population (Table 3). Low tubular function and increased use of nephrotoxic drugs, known to induce non-oliguric acute kidney injury (AKI), may account for this trend in preterm newborns [3]. In our study, stage classification of AKI found align with those found by [20], who analyzed data showing the median age of neonates with AKI was 3.49±0.23 days. Another research by [21] reported that the average time from birth to the onset of AKI was 2.8±1.8 days, and that of the 449 infants who had AKI early on, 79 (18%) experienced a second episode during the first week of life. [3] found that the incidence of AKI was highest during the first week of life for the overall group. Regarding antibiotics in our study, we found that nephrotoxic antibiotics, especially ciprofloxacin, levofloxacin, and

Polymyxin, were significantly associated with the development of AKI (Table 4). The risk of acute renal damage was shown to be doubled with the use of quinolones in a study conducted by [22]. The increased risk of nephrotoxicity shown with Polymyxin treatment was also validated by [23] (OR 2.23 (95% CI 1.58e3.15)). Regarding the duration of hospital admission in our study, AKI significantly prolonged the duration of hospital admission. Another research found that newborns with AKI stayed in the NICU for 11.7 days longer than those without AKI. This was found in a prospective cohort study of [24]. The AWAKEN research revealed similar results [3]. However, research conducted by [12] in 2018 showed that newborn AKI was not linked to more extended hospital stays. AKI is an independent risk factor of mortality in neonates. Sepsis and HIE are significant mortality cofactors in AKI. Our study showed that the need for inotropes, respiratory support, development of AKI, shock, and sepsis were significantly associated with mortality in the study population. In our study, 77 (75.5%) of 102 AKI patients died, and 25 (24.5%) survived despite 57 (56%) patients with AKI improved, 32 (31%) patients deteriorated, and 13 (13%) patients had stationary course till death. This means that there are factors other than AKI affecting survival rate. The non-survival rate was significantly higher in infants with higher neonatal AKI stages. In our study, there was a significant difference between the mortality rate among AKI patients (75.5%) and the mortality rate among non-AKI patients (26.8%). This mortality rate in our study is much higher than observed in other studies. Mortality rates of 24.4% were observed by [25] after reviewing the outcomes of 45 term and preterm children with AKI and no heart illness. It was also agreed upon by [12] that newborn acute kidney injury was substantially related to death and that the total mortality rate was 28.3 percent. When combined with sepsis, AKI may increase mortality by as much as 70.2% [26]. Our findings corroborated those of [10], who reported that 61.9% of preterm infant deaths were attributable to neonatal AKI. In our cohort, 23 out of 102 patients with AKI (22.5%) needed peritoneal dialysis. The renal replacement therapy (RRT) rate noted in our cohort is much higher than those reported in previous studies. For instance, fewer than 1% of newborns with AKI required RRT, as written by [27]. Still, the incidence of RRT ranged from 1% to 10% in neonates undergoing congenital heart disease repair, as described by [28] (Table 5). We also noted that there are several significant caveats to our research. Due to many factors, the current results may not be generalizable to other NICUs. First, this was single-center observational research in a quartet NICU offering level II, III, and IV newborn treatment. Second, we used a weak marker of AKI in neonates (both SCr and UOP) to define AKI; this means that the actual incidence of AKI may be greater than reported. Third, we may have overlooked some AKI patients because we used SCr measurements collected beyond the first 72 hours of life to stage AKI rather than during the first 72 hours [29] (Table 6). We also had trouble categorizing some neonates with normal or low creatinine levels because they had low urine output (considered as AKI by KDIGO). Creatinine levels were measured more often in newborns with neonatal acute kidney injury (AKI) than those without, suggesting that the reported incidence may be higher than the actual rate. However, the research's strengths and trustworthiness come from its prospective design, inclusion of many neonates across a one-year study period, and rigorous data collection.

3.1. Ethical approval

The FM-BSU REC has approved the work from the ethical point of view on its meeting dated 7th of June 2020, Approval number: FMBSUREC/07062020/Morsy.

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