Original Article

Incidence and Risk Factors for Acute Kidney Injury in Critically ill Neonates Admitted in Neonatal Intensive Care Unit

Risk Factors for Acute Kidney Injury

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ABSTRACT

Objective: To find the incidence and risk factors of AKI among the critically ill neonates in a public sector tertiary care hospital in Karachi.

Study Design: prospective study

Place and Duration of Study: This study was conducted at the public sector Hospital National Institute of Child Health, Karachi, Pakistan from January, 2022 to April, 2022.

Materials and Methods: 300 neonates admitted to NICU were carefully monitored for morbidities that can lead to AKI. 95% confidence interval was calculated, considering a p-value ≤0.05 as significant.

Results: Out of 300 neonates, 80 (26.66%) developed AKI. 59% were full term. Mean age with and without AKI at presentation was 7+3.83 and 4±1.99 days which was statistically significant (p=0.001). The BW ranged from 1200 to 3300 grams with a mean ±SD of 2120 ± 420 grams. The most common risk factors were sepsis (67.5%), nephrotoxic drugs (55%), and mechanical ventilation (51.3 %) followed by perinatal asphyxia (47.5%). The mortality rate was higher in patients with mechanical ventilation (P< 0.001), sepsis (P=0.008), nephrotoxic agent use (P=0.008) and birth asphyxia (p=0.001).

Conclusion: This study suggested that early recognition and better management of risk factors like sepsis, tetanus, nephrotoxic drugs, mechanical ventilation and birth asphyxia can improve the outcomes.

Key Words: Risk Factors, Acute Kidney Injury, Neonates, Intensive Care Unit

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INTRODUCTION

Acute kidney injury (AKI) can be defined as a sudden reduction in kidney function which results in fluid and electrolyte imbalance as well as uremia which ultimately leads to lethal complications like hypertension, hyperkalemia and metabolic acidosis [1,2]. It is one of the most commonly encountered problems in newborns admitted to the neonatal intensive care unit (NICU) and accounts for 6% to 24% of the NICU admissions [3]. AKI has been considered to be an independent risk factor for morbidity and mortality resulting in increased length of hospital stay in neonates [4]. An international multicenter study confirmed higher mortality rates in newborns suffering from AKI (9.7%) as compared to the non-AKI (1.4%) group and approximately 40% of survived neonates developed everlasting kidney damage [5,6].

AKI can be divided into oliguric (urine output of <1 ml/kg/h) and non-oliguric (urine output of >1 ml/kg/h) subtypes [7]. It is common in neonates presenting with premature birth, perinatal asphyxia, respiratory distress syndrome, hemodynamic instability, patent ducts arteriosus, renal venous thrombosis, bronchopulmonary dysplasia and maternal as well as neonatal nephrotoxic medication exposure [7-9].

As previous literature reported that the incidence of acute kidney injury in neonates admitted to NICU varied from one geographical area to another. Studies regarding the prevalence and risk factors of AKI among critically ill neonates are very scarce in underdeveloped countries like Pakistan. So it is important to determine the burden imposed by AKI and its risk factors in our local population.

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MATERIALS AND METHODS

This longitudinal prospective study was conducted at the NICU at the National Institute of Child Health, Karachi from January, 2022 to April, 2022. This was initiated after approval from IERB and obtaining consent from the parent. AKI was considered when serum creatinine (Cr) >1.5 mg/dl and/or blood urea nitrogen (BUN) >20 mg/dl on two different times at least 12 hours apart from each other [5].

300 neonates admitted to NICU for different clinical indications were enrolled in the study. A consecutive non-probability sampling technique was used until the desired sample size was achieved. Inclusion criteria were neonates up to 28 days of life, referred from other hospitals and length of stay > 24 hours. Exclusion criteria include multiple congenital anomalies, all syndromic babies, neonates on GFR alternating drugs such as ACE inhibitors and maternal history of AKI.

Basic demographics and clinical data, including history and clinical examination, were collected in a specifically pre-designed proforma. Investigations that included creatinine, and blood urea nitrogen (BUN) at admission and 24 hours apart were done.

All patients were monitored for AKI occurrence up to 7 days of admission. Short-term outcome of neonates was measured as survival and death, Data was entered on excel 2016 and analyzed using SPSS version 24. Mean ± SD/ Median (IQR) was reported on the basis of normality for quantitative variables such as age and baseline creatinine. However, qualitative variables such as gender, the reason for NICU admission, diagnosis at the time of admission, acute kidney injury and risk factors (age, gender, nephrotoxic drugs) was reported as frequency and percentage. Chi-Square or Fisher exact test was done for analysis and a 95% confidence interval was reported, considering a p-value ≤0.05 as significant.

RESULTS

A total of 300 neonates were examined in this study and AKI occurred in 80 (26.66%) patients, 177 (59%) and 123 (41%) cases were full-term and preterm neonates, respectively, the difference was significant (p=0.004).

The mean ± SD age of the patients whether suffering from AKI or not on admission was estimated at 7±3.83 and 4±1.99 days respectively. The birth weight ranged from 1200 to 3300 grams with a mean ± SD of 2120 ± 420 grams. The difference between mean birth weight and gestational age of AKI and non-AKI babies was statistically significant (2.4 kg v/s 2.0 kg, p-value < 0.02: 36.95 weeks v/s 35.28 weeks, p=0.001). there was no variance in gender between patients with or without AKI (p=0.43).

One baby out of 7 babies < 1500 gram had AKI, 43 babies out of 229 babies between birth weights 1500 - <2500 gram had AKI, and 36 out of 64 babies with birth weight 2500 gram or more had AKI. The demographic data of the studied cases are shown in Table 1.

Table No.1: Demographic features of neonates admitted to the neonatal intensive care unit

		AKI	Non-AKI	p-value
Gestational Age	Term	58	119	0.004
	Preterm	22	101	
Sex	Male	47	118	0.43
	Female	33	102	
Mode of delivery	SVD	44	135	0.32
	CS	36	85	

80 cases diagnosed with AKI, there were 52 cases with multi-factorial predisposing factors and 28 cases with a single risk. The most common risk factors for AKI were sepsis (67.5%) mechanical ventilation (51.3%) followed by birth asphyxia (47.5%).

The distribution of various factors across both groups is given in Table 2.

Table No.2: Predisposing factors for acute kidney injury

	AKI (80)	Non-AKI (220)	p-value
Sepsis	54 (67.5)	117 (53.2)	0.027
Birth asphyxia	38 (47.5)	70 (31.8	0.012
Meconium aspiration	16 (20)	22 (10)	0.021
RDS	16 (20)	29 (13.2)	0.144
Neonatal jaundice	16 (20)	34 (15.5)	0.35
CHD	24 (30%)	45(22%)	0.082
mechanical ventilation	41(51.3 %)	68 (30.9%)	0.001
nephrotoxic drugs	44 (55%)	85(38.6%)	0.01
Tetanus	9 (11.3)	5 (2.3)	0.001

However, there was no statistical significance between the AKI and non-AKI groups except for sepsis, birth asphyxia, mechanical ventilation, nephrotoxic drugs and tetanus.

In total, 51 (17%) neonates died. 80 neonates developed AKI out of which 22 (27.5%) cases expired. On the other hand, 30 out of 220 (13.6%) with no evidence of AKI expired. The difference was statistically significant (p<0.010). Various factors were studied in AKI groups in regard to mortality. The significant morbidities and factors in patients who expired from AKI patients were as follows i.e. mechanical ventilator (p<0.001), those with sepsis (p=0.008), nephrotoxic agent use (p=0.008) and with birth asphyxia (p=0.001).

DISCUSSION

AKI can be developed in high-risk neonates leading to further morbidity and can even be fatal [2]. In research

by Noami A et. al neonates who were critically ill and had AKI had a mortality rate of 70.6% compared to those who did not suffer from AKI [9]. In this study neonates who developed AKI were 26.6% which is similar to a study carried out by Charlton et. al [2]. Similarly, the multinational multicenter retrospective cohort study AWAKEN had also concluded about 30% of AKI coincided with a study of Tanzania i.e. 31.5% [6,9]. As a fact, the incidence of AKI is multifactorial and may affect every neonate differently admitted under similar conditions.

In this study neonate who developed AKI were 80 of which 47 were males (58.75%) and 33 were females thus impact of gender on the incidence of AKI was not significant. Various studies have concluded that the occurrence of AKI in the boys was more than in the girls. [3,5-6,10]. The higher incidence of AKI can be because of the higher susceptibility of boys to have peri-natal disorders such as sepsis and respiratory distress syndrome [11].

A study by Al Gadeep et. al, reported that 67.7% of low birth weight (1500-2500g) neonates had AKI [12]. On the contrary, our study in which 36 out of 64 (56.6%) normal birth weight neonates had AKI. However, the higher rate in normal birth weight neonates can be a result of maternal infections, babies born with meconium-stained fluids, and hypoxic-ischemic encephalopathy due to outborn deliveries. Bamsai et. al also supports our study that full-term neonates were at a higher risk of AKI [3].

Many studies reported sepsis as a leading factor of AKI. Neonates with sepsis are thought to be susceptible to AKI due to hypotension. In this study, 67.5% (54) of neonates suffering from sepsis had acute kidney injury. Similarly, Youssef et. al found that almost 63% of neonates with sepsis had AKI, therefore susceptibility of AKI in neonates suffering from sepsis is high [11]. However, a few of the research carried out in India and Tanzania had a lower rate of incidence of AKI due to sepsis i.e. 39.25% and 22.4% respectively [9,13].

Moreover, the administration of nephrotoxic drugs also contributes to AKI. Studies showed that these drugs cause inflammation in the glomerulus, proximal tubules, and surrounding cellular matrix. This inflammation may ultimately fiberize the kidney tissue resulting in AKI [14-15]. During our study, about 55% of neonates had AKI after they were administered such nephrotoxic drugs. This is in line with a study done by Leghrouz et al. [8]. In our setup amikacin was administered as a first-line drug in neonates as most of the organisms in this age group are susceptible to it whereas 44% of patients received other nephrotoxic drugs i.e. meropenem, vancomycin, colomycin, ceftazidime and amphotericin B. Various studies further justified that these drugs significantly contribute to AKI ($p<0.001$) [12,16].

Furthermore, mechanical ventilation is a life-saving procedure. 51.3% of neonates had AKI after mechanical ventilation which is in line with a study carried out by El Badaway et al. which was 56% [5]. However, the incidence can be diminished by early interventions and by improving intensive care unit management in developed countries such as China it was found that only 15.1% of ventilated babies developed AKI. Y. fan et al. also concluded that the highest oxygen concentration contributed to AKI [17]. Mechanical ventilation contributes to AKI as it decreases renal blood flow and increases renal vascular resistances furthermore it causes hypercapnia or hypoxemia which causes activation or inactivation of vasoactive substances such as nitric oxide and angiotensin II. It can further cause barotrauma leading to the release of inflammatory mediators and contributing to a systemic inflammatory reaction [9].

Perinatal asphyxia was also a major cause of AKI in this study (47.5%) which is supported by Gupta et al. (54%) and Kaur et al. (56%) [18,19]. A recent study also showed a significant association o perinatal asphyxia with AKI because perinatal asphyxia causes acute tubular injury and reperfusion injury following hypoxia [8,10]. Another study also supports our observation and regards perinatal asphyxia as a major cause of AKI even higher than sepsis [6].

Consequently, lack of awareness of mother immunization coupled with the unsanitary conditions during deliveries at home causes umbilical cord infection and results in neonatal tetanus. There is scarce knowledge about neonatal tetanus published yet. Our data shows neonatal tetanus is majorly associated with acute kidney injury. Moreover, RDS, congenital heart disease and hyperbilirubinemia were insignificant risk factors for AKI in our research although according to a study in the USA very low birth weight neonates had 96% of AKI because of RDS [4].

It was found that the death rate was significant in babies who underwent mechanical ventilation i.e. ($p < 0.001$), various studies supported our finding such as a study carried out in Western India neonates had a greater chance to survive who were not mechanically ventilated [3]. Neonates with birth asphyxia along with AKI also accounted for higher mortality as compared to those without AKI [20] in our observation it was statistically significant ($p < 0.001$), Nandhagopal et. al also reported 71% mortality in such neonates [10]. Likewise, Selewski and colleagues also reported a higher incidence of mortality in asphyxiated neonates with AKI (14% vs 3%) [20]. Sepsis and nephrotoxic drugs were also significant factors in correlation with mortality ($p<0.008$). This coincides with research by Gohiya et al. that justifies that neonates who underwent sepsis had a higher risk of stage III, AKI which in turn led to more risk of mortality [13]. Similarly, another

study carried out in Egypt reported quite high mortality in septic neonates with AKI i.e. 50-78% [11].

CONCLUSION

AKI occurred in approximately half of the neonates admitted to the neonatal intensive care unit during the study period. Term neonates and those having normal birth weight were at higher risk of AKI. In this prospective study, critically ill neonates with predisposing factors such as sepsis, birth asphyxia, mechanical ventilation, nephrotoxic drugs and tetanus accounted for 43% of mortality. Therefore, cautious monitoring of kidney function and better nursing care of critically ill neonates can drop the rate of mortality dramatically.

Author's Contribution:

Concept & Design of Study:	Farjam Ahmed Zakai
Drafting:	Mashal Khan, Mehmood Shaikh
Data Analysis:	Muhammad Hanif, Muhammad Ashfaq, Syed Habib Ahmed
Revisiting Critically:	Farjam Ahmed Zakai, Mashal Khan
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