ARC Journal of Pediatrics
Volume 8, Issue 1, 2022, PP 1-14
ISSN 2455-5711
DOI: https://doi.org/10.20431/2455-5711.0801001
www.arcjournals.org

Epidemiology and Clinical Evolution of Newborns with Acute Kidney Injury in Intesive Care Unit

Giulia Gabriela NorcioScapini[1]*, Nilzete Liberato Bresolin[2], Andréa Benincá de Almeida[3]

[1]*Medical School student at the Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil.*

[2]*Assistant Professor at the Federal University of Santa Catarina, department of Pediatrics, Florianópolis, Santa Catarina, Brazil.*

[3]*Neonatologist and medical head of the Neonatal Intensive Care Unit of Hospital Infantil Joana de Gusmão, Florianópolis, Santa Catarina, Brazil*

Corresponding Author:Giulia Gabriela Norcio Scapini,1Medical School student at the Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil.*

Abstract:*Introduction: Acute kidney injury (AKI) is common in hospitalized neonates and associated with increased morbidity and mortality. The aim of this study is to describe the clinical epidemiological profile of AKI in neonatal intensive care unit (NICU), to analyze factors associated with death and predictors for chronic kidney disease (CKD). Methods: This is a single-center retrospective cohort study conducted with data from medical records of neonates with AKI in NICU between 2018 and 2020. The research ethics committee of the institution approved the study. Results: 66 (20,8%) of the 316 neonates admitted to the NICU had AKI. 53% of those had oliguria and 84.8% were exposed to nephrotoxic drugs. Extreme preterm and preterm newborns had 6.2 and 3.4 times higher odds of death compared to full-term. Perinatal asphyxia was associated with higher odds of death (OR=7.2), as were APGAR < 7 in the first minute of life (OR=6.9), oliguria (OR=4.4), vasoactive drugs (VAD) use (OR=8.3), and severe AKI (OR= 3.7). The mortality of neonatal AKI was 31.8%. Conclusion: AKI is a common event in the NICU, with high mortality rates. Factors associated with higher OR for death in neonatal AKI were prematurity, perinatal asphyxia, severe AKI, oliguria and VAD use.*

Key Words:*Acute Kidney Injury; Neonate; KDIGO; Intensive care; Prognosis; Mortality.*

1. INTRODUCTION

Acute Kidney Injury (AKI), formerly known as Acute Renal Failure (ARF), consists of a sudden decline in renal function, leading to disturbances in the balance of fluids, electrolytes, and residual metabolic products [1, 2]. Due to particularities of renal physiology in the first days of life, neonates have a higher propensity to develop AKI. Their kidneys function with a very low glomerular filtration rate (GFR), maintained by a tenuous balance between vasodilator and vasoconstrictor forces, which is limiting factor for the physiological adaptation to the possible endogenous and exogenous stressors that mark this period [3, 4]

The incidence of neonatal AKI is not well stablished. Research shows that 8 to 24% of patients admitted to neonatal intensive care units (NICU) develop this injury [4, 5]. The variability of epidemiological data is due to the lack of a standardization of AKI diagnostic criteria. In more recent studies, which considered the decrease in urine output, the documented incidence of the disease was higher than in older studies, which evaluated only the changes in serum creatinine (sCr) levels [6, 7].

The diagnosis of neonatal AKI is based on two main parameters: decrease in urine output an increase in sCr. These changes alone have low sensitivity in the beginning of the condition, since sCr might not increase until 25 to 50% of renal function has already been compromised and the urine output might not decrease [8, 9]. Besides that, the particularities of neonatal renal physiology make the interpretation of newborn (NB) sCr levels difficult, as they reflect the maternal levels until the first 48-72 hours of life and vary according to the gestational age [5].

According to KDIGO, the most accepted for diagnosis nowadays, neonatal AKI is defined as: increase in sCr of 0.3mg/dL or more, or an increase sCr of 1.5 times or more over the lowest recorded value, or a urine output of less than 1 mL/kg/h on days 2-7 of the postnatal period [10, 11].

The future impacts of AKI can be severe. Studies that consider the current definitions of AKI show that even small degrees of injury are associated with increase in morbidity and mortality in children and adults [12, 13]. One of the evidenced consequences is that approximately 50% of newborns who had AKI are at risk for developing chronic kidney dysfunction (CKD) in adulthood, which increases with the severity of the diagnosed AKI [3, 9, 10, 14].

For long-term prognostic assessment, indicators include hypertension, presence of proteinuria, microalbuminuria, decrease in the capacity of urine concentration, and other signs of impaired tubular function (all of which can be understood as CKD characteristics), besides impaired renal growth. From the prognostic knowledge, NBs who develop AKI require long-term follow-up, with monitoring of blood pressure, renal function, and urine analysis [3].

The present study aims to describe the clinical epidemiological profile of AKI in neonates in the intensive care unit, analyze the factors associated with death and the prevalence of predictors for chronic kidney disease (CKD).

2. METHODS

This is a descriptive, retrospective cohort study conducted at the Neonatal Intensive Care Unit of the Hospital Infantil Joana de Gusmão (HIJG) inFlorianópolis, Santa Catarina, Brazil.

A detailed research design was prepared and submitted to the Research Ethics Committeeof the Hospital Infantil Joana de Gusmão (REC-HIJG). Data were collected only after approval of the study by the REC-HIJG, with authorizationto waive the Informed Consent Form (ICF) due to the retrospective nature of the research. The data collected werekept confidential in the computer program Microsoft® Excel 2010 under password protection. Only the researchers had access.

To compose the sample, medical records of all neonates admitted to the HIJG NICU of between January 2018 and March 2020 were reviewed (316 neonates). After careful analysis, were included in the research the patients who meet the criteria for AKI diagnosis by KDIGO guidelines in the classification for neonatal population [11] – MODIFIED [12] according to the Table 1. Patients who did not present diagnostic criteria for AKI by the neonatal KDIGO classification were excluded from the research.

Table1. *Neonatal classification KDIGO of AKI*

Stage	Serum Cr	Urine Output
0	No change in sCr or an increase<0.3 mg/dL	≥ 1.0 mL/kg/h
1	Increase insCr ≥ 0.3 mg/dL in 48 h orincrease ofsCr ≥1.5 – 1.9 × reference of sCr in 7 d	> 0.5 mL/kg/h and< 1.0 mL/kg/h up to 24h
2	Increase in sCr ≥2.0 – 2.9 × reference of sCr*	> 0.3 mL/kg/h and≤ 0.5 mL/kg/h by time ≥ 24 h
3	Increase in sCr ≥3 × referenceofsCr* orsCr≥2.5 mg/dL** or receive dialysis	≤ 0.3mL/kg/h by time ≥24 h or anuria by time ≥12 h

Differences between the definition of neonatal AKI and KDIGO include:

*The reference sCr will be defined as the lowest recorded value.

** The value of sCr2.5 mg/dL represents less than 10 ml/min/1.73m².

After diagnostic definition and AKI classification, the data were collected based on the data collection instrument (APPENDIX 1) and simultaneously tabulated in the Microsoft Excel program.

The analyzed variables were as follows: sex, gestational age, birth conditions (APGAR, birth weight, perinatal asphyxia), AKI grade classification according to KDIGO, presence or absence of cardiac involvement with evaluation by transthoracic echocardiogram (TTE), presence of renal structural changes with ultrasound evaluation of kidneys and

urinary tract, use of nephrotoxic drugs (NTD), use of vasoactive drugs (VAD) and need for mechanical ventilation (MV), need for renal replacement therapy (RRT) and hospitalization outcome (discharge ordeath). For descriptive statistics, it was recorded the length of hospital and NICU stay,MV,exposure to NDTs, and time to diagnosis of AKI in days.

The AKI grade classification according to the modified KDIGO was based on laboratory data of sCr dosage and urine output measurements recorded in medical records. For the calculation of sCr variation, a minimum of two consecutive dosages were required after 72h of life, with a maximum interval of 7 days between the two, being defined as sCrbaseline the lowest previous value. Isolated absolute values of sCr were considered only when higher than 2.5, configuring KDIGO 3. Measurements of UO were included only when documented for at least 12 hours in cases of anuria, and for at least 24 hours in cases of oliguria.

As for gestational age (GA), NBs were categorized as “full-term NB” - FTNB (GAof 37 weeks to 41 weeks and 6 days), “preterm NB” - PTNB (GAof 30 weeks to 36 weeks and 6 days) and “extreme preterm NB” - EPTNB (GAless than 30 weeks).

For the classification of birth weight, participants were divided into “normal weight” - NW (weight> 2500g), low birth weight - LBW (between 1500g and 2500g), very low birth weight - VLBW (between 1000g and 1500g) and extreme low birth weight - ELBW (weight< 1000g). The classification of weight for gestational age had as reference the Intergrowth 21st curve [15], so that NBs were divided as “small for gestational age (SGA), “appropriate for gestational age” (AGA) and “large for gestational age” (LGA).

Nephrotoxic medications were defined based on the Goldstein study[16]. The definition of hypertension was the same used by the NICU service of HIJG, described by Dionne [17].

Statistical analysis was performed in IBM SPSS Statistics softwarefor Macintosh version 20.0 (IBM Corp, 2011). Descriptive statistics was employed using measures of central tendency, dispersion, and frequencies. For the nominal and ordinal qualitative variables, the absolute and relative frequencies and 95% confidence interval (95% CI) of the proportions were presented.The proportions were compared using 95% CI analysis. The association between qualitative variables was verified using the chi-square test. The magnitudes of associations were reported by means of Cramer’s V. The odds ratio (OR) for the occurrence of death as a function of the study covariates was calculated for the covariates with significance lower than 0.10 in the chi-square test. The significance level adopted was 5% ($p < 0.05$).

3. RESULTS

Between January 2018 and March 2020, 316 neonates were admitted to the NICU of HIJG. Of these, 66 had diagnostic criteria for AKI according to KDIGO guidelines – modified for neonatal population, which corresponds to an incidence of AKI of 20.8%. The study analyzed the data regarding the 66 participants with AKI diagnosis (KDIGO ≥ 1).

Regarding the epidemiological profile of the participants, the most prevalent gender was male, with 49 individuals (74.2). The mean gestational age at birth was 35.3 weeks, with standard deviation of 4.5 (95% CI 34.0-36.5). Regarding the classification for gestational age at birth, 30 participants were FTNB (45.5%), 27 werePTNB (40.9%) and 9 were EPTNB (13.6%). There were no post-term NB admitted to the NICU with a diagnosis of AKI in the studied period.

On birth weight classification, 33 neonates (50%) were normal weight, 20 (30.3%) were LBW, 4 (6.1%) wereVLBWand 9 (13.6%) were ELBW. In the classification of weight for gestational age, most participants (71.2%) were classified as SGA.

When the birth conditions were analyzed, it was found that 39 NBs (59.1%) had APGAR in the first minute of life greater than 7 and 27 NBs (40.9%) less than 7. In the fifth minute of life, only 8 patients (12%) had APGAR less than 7. Most participants (57.6%) suffered from perinatal asphyxia, requiring resuscitation maneuvers and/or oxygen support after birth. Of the 66 patients studied, 32 (51.5%) had diagnosis of congenital malformations evidenced by prenatal ultrasonography.

The mean life spanat diagnosis of AKI was 10.4 days, with a median of 6 daysand standard deviation of 10.8. Of the 66 patients, 36 (54.5%) were diagnosed with AKI in the first 7 days after birth. Oliguric AKI was documented in 35 participants (53%),

however, only 6 participants (9%) were diagnosed exclusively by UO and 29 (43.9%) had both sCr and UO changes. As for the degree of AKI, 29 NBs (43.9%) were classified as KDIGO 1, 11 (16.7%) as KDIGO 2 and 26 (39.4%) as KDIGO 3 (Table 2).

Table2.*Clinical-epidemiological profile of patients diagnosed with AKI at the NICU of Hospital Infantil Joana de Gusmãobetween January 2018 and March 2020.*

Variables	n / mean	%
Sex		
Female	17	25.8
Male	49	74.2
Gestational age (weeks)	35.2±4.5	
GA classification		
FTNB	30	45.5
PTNB	27	40.9
EPTNB	9	13.6
Weight at birth		
NW	33	50.0
LBW	20	30.3
VLBW	4	6.1
ELBW	9	13.6
Weight for GA		
SGA	11	16.7
AGA	47	71.2
LGA	8	12.1
APGAR 1st minute		
≥ 7	39	59.1
< 7	27	40.9
APGAR 5th minute		
≥ 7	58	87.9
<7	8	12.1
Perinatal Asphyxia		
Yes	38	57.6
No	27	40.9
Not informed	1	1.5
Average lifetime at diagnosis of AKI (days)	10.4±10.8	
KDIGO		
1	29	43.9
2	11	16.7
3	26	39.4
Oliguric AKI		
Yes	35	53.0
No	31	47.0
TOTAL	66	100.0

The length of hospitalization varied from 1 day to 232 days, with a mean of 47 days, median of 33 days, and standard deviation of 49 (95% CI 34.3-61.4). The mean length of hospitalization in NICU was 31 days, with a median of 18 days and standard deviation of 35 (95% CI 21.8-41.5). Throughout the NICU stay, 54 (81.8%) of the NBs required mechanical ventilation, with a mean time of MV of 12 days, standard deviation of 18.6 (95% CI 7.5-17.8). Among the participants, 43 (65.2%) used VAD.

Nephrotoxic medications were used in 56 NBs (84.4%). The mean number of NTDto which

each NB was exposed was 2.5 drugs, with standard deviation of 1.8 (95% CI 2.0-3.0) and the mean time of exposure was 20 days, with standard deviation of 15.8 (95% CI 15.7-24.4). The most frequent NTDs were Gentamicin (44 patients – 78.5%), Vancomycin (24 patients – 42.8%) and Piperacillin + Tazobactam (21 patients – 37.5%). Of the 66 patients studied, 21 (31.8%) died during the same hospitalization (Table 3).

Table3.*Clinical variables throughout the hospitalization of patients with AKI diagnosis in the NICO of Hospital Infantil Joana de Gusmãobetween January 2018 andMarch 2020.*

Variable	n / mean	%	95% CI
Mean length of hospitalization (days)	47.8±49		34.3-61.4
Mean length of hospitalization in NICU (days)	31.6±35.8		21.8-41.5
Need for mechanical ventilation			
Yes	54	81.8	
No	12	18.2	
Mean time of mechanical ventilation (days)	12±18.6		7.5-17.8
Need for Vasoactive Drugs (VAD)			
Yes	43	65.2	
No	23	34.8	
Exposure to NDT			
Yes	56	84.8	
No	10	18.2	
Mean number of NDT	2.5±1.8		2.0-3.0
Mean time of exposure to NDT (days)	20.1±15.8		15.7-24.4
Death			
Yes	21	31.8	
No	45	68.2	
TOTAL	66	100.0	

When the possible risk predictors for CKD were analyzed, 17 patients (26.2%) had high BPat the diagnosis of AKI. Of the 45 NBs who were discharged, 15 (33.3%) remained with high BPat discharge. As for the dosage of sCrat discharge, 17 patients (37.8%) had significantly higher values than the baseline SCR, according to KDIGO guidelines.

Regarding the need for RRT, the method used in the participants was peritoneal dialysis by Tenckhoffcatheter, required in 7 participants (10.6%), of whom2 (28.5%) were discharged with the need for dialysisand 4 (57.1%) evolved to death (Table 4).

Of the total number of patients discharged, only 11 (24.4%) were referred for follow-up in the hospital pediatric nephrology outpatient clinic. Among the patients referred to the outpatient clinic, 8 (72.7%) had AKI KDIGO 3and 3 (27.3%) had AKI KDIGO 1.

Table4. *Prevalence of risk predictors for CKD in patients with AKI diagnosis at the NICU from Hospital Infantil Joana de Gusmãobetween January 2018 and March 2020.*

Risk factors	n	Percentage	Valid percentage
High BP at AKI diagnosis			
Yes	17	25.8	26.2
No	48	72.7	73.8
Not informed	1	1.5	
High BP at hospital discharge			
Yes	15	22.7	33.3
No	30	45.5	66.7
Not applicable(death)	21	31.8	
High SCR at hospital discharge			
Yes	17	25.8	37.8
No	28	42.4	62.2
Not applicable (death)	21	31.8	
Need for RRT			
Yes	7	10.6	

No	59	89.4	
TOTAL	66	100.0	

For the associative analysis, clinical-epidemiological variables were related to death in patients with AKI diagnosis during NICU hospitalization. Those with statistically significant associations to the studied outcome were gestational age, APGAR less than 7 in the first minute of life, perinatal asphyxia, moderate/severe AKI grade(KDIGO 2 or 3), oliguric acute kidney injury, need for MV and need for VAD.

There was no statistically significant association between death and gender (p=0.471). A weak statistically significant association was observed between death and GA (p=0.032, Cramer's V=0.317).Among the categories of GA, it was observed that EPTNB had 6.2 more chances of evolving to death when compared to FTNB (95% CI 1.227-31.838, p=0.027). The PTNB, on the other hand, were3.4 times more likely to die when compared to FTNB (95% CI 1.005-11.753, p=0.049).

The weight classification for GA showed no significant differences for the studied outcome (p=1.000). Of the neonates who died, 66.6% were LBW or VLBW or ELBW. However, this variable was not significantly associated to the studied outcome (p=0.064).

When birth conditions were evaluated, a statistically significant association of moderate magnitude was observed between APGAR in the first minute of life and death (p=0.001, Cramer's V=0.424) and between birth asphyxia and death (p=0.003, Cramer's V=0.382). APGAR less than 7 in the first minute was shown to be relevant for the occurrence of death, with 6.9 times more chances than the infants with APGAR greater than or equal to 7 in the first minute of life (95% CI 2.167 – 21.810, p=0.008). The group of newborns who suffered from perinatal asphyxia requiring resuscitation maneuvers and/or supplementary O2 had 7.2 times higher odds of the unfavorable outcome (95% CI 1.850-28.016, p=0.004).

As for the degree of AKI, to obtain results with greater statistical power, the participants were grouped intoKDIGO 1 – mild AKI; and KDIGO 2/3 – severe AKI. There was a statistically significant association of weak magnitude between death and severe AKI (p=0.034, Cramer's V=0.024). It was observed that patients with classification AKI KDIGO 2 or 3 were3.7 times more likely to die than patients classified as KDIGO 1 (95% CI 1.114 – 11.695, p=0.029).

The occurrence of oliguric AKI was statistically associated with a worse prognosis (p=0.010, Cramer's V=0.317). Oliguric patients were 4.4 times more likely to die than non-oliguric patients(95% CI 1.365 – 14.045, p=0.013).

The need for MV throughout the hospitalization showed a weak statistical association with the unfavorable outcome (p=0.007, Cramer's V=0.322). The exposure to VAD, on the other hand, was shown to be a factor associated with worse prognosis (p=0.005, Cramer's V=0.363). Patients exposed to VAD were 8.3 timesmore likely to die when compared to NBs without the need for these medications (95% CI 1.729 – 39.968, p=0.008). The need for RRT had no statistically significant association with death (p=0.196), was well as exposure to nephrotoxic medications (p=0.714) (Table 5).

Table5.*Cases of death according to clinic-epidemiological variables of neonates with AKI diagnosis at the NICU from Hospital Infantil Joana de Gusmãobetween January 2018 and March 2020.*

Variables	**Death**		**P value**	**Cramer's V**	**OR**	**95% CI**
	Yes	**No**				
	n(%)	**n(%)**				
Sex						
Female	6 (28.6)	11 (24.4)	0.471			
Male	15 (71.4)	34 (75.6)				
Gestational age						
FTNB	5 (23.8)	25 (55.6)			1	
PTNB	11 (52.4)	16 (35.6)	0.037	0.317	3.4	1.00-11.75
EPTNB	5 (23.8)	4 (8.9)	0.027		6.2	1.22-31.83
Weight for GA						
SGA	3 (16.7)	8 (17.8)	1.000			

AGA	16 (71.2)	31 (68.9)				
LGA	2 (12.1)	6 (13.3)				
Low birth weight						
Yes	14 (66.7)	19 (42.2)	0.064			
No	7 (33.3)	26 (57.8)				
APGAR 1st minute						
≥ 7	6 (28.6)	33 (73.3)	0.008		1	
< 7	15 (71.4)	12 (26.7)		0.424	6.9	2.16-21.81
Perinatal asphyxia						
Yes	18 (85.7)	20 (45.5)	0.003	0.382	7.2	1.85-28.01
No	3 (14.3)	24 (54.5)			1	
KDIGO						
1	5 (23.8)	24 (53.3)	0.034	0.024	1	
2/3	16 (76.2)	21 (46.7)			3.7	1.14-11.69
Oliguric AKI						
Yes	16 (76.2)	19 (42.2)	0.01	0.317	4.4	1.34-14.4
No	5 (23.8)	26 (57.8)			1	
Need for MV						
Yes	21 (100)	33 (73.3)	0.007	0.322		
No	0 (0)	12 (26.7)				
Need for VAD						
Yes	19 (90,5)	24 (53,3)	0,005	0,363	8,3	1,72-39-96
No	2 (9,5)	21 (46,7)			1	
RRT						
Yes	4 (19.0)	3 (6.7)	0.196			
No	17 (81.0)	42 (93.3)				
Exposure to NTD						
Yes	17 (81.0)	39 (86.4)	0.714			
No	4 (19.0)	6 (13.3)				

4. DISCUSSION

4.1. Definition and Epidemiology

Neonatal AKI is a common condition in NICU inpatients, defined as an independent risk factor for mortality in this age group[5]. The average incidence of neonatal AKI documented in the literature ranges from 6.5% and 56%, depending on the diagnostic criteria used [18, 19]. In this study, the incidence found of20.8% is similar to the average reported in other studies that coveringcritically ill neonates [12, 18, 20].

In the multicenter multinationalobservational cohort AWAKEN, the incidence of neonatal AKI among the participant centers ranged from 2.5 and 74.1%, even with a single AKI diagnostic definition (KDIGO-modificado-2012). It is believed that such variability is due to the different frequencies of sCr dosages during hospitalization, as well as UO monitoring. On this, Shalabyclaims that a higher frequency in sCr dosing increases the diagnostic probability of AKI,reflecting,therefore,a better standard of care [19]. The adequate monitoring of UO is also crucial: the AWAKEN study showed that 37.1% of AKI diagnoses would be missed if urine output was not monitored [12], in our study, 9% of diagnoses would be lost if the UO was not recorded.

As for the gender of neonatal AKI patients, the higher proportion of severity in male NBs (74.2%) was also reported by Timovska (68%) and Kriplani (68.5%) [18, 21]. Similar data are seen in studies in children and adults [20]. The higher prevalence of AKI documented in males is believed to result from risk factors thar are more common in this gender, such as neonatal sepsis and respiratory distress syndrome of the newborn [18].

Birth conditions

Prematurity is a well-stablished risk factor for the occurrence of AKI in the neonatal period, resulting from an incomplete nephrogenesis process and less number of nephrons [5, 22, 23]. The association of lower gestational ages with more severe cases of AKI, described in several studies, was confirmed in this study: EPTNB and PTNB had 6.2- and 3.4-timesgreater chances of death in relation to TNB, respectively [12, 19, 24].

In a prospective cohort study that exclusively followed extreme preterm infants with AKI, it was evident that there is a higher incidence of severe AKI the younger the gestational age. NBs with GA of 24 weeks had rates of severe AKI 2 and 3 times higher than NBs at26 or 27 weeks, respectively. It should be noted that the aforementioned research used other biochemical markers of AKI besides sCr [24]. According to Bresolin, the particularities in the renal physiology of premature infants make the definition of AKI by means of the sCr and UO uncertain,raising the diagnostic difficulty and the standardization of studies in this group [25].

The association between low birth weight and neonatal AKI is a widely studied topic. In a prospective cohort that followed ELBW NBs over 10 years, the prevalence of AKI was 26% and the mortality in the group with AKI was 54%, versus 20% in the group without AKI [23]. In a case-control study of deaths in VLBW NBs it was observed that, after adjustment for confounding factors, the relative or absolute increase in sCrincreased the changes of death, supporting the hypothesis that AKI is an independent risk factor for mortality of VLBW NBs [9]. Similarly, the present study showed that of the 21 neonates who died, 66.6% were LBW, VLBW or ELBW, however, this variable was not statistically significant for the outcome ($p=0.06$).

As for the clinical conditions at birth, low APGAR scores at the first and fifth minutes have been related to a higher incidence of AKI in neonates. In a retrospective cohort, first and fifth minutes APGAR scores were significantly lower in NBs with AKI than in the group without AKI ($p<0.001$) [26]. A prospective study at the NICU from the Alabama University followed ELBW NBs and reached to the same conclusion [27]. The association of APGAR less than 7 at the 1st minute in patients with AKI with higher chances of death (OR 6.9), compared to NBs with AKI and APGAR greater than 7 at the 1st minute, was only reported in this study, with no previous reports in the literature.

Perinatal asphyxia is the most common isolated cause of AKI and is configured as a factor of worse prognosis in these patients. In the present study, 57.6% of the participants suffered from perinatal asphyxia. These NBs were 7.2 times more likely to die than those with AKI without perinatal asphyxia. Regarding the treatment for this grievance, Bhat et al in a randomized clinical trial with follow-up up to 1 year of life showed that the group with perinatal asphyxia who received Theophylline in the first hour had a lower incidence of severe renal dysfunction and higher GFR. Despite evidence of high morbidity and mortality in cases ofrenal injury induced by perinatal asphyxia and the existence of clinical treatment, there are limitations of specific markers of this condition, making the diagnosis and early treatment difficult [21, 28].

4.2. AKI Diagnosis

Few studies use UO definitions for the diagnosis of AKI. This is mainly dueto the difficulty in measuring and correctly monitoring this parameter [19, 25]. In this study, a good part of NBs (47%) had non-oliguric AKI diagnose exclusively by sCr variations. Still, the proportion of neonates with oliguric AKI (53%) was higher than that found in other studies: 21%, 29.9% and 40% [19, 12, 26]. Accurate measurementand recording in the studied institution may have contributed to a higher diagnosis of oliguria in patients admitted to the NICU. It is important to emphasize that, although not very sensitive, oliguria serves as an indicator of increased mortality and may be the only alteration in AKI [12, 20]. In a study with 496 critically ill children with AKI, 90 (18.1%) children were diagnosedonly with altered urine output and 63 (12.7%) had both criteria altered [7].In the present study thepatients with oliguric kidney injury showed a 4.4 times greater chance of dying compared to those who were not oliguric.

4.3. Clinical Variables in Hospitalization

Throughout hospitalization, the factors considered significant for the studied outcome in NBs with AKI were the need for MV and exposure to VAD.

The association between MV and AKI has been reported in the literature as both etiology and as consequence [25, 29, 30]. Of the 66 neonates with AKI in this study, 54 (81%) required MV. This clinical parameter showed a statistically significant association of weak magnitude with death. The mean MV time was 12 days, similar to what was found by Kriplani - 11 days in patients with AKI, versus 4 days in the patients without AKI [21]. On this, a retrospective cohort study with 2,106 children showed AKI as an independent risk factor for prolonged mechanical ventilation time but highlightedthat the physiological explanation of this fact is complex, and the collinearity between the two statistical parameters cannot be ruled out [30]. According to Bresolin, hypoxemia, hypercapnia, and positive pressure ventilation are factors that act directly and indirectly on the kidney, reducing its perfusion and glomerular filtration [25].

The relationshipbetween the need for VAD and AKI is widely studied, both as a risk factor for injury and death [27, 31, 32, 33]. According to DeZan, exposure of neonates to a large number for VAD is associated with severe cases of AKI and may be a marker of worse prognosis [34]. In different studies, the need for VAD has been considered the greatest predictor of mortality [20, 25, 32, 35]. In this study, the results agree with the literature: patients with need for VAD had 8.3 times higherodds of death than those who did not require them, being the variable with the highest odds ratio for death.

It is also known that the exposure to nephrotoxic medications is an important etiologic factor of AKI, especially in neonates, and that the risk increases according to the number of NTD used. The most prevalent mechanisms of AKI secondary to NTD are reduced GFR, acute tubular necrosis, acute interstitial nephritis, and renal tubular obstruction [1, 16, 36]. In this study, exposure to NTD was frequent: of the 66 individuals with AKI, 56 (84.8%) were exposed to a mean number of 2.5 drugsfor a mean time of 20 days. Similar epidemiological data were observed in a study with 107 ELBW NBs, of whom87% were exposed to at least one NTD, the most frequent medication being gentamicin (86%) [5]. Despite the high prevalence of NBs with AKI exposed to NTD, this was not associated with the worse prognosis in the study.

In a prospective study (NINJA), automated electronic monitoring was stablished to identify children exposed to three or more nephrotoxins, who were then subjected to daily dosages of sCr. At the end of the study, it was found that there wasa 38% reduction in exposure to NTD and 64% decrease in the incidence of AKI. A similar study reproduced in neonates (Baby-NINJA) showed that a decrease in NTD exposition resulted in a decrease in the percentage of nephrotoxin-induced AKI from 30.9% to 11%. It is clear, therefore, the need for monitoring neonates at risk for AKI from exposure to a high number of NTD, since usually this type of AKI is reversible with withdrawal of the causative agent [33, 35].

4.4. Prognosis

The prognosis for patients with neonatal AKI is variable, with possibilities for complete recovery of renal function, need for RRT in the acute phase and/or after discharge, risk of progression to CKD and increased risk of death [35, 36]. In this study, parameters cited in the literature were evaluated as possible predictors of CKD risk: decreased GFR (elevatedsCr at discharge), hypertension at discharge and need for RRT during hospitalization [36, 37]. Of the 45 patients who did not die, the prevalence of risk predictors for CKD was high: 15 NBs(33.3%) had hypertension at discharge and 17 (37.8%) had increased sCr values. However, only11 (24.2%) were referred for longitudinal follow-up at the hospital's nephrology outpatient clinic.

In the literature, the need for RRT in patients with AKI is defined as indicator of poor prognosis [12]. In the present study, of the 66 patients with AKI, 7 (10.6%) had an indication for dialysis. Of these, 4 (57.1%) died. However, the sample size was not sufficient to stablish a statistical association between need for RRT and death.

The higher risk of death in NBs with AKI when compared to those without AKI is well stablished. In this study, the mortality found was 31.8%, similar to that described by Timovska (32%), Askenazi (28%) and Bresolin (33%) [18, 24, 25]. In addition, it was found that NBs with severe AKI were3.7 times more likelyto die than those with mild AKI. On this subject, studies show that mortality increases with the presence of AKI and

correlates with the severity of kidney injury [24, 38].

4.5. Limitations of the study

The present study has limitations. The retrospective naturemakes the analysis of causal associations between the variables less clear, which makes it difficult to analyzethe temporal relationship between the studied aspects and to exclude collinearity between the statistical parameters, since critically ill NBs often have several conditions known to be associated with death. Furthermore, the fact that this is a single-center study might generate a selection bias, since the studied hospital is a state reference and receives cases of higher complexity. On the other hand, the high complexity of the service facilitates data collection, since the request and recording of laboratory tests and urine output are well stablished in the NICU routine. In addition, the small sample size (66 neonates with AKI) limited the possibility of statistical analysis. It is believed that with a larger sample, more significant associations would be found, especially in the variables that present three or more subgroups.

5. Conclusion

Neonatal AKI is common in the NICU setting.In the present study, the incidence of AKI was 20.8%and, in these patients, the mortality rate was 31.8%. Most NBs with AKI were exposed to nephrotoxic drugs (84.8%). For its diagnosis, the particularities of the renal physiology in the first days of life should be considered and the evaluation of UO and the sCr variations are essential.

After diagnosis, knowledge of prognostic factors is essential for a good patient care. The independent variables associated with death in NBs with AKI in this study were: prematurity, history of APGAR < 7 in the first minute, perinatal asphyxia, oliguric AKI, severe AKI and need of VAD, data in agreement with the literature on the subject.

At the time of discharge, it is important to pay attention to parameters known in literature as risk indicators for the developing of chronic kidney disease in adulthood, such as decreased GFR (elevatedsCr), hypertension, and need for RRT during hospitalization. These changes were prevalent in the studied individuals and, yet the referral rateto the nephrology outpatient clinic was low. For posterior studies, a longitudinal follow-up of patients who presented neonatal AKI is suggested in order to assess progression to CKD.

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Data availability

All data analyzed in the study may be made available by the authors upon reasonable request.

Ethical approval

The study was approved by the HIJG Research Ethics Committee, under CAAE registration number: 32355520.9.0000.5361, and was carried out according to the current guidelines and regulatory standards for research involving human subjects (Resolution 466/12 of the National Health Council).

Authors' contribution

SCAPINI GGN performed the acquisition and analysis of data and writing of the article. BRESOLIN NL and ALMEIDA AB contributed to the study design and critical review of the article. All of them approved the final version to the published and take responsibility for all aspects of the study.

Consent to participate

Due to the characteristics of the study, the participation consent form was waived.

APPENDIX 1

DATA COLLECTION TOOL

Project Title: Epidemiology and clinical Evolution of newborns with AKI in intensive care unit.

Responsible Researchers: NilzeteLiberatoBresolinand Giulia Gabriela NorcioScapini.

Phone number for contact: (49) 99973-2423

Subject Registration

Study ID: _____

Includes patient number (first patient is 001 and then numbered sequence).

Data study collection started: __/ __/ ____

Date the first patient was entered into the study (just use today's default for when you first enter the system)

Gender: ____*(Enter as M or F)*

Date of birth: __/ __/ ____*(Use calendaror dd-mm-yyyy)*

Date of AKI diagnosis

Date of diagnosis (dd-mm-yyyy): __/ __/ ____ (*Use calendar or dd-mm-yyyy)*

Enter the date the patient was first diagnosed with acute kidney injury (AKI) by KDIGO (ignore hours and minutes; no end date needed)

KDIGO score: ___

Enter the numerical KDIGO score. Use 0, 1, 2 or 3.

General History and Health Care

Ethnicity: _____

Non-Hispanic Caucasian, Caucasian-Hispanic, non-Hispanic Black, Hispanic Black, Asian, American Indian/Alaska Native, mixed ethnicity, other.

Birth History

Weight at birth: _____ g Height at birth: _____ cm

Birth weight classification: _____ (*Classify intoSGA, AGA, LGA).*

Apgar 1^{st}/5^{th}min: ____/____ *(Put number 0 if caregivers do not know).*

Asphyxia ate the time of delivery? YES( ) NO ( )

Gestational age: _____ weeks

Gestational History

Drugs used during gestation: _____

Renal changes diagnosed by prenatal USG: _____

Prior and Family Morbid History (parents' report)

Are you aware of the health history of the child's birth family?

YES( ) NO ( )

Including living and deceased, have any members of the child's birth family (parents, grandparents, siblings) been told by a health care provider that they had kidney disease?

YES( ) NO ( ) NOT APPLICABLE ( )

Which family members?

Family Member	Disease

May put unknown for when the Family does not know the nature of the kidney disease.

Does the child have any illness prior to the diagnosis of AKI? YES( ) NO ( )

Specify (you may list more than one if applicable): _____

Physical Examination

Length: _____ cm Weight: _____ kg Blood Pressure: ___/___ mmHg

Hospitalization

Date (dd-mm-yyyy): __/ __/ ____ *(Place the date of hospitalization)*

How many days was the patient hospitalized? _____

Include all days in the hospital. If admitted on Tuesday and released on Wednesday, consider 2 days.

How many days did the patient stay in the ICU? _____

Include all ICU days. If admitted on Tuesday and discharged on Wednesday, consider 2 days. Write "0" if patient did not stay in ICU.

What was the primary indication for admission? _____

For example: edema, peritonitis, thrombosis, acute renal failure, hypertension, infection.

What was the second reason for hospitalization? _____

For example: edema, peritonitis, thrombosis, acute renal failure, hypertension, infection, sepsis. Leave blank if there is no secondary reason.

Management

Nephrotoxic drugs used during ICU stay (list them all): _____

Designate the time of the use of each drug beside in days.

Was mechanical ventilation needed? YES( ) NO ( )

If yes, how long? _____ (*Enter the days in which MV was needed)*

Were vasoactive drugs needed? YES( ) NO ( )

List which vasoactive drugs were used: _____

Did you have hydric overload at the time of AKI? YES( ) NO ( )

Did you have fluid overload at the time of discharge/death? YES( ) NO ( )

Infection

Did the patient have an infection during this admission? YES( ) NO ( )

If yes, type of infection/location: _____

For example: peritonitis, pneumonia, cellulitis, urinary tract, infection, gastroenteritis, among others.

If yes, etiologic agent: _____

For example: Streptococcus pneumoniae, E. coli, Influenza, unknown, among others.

Acute renal failure

Did the patient require renal replacement therapy during admission? YES( ) NO ( )
Highest Creatinine during hospitalization: _____ mg/dL
Place NA if you have only one creatinine value during hospitalization.
Lowest Creatinine during hospitalization: _____ mg/dL
What is the most likely cause of the acute kidney injury?_____
Dialysis Therapy: YES( ) NO ( )
If yes, which? _____
Why? _____

Complications

During hospitalization, what are the complications for the patient's health condition? _____

Urine Output

Change found in urine output according to KDIGO: _____
If no change, put 00.

Laboratory tests

Creatinine 1st value: ____ mg/dL Hourslived at the time of collection:____
Creatinine 2nd value: ____ mg/dL Hourslives at the time of collection:____
Latic Acid: _____
Enter the value or NA for not performed.
Metabolic acidosis? YES( ) NO ( )
Metabolic disorder? YES( ) NO ( )
If yes, which disorder? _____ *(Ca, K, P, Na, Cl)*

Image

Does it have echocardiogram? YES( ) NO ( )
If yes, what is the diagnostic conclusion? _____

Citation: *Giulia Gabriela Norcio Scapini, Et,al., "Epidemiology and Clinical Evolution of Newborns with Acute Kidney Injury in Intesive Care Unit" ARC Journal of Pediatrics (AJPDS) 8, no. 1, 2023, pp. 1-14. DOI: https://doi.org/10.20431/2455-5711.0801001*

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