Frequency, Risk Factors, Clinical Course, and Effect on Mortality of Acute Kidney Injury in Newborns

Gazi Arslan[1], **Gizem Yildiz**[2]

[1]Division of Pediatric Intensive Care, Department of Pediatrics, Dokuz Eylul University School of Medicine, Izmir, Turkey
[2]Division of Pediatric Nephrology, Department of Pediatrics, Dokuz Eylul University School of Medicine, Izmir, Turkey

10.5222/TP.2020.43531

Cite as: Arslan G, Yildiz G. Frequency, risk factors, clinical course, and effect on mortality of acute kidney injury in newborns. Trends in Pediatrics 2020;1(1):17-21.

Received: 25 August 2020
Accepted: 12 September 2020
Publication date: 30 September 2020

Keywords: Acute kidney injury, neonatal intensive care unit, mortality

This study was presented as an oral presentation at the 50th ERA-EDTA Congress, Istanbul in 2013.

Gazi Arslan
Division of Pediatric Intensive Care, Department of Pediatrics,
Dokuz Eylul University School of Medicine,
Balçova, 35340 İzmir - Turkey
ORCID: 0000-0002-8616-3761
✉ gaziarslan@gmail.com

G. Yildiz 0000-0001-9513-6661

ABSTRACT

Objective: *Acute kidney injury (AKI) is still an important cause of morbidity and mortality in the neonatal period, despite recent improvements on perinatal care. In this study, the frequency, etiological causes, clinical characteristics, and mortality of newborns with AKI in a tertiary neonatal intensive unit (NICU) were investigated.*
Methods: *Medical records of newborns admitted between 2007 and 2011 were evaluated and patients who developed AKI in the first 28 days of life were determined. Clinical characteristics, primary cause, mortality, and highest creatinine of newborns with AKI were recorded.*
Results: *It was determined that 94 of 677 (13.9%) patients (80% of them in the first seven days of life) developed AKI. Hypovolemia, birth asphyxia, congenital heart disease, sepsis, and genitourinary system (GUS) anomalies were found to be the most frequent causes of AKI. The incidence of AKI and mortality rates were higher in patients with gestational age under 28 week and birth weight under 1000 g. Mortality tends to rise in the presence of AKI regardless of the underlying disease, but this was statistically significant only for sepsis and cardiac disease. The presence of AKI increases length of stay and, the creatinine level was found to be lower in those who survived.*
Conclusions: *AKI is still an important morbidity in patients treated in NICU despite improvement on perinatal care. Low birth weight, prematurity, birth asphyxia, sepsis, hypovolemia, cardiac diseases, and GUS anomalies were common causes and mortality increases in patients with AKI regardless of gestational age, birth weight, and underlying etiology.*

INTRODUCTION

Diagnosis of acute kidney injury (AKI) in newborns is challenging due to difficulties in monitoring urine output, serum creatinine levels reflecting maternal serum creatinine level in the first days of life, and the frequent occurrence of non-oliguric renal failure. The incidence of AKI in the neonatal period varies according to the birth weight, gestational age, the severity and number of concomitant diseases. With the development of neonatal and perinatal care, the survival rates of critically ill newborns have increased. However, this also increases the incidence of AKI [(1)]. There are few studies showing the relationship between etiological causes and mortality of AKI in newborns admitted to the neonatal intensive care unit (NICU). In these studies, most causes of AKI in the neonatal period were sepsis, hypovolemia, birth asphyxia, congenital heart disease (CHD), genitourinary system (GUS) anomalies, and drugs. However, their relationship with AKI and their effects on mortality are not well established [(1-4)]. Although AKI in the neonatal period may cause chronic kidney disease [(5-8)], but there are few studies of AKI and long-term effects in this patient group. The aim of this study is to determine the relationship, incidence, etiological causes, clinical course, mortality rates and mortality risk factors of AKI in newborns.

AKI is the accumulation of harmful wastes in the body and reduced kidney function resulting in fluid retention. Clinical manifestations can range from mild dysfunction to severe anuric renal failure. A decrease in urine output or an abnormal elevation in

serum creatinine supports the diagnosis [2]. In order to diagnose and stage AKI in other pediatric age groups, Akcan-Arıkan et al. modified the RIFLE (risk, injury, failure, loss, end-stage disease) criteria and pediatric RIFLE (pRIFLE) criteria were developed [9]. However, there is not enough data about using those criteria's in the newborn age group.

MATERIAL and METHODS

This study was conducted in accordance with the amended Declaration of Helsinki, approved by the Local Ethical Committee. Medical records of all newborns admitted to the NICU between 2007-2011 were evaluated and those having AKI within 0-28 days of life were determined. The referral status, birth weight, gestational age, mode of delivery, clinical characteristics, presence of maternal morbidity, length of stay, and mortality status were recorded. In addition to other data, main disease-causing AKI was determined, the highest creatinine level and prognosis were recorded. AKI was defined as a two-fold increase between two measurements or a serum creatinine level of >1.5 mg/dL. The etiology of AKI was determined by the underlying disease. In the presence of more than one etiological factor, the primary etiological factor was determined by clinical decision.

Categorical and continuous variable were reported as frequencies and percentiles and means with standard deviations (SD) or medians with interquartile ranges (IQRs). The Mann-Whitney U test was used to compare non-parametric variables and Student's t test was performed for parametric data. Multivariate regression analysis was used to determine risk factors for mortality. All data obtained were analyzed using an IBM SPSS V15.0 program and P-values ≤0.05 were considered significant for all comparisons.

RESULTS

Total of 677 patients were included to the study during the study period. High creatinine value for age was found in 94 (13.9%) patients. Table 1 shows the risk factors related to AKI for newborns admitted to the NICU. AKI incidence was higher in patients with birth weight under 1000 g weight and gestational age under 28 weeks.

The time of the occurrence of AKI according to the underlying etiology and the mortality rates in those patients are shown in Table 2.

Mortality increased in patients with AKI regardless of birth weight and gestational age. Mortality tends to increase in the presence of AKI regardless of the underlying disease, but this was statistically significant only for sepsis and cardiac disease (Table 3).

Table 1. Risk factors related to AKI

	Acute Kidney Injury		
Characteristics	**No**	**Yes**	**P**
Gender			
Male - no. (%)	338 (86.2%)	54 (13.8%)	0.923
Female - no. (%)	245 (86%)	40 (86%)	
Birth Weight			
<1000 gr - no. (%)	66 (63.5%)	38 (36.5%)	<0.001
1000-1500 gr - no. (%)	133 (88.7%)	17 (11.3%)	
1500-2000 gr - no. (%)	124 (89.9%)	14 (11.1%)	
2000-2500 gr - no. (%)	81 (91%)	8 (9%)	
>2500 gr - no. (%)	179 (91.3%)	17 (8.7%)	
Gestational Age			
<28 week - no. (%)	54 (61.4%)	34 (38.6%)	<0.001
28-32 week - no. (%)	203 (87.1%)	30 (12.9%)	
33-37 week - no. (%)	202 (92.2%)	17 (7.8%)	
>37 week - no. (%)	81 (90.5%)	8 (9.5%)	
Route of Delivery			
C/S - no. (%)	470 (86.7%)	72 (13.3%)	0.365
NSPD - no. (%)	113 (83.7%)	22 (16.3%)	
Maternal Morbidity			
No - no. (%)	347 (87%)	52 (13%)	0.442
Yes - no. (%)	236 (84.9%)	42 (15.1%)	

Table 2. AKI etiology and mortality rates by age groups

	Age (days)				
Characteristics (n)	**0-2**	**3-7**	**8-15**	**16-30**	**Mortality n (%)**
Sepsis (27)	1	12	8	6	9 (33.3)
Birth Asphyxia (23)	20	3	-	-	8 (34.8)
Hypovolemia (19)	6	9	2	2	5 (26.3)
Congenital Heart Disease (14)	7	6	-	1	7 (50)
Genitourinary Anomalies (5)	4	1	-	-	2 (40)
Other (6)	2	3	1	-	3 (50)

Table 3. Primary etiological and risk factors and mortality rates leading to AKI

Characteristics	Acute Kidney Injury	n	Mortality n (%)	P	OR
Sepsis	Yes	27	9 (33.3)	<0.001	7.9
	No	203	12 (5.9)		
Birth Asphyxia	Yes	23	8 (34.7)	0.619	-
	No	55	16 (29)		
Hypovolemia	Yes	19	5 (26.3)	0.223	-
	No	25	3 (12)		
Congenital Heart Disease	Yes	14	7	<0.001	5.6
	No	265	40		
Genitourinary Anomalies	Yes	5	2	0.140	-
	No	15	1		
Birth Weight					
<1000 gr	Yes	38	16 (42.1)	<0.324	-
>1000 gr	Yes	56	18 (32.1)		

DISCUSSION

Acute kidney injury in newborns is generally defined by determining the urine output and serum creatinine level. However, there is no single serum creatinine value agreed upon. Different definitions are used in the literature. Mostly, increase in serum creatinine level was defined as AKI, while in some studies only the renal replacement therapy requirement was defined as AKI [10]. Recently, studies on new biomarkers have been intensified due to the disadvantages of serum creatinine level in the diagnosis of AKI. These include serum and urine neutrophil gelatinase-associated lipocalin, urine liver fatty acid binding protein, serum and urine cystatin-C, urine interleukin-18, urine aprotinin, urine netrin-1, kidney damage molecule-1, beta-2 microglobulin and osteopontin [5]. In 2013, a working group concluded Kidney Disease Improving Global Outcomes (KDIGO) criteria for the definition of AKI. According to KDIGO criteria, AKI was defined as ≥ 0.3 rise or ≥ 1.5-1.9 × rise from baseline serum creatinine level (defined as previous lowest/trough value) [27]. Due to the retrospective nature of our study, it is not possible to use the above-mentioned new biomarkers and KDIGO criteria for the diagnosis of AKI. Therefore, AKI was defined as a serum creatinine level >1.5 mg/dl or a 2-fold increase between any 2 measurements despite a serum creatinine level of <1.5 mg/dl [4]. The incidence of AKI in our study was found to be 13.9%. Moghal et al. found that the incidence of AKI was higher in critically ill patients in newborns than in other age groups [11]. However, in several studies, the incidence of AKI in critically ill newborns has been found in a wide range of 1-31%. This was interpreted as there was no consensus on the diagnosis of AKI.

When the development time of AKI were examined, it was found that AKI developed with a rate of 78.8% in the first week of life, while the most common etiological reasons were birth asphyxia, hypovolemia, CHD, GUS anomalies and drugs (aminoglycosides, indomethacin, ibuprofen), but the relationship between AKI and their effects on mortality are not well known [13-19]. In a study conducted in India, the incidence of AKI was found to be 26% in 200 newborns with sepsis and it was observed that mortality was higher in patients with AKI [20]. Birth asphyxia has been defined as the most common cause of AKI in many studies. While Aggarwal et al. found the inci-

dence of AKI to be 54% in patients with 5th minute Apgar scores of 6 and below [15], Korlowicz et al. [16] found the incidence of AKI to be 66% in term newborns exposed to severe birth asphyxia. In patients with hypoxic ischemic encephalopathy, a significant relationship was found between AKI and the severity of the neurological disease and serum creatinine level and the neurological outcome of the patients [21]. Studies investigating the incidence of AKI in newborns with CHD, Mortazavi et al. [22] found the incidence of AKI to be 21% in newborns with heart disease, whereas in another study, the incidence of AKI in congenital heart diseases was reported to vary between 5-20% [23]. The incidence of AKI was found to be 24% in premature babies of <30 weeks of age who were given indomethacin treatment due to patent ductus arteriosus [24]. It is controversial whether AKI in these patients is caused by patent ductus arteriosus induced circulatory disorder or indomethacin treatment.

There is no specific treatment for AKI that occurs in the neonatal period, underlying factors need to be treated. In postrenal AKI, the treatment is usually surgical intervention. Renal replacement therapy is the most effective modality in AKI [25].

It is known that mortality increases with acute kidney damage in neonatal period. Studies examining the relationship between mortality and AKI, the mortality rate was found between 6% and 58% depending on the underlying diseases [26]. AKI is not usually directly causing mortality, and the disease that causes death and the etiology of AKI may not be the same. Therefore, mortality rates in AKI are mostly associated with the underlying disease [10].

The limitation of the study is the AKI criteria we used. We defined AKI as serum creatinine level > 1.5 mg/dl or a 2-fold increase between any 2 measurements despite a serum creatinine level of < 1.5 mg/dl. However, KDIGO criteria defined in 2013 for the diagnose of AKI, this may cause underdiagnose and lower incidence of AKI.

CONCLUSION

AKI is more common in critically ill newborns than in other age groups. The development of perinatal care has increased the survival rates and the incidence of AKI in critically ill newborns. However, diagnosing AKI in newborns is more difficult than in other age groups. The frequency of AKI in the neonatal period varies according to the gestational age, birth weight, severity of comorbid diseases and NICU possibilities. Most common causes of AKI in the neonatal intensive care unit are sepsis, hypovolemia, birth asphyxia, CHD, GUS anomalies and nephrotoxic drugs. It is known that mortality rates increase in newborns with acute kidney damage. On the other hand, AKI in the neonatal period can cause chronic kidney disease that requires lifelong follow-up and treatment.

Ethics Committee Approval: Local Ethical Committee at Dokuz Eylul University (2012/10-35).
Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding: The authors received no financial support for the research, authorship, and/or publication of this article.
Informed Consent: Parents of the patient provided informed consent to publish the report.

REFERENCES

1. Vachvanischsanong P, Mcneil E, Dissaneevate S, Dissaneevate P, Chanvitan P. Neonatal Acute Kidney İnjury in a tertiary center in a developing country. Nephrol Dial Transplant. 2012;27:973-7. https://doi.org/10.1093/ndt/gfr477
2. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: What do we know? What do we need to learn? Pediatr Nephrol. 2009;24:265-74. https://doi.org/10.1007/s00467-008-1060-2
3. Bailey D, Phan V, Litalien C, Ducruet T, Merouani A, Lacroix J, Gauvin F. Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. Pediatr Crit Care Med. 2007;8:29-35. https://doi.org/10.1097/01.pcc.0000256612.40265.67
4. Agras PI, Tarcan A, Baskin E, Cengiz N, Gürakan B, Saatçi U. Acute renal failure in the neonatal period. Ren Fail. 2004;26:305-9. https://doi.org/10.1081/JDI-200026749
5. Jennifer G, Jetton and David J, Askenazi. Update on acute kidney injury in the neonate. Curr Opin Peditr. 2012;24:191-6. https://doi.org/10.1097/MOP.0b013e32834f62d5
6. Abitbol CL, Bauer CR, Montane B, Chandar J, Duara S, Zilleruelo G. Long-term follow-up of extremely low birth weight infants with neonatal renal failure. Pediatr Nephrol. 2003;18:887-93. https://doi.org/10.1007/s00467-003-1186-1
7. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S,

Goldstein SL. 3-5-year longitudinal follow-up of pediatric patients after acute renal failure. Kidney Int. 2006;69:184-9. https://doi.org/10.1038/sj.ki.5000032
8. Chertow GM, Soroko SH, Paganini EP, Cho KC, Himmelfarb J. İkizler TA. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. Kidney İnt. 2006;70:1120-6. https://doi.org/10.1038/sj.ki.5001579
9. Akcan-Arıkan A, Zappitelli M, Loftis LL. Modified RİFLE criteria in critically ill children with acute kidney injury. Kidney İnt. 2007;71:1028-35. https://doi.org/10.1038/sj.ki.5002231
10. Hoste EA. Kellum JA. Acute kidney injury: epidemiology and diagnostic criteria. Curr Opin Crit Care. 2006;12:531-7. https://doi.org/10.1097/MCC.0b013e3280102af7
11. Moghal NE, Brocklebank JT, Meadow SR. A review of acute renal failure in children: incidence, etiology, and outcome. Clin Nephrol. 1998;49:91-5.
12. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. Pediatr Res. 2011;69:354-8. https://doi.org/10.1203/PDR.0b013e31820b95ca
13. Mortazavi F, Hosseinpour SAkha S, Nejati N. Acute kidney failure in neonatal period. Iran J Kidney Dis. 2009;3:136-40.
14. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian Pediatr. 2005;42:928-34.
15. Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of renal functions in asphyxiated newborns. J Trop Pediatr. 2005;51:295-9. https://doi.org/10.1093/tropej/fmi017
16. Korlowicz MG, Adelman RD. Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol. 1995;9:718-22. https://doi.org/10.1007/BF00868721
17. Andreoli SP. Acute renal failure in the newborn. Semin Perinatol. 2004;28:112-23. https://doi.org/10.1053/j.semperi.2003.11.003
18. Subramanian S, Agarwal R, Deorari AK, Paul VK, Bagga A. Acute renal failure in neonates. Indian J Pediatr. 2008;75:385-91. https://doi.org/10.1007/s12098-008-0043-4
19. Morelli S, Ricci Z, Di Chiara L, Stazi GV, Polito A, Vitale V, Giorni C, Iacoella C, Picardo S. Renal replacement therapy in neonates with congenital heart disease. Contrib Nephrol. 2007;156:428-33. https://doi.org/10.1159/000102134
20. Mathur NB, Agarwal HS, Maria A. Acute renal failure in neonatal sepsis. Indian J Pediatr. 2006;73:499-502. https://doi.org/10.1007/BF02759894
21. Nouri S, Mahdhaoui N, Bleizig S, Zakhama R, Salem N, Ben Dhafer S, Methlouthi J, Seboui H. Acute renal failure in full term neonates with perinatal asphyxia. Prospective study of 87 cases. Arch Pediatr. 2008;15:229-35. https://doi.org/10.1016/j.arcped.2008.01.011
22. Mortazavi F, Hosseinpour SAkha S, Nejati N. Acute kidney failure in neonatal period. Iran J Kidney Dis. 2009;3:136-40.
23. Morelli S, Ricci Z, Di Chiara L, Stazi GV, Polito A, Vitale V, Giorni C, Iacoella C, Picardo S. Renal replacement therapy in neonates with congenital heart disease. Contrib Nephrol. 2007;156:428-33. https://doi.org/10.1159/000102134
24. Akima S, Kent A, Reynolds GJ, Gallagher M, Falk MC. Indomethacin, and renal impairment in neonates. Pediatr Nephrol. 2004;19:490-3. https://doi.org/10.1007/s00467-003-1402-z
25. Moghal NE, Embleton ND. Management of acute renal failure in the newborn. Semin Fatal Neonatal Med. 2006;11:207-13. https://doi.org/10.1016/j.siny.2006.01.007
26. Subramanian S, Agarwal R, Deorari AK, Paul VK, Bagga A. Acute renal failure in neonates. Indian J Pediatr. 2008;75:385-91. https://doi.org/10.1007/s12098-008-0043-4
27. Zappitelli M, Ambalavanan N, Askenazi DJ, Moxey-Mims MM, Kimmel PL, Star RA, Abitbol CL, Brophy PD, Hidalgo G, Hanna M, Morgan CM, Raju TNK, Ray P, Reyes-Bou Z, Roushdi A, Goldstein SL. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. Pediatr Res. 2017;82(4):569-73. https://doi.org/10.1038/pr.2017.136