The Long-Term Renal Functions After An Episode of Acute Kidney Injury in Children

Çocuklarda Akut Böbrek Hasarı Sonrası Uzun Dönem Böbrek Fonksiyonları

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ABSTRACT

Objective: It is widely accepted that an acute kidney injury (AKI) episode has long-term consequences such as chronic kidney disease. But the risk factors for poor renal outcome after an AKI episode are not well defined in paediatric age group. The aim of this study is to evaluate the first and fifth-year renal functions of the patients who undergo AKI during their hospital admission and to determine the risk factors affecting renal functions.

Material and Methods: 219 patients who underwent AKI from 2008 to 2012 were included in this study. 62 patients survived less than 1 year. The first and the fifth-year serum creatinine concentrations of the remaining 157 patients were reviewed retrospectively.

Results: Patients who were ≤2 years of age and patients who were in Failure+Loss group at the time of AKI had significantly lower estimated Glomerular Filtration Rate (eGFR) values in the first and fifth year after AKI compared to patients who were>2 years of age and patients who were in Risk+Injury group. 25.7% and 40.3% of the patients had abnormal eGFR in the first and fifth year after AKI respectively. In a logistic regression model, factors associated with having abnormal eGFR in the first and fifth year after AKI included younger age but not an advanced degree of AKI.

Conclusion: The previous episode of AKI could cause harmful effects on renal functions of children in the long term. Younger age and advanced stage of AKI are associated with worse renal functions after an episode of AKI.

Key Words: Acute Kidney Injury, Acute Renal Failure, Chronic Kidney Disease, Paediatrics, Renal Function

ÖZ

Amaç: Geçirilmiş Akut Böbrek Hasarı (ABH) atağının kronik böbrek hastalığı gibi uzun vadeli sonuçları olduğu yaygın olarak kabul edilmektedir. Ancak ABH atağından sonra gelişen böbrek fonksiyonlarındaki bozulma için risk faktörleri pediatrik yaş grubunda iyi tanımlanmamıştır. Bu çalışmanın amacı, hastane yatışlarında ABH atağından geçen çocukların 1. ve 5. yıl böbrek fonksiyonlarını değerlendirmek ve böbrek fonksiyonlarını etkileyen risk faktörlerini belirlemektir.

Gereç ve Yöntemler: 2008-2012 yılları arasında ABH atağı geçiren 219 hasta çalışmaya dâhil edildi. 62 hasta 1 yıldan az yaşadı. Geriye kalan 157 hastanın 1. ve 5. yıldaki serum kreatinin konsantrasyonları geriye dönük olarak incelendi.

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Bulgular: ABH atağı sırasında ≤2 yaş olan ve Yetmezlik + Kayıp grubunda olan hastaların ABH sonrası birinci ve beşinci yıllardaki hesaplanmış Glomerular Filtrasyon Hızı (hGFH) değerleri ABH atağı sırasında > 2 yaş olan ve Risk + Hasar grubunda olan hastalara göre anlamlı olarak daha düşüktü. Hastaların % 25.7'sinde ve % 40.3'ünde ABH sonrası sırasıyla 1. ve 5. yılda düşük hGFH vardı. Lojistik regresyon modelinde, ABH'dan sonraki 1. ve 5. yılda düşük hGFH'ya sahip olmakla ilişkili faktörler küçük yaşta ABH atağı geçirmek olarak bulundu; fakat ABH'nın derecesi düşük hGFH'nı etkilemiyordu.

Sonuç: Geçirilmiş ABH atağı, çocuklarda uzun dönem böbrek fonksiyonlarını olumsuz yönde etkileyebilir. ABH atağı sırasında infant yaş grubunda olmak ve ileri ABH evresine sahip olmak, uzun dönemde, kötü böbrek fonksiyonları ile ilişkilidir.

Anahtar Sözcükler: Akut Böbrek Hasarı, Akut Böbrek Yetmezliği, Kronik Böbrek Hastalığı, Pediatri, Renal Fonksiyon

INTRODUCTION

Paediatric acute kidney injury (AKI) is an important health problem since its incidence has been increasing all over the world (1) In recent years, there have been significant changes in the epidemiology of childhood AKI. Previously AKI was mostly due to primary renal diseases but now it appears to be a complication of frequent hospitalizations due to complex chronic conditions of the patients (2, 3).

It has been shown several times that AKI is associated with increased mortality, morbidity, and prolonged hospitalizations (4-7). Previously, AKI was considered as a transient condition. Recent studies support the hypothesis that a previous episode of AKI may cause long-term renal damage (8-10). There has been good evidence on the relationship between AKI and chronic kidney disease (CKD) in adults (11). There are a few studies on this relationship in paediatrics. The aim of this study was to evaluate the renal functions in the first and fifth year after an AKI episode in patients who were treated for AKI in our hospital and to determine the risk factors affecting renal functions.

MATERIALS and METHODS

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the Medical Specialist Education Board of Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital and Kecioren Ethics Committee (09.05.2019-2019/5).

219 patients who had been referred to the paediatric nephrology division of Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital during their inpatient treatment from January 2008 to December 2012 were included in this study. Inclusion criterion were being older than 1 month of age and younger than 18 years of age, and not having CKD previously. Fifty-nine patients died at their hospital stay. Three patients survived less than one year after hospital discharge. The first and fifth year serum creatinine concentrations of the remaining 157 patients were reviewed retrospectively. AKI was defined using pRIFLE criteria, using estimated Glomerular Filtration Rate (eGFR) based on the Pottel Formula (eGFR = 107.3/(Serum Creatinine/Serum Creatinine for healthy children of a particular age), urine output and the duration of AKI (12,13). The Pottel Formula was used to estimate the glomerular filtration rate of the patients instead of the Schwartz formula (13). The problem of reaching height information from medical charts was the underlying reason why the Pottel Formula was chosen. We should note that Pottel et al.(13) has shown that the height independent formula has a good correlation with the Schwartz formula. Their research has revealed that height independent formulas are comparable with the height dependent formulas to estimate GFR in children with acute kidney injury (14).

Patients were divided into 2 groups as patients who are in the Risk+Injury group and patients who were in the Failure+Loss group in pRIFLE classification. eGFR below than 90 ml/min/1.73 m^2 was accepted as abnormal eGFR. The aetiology of AKI was defined using ESPN/ERA-EDTA classification (15). In the ESPN/ERA-EDTA classification, there are five major categories. In the glomerular disease category (Category 1), there are several diseases, such as glomerulonephritis, IgA nephropathy, and systemic vasculitis. Tubulointerstitial nephritis, toxic nephropathy and urolithiasis belong to the tubulointerstitial disease category (Category 2). The systemic diseases affecting the kidney category (Category 3) includes several diseases, such as thrombosis of renal vein, amyloid nephropathy, and haemolytic uraemic syndrome. In the familial/hereditary nephropathies category (Category 4), there are diseases, such as polycystic kidney disease, cystinosis, and renal tubular acidosis. The fifth category is miscellaneous renal disorders that includes diseases, such as acute kidney injury due to hypovolaemia, acute kidney injury due to circulatory failure, acute kidney injury due to sepsis and acute pyelonephritis.

Patients were classified into two groups according to their age as follows: While the first group covered the patients who were older than 1 month and younger than 2 years old, the second group consisted of patients older than 2 years old. The patients were also classified as having AKI at the time of admission and having AKI during inpatient treatment. Prerenal, intrinsic or, obstructive AKI were defined by the clinical evaluation of the patients. Patients were also classified according to undergoing renal replacement therapy (RRT) or not, having an underlying condition or not and being hospitalized in paediatric intensive care unit (PICU) or non-PICU.

The statistical analysis was performed in SPSS for Windows 15.0. χ^2 test was used to find differences between groups

for categorical variables. A Student's t-test was used to find differences between groups for numeric variables. Multiple logistic regressions were performed to find the risk factors for abnormal eGFR. P-values less than 0.05 were considered significant.

RESULTS

Serum creatinine concentrations of 74 patients (42 male, 32 female) could be reached in the first year after AKI. The median age of patients was 6.9 years (IQR: 2.9-12.7) in the first year after AKI. The mean eGFR was 106.6±33.4 ml/min/1.73 m^2. In this study, the findings showed that among 74 patients, 12 patients were in the 'Risk' group, 25 patients were in the 'Injury' group, 33 patients were in the 'Failure' group, and four patients were in the 'Loss' group at the time of AKI. Patients in the 'Failure' group were significantly younger than the patients in the other three groups in the first year after AKI (p<0.01). The eGFR in the first year after AKI was significantly lower in patients in the 'Failure' group at AKI (p=0.03). The causes of AKI were as follows in 74 patients: 19 patients (25.7%) had AKI previous year because of glomerulonephritis. Twelve patients (16.2%) underwent AKI in the previous year due to tubulointerstitial diseases, 13 patients (17.6%) due to systemic diseases affecting the kidney, namely haemolytic uremic syndrome, and 30 patients (40.5%) due to miscellaneous renal disorders. There was no patient in the familial/hereditary nephropathies category. The patients whose AKI causes were HUS and miscellaneous renal disorders were significantly younger than the patients whose AKI causes were glomerular diseases and tubulointerstitial diseases (p< 0.01). The eGFR in the first year did not differ with the cause of AKI (p=0.07) (Table I).

Table II shows the comparison of the mean eGFR values of patients in subgroups. According to this comparison patients who were ≤2 years of age and patients who were in the Failure+Loss group had significantly lower eGFR values in the first year after AKI compared to patients who were>2 years of age and patients who were in the Risk+Injury group at the time of AKI.

Serum creatinine concentrations of 62 patients (34 male, 28 female) could be reached in the fifth year after AKI. The median age of the patients was 10.3 years (IQR: 6.7-14.8) in the fifth year after AKI and the mean eGFR was 101±25.6 ml/min/1.73 m^2. In this study, among these 62 patients,10 patients were in the 'Risk' group, 21 patients were in the 'Injury' group, 28 patients were in the 'Failure' group and three patients were in the 'Loss' group at the time of AKI. Patients in the 'Failure' group were significantly younger than the patients in the other three groups (p<0.01). The eGFR in the fifth-year after AKI did not differ between the pRIFLE stages. The causes of AKI were as follows in 62 patients: 16 patients (25.8%) had AKI before five years due to glomerulonephritis. Eleven patients (17.7%) underwent AKI before five years due to tubulointerstitial diseases, 11 patients (17.7%) due to systemic diseases affecting the kidney, namely haemolytic uremic syndrome, and 24 patients (38.7%) due to miscellaneous renal disorders. The patients, whose AKI causes were HUS and miscellaneous renal disorders, were significantly younger than the patients whose AKI cause were glomerular diseases and tubulointerstitial diseases (p< 0.01). The eGFR in the fifth-year did not differ with the cause of AKI (Table I) (p=0.07).

Similar to the first year eGFR, the fifth year eGFR was significantly lower in the Failure+Loss group compared to the Risk+Injury group. The fifth year eGFR of the group who had AKI ≤2 years

Table I: Age and eGFR of the patients classified according to PRIFLE stage and the aetiology of AKI in the first and fifth year after AKI.

First year after AKI					
pRIFLE stage	**Risk (n=12)**	**Injury (n=25)**	**Failure (n=33)**	**Loss (n=4)**	**p**
Age in the first year after AKI (year), median (IQR)	9.2 (13.0)	9.2 (7.5)	2.9 (4.5)	11.1 (6.6)	<0.01
eGFR in the first year after AKI(ml/min/1.73 m^2) mean±SD	122.9±32.7	114.9±34.0	94.4±28.3	107.5±45.3	0.03
AKI aetiology*	**Category 1 (n=19)**	**Category 2 (n=12)**	**Category 3 (n=13)**	**Category 5 (n=30)**	**p**
Age in the first year after AKI (year) median (IQR)	11.7 (8.5)	10.6 (9.0)	4.0 (5.4)	93.7 (5.3)	<0.01
eGFR in the first year after AKI (ml/min/1.73 m^2) mean±SD	116.1±40	122.5±35.5	98.1±36.1	98.1±22.7	0.07
Fifth year after AKI					
pRIFLE stage	**Risk (n=10)**	**Injury (n=21)**	**Failure (n=28)**	**Loss (n=3)**	**p**
Age in the fifth year after AKI (year), median (IQR)	14.7 (11.6)	12.5 (7.0)	7.8 (4.1)	15.3 (3.0)	<0.01
eGFR in the fifth year after AKI (ml/min/1.73 m^2) mean±SD	103.2±27.2	109.6±25.8	93.3±22.8	104.8±37.0	0.17
AKI aetiology*	**Category 1 (n=16)**	**Category 2 (n=11)**	**Category 3 (n=11)**	**Category 5 (n=24)**	**p**
Age in the fifth year after AKI (year), median (IQR)	14.1 (5.0)	12.5 (8.4)	8.0 (3.3)	6.8 (7.3)	<0.01
eGFR in the fifth year after AKI (ml/min/1.73 m^2) mean±SD	111.3±22.5	104.1±26.8	88.3±16.6	98.5±28.6	0.13

***Category 1:** *Glomerular diseases,* **Category 2:** *Tubulointerstitial diseases,* **Category 3:** *Systemic diseases affecting the kidney,* **Category 5:** *Miscellaneous renal disorders. There were no patients in the category 4 (familial/hereditary nephropathies)*

Table II: eGFR in the first and fifth year classified according to the RRT status, pRIFLE stage, AKI type, age groups, managing in PICU, AKI place and having an underlying disease.

	eGFR in the first year (ml/min/1.73 m²)	p	eGFR in the fifth year (ml/min/1.73 m²)	p
Receiving RRT *				
Yes	102.6±31.9	0.711	92.3±23.5	0.078
No	108.5±34.2		104.9±25.9	
pRIFLE stage*				
Risk+Injury	117.5±33.4	0.005	107.5±26.0	0.043
Failure+Loss	95.8±30.1		94.4±23.9	
AKI type*				
Prerenal	100.9±26.1	0.247	100.8±29.2	0.903
Intrinsic	110.0±38.2		100.0±22.2	
Obstructive	136.9±38.2		120.7±22.2	
Age at AKI*				
≤2 years of age	86.7±17.8	0.000	86.8±25.4	0.004
>2 years of age	114.6±34.9		106.8±23.6	
Managing in PICU*				
PICU	102.1±13.9	0.425	96.9±28.1	0.607
Non-PICU	107.3±35.2		101.7±25.4	
AKI place*				
AKI at admission	106.1±34.6	0.792	97.9±22.6	0.193
AKI during inpatient treatment	108.4±30.2		109.1±31.6	
Underlying disease*				
Without underlying disease	109.0±36.6	0.743	99.3±23.1	0.575
With underlying disease	104.1±29.6		103.1±28.5	

AKI: *Acute Kidney Injury,* ***eGFR:*** *estimated Glomerular Filtration Rate,* ***PICU:*** *paediatric Intensive Care Unit,* ***pRIFLE:*** *paediatric Risk, Injury, Failure, Loss and End Stage Renal Disease,* ***RRT:*** *Renal Replacement Therapy,* *******Drop-out rates in all subgroups were similar.*

Table III: Logistic regression analysis of risk factors of having an abnormal eGFR

	Factors	OR	95% CI		p
			Lower	Upper	
abnormal eGFR in the first year	younger age	5.29	1.63	17.14	0.005
	pRIFLE stage	3.16	0.93	10.70	0.065
abnormal eGFR in the fifth year	younger age	6.17	1.78	21.47	0.004
	pRIFLE stage	2.06	0.66	6.41	0.214

eGFR: *estimated Glomerular Filtration Rate,* ***pRIFLE:*** *paediatric Risk, Injury, Failure, Loss and End Stage Renal Disease*

of age was significantly lower than the group who had AKI >2 years of age (Table II).

Nineteen patients (19/74, 25.7%) had abnormal eGFR in the first year after AKI. 25 patients (25/62, 40.3%) had abnormal eGFR in the fifth year after AKI. Significantly more patients in ≤2 years of age at AKI group had abnormal eGFR in the first year compared to >2 years of age group (n=11, 52.4% to n=8, 15.1% respectively, p=0.001, Figure 1). 13 patients (13/18, 72.2%) in ≤2 years of age group had abnormal eGFR in the fifth year, whereas 12 patients (12/44, 27.3%) in >2 years of age group had abnormal eGFR in the fifth year (p=0.001, Figure 1). Significantly more patients in the Failure+Loss group had abnormal eGFR in the first year compared to patients in the Risk+Injury group (n=14, 37.8% to n=5, 13.5% respectively, p=0.017, Figure 2). 9 patients (29.0%) in the Risk+Injury group had abnormal eGFR in the fifth year, whereas 16 patients (51.6%) in the Failure+Loss group had abnormal eGFR in the fifth year (p=0.070, Figure 2). In a logistic regression model, factors associated with having abnormal eGFR included younger age but not having an AKI degree of Failure+Loss (Table III).

DISCUSSION

This study showed that 25% and 40% of the patients, who underwent an AKI episode, had an abnormal eGFR in the first and fifth year respectively. The most important factor that affected having an abnormal eGFR was being ≤2 years of age at the time of AKI.

Because the incidence and the number of paediatric AKI survivors increase, there is a paramount need to identify the long-term outcome of these patients and factors influencing this outcome. It is widely accepted that an AKI is not a temporary event, thus have long-term consequences such as CKD. In this

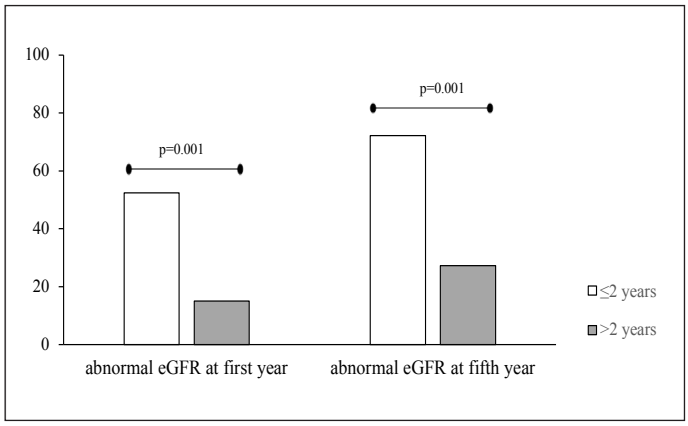

Figure 1: The rate of children who underwent AKI and had abnormal AKI in the first and fifth year after AKI, classified according to the age group. Significantly more patients in ≤2 years of age at AKI group had abnormal eGFR in the first and fifth year compared to >2 years of age group.

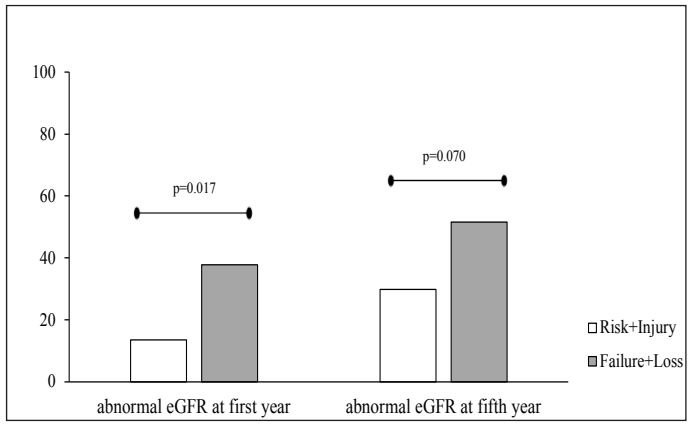

Figure 2: The rate of children who underwent AKI and had abnormal AKI in the first and fifth year after AKI, classified according to the pRIFLE stage. Significantly more patients in Failure+Loss group had abnormal eGFR in the first year compared to Risk+Injury group. The rate of children with abnormal eGFR in the fifth year was comparable between Risk+Injury and Failure+Loss group.

study we examined factors included AKI aetiology, receiving RRT, pRIFLE stage, having a prerenal or intrinsic type of AKI, age at AKI, being managed in PICU, having AKI at admission or during inpatient treatment and having an underlying condition. Among these factors age at AKI and pRIFLE stage were the factors that affects the first and fifth year eGFR after AKI.

In the literature, there is evidence that younger children with AKI have worse survival rates than the other paediatric age groups with AKI (16). Similar to the literature, in the previous study, we reported that patients who had AKI under 2 years of age had poor survival (17). But the effect of age at AKI on the long-term outcome after AKI is not well examined in paediatric age group. To our knowledge, this is the first study underlying the effects of younger age on long term renal function after AKI in the literature. In our cohort, the rate of having an abnormal eGFR in the fifth-year reached 72% in patients who underwent AKI under two years of age. Some studies show that neonatal AKI has a worse outcome, but they do not compare their results with the other age groups (18,19). Factors reported in the literature about the progression to CKD after neonatal AKI are as follows: low nephron numbers and incomplete nephrogenesis of neonates and recurrent AKI episodes, extrauterine growth restriction, hypertension and obesity in the postnatal period. Low nephron numbers arise from prematurity, low birth weight, and intrauterine growth restriction. However, it is still unknown whether a renal failure is a culprit or outcome of low nephron number (20, 21). Extrauterine growth restriction and clinical circumstances, such as recurrent AKI episodes, hypertension and obesity, may affect nephrogenesis, childhood renal function, and long-term risk of CKD. As observational studies have found high rates of CKD in survivors of neonatal AKI, it has paramount significance to detect neonatal status and birthweight of the children who undergo an AKI episode. Unfortunately, in this study, we did not examine birth weights and the status of undergoing AKI in their neonatal period of this cohort. Further prospective longitudinal studies are needed on the effects of birth weight and having an AKI episode in the neonatal/infant age group on renal outcome after AKI. Authors recommend that neonates who underwent an AKI episode should be followed up closely to improve long term renal outcome (19,21). Our results show that having an AKI episode in infant age is associated with a decrease in eGFR in the first and fifth-year after AKI. We suggest that both neonatal survivors of AKI and also the infants who undergo AKI before the age of two should be closely followed up to implement reno-protective interventions.

Although the pRIFLE stage did not affect survival in our previous report, it affected the first and fifth-year eGFR after AKI. Some adult studies conclude that the severity of AKI is a significant predictor of CKD progression (22-24). We should state that there are conflicting results in the association of AKI severity and progression to CKD in children. Al-Qatibi et al. (25) found that the severity of renal impairment at baseline did not affect the risk of long-term renal impairment. On the other hand, Keenswijk et al. reported that being in the 'Failure' group at the time of AKI was significantly associated with CKD in the sixth month after AKI in children (26).

We did not find PICU admission and receiving RRT as risk factors for abnormal eGFR. The factors were associated with worse patient survival in our previous report (17). Some studies investigated patients who had AKI during their PICU admission had a high incidence of reduction in the GFR and proteinuria in the long term (25). Studies about paediatric AKI are conducted either in critically ill children or non-critically ill children. Thus, the literature on the comparison of long-term outcomes of AKI in critically and non-critically children is scarce. However, in line with our results, Mammen et al.(10) reported that 40% of the patients who underwent an AKI episode in PICU had a decreased eGFR in the long-term. Although undergoing RRT was defined as a crucial risk factor for long-term renal

dysfunction, our results showed no effect of RRT on abnormal eGFR in the first and fifth-year after AKI (10,27). The underlying reason for this outcome needs further investigation.

This study has some limitations, such as its retrospective nature and high dropout rates during follow up. Another limitation of the study is that the original definition of paediatric RIFLE criteria used the Schwartz formula, but we used the Pottel formula instead because of the problem of reaching height information from medical charts. We also did not investigate other significant renal outcomes, such as albuminuria and hypertension in the children involved in this study. On the other hand, we noticed that there were lots of gaps in renal outcome after paediatric AKI in the literature. Thus, we tried to define factors that affect long term renal outcome after paediatric AKI with this study.

CONCLUSION

To sum up, we have shown that a previous episode of AKI could cause harmful effects on renal functions in children in the long term. Factors, such as advanced stage of AKI and younger age are associated with worse first and fifth-year renal functions after an episode of AKI in children. We propose that children who had an advanced stage of AKI and who had AKI at a younger age should be closely followed up to implement reno-protective interventions.

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