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ORIGINAL ARTICLE

Acute kidney injury with replacement kidney therapy in the Pediatric Intensive Care Unit of children's hospital Dr. Jeser Amarante Faria

Ana Luiza da Silva Wendhausen¹, Artur Ricardo Wendhausen², Flávia Helena Bergmann Julião²

Keywords:

Renal replacement therapy,
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Abstract

Introduction: Acute kidney injury (AKI) is defined as a sudden reduction in kidney function, which ranges from mild changes in kidney biomarkers to severe conditions that require renal replacement therapy (RRT). RRT is the most effective treatment for patients with severe AKI, and the most used RRT methods are: conventional hemodialysis (HD), continuous hemodialysis and peritoneal dialysis (PD). **Objectives:** This study aims to analyze the epidemiological profile and outcome of patients diagnosed with Acute Kidney Injury undergoing renal replacement therapy in the Intensive Care Unit. **Methods:** For this, a descriptive, observational, cross-sectional study was carried out through the retrospective collection of data obtained through the electronic medical record system. **Results:** Among the hospitalizations during the study period, 3.67% required RRT due to AKI, with sepsis as the main cause (48.57%). Most patients underwent RRT through HD. The mortality rate was 45.7%, showing higher mortality in those who developed AKI during hospitalization compared to those who were already admitted with AKI. **Conclusion:** It is possible to conclude that most patients undergoing RRT due to AKI are under 2 years of age and more than 50% have comorbidities. The presence of comorbidities and PIM2 are related to mortality.

¹ Universidade da Região de Joinville - UNIVILLE - Joinville - Santa Catarina - Brazil.

² Hospital Infantil Dr. Jeser Amarante Faria, Unidade de Terapia Intensiva - Joinville - Santa Catarina - Brazil.

Correspondence to:

Ana Luiza da Silva Wendhausen.

Universidade da Região de Joinville. Rua Paulo Malschitzki, Zona Industrial Norte, Joinville, SC, Brazil. CEP: 89219-710. E-mail: wendhausen.ana@gmail.com

INTRODUCTION

Acute kidney injury (AKI) is defined as a sudden decrease in kidney function with varying degrees of severity, ranging from mild alterations in kidney biomarkers to severe disease requiring renal replacement therapy (RRT). Prevalence of AKI has increased in both developed and developing countries. This multifactorial condition has been associated with high morbidity and mortality in critically ill patients^{1,2}.

AKI is a very common condition in hospitalized children. Data suggest that 5% of children with non-critical conditions and up to 27% of children with critical conditions experience AKI at some point during hospitalization². An epidemiology study carried out by the Latin American Society of Nephrology and Hypertension in 2004-2012 found death rates between 18% and 70.4% in pediatric patients with AKI in Latin America. The most common etiologies were hemolytic-uremic syndrome (HUS), heart disease and critical illness³. In Brazil, a retrospective study from 2008 reported an overall mortality of 53.3% in children aged 0-12 years with AKI requiring dialysis¹.

In addition to high mortality, children with AKI go through longer periods of hospitalization and often require intensive care. Patients surviving AKI are still a high risk of developing chronic kidney disease (proteinuria, hypertension and reduced glomerular filtration rate)⁴.

The need to standardize the criteria for AKI resulted in classifications initially thought for adults and later adapted for children. The most recent classification system, and also the most recommended in pediatrics, is the KDIGO (Kidney Disease: Improving Global Outcome). Published in 2012, the KDIGO is used to categorize patients into three stages depending on disease severity. The criteria analyzed are increases in serum creatinine and/or decreases in 24-hour urinary output^{1,5,6}.

RRT is the most effective treatment for severe AKI in critically ill patients. It aims to correct metabolic disorders resulting from renal dysfunction, electrolyte and fluid balance, preservation and assistance in the recovery from organ dysfunctions associated with kidney damage. RRT includes conventional (HD) or intermittent hemodialysis, continuous hemodialysis and peritoneal dialysis (PD). The choice of method depends on the objective of treatment, the availability of materials and specialized staff, and the patient's clinical condition¹. Since it is a complex and costly therapy, access to RRT has been less than ideal in low- and middle-income countries. In this context, peritoneal dialysis comes up as the most used therapy in patients with acute disease due to ease-of-use and affordability^{1,7}.

Recent research has looked into how to predict or detect risks for AKI earlier in order to avoid or mitigate the damage caused by the disease. More specific and sensitive

biomarkers, capable of detecting the onset of kidney injury earlier than the increase in serum creatinine, have been studied. These markers include urine neutrophil gelatinase-associated lipocalin (NGAL), used to detect early tubular damage. When associated with other biomarkers such as Cystatin C (CysC), more accurate data is gathered on the pathophysiology of the disease, improving prognostic capabilities. Following this trend, the renal angina methodology was developed in 2010. This clinical scale identifies patients at high risk of AKI and serves as a screening tool to indicate biomarker levels^{1,4,8}.

From an epidemiological point of view, especially in Brazil, there is a lack of large studies on AKI in the pediatric population. Since AKI is a serious condition with high morbidity and mortality that imposes a substantial financial burden on the healthcare system, the analysis of the epidemiological profile and outcomes of patients on RRT allows the establishment of improved public health policy and a more rational approach to the resources needed to treat patients with AKI, consequently decreasing the impact of the disease on affected individuals.

METHODS

This descriptive observational cross-sectional study was carried from January 1, 2016 to August 31, 2020. We collected retrospective data stored in a TASY electronic medical records system.

The study included patients aged 28 days to 17 years diagnosed with acute kidney injury admitted to the Pediatric Intensive Care Unit who, at some point, underwent RRT. Patients aged 28 days or less, individuals diagnosed with or progressing to chronic kidney disease (CKD), patients with medical records with missing, incorrect or insufficient data, were excluded from the study.

The variables collected were age, gender, disease etiology, city of residence, initial dialysis method and whether they were converted to other types of dialysis, PIM2 (Paediatric Index of Mortality %), KDIGO score at the time of RRT prescription, previous comorbidities, total time on RRT, time on mechanical ventilation (MV), whether they received vasoactive drugs (VAD) at any point during hospitalization, length of stay in the ICU and outcome (discharge or death).

The etiology of AKI was defined according to the classification proposed by the ESPN/ERA-EDTA (European Society for Pediatric Nephrology / European Renal Association- European Dialysis and Transplant). This classification segregates patients into five categories: glomerular disease, tubulointerstitial nephritis, systemic diseases with renal involvement (HUS, lupus), familial nephropathy, others (sepsis, hypovolemia, shock, pyelonephritis).

Comorbid conditions existing prior to the diagnosis of AKI were categorized into neuropathy, heart disease, oncologic condition, genetic syndrome, prematurity, endocrine disease, and others.

Patients were categorized into the following age groups at the time of AKI diagnosis: 29 days to 2 years, 2 to 5 years, 5 to 10 years, over 10 years. They were also categorized into individuals with AKI at the time of admission and individuals who developed AKI at some point during their stay in the ICU.

The database was built with Microsoft Excel. Statistical analysis was carried out on SPSS (Statistical Package for the Social Science).

The study complied with the Guidelines for Research involving human beings, contained in resolution 466/2012 of the National Health Council. The Ethics Committee for Research with Human Beings of the Hans Dieter Schmidt Hospital approved the study and granted it certificate number 35713720.0.0000.5363.

This study did not pose any direct risks to the enrolled patients. It did not change the therapeutic approaches or treatments prescribed to patients. Since this was an observational descriptive study, it did not require patient consent. In accordance with ANVISA resolution RDC 96/2008, the authors declare that the study did not entail conflicts of interest.

RESULTS

A total of 1,905 patients were admitted to the PICU at HJAF from January 1, 2016 to August 31, 2020 (56 months). In this time period, 70 patients underwent RRT for AKI, 33 males (47.1%) and 37 females (52.9%). Mean age was 4.87 years (SD: ± 4.61). According to the distribution by age group, 25 (35.72%) patients were between 29 days and two years old, 17 (24.28%) between two and five years old, 14 (20%) between five and 10 years old, and 14 (20%) were over 10 years old.

An average 1.25 patients/month underwent RRT. The year with the highest number of admissions was 2019 (32.85%), with an average of 1.91 patients/month. Half of the studied population came from the North of the state, followed by the West with 20%, the Vale do Itajaí region with 15.71%, the South with 7.14%, the Greater Florianópolis with 5.71%, and the Serrana region with 1.42%.

According to etiology, the causes of AKI were: glomerular disease in three patients (4.28%); systemic disease with kidney involvement in 25 patients (35.71%). HUS was the main cause of AKI for systemic disease, with 18 patients (25.71%). Forty-two patients (60%) were described as having other causes of AKI, among which sepsis accounted for 34 patients (48.57%).

At the time of admission, 46 (65.71%) children had been diagnosed with AKI, while 24 (34.28%) had AKI at some point during hospitalization. According to the KDIGO classification, at the time of RRT prescription, 53 (75.71%) had stage 3, nine (12.85%) had stage 2, and eight (11.42%) had stage 1 disease. Thirty-nine patients were initially prescribed HD and 31 PD, of which 13 (41.9%) were converted to HD at some point during hospitalization.

Thirty-six of the 70 patients (51.42%) had other conditions prior to AKI, with oncologic conditions diseases accounting for approximately 17% of the cases, followed by neuropathy, heart disease, prematurity, genetic syndrome, endocrine diseases and other comorbid conditions.

More than 87% of the patients underwent MV and spent 14.18 days (SD: ± 15.51) on average on a ventilator, ranging from one to 75 days. VADs were prescribed to 55 (78.57%) children. Only nine did not require ventilatory support and 15 were not prescribed VADs.

The average length of stay in the ICU was 17.31 days (SD: ± 16.89), ranging from one to 75 days. The average length of stay was 13.81 days for the patients who died and 20.26 days for the patients who were discharged. Overall mean time on RRT was 8.86 days (SD: ± 9.82); mean time on RRT for the patients who died was 5.66 days and 11.55 days for the patients who were discharged.

Mean PIM2 was 21.41% (SD: ± 24.46); mean PIM2 for the patients who died was 33.27% and 11.42% for the patients who were discharged. The mortality rate was 45.7%; seven of the 32 patients who died had already recovered kidney function (Table 1).

When the study population was compared for outcomes (Table 2), statistically significant associations ($p < 0.05$) were found with PIM2 ($p < 0.001$), presence of comorbidity ($p = 0.009$) and time on RRT ($p = 0.008$). The other characteristics (KDIGO, age group, AKI on admission) were not statistically associated with patient outcomes.

The analyzed association revealed that systemic diseases with renal involvement, represented mainly by HUS, were associated with a greater number of discharges than deaths. Diseases in the "other" category and sepsis in particular were more strongly associated with death (Table 3).

DISCUSSION

The present study showed that 1.25 patients/month required RRT for AKI, or 3.67% of PICU admissions in the studied time period. Other studies found rates between 0.29 and 5.16 patients/month, with a range of 1.2 to 7.17% of ICU patients needing RRT⁹⁻¹⁷.

As in other studies, in ours the age group most affected by AKI was the youngest, comprising individuals aged 29

Table 1. Study population characteristics.

	N (%)	Mean (DP)
Age		4.87 (4.61)
Gender		
Female	37 (52.9)	
Male	33 (47.1)	
Comorbidity		
Oncologic condition	12 (17.14)	
Neuropathy	6 (8.57)	
Cardiopathy	3 (4.28)	
Prematurity	3 (4.28)	
Genetic syndrome	3 (4.28)	
Endocrine disease	1 (1.42)	
Other	8 (11.42)	
Region of residence		
North	35 (50)	
West	14 (20)	
Vale do Itajaí	11 (15.71)	
South	5 (7.14)	
Great Florianópolis	4 (5.71)	
Serrana	1 (1.42)	
KDIGO		
1	8 (11.42)	
2	9 (12.85)	
3	53 (75.71)	
MV	61 (87.14)	
Time on MV		14.18 (15.51)
VAD	55 (78.57)	
Length of stay		17.31 (16.89)
PIM2		21.41 (24.46)

Abbreviations: SD, standard deviation; MV, mechanical ventilation, VAD, vasoactive drug; PIM-2, Paediatric Index of Mortality-2. Orders of magnitude: Age, years; Length of stay, days; Mechanical ventilation time, days.

Table 2. Associations between study population characteristics and outcomes.

	Death (n=32)	Discharge (n=36)	P
PIM2 (mean)	33.26	11.41	<0.001 ^a
Comorbidity (N) (%)	22 (68.75)	14 (38.88)	0.009 ^b
KDIGO (mean)	2.47	2.79	0.059 ^c
Time on RRT (mean)	5.65	11.55	0.008 ^a
Age range (mean)	2.45	2.43	0.438 ^b
AKI on admission (N) (%)	17 (53.12)	29 (80.55)	0.48 ^b

Abbreviations: RRT, Renal replacement therapy; AKI, acute kidney injury; PIM-2, Paediatric Index of Mortality-2. Orders of magnitude: Age, years; time on RRT, days. Statistical tests: ^a T-Test; ^b Chi-square; ^c Mann-Whitney.

Table 3. Statistically significant associations between etiology and outcomes ($p=0.001$).

	Death (n=32)	Discharge (n=36)	P
Other (N) (%)	27 (84.37)	15 (41.66)	
Systemic diseases with renal involvement (N) (%)	4 (12.50)	21 (58.33)	0.001 ^b
Glomerular disease (N) (%)	1 (3.12)	2 (5.55)	

Statistical test: ^b Chi-square.

days to two years (35.72%). According to the literature, AKI occurs predominantly at the ends of the pediatric age range, i.e., in adolescents and infants under one month of age^{2,18,19}. The average age of individuals with AKI in our study was 4.87 years; mean age varies widely in the literature. There was no significant difference between genders, although most articles point to a slight predominance of disease in males^{9,12,20,21}.

Contrary to our study, some authors described a relationship between mortality and younger age, especially in individuals younger than one year. This association is reportedly stronger in populations that include individuals younger than one month^{9,11,22}.

The year with the highest number of admissions was 2019, the year in which the Hospital became the only referral center for pediatric RRT in the entire state. Most patients came from the North region, where the Hospital is located.

Sepsis was the main cause of AKI in our study, followed by HUS and glomerulopathies. This study was carried out in a PICU with predominantly clinical patients, with rare postoperative admissions. Therefore, there were no data available on the use of RRT in surgical complications.

The etiology of AKI varies widely between developed and developing countries. In developed countries, AKI is more associated with hospital-acquired illnesses and the consequences of treatment for critically ill patients (heart surgery post-operative care, sepsis, transplantation, tumor lysis syndrome, exposure to nephrotoxic drugs). Improvements in the care and survival of critically ill patients has caused AKI to be increasingly associated with systemic diseases such as sepsis, multiple organ damage and the therapies prescribed for these conditions^{2,23}.

Conversely, developing countries have a higher incidence of AKI resulting from community-acquired conditions such as post-infectious glomerulonephritis, hypovolemia, toxicity/poisoning and sepsis.

The Spanish multicenter study by Pol et al. described postoperative complications as the main cause of AKI, followed by sepsis and kidney disease¹⁶. A multicenter study carried out in China reported urolithiasis, dehydration and nephrotic syndrome were the main causes of AKI²¹. A review carried out in sub-Saharan Africa found malaria as the main etiology, followed by dehydration due to gastroenteritis²⁴. A study conducted

in Turkey described sepsis as the main cause, followed by hypovolemia and shock, tubulointerstitial disease and HUS¹¹.

Our study found a statistically significant correlation between etiology of AKI and outcomes, with sepsis showing a stronger association with death. As described in the literature, sepsis is the most significant cause of death in children with AKI^{19,25}.

Since ours is a referral center for RRT, most of the patients included in the study had been diagnosed with AKI prior to admission. This data varies substantially in the literature, but this is a trend in developing countries, in which community-acquired AKI is the most prevalent form of disease²⁴. The same occurs with the degree of renal impairment, which in developing countries is more severe at the time of diagnosis^{11,14,18,23,25}. In our study, most of the patients had advanced kidney disease according to the KDIGO classification at the time of diagnosis.

We found no statistically significant association between the KDIGO classification and patient outcomes. The literature varies widely in descriptions of an association between death rates and degree of renal impairment. Two articles presented interesting data regarding the classification of kidney injury. Kari et al. found lower death rates in patients with stage 1 or 2 disease according to the KDIGO classification undergoing RRT compared to individuals with in stage 3 disease, indicating that patients with less severe kidney damage benefited more from RRT²⁵. Kaddourah et al. evaluated progression of the KDIGO scores over a week in critically ill hospitalized patients, and found that individuals with stage 1 disease on the first day were more likely to progress to stages 2 or 3 compared to patients without a diagnosis of AKI on the first day¹⁵.

As in our study, several other centers do not have an AKI treatment protocol, which may impair the assessment of the degree of kidney injury and patient outcomes. However, the severity of AKI is associated with a greater probability and duration of RRT, longer MV time, and consequently longer hospital stays^{4,9,12,23,25}.

More than 50% of the patients had chronic clinical conditions prior to the diagnosis of AKI. Other authors have described similar proportions in their studies, with a predominance of heart disease, neuropathy and lung disease. The presence of comorbid conditions is a risk factor for AKI that has been also associated with higher death rates among patients undergoing RRT^{9,11,23}. Our study found a statistically significant association between presence of comorbid conditions and death.

The mode of RRT in the majority of our patients was HD. This is due to the fact that many patients who are referred to our service had failed treatment attempts with PD. Among those who started PD upon admission, 41.9% had device failure and converted to HD. There is a preference for PD in the literature due to ease of use and affordability^{11,16}. Continuous hemodialysis is preferentially prescribed to critically ill patients, since it generates less hemodynamic instability; however, it is an expensive method not available in our service.

As described in the literature, we found a high incidence of MV and use of VADs in patients undergoing RRT. The average length of stay and time on RRT was shorter in the patients who died. The mean time on MV, length of hospitalization and time on RRT were higher than those found in the literature, although the articles included in our references did not establish comparisons against a population that exclusively underwent RRT, as we did in our study^{9,24,25}.

In the population studied by Bresolin et al., 100% of the children who died were prescribed VADs and MV¹⁷. In a Brazilian study enrolling pediatric patients hospitalized for sepsis and AKI, more than 70% of the population required MV, more than 98% took VADs and 42.8% needed RRT. Among those who required RRT, more than 92% were on MV and all took VADs. And as in our study, the patients who died had shorter hospital stays²¹. In a North American review, Sutherland et al. compared the lengths of stay between different groups of patients with AKI and found that the ones referred to an ICU had longer stays than those with AKI who required RRT, and that patients with AKI not transferred to an ICU and who did not require RRT had shorter hospital stays¹⁸.

Several studies demonstrate that AKI is an independent risk factor for prolonged ICU stay, longer time on MV and increased mortality among critically ill patients^{2,20,25}.

Differently from developed countries, in which the death rates for patients with AKI range between 11% and 27% with higher values in groups undergoing RRT, the death rate in our population was 45.7%. In developing countries, death rates may be as high as 86.5%^{1,9,18,23,26}. A review carried out in Latin America including pediatric patients with AKI described death rates ranging from 18% to 70.4%³. Bresolin et al. reported a death rate of 68.5% in children undergoing RRT at a pediatric hospital in southern Brazil¹⁷.

Comparative studies including critical patients found that individuals with AKI have longer hospital stays, mortality scores, higher incidence of shock and respiratory failure, and death mortality rate compared to critically ill patients without AKI^{11,12,18,25}. Our study did not find a statistically significant association between time of onset of AKI and patient outcome, although, as in other articles, higher death rates were seen among patients who developed AKI during hospitalization compared to individuals who had AKI on admission^{11,23,26}.

The use of RRT in critically ill patients is strongly associated with death, with a risk three to nine times higher compared to patients with AKI who did not need RRT^{21,22}. There was a statistically significant difference between time on RRT time and outcome, with lower averages in patients who died.

In addition to short-term mortality, a Canadian study prospectively evaluated the death rates of patients hospitalized in a PICU. The comparison demonstrated that the individuals with AKI on admission had a higher death rate both after 30 days of hospital discharge and during a follow-up period of five to seven years²⁰.

The average mortality score found in our study was 21.41%, which is higher than the one reported in other studies that used the PIM2, with averages between 13.1% and 16.5% in patients with AKI. There are no specific data covering only patients undergoing RRT as in our study^{9,19}. However, all studies that investigated pediatric mortality rates found higher values in patients with AKI^{16,19,25}. As other authors, we found a statistically significant association between PIM2 and death.

CONCLUSION

Our study found that critically ill pediatric patients undergoing RRT for AKI are mostly under two years of age and more than 50% have at least one comorbid condition. Mechanical ventilation and use of vasoactive drugs were prescribed to more than 78% of our population. Average length of hospital stay and time on RRT were greater in patients discharged from the ICU.

Overall mortality was 45.7%. Sepsis was the main cause of AKI. PIM2 and presence of comorbid conditions were positively associated with mortality.

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