

# Study of acute kidney injury in children with nephrotic syndrome in a rural tertiary care hospital



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Submission: 12-02-2024

Revision: 24-03-2024

Publication: 01-05-2024

## ABSTRACT

**Background:** Acute kidney injury (AKI) is a common comorbidity in critically ill children and is associated with an increased risk of morbidity and mortality in children with nephrotic syndrome. The etiology of AKI in nephrotic syndrome is complex and multifactorial. **Aims and Objectives:** To determine the proportion, risk factors, and outcomes of patients with AKI in children hospitalized with nephrotic syndrome. **Materials and Methods:** This cross-sectional study was done on children between 1 month and 14 years of age attending the pediatric department for 1 year from October 2020 to June 15, 2022. Detailed history, physical examination, and investigations were done in children with nephrotic syndrome as per pro forma. Information was collected on demographic variables, vital signs, anthropometry, diagnosis, comorbidities, therapies, presence of hypovolemia, sepsis or shock, use of diuretics or nephrotoxic medications, need for oxygen, mechanical ventilation, vasopressors or renal replacement therapy, length of hospital stay, and outcome at discharge. For those children having AKI, clinical outcomes were measured in terms of duration of hospital stay, recovery of S.creatinine, and urine output. **Results:** A total of 64 patients with nephrotic syndrome were enrolled in this study. Fifteen patients had AKI (23.4%) among children with nephrotic syndrome. The most common etiology being sepsis accounting for 4 out of 15 (26.7%) of total cases followed by acute respiratory distress syndrome (13.3%), nephrotoxic medications (13.3%), renal parenchymal disease (13.3%), Post-streptococcal glomerulonephritis (13.3% each) and Sickle cell disease with nephritis and acute fulminant hepatitis (6.7%). There was significantly more mortality among subjects with stage 2 (14.3%) and 3 (14.3%) kidney disease. **Conclusion:** AKI is common in our children with nephrotic syndrome and the main risk factors of AKI include sepsis, gross hematuria, urinary tract infections, peritonitis, and exposure to potentially nephrotoxic medications. There is a need to identify the patients with nephrotic syndrome at risk of AKI and apply strategies to prevent AKI in focused at-risk groups.

**Key words:** Urine output; Nephrotic syndrome; Acute kidney injury

## INTRODUCTION

Nephrotic syndrome is a common renal disease worldwide, and it is also an important chronic disorder in children. Its incidence is reported to be 2–3/100,000 children per year.<sup>1</sup> For decades the term “Acute Renal Failure (ARF)” has been used for denoting a sudden and potentially reversible inability of the kidneys for performing their

normal homeostatic functions. It refers to damage that has already occurred and does not leave any capacity for early detection of injury or intervention, to prevent failure. ARF is associated with severe morbidity especially in children due to the existence of more than 30 definitions of ARF in literature, leading to large variations in the reported incidence and outcome, the term ARF was replaced by acute kidney injury (AKI) to provide uniform definition

### Access this article online

**Website:**

<http://nepjol.info/index.php/AJMS>

**DOI:** 10.3126/ajms.v15i5.62711

**E-ISSN:** 2091-0576

**P-ISSN:** 2467-9100

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and classification and standardize patient care.<sup>2,3</sup> Acute kidney injury (AKI) is a common comorbidity in critically ill children and is associated with an increased risk of morbidity and mortality.<sup>4</sup> Some factors, such as age and sex are non-modifiable whereas others, including exposure to medications, are controllable and present the opportunity to decrease the risk of AKI admitted to intensive care unit (ICU). The incidence of AKI in nephrotic syndrome varies widely in critically ill children from 10% to 80%.<sup>5</sup> Until recent years most information on the epidemiology of AKI in the nephrotic syndrome came from case reports. A recent study by Rheault et al.<sup>6</sup> using data from the Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP-KID)<sup>7</sup> reported a 158% increase in the frequency of nephrotic syndrome hospitalizations complicated by AKI between 2000 and 2009. The frequency of hospitalizations secondary to other complications seen with nephrotic syndrome such as infection and thromboembolism remained stable during the same period. There are few studies in AKI in hospitalized children with nephrotic syndrome and most are retrospective<sup>6,8,11,12</sup> and in Indian children studies are limited.<sup>8-11</sup> Hence, this study was planned to determine the proportion, risk factors, and outcomes of patients with AKI in children hospitalized with nephrotic syndrome in a rural tertiary care hospital.

### Aims and objectives

1. To determine the proportion of AKI in Nephrotic Syndrome by using the KDIGO criteria.
2. To evaluate the Risk factors associated with the development of AKI.
3. To determine the association of AKI with outcome including length of stay.

## MATERIALS AND METHODS

This was a prospective observational study conducted after clearance from the Board of Studies and Ethical Committee (No.-EC/OA-67/2020) in the Department of Paediatrics, Shaheed Hasan Khan Mewati Government Medical College, Nalhar, Nuh, Haryana. The study population included patients aged 1 month–14 years of age admitted in wards and pediatric ICU (PICU) (October 2020–June 15, 2022). The study population has been calculated using G-power software with 80% of the power and 5% of the significance level. The total sample size was determined to be 64 patients. Inclusion criteria were patients 1 month–14 years of age admitted in pediatric wards and PICU with nephrotic syndrome and exclusion criteria included children on renal replacement therapy, with increased serum creatinine at admission, hospital length of stay <1 day and only one serum creatinine value are available.

Detailed history, physical examination, and investigations were done in children with nephrotic syndrome as per pro forma. Information was collected on demographic variables, vital signs, anthropometry, diagnosis, comorbidities, therapies, presence of hypovolemia, sepsis or shock, use of diuretics or nephrotoxic medications, need for oxygen, mechanical ventilation, vasopressors or renal replacement therapy, length of hospital stay, and outcome at discharge. Serum creatinine was estimated using the modified Jaffe method, the sample was collected within 24 h of admission and subsequently on days 1, 3, 5, 7, 10 or at discharge and 24 h urine output monitoring was done. AKI was defined and staged as recommended by the Kidney Diseases Improving Global Outcomes (KDIGO) guidelines as an abrupt (within 48 h) reduction in kidney function with an absolute increase in serum creatinine concentration by either >0.3 mg/dL or increase of >50% (1.5-fold from baseline) or reduction in urine output (documented oliguria of <0.5 mL/kg/h for 6 h).

- Baseline serum creatinine value was defined as the most recent creatinine value before admission obtained within the prior 6 months. If no prior creatinine value is available, then the lowest creatinine value obtained during the hospitalization was defined as the baseline value
- For those children having AKI, clinical outcomes were measured in terms of duration of hospital stay, recovery of S. creatinine, and urine output. AKI was managed as per the protocol
- Nephrotoxic medication exposure was defined as the administration of medication before admission, 1 week at the maximum, following which the child developed a decrease in urine output and an increase in serum creatinine.

### Statistical analysis

The statistical analysis was performed by the statistical software SPSS 25.0. The quantitative (numerical variables) were present in the form of mean and SD and the Qualitative (categorical variables) were present in the form of frequency and percentage. The Student *t*-test was used for comparing the mean values between the two groups, whereas the Chi-square test was applied for comparing the frequency. The P was considered to be significant when <0.05. Receiver operator characteristic curves were used to categorize continuous variables at baseline for their prediction of AKI. The odds ratio for risk factors for AKI was determined using logistic regression; variables with P<0.1 were included in multivariable analysis. The software used for the statistical analysis was SPSS (Statistical Package for Social Sciences) version 25.0 and MedCalc software.

## RESULTS

A total of 64 patients with nephrotic syndrome were enrolled in this study, 13 patients were 0–<1 year, 16 were 1–3 years, and 35 were in the 3–7 years of age group. There were 43 (67.2%) male patients and 21 (32.8%) female patients with maximum age of presentation being 7 years. The mean age of male patients was  $7.24 \pm 5.58$  years; female patients were  $7.19 \pm 5.84$  years' overall study population was  $7.23 \pm 5.62$  years.

Of 64 patients, 15 patients had AKI. The prevalence of AKI was 23.4% among children with nephrotic syndrome. The most common etiology is sepsis accounting for 4 out of 15 (26.7%) of total cases, followed by acute respiratory distress syndrome (ARDS) (13.3%), nephrotoxic medications (13.3%), renal parenchymal disease (13.3%), post-streptococcal glomerulonephritis (PSGN) (13.3% each), and sickle cell disease with nephritis and acute fulminant hepatitis (6.7%) Table 1.

As per KDIGO criteria, stage 1 was found among 1 (6.7%) whereas stages 2 and 3 were found among 7 (46.7%) patients each. As per outcome, 2 (13.3%) had been discharge against medical advice (DAMA), 8 (53.3%) were discharged, 2 (13.3%) expired, and 3 (20.0%) were referred. Mortality was significantly more among subjects with nephrotoxic medications (50%) and sepsis (25%). There was metabolic acidosis among 2 (13.3%), hyperkalemia among 1 (6.7%), and hypernatremia among 3 (20.0%) patients. The mean duration of stay (in days) among the study population was  $6.40 \pm 4.41$ . The mean age was significantly more among discharged patients ( $6.70 \pm 5.22$  years) compared to referred patients ( $6.59 \pm 5.99$ ) which was significantly more than expired patients ( $6.07 \pm 6.71$ ) compared to DAMA patients ( $4.78 \pm 4.51$  years). The mean duration of stay (in days) was significantly more among discharged patients. Mechanical ventilation was done for 4 (26.6%), and inotropic support was provided for 6 (40.0%). There was significantly more mortality among subjects with stage 2 (14.3%) and 3 (14.3%) kidney disease.

## DISCUSSION

In the present study, there were 43 (67.2%) male patients and 21 (32.8%) female patients of nephrotic syndrome with the maximum age of presentation being 7 years. The mean age of male patients was  $7.24 \pm 5.58$  years, female patients were  $7.19 \pm 5.84$  years, and overall study population was  $7.23 \pm 5.62$  years. Fifteen out of 64 patients had AKI in which 4 (26.6%) were <1 year of age, 2 (13.33%) between 1 and 3 years of age, and 9 (60%) between 3 and 7 years. Kumar et al.<sup>13</sup> stated that there were 64.8% of

**Table 1: Distribution of study population according to etiology/risk factors**

Etiology/Risk factors	Frequency	Percentage
Acute fulminant hepatitis	1	6.7
Acute respiratory distress syndrome	2	13.3
Nephrotoxic medications	2	13.3
Malignant HTN	1	6.7
Renal parenchymal disease	2	13.3
Sepsis	4	26.7
PSGN	2	13.3
Sickle cell disease with nephritis	1	6.7

HTN: Hypertension, PSGN: Post-streptococcal glomerulonephritis

males with mean age at diagnosis of nephrotic syndrome for the study population was 37.4 months, and the mean age at enrolment was 59.5 months with 85.2% between 2 and 12 years of age. Sutherland et al.<sup>14</sup> found the highest AKI incidence was among 15–18-year-old hospitalized children in general. However, this study found that the risk of AKI in children with nephrotic syndrome did not differ significantly by age at admission and sex. This was also seen in the study by Rheault et al.<sup>6</sup> In our study, the prevalence of AKI among children with nephrotic syndrome was 23.4% as per KIDGO criteria. Stage 1 was found among 1 (6.7%), stage 2 and stage 3 were found among 7 (46.7%). According to the pRIFLE criteria, the prevalence of AKI-NS at admission in the study by Anigilaje and Ibraheem<sup>15</sup> was 25.3%. Sharma et al.<sup>9</sup> also reported a similar 23.6% for AKI in children with NS in India. However, the burden of AKI-NS varies from 0.8% to 58.6% in other studies.<sup>6,9,14,16-18</sup> The prevalence of 0.8% was reported by Kilis-Pstrusinska et al., in Poland and also higher than the 8.5–9.1% noted from the data of the HCUP-KID.<sup>7,8</sup> Kim et al.<sup>11</sup> found that one-third (32.2%) of childhood-onset nephrotic syndrome hospitalizations were complicated by AKI. There was a lower incidence of AKI in the present study. The explanation may be related to a selection bias, with a high concentration of patients with more severe nephrotic syndrome and where many of the patients were aggressively treated with CNIs and RASis. CNIs and RASis are well-known nephrotoxic agents.<sup>6,10</sup> Nevertheless, the high AKI incidence is concerning, and close monitoring is needed to appropriately treat patients with AKI, especially in the early period of hospitalization considering that the median onset of AKI was day 0 of hospitalization. Kim et al.<sup>11</sup> found longer hospital stays in the AKI group than in the non-AKI group (median 12 vs. 6 days,  $P=0.002$ ), which would result in higher medical costs and increased possibility of hospital-acquired infections and other related complications.<sup>11</sup> In the current study, the most common etiology being sepsis accounting four out of 15 (26.7%) of total cases, renal parenchymal disease (13.3%), PSGN (13.3%), ARDS (13.3%), nephrotoxic medication (13.3%), sickle disease with interstitial nephritis

(6.7%), acute fulminant hepatitis (6.7%), and malignant hypertension (6.7%). Anigilaje and Ibraheem<sup>15</sup> found that nephrotic syndrome children with no sepsis were at significantly reduced odds of having AKI. In other words, the risk of AKI is less among nephrotic syndrome without sepsis, supporting the inflammatory role of sepsis in the pathogenesis of AKI. In addition, Sutherland et al.<sup>14</sup> also found septicemia to be associated with AKI in their study. In our study, the mean duration of stay (in days) among the study population was  $6.40 \pm 4.41$ . The mean duration of stay (in days) was significantly more among discharged patients ( $7.72 \pm 3.66$ ). Kushwah et al.<sup>19</sup> found that AKI was associated with a median of 5 days longer hospital stay as compared to patients without AKI that was further prolonged for patients with stage 3 AKI (data not shown). While the majority of stage 1 and 2 AKI recovered renal function partially or completely, stage 3 AKI had a poor outcome, similar to that reported by other authors. Sharma et al.<sup>9</sup> found that the mean time to recovery was prolonged with more severe AKI. Rheault et al.<sup>20</sup> found that children with more severe stages of AKI had longer hospitalizations. Sutherland et al.<sup>14</sup> found that AKI in hospitalized children was associated with a prolonged length of stay.

#### Limitations of the study

In spite of every sincere effort, our study has lacunae. The notable shortcomings of the study are:

1. The sample size was small. Only 64 patients are not sufficient for this study.
2. The study has been done in a single center.
3. The study was carried out in a tertiary care hospital, so hospital bias cannot be ruled out.

#### CONCLUSION

AKI is common in our children with nephrotic syndrome. This should be concerning, and the need for close observation to allow for prompt diagnosis of AKI and management cannot, therefore, be over-emphasized. We found the main risk factors of AKI to include sepsis, gross hematuria, urinary tract infections, peritonitis, and exposure to potentially nephrotoxic medications. While efforts at recognizing these risk factors of AKI among our children with nephrotic syndrome are important, we also propose a large prospective multicenter study to characterize the risk factors of AKI and its long-term outcomes among Indian children with nephrotic syndrome. AKI was associated with prolonged duration of hospital stay, reduced eGFR at discharge, and short-term follow up. Our findings highlight the need to identify the patients with nephrotic syndrome at risk of AKI and apply strategies to prevent AKI in focused at-risk groups.

#### ACKNOWLEDGMENT

The authors thank study patients and staff of department of Pediatrics of SHKM, Government Medical College, Nuh for continuous support and help.

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<https://doi.org/10.1007/s00467-013-2607-4>

**Authors Contribution:**

**MY, RJ, B-** Conceptualized the study, collected and interpreted the data, and prepared the initial manuscript; **RJ, B, MY-** Supervised the study, revived literature, and revised the initial manuscript. All authors approved the final version of the manuscript and are accountable for all aspects related to the study.

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**Source of Support:** Nil, **Conflicts of Interest:** None declared.