International Journal of Contemporary Pediatrics
Maheshwari UM et al. Int J Contemp Pediatr. 2023 Jun;10(6):785-789
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20231406

Original Research Article

Comparison of profile and short-term outcome of acute kidney injury between steroid sensitive and steroid resistant nephrotic syndrome

Uma Maheshwari M.[1]*, Alpana Ohri[1], Amish Udani[1], Chintan Shah[2]

[1]Department of Pediatric Nephrology, B. J. Wadia Hospital for Children, Mumbai, Maharashtra, India
[2]B. J. Wadia Hospital for Children, Mumbai, Maharashtra, India

Received: 13 April 2023
Revised: 24 April 2023
Accepted: 28 April 2023

***Correspondence:**
Dr. Uma Maheshwari M.,
E-mail: druma25sep@gmail.com

ABSTRACT

Background: Acute kidney injury (AKI), a severe complication of nephrotic syndrome (NS) is being more prevalent in recent times. Objectives were: 1) Determine incidence, etiology, short term outcome of AKI in children hospitalised with NS. 2) Compare above variables in steroid sensitive nephrotic syndrome (SSNS) versus steroid resistant nephrotic syndrome (SRNS).
Methods: Prospective observational study over 18 months including all consecutive nephrotics hospitalized with AKI. AKI defined according to KDIGO criteria with baseline creatinine taken as lowest value in last 6 months/ nadir during stay. Secondary NS were excluded. Demographics, clinical features, labs, hospital course, treatment and follow up at 3 months were recorded. SSNS and SRNS were compared.
Results: The incidence of AKI in hospitalised nephrotics (30/304) was 9.8%, 30 patients (16 boys) with mean age 4.08 years (± 4.04 SD). Common etiologies of AKI were infection (60%), nephrotoxic drugs, hypovolemia, and thrombosis in decreasing order. Nephrotics developing AKI had a longer hospital stay versus those without AKI ($p<0.001$). The 2/30 patients died (6%), 10/30 (33.3%) required PICU, 7/30 (26%) needed RRT. Among discharged patients 4/28(14.28%) had persistent deranged renal functions at 3 months follow up, all of whom belonged to SRNS category. Comparison of 14 patients in SSNS with 16 in SRNS showed UTI (31.3%), drugs (25%), systemic infection (31.3%), thrombosis (12.5%) as etiologies in SRNS. Systemic infection (42.9%), drugs (21.4%), UTI (14.3%) and hypovolemia (21.4%) were causes in SSNS. Mortality rate, need for PICU ($p=1.0$), RRT ($p=1.0$) was similar (6%,37.5%, 25%) Vs (7%,28.5%, 21.4%).
Conclusions: AKI is seen in up to a tenth of children with NS equally in SSNS and SRNS. While etiology and severity of AKI in the 2 groups is similar, short-term outcome in SRNS is more ominous.

Keywords: NS, AKI, Short term outcome of SRNS

INTRODUCTION

Nephrotic syndrome (NS) is characterised by massive proteinuria (3-4+ protein), hypoalbuminemia and oedema with hyperlipidemia. Incidence of NS is 1-3 per 1,00,000 children per year. In 3-5% cases, NS may be secondary to a systemic disorder (SLE, HSP, hepatitis B). A male preponderance is noted and it usually occurs between 2-7 years of age in children.[1] In 10-15% cases, non-response to steroids even after 6 weeks of therapy is noted. The incidence of AKI varies from 8.5-56% according to various studies.[2] Acute renal failure may occur secondary to infections, nephrotoxic medication exposure, hypovolemia and bilateral renal vein thrombosis. AKI in NS is multi-factorial in origin.[3] Mostly reduction in glomerular filtration is reversible in NS, but in some cases, this episode may lead to progression to chronic kidney disease.[2] AKI has increased the morbidity in terms of prolonged hospital stay and intensive care in recent times. Due to the scant prospective study in our region,

we studied the incidence, etiology, clinical course and outcome of AKI in hospitalised children with NS.

Aims and objectives

Aim and objectives were to study the incidence, etiology, clinical course and short-term outcome of AKI in children with NS and to compare the etiology, clinical course, short term outcome between SSNS and SRNS.

METHODS

Study type

Study type was of single centre prospective observational study.

Place of study

Study conducted at B. J. Wadia hospital for children, Mumbai.

Study period

Study carried out from June 2021-Dec 2022.

Inclusion criteria

All consecutive admissions with NS < 18 years of age, who had presented with AKI during the past 18 months were included in study.

Exclusion criteria

Children who had progressed to CKD with EGFR <30 ml/min/1.73 m^2, secondary causes of NS, congenital NS, admitted for rituximab infusion, renal biopsy were excluded.

Ethical approval obtained.

Sample size

Sample size of the study was determined using SAS 9.2 package. Minimum sample size=29, power=80%, alpha=0.05.

Statistical test

Z test for binomial proportion.

Among the 304 nephrotic admissions, 30 patients with AKI were included as per the above criteria and their clinical course studied.

Criteria for diagnosis of NS was according to ISPN guidelines-heavy proteinuria (3+,4+), hypoalbuminemia (<3 g/dl) and edema.[4]

***Frequent relapses*:** Two or more relapses in initial six months or more than three relapses in any 6 months or four or more relapses in a year.[4]

Steroid dependence: Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.

Steroid resistance: Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg/day for 6 weeks.[5]

Diagnosis of AKI was done according to KDIGO clinical practice guideline for AKI.[6]

Severity of AKI will be classified according to KDIGO criteria. Stage 1-3.

Stage 1: Increase in S. Cr ≥ 0.3 mg/dl (in 48 hours) or 1.5 to 1.9 multiplied by baseline (in 7 days). *Stage 2:* 2.0 to 2.9 multiplied by baseline S Creatinine. *Stage 3:* 3.0 or more multiplied by baseline or increase in S. Cr ≥4.0 mg/dl; or beginning of renal replacement therapy regardless of a previous KDIGO stage. Or eGFR <35 ml/min per 1.73 m^2.

Baseline serum creatinine taken as the most recent S. Cr value within last six months, including the day of admission (If no prior creatinine value was available) whichever is the lowest. Patients with deranged S. Cr at admission monitored daily for change in S. Cr level till two subsequent values became normal for age or static; whichever occurred earlier.

Serum creatinine (S. Cr) would be estimated by sarcosine oxidase (enzymatic) method.

Detailed proforma made recording the demographic details, age of onset of NS, presence of atypical features, prior drug history which includes the use of alternative medicine (s), diuretic, immunosuppressant, any contrast exposure (especially in the past 72 hrs).[7]

Also, KDIGO stage at diagnosis, and highest KDIGO stage reached noted.

Details at examination were taken which includes vitals, signs of hypovolemia, hypertension.

eGFR was calculated using the modified Schwartz formula with a constant of 0.413.

Lab investigations including the biochemistry (creatinine, BUN), Serum albumin, urine routine, septic parameters including CRP, urine and blood culture, urine for eosinophils, urine for fungal hyphae, ultrasonography, ascitic tap done.

Infections were diagnosed based on local criteria for cellulitis, peritonitis-ascitic tap was done, inflammatory

markers and chest x ray for pneumonia, urine culture for urinary tract infection, elevated CRP, WBC count and blood culture for sepsis. ACE inhibitors and Calcineurin inhibitors were not included in etiology as all SRNS patients had h/o intake of these drugs and causality could not be established.[8]

Biopsy done in cases where it was indicated.

Clinical course of AKI studied in terms of progression of AKI from one stage to another, requirement of renal replacement therapy including its type and duration and requirement of PICU admission.

Clinical outcome measured in terms of creatinine levels at discharge, duration of hospital stays and mortality. Short term outcome at 3 months also noted.

Statistical analysis

Data were analysed using SPSS V15.0 (Statistical package for social sciences, version 15.0) package. Data were given as mean ± SD for continuous data and Number and Percentage for categorical data. Student's unpaired t test was applied to compare means between 2 groups. Fisher exact probability tests were applied to compare percentages for categorical data between 2 groups. Chi square test was applied to compare percentages for categorical data of 2 groups. All statistical tests were two tailed. Alpha (α) level of significance was taken as $p \leq 0.05$.

RESULTS

The incidence of AKI in NS in hospitalised children found to be 9.8% (30/304). The mean age at presentation of AKI is 4.08 years with S. D=4.04, of which 18(60%) were boys.16/30 (54%) had steroid resistant NS and 14 (46%) had SSNS.

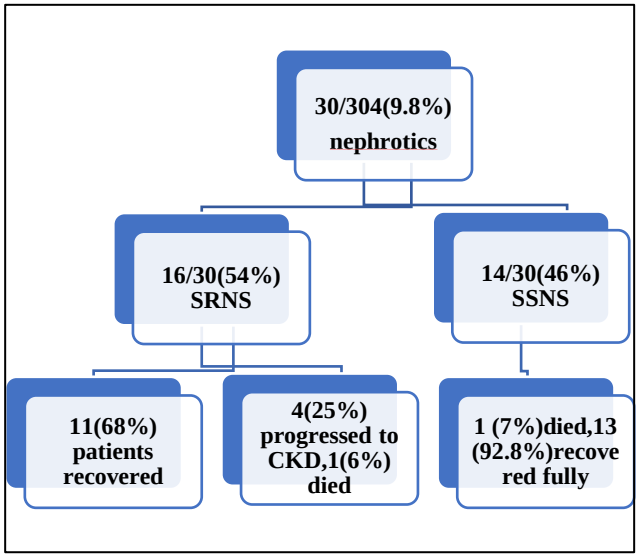

Figure 1: Algorithm of results.

Etiology of AKI found to be infection-11/30 (36%), UTI-7/30 (23%), drug induced AKI-7/30 (23%), hypovolemia-3/30 (10%) and thrombosis-2/30 (6%) (Figure 2). Infections included sepsis, cellulitis, peritonitis, acute gastroenteritis, pneumonia other than UTI which was recorded separately.

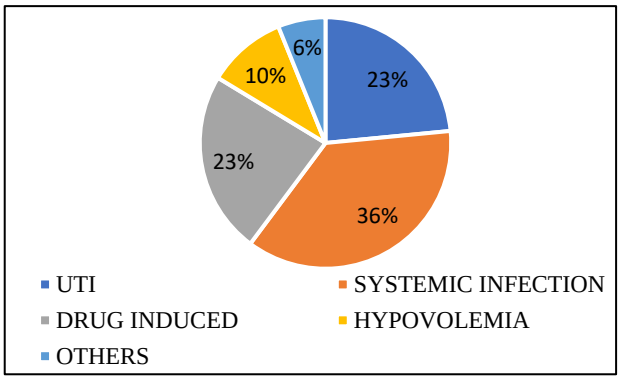

Figure 2: Etiology of AKI.

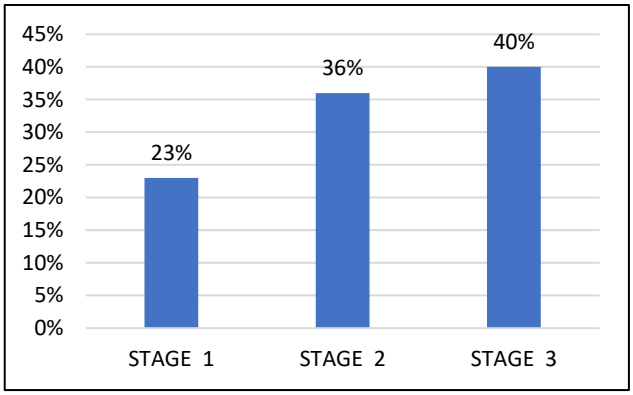

Figure 3: Stage of AKI.

The 40% patients presented with stage 3 AKI at onset, 36%-stage 2 and 23%- stage 1 (Figure 3) and the mean day of onset of AKI was day 2.33 days. The 26% (8/30) patients presented with AKI after 48 hrs of admission, 5/8 caused by infection,3/8 due to nephrotoxic drugs all of whom had recovered.

The 7/30 (23%) patients required renal replacement therapy (RRT). All 16 SRNS patients had a prior renal biopsy done at diagnosis of steroid resistance-among which 10 had FSGS,5 had MCNS and 1 had mesangio-proliferative type finding. The 2/16 patients with SRNS underwent biopsy after AKI, had severe tubular injury.

The 10/30 patients (33%) required intensive care, 9/30 (30%) required assisted ventilation, of which 2/30 (6.6%) patients died 1 each in SRNS and SSNS group.

Time for renal recovery is prolonged if stage of AKI at onset is stage 3 (p=0.045). Patients with AKI due to infection (OR=4) has more probability to recover compared to other causes. Mean duration of hospital stay

17.37 days. The 4/28(14.2%) patients had EGFR<90 ml/min/1.73 m^2 at discharge and at 3 months follow up, all 4 patients had EGFR <60 ml/min/1.73 m^2 (CKD stage 3 and higher).

Comparison between SRNS vs SSNS

The 16/30 (54%) had SRNS and 14/30(46%) had SSNS.

Aetiology in SRNS group were-infection (31.3%), drug induced AKI (25%), UTI (31.3%) and thrombosis (12.5%) and SSNS group-infection (42.9%), drug induced (21.4%), hypovolemia (21.4%) and UTI (14.3%) which was similar (p=0.17).

The 81.3% patients reached stage 3 AKI in SRNS group and 85.7% had stage 3 AKI in SSNS group (p=1.0).

Renal replacement therapy required in 25% patients in SRNS group versus 21.4% in SSNS group (p=1.0).

Mortality was similar in both the groups as 1 patient in each group had died (p=1.0).

The 4/28 (14.2% had EGFR<60 ml/min/1.73m^2 (chronic kidney disease stage 3 or higher) at 3 months follow up all the 4 belonged to SRNS group.

Table 1: SRNS versus SSNS.

	P value
Etiology	P=0.17 (not significant)
Stage of AKI	P=1.0 (not significant)
RRT requirement	P=1.0 (not significant)
Mortality	P=1.0 (not significant)
Outcome (at discharge)	P=0.046 (significant)

Table 2: Comparison of different variables between SRNS and SSNS.

Variables	Group I (n=16), SRNS	Group II (n=14), SSNS	Significance and p value
Mean age of onset of NS	5.43±4.88 years	2.71±2.34 years	T=1.9, NS, p=0.07
Mean age of present-ation of AKI	6.81±4.67 years	4.30±4.29 years	T=1.5, NS, p=0.1
Mean duration of hospital stay	19.19±11.0 1 days	15.29±6.84 days	T=1.1, NS, p=0.3
Mean time for renal recovery	14.63±10.9 1 days	9.64±7.52 days	T=1.4, NS, p=0.2
Mean no. of days of stay in PICU	2.56±4.12 days	3.36±7.55 days	T=0.4, NS, p=0. 7

DISCUSSION

AKI has increased in incidence in recent times as reported by HCUP-KIDS data in North America and by other Indian studies. Our study reports an incidence of 9.8% over 18 months comparable to other studies.[9]

Our study included AKI at admission as well as during the hospital stay in contrast to other study, which included AKI only at admission.[8]

We noted that 40% patients had stage 3 AKI at onset and mean day of onset was day 2 of admission and day of peak creatinine was day 4. Reason for higher stage of AKI at onset may be due to multiple factors like receiving nephrotoxic medications before admission and severity of infection at admission.

Age, sex and type of NS of patients studied were similar to other Indian studies.[10-11]

Infection (59%)-both UTI and systemic infection was found to be the commonest cause of AKI followed by nephrotoxic medication exposure (23.3%) comparable to other studies. Nephrotoxic medications which were noted include contrast (3), nephrotoxic antibiotics (4), alternate medications (2), NSAIDs (1) and diuretics (6) (Figure 4). SRNS patients were already receiving Calcineurin and ACE inhibitors, which was stopped intermittently at onset of AKI.

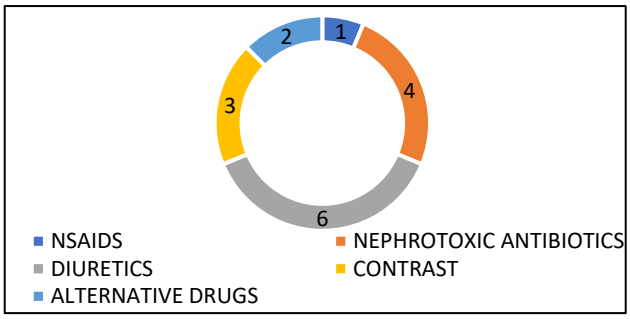

Figure 4: Drugs implicated.

Only 2 patients gave h/o amikacin and 1 patient gave h/o NSAID use, as aminoglycoside are discouraged as first line antibiotic in our hospital and NSAID is avoided.3 patients had h/o contrast -for HRCT Chest to rule out Pneumonia/tuberculosis which was necessary.

In our study, urinary tract infection found to be the commonest infection (23%), followed by spontaneous bacterial peritonitis, sepsis, acute gastroenteritis and cellulitis in the decreasing order in contrast to the other Indian studies who found cellulitis and peritonitis to be the commonest infection causing AKI.[8,11]

Hypovolemia was seen only in SSNS, and thrombosis in SRNS. Both patients with thrombosis had IVC thrombus which could has caused AKI due to hypovolemia.

The 4/28 (14.2%) patients, all 4 who belonged to SRNS category progressed to chronic kidney disease<60 ml/min/1.73 m^2 at 3 months follow up. While the incidence of progression to CKD was 41% in another Asian study, which also found that infection, drug toxicity, SRNS and FSGS to be the causes.[12,13]

The mean duration of hospital stay was 17.3 days which is significantly prolonged than in patients without AKI (8 days) (p<0.001). We also found that time for renal recovery was prolonged if the stage of AKI is higher (p=0.043). Another Indian study also showed that time for recovery was prolonged with severe AKI.[8]

Mortality rate in our study was 6.6% (2/30), the reason being septic shock, 1 in each subgroup.

There are very few studies comparing AKI in SRNS versus SSNS. The etiology, severity of AKI and mortality were similar among the two groups.

There is significant difference in the immediate outcome (discharge EGFR<90 ml/min/1.73 m^2) between the two groups (p=0.045). The 4/16 (25%) patients with SRNS had progressed to CKD (EGFR<60 ml/min/1.73 m^2) at 3 months follow up. This shows that SRNS patients who are already on nephrotoxic drugs like calcineurin inhibitor and ACE inhibitors, after an episode of AKI,may progress to CKD.

Limitations

This study did not include calcineurin inhibitors and ACE inhibitors as the cause, as patients had received it for a longer duration, and cannot be proven as the cause for AKI. Follow up was done only for 3 months, long term follow up is needed to study the outcome better.

CONCLUSION

Infection and nephrotoxic medication exposure were the most common causes of AKI in children hospitalised with NS. Children with severe AKI at onset required longer time to recover. The 33% required PICU admission and 6.6% was the mortality rate. Etiology, severity and mortality were similar in both subgroups. Hypovolemia was seen only in SSNS, thrombosis seen in SRNS group. Patients with SRNS had adverse renal outcome than the patients with SSNS.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein SL. Pediatric Nephrology. 7th edition. 2016.
2. Lionaki S, Liapis G, Boletis JN. Pathogenesis and Management of Acute Kidney injury in patients with Nephrotic Syndrome due to Primary Glomerulopathies. Medicina (Kaunas). 2019;55(7):365.
3. Menon S. Acute kidney injury in nephrotic syndrome. Front Pediatr. 2018;6:428.
4. Sinha A, Bagga A. Clinical practice guidelines for nephrotic syndrome: consensus is emerging. Pediatr Nephrol. 2022;37:2975-84.
5. Vasudevan A, Thergaonkar R, Mantan M, Sharma J, Khandelwal P et al. Consensus guidelines on management of steroid resistant nephrotic syndrome. Indian Pediatr. 2021;58(7):650-66.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int. 2012;2(S):1-138.
7. Moffett B, Goldstein SL. Acute Kidney Injury and Increasing Nephrotoxic Medication Exposure in Noncritically -ill children. Clin J Am Society Nephrol. 2011;6(4):856-63.
8. Sharma M, Mahanta A, Barman AK, Mahanta PJ. Acute Kidney injury in children with nephrotic syndrome: a single centre study. Clin Kidney J. 2018;11(5);655-58.
9. Rheault MN, Zhang L, Selewski DT, Kallash M, Tran CL. AKI in Children Hospitalized with Nephrotic Syndrome. Clin J Am Soc Nephrol. 2015;10(12):2110-8.
10. Prasad BS, Kumar M, Dabas A, Mishra KS. Profile of Acute Kidney Injury in Hospitalized Children with Idiopathic Nephrotic Syndrome. Indian Pediatr J. 2019;56:119-22.
11. Kushwaha S, Yadav M, Hari P, Meena J, Sinha A. Incidence and Determinants of Acute Kidney Injury in Patients with Nephrotic Syndrome. Asian J Pediatr Nephrol. 2019:2(2);75-81.
12. Yaseen A, Tresa V, Lanewala AA, Hashmi S, Ali I. Acute Kidney injury in idiopathic nephrotic syndrome of childhood is a major risk factor for the development of chronic kidney disease. Renal Failure. 2017;39(1):323-7.
13. Young KM, Myung HC, Ji HKYo HA, Hyun JC. Acute Kidney injury in childhood onset nephrotic syndrome: Incidence and risk factors in hospitalised patients. Kidney Res Clin Pract. 2018;37(4):347-55.

Cite this article as: Maheshwari UM, Ohri A, Udani A, Shah C. Comparison of profile and short-term outcome of acute kidney injury between steroid sensitive and steroid resistant nephrotic syndrome. Int J Contemp Pediatr 2023;10:785-9.