

# Pediatric Nephrotic Syndrome in a Cameroonian Cohorte: The Beast to Slaughter

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## Abstract

**Background:** Idiopathic nephrotic syndrome (INS) is a frequent pathology in children. There is little data on the future of NS in children in sub-Saharan Africa, particularly Cameroon. The aim of our study is to report the prognosis of children treated for nephrotic syndrome in the city of Yaoundé. **Method:** This was an analytical cross-sectional study with retrospective collection in 4 reference hospitals in the Cameroonian capital over a period of five years from January 1, 2018 to December 31, 2022. We included all medical records of patients treated for idiopathic INS. We excluded incomplete records and those with a history of chronic kidney disease. The sociodemographic, clinical, paraclinical, and therapeutic data, as well as the short-term evolution were collected in the files. Data was analysed using the software statistical package for social sciences version 25.0. Statistical significance was set at a p-value <0.05. **Results:** A total of 131 children (58% boys) were included in our study over a period of 5 years. The median age was 8 [6 - 11] years. Median proteinuria was 5 g/24h [3 - 8.4], median serum protein was 39 [34 - 46] g/l and median estimated glomerular filtration rate was 130.36 [68 - 174.6] ml/min/1.73m<sup>2</sup>. During steroid therapy, 45.07% were in partial remission at 2 months, 16.9% were in complete remission at 4 and 6 months, and 37.25% had relapsed. Steroid sensitivity was reported in 28.17% of cases, steroid resistance in 64.78% of cases and steroid dependent in 7.04% of cases. The mortality rate was 12.97%. Survival time averaged 48.2 months, with an overall crude survival rate of 99.2% at 3 and 6 months and 98.4% at 1 year. Regarding renal survival, renal function was impaired in 8.33% of patients at 6

months and 9% at 12 months. **Conclusion:** Idiopathic nephrotic syndrome is a common disease in children. Its evolution depends on corticosteroid therapy. The long-term prognosis is dominated by the risk of progression to end-stage kidney disease or even death. Rigorous and affordable follow-up is essential to reduce the number of patients lost to follow-up and the occurrence of complications.

## Keywords

Idiopathic Nephrotic Syndrome, Outcome, Mortality, End-Stage Kidney Disease, Children, Cameroon

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## 1. Background

Idiopathic nephrotic syndrome (INS) is the most common glomerular disease in childhood worldwide. It is one of the most common causes of childhood renal disease in Africa [1] [2]. It is a podocytopathy resulting in foot process effacement responsible for the triad: edema, massive or nephrotic-range proteinuria and hypoalbuminemia. In 90% of children, there is no cause: this is called idiopathic nephrotic syndrome or nephrosis. In this picture, steroids are used to induce remission and then reduce progression to end-stage renal failure (ESRD) and mortality. The prognosis for childhood INS is best predicted by the patient's response to initial treatment and the frequency of relapses during the first year after treatment. Unfortunately, it has been widely reported that black children have a poor response to steroids [2] [3]. There is a high incidence of steroid resistance regardless of histopathological pattern in black children in South Africa [4]. Few reports from West Africa and Nigeria have shown steroid sensitivity similar to Asian and European series [5]-[7].

In the absence of renal disease registries, data on INS are scarce in most sub-Saharan African (SSA) countries [1]. Cameroon, a SSA country located in Central Africa, where public awareness of the renal disease remains limited and treatment costs are not subsidised, has a high burden of chronic kidney disease in children. Chronic glomerulonephritis was the most common aetiology [8]. Fouda *et al.* previously reported that the incidence of INS was 1.5%, with frequent loss to follow-up within 3 months and a mortality rate of 27% [9]. The aim of our study was to report the early and one-year prognosis of children with idiopathic NS in this setting.

## 2. Methods

### 2.1. Study Design and Setting

This study was a cross-sectional study conducted in 4 public hospitals: Yaoundé General Hospital (YGH), Yaoundé Gynaecology, Obstetrics and Paediatrics Hospital (YGOPH), University Teaching Hospital of Yaoundé (UTHY) and Mother

and Child Centre of Chantal Biya Foundation (CME-FCB). These 4 hospitals are reference centres for specialised paediatric pathologies. They all have a nephrology unit.

## 2.2. Data Collection Tools and Procedures

The study included all records of paediatric INS received from 1 January 2018 to 31 December 2022, a period of 5 years, and included all children aged 2 to 15 years admitted to the paediatric and nephrology departments of the different hospitals. The following were excluded 1) those whose records were incomplete (no aetiological investigation, no proteinuria and no creatinine); 2) those with a history of chronic kidney disease; 3) less than 4 weeks of follow-up after the start of steroid therapy. We collected socio-demographic, clinical and biological data, including age at the onset of the disease, the presence of haematuria, blood pressure and the result of serum albumin and creatinine at the time of the diagnosis of INS. The following definitions were considered:

- Nephrotic syndrome (NS): the presence of generalised oedema, massive proteinuria ( $\geq 3$  + dipstick proteinuria, proteinuria on 24-hour urine  $> 1000$  mg/m<sup>2</sup>/day or urine protein-creatinine ratio  $> 2$  g/g) and hypoalbuminaemia (serum albumin  $< 25$  g/l);
- Idiopathic nephrotic syndrome: NS with negative etiologies workup including HIV, HBV, HCV, Syphilis, malaria, filariasis, haemopathies or systemic diseases;
- Remission: This was confirmed at 8 weeks and is considered complete in case of negative dipstick proteinuria and proteinuria below 200 mg/g (20 mg/mmol). Remission was considered as partial in case of proteinuria reduction by at least 50% or more of the initial value or proteinuria between 200 and 2000 mg/g (20 - 200 mg/mmol) associated with serum albumin levels greater than or equal to 30 g/l; otherwise, there is no remission;
- Steroid response: as defined by the KDIGO can be either steroid-sensitive (SSNS) when there is a remission within 4 weeks or steroid-resistant (SRNS) otherwise; 2 consecutive relapses during treatment or within 15 days of prednisone discontinuation was considered as a steroid-dependent NS (SDNS):
- Hypoalbuminemia was defined as an albumin level of less than 30 g/l;
- Anemia was defined as a hemoglobin level of less than the 5<sup>th</sup> percentile for age;
- High blood pressure was confirmed when average blood pressure measured multiple times over three visits or more is at or above the 95th percentile for their age, sex and height;
- Renal impairment was defined by a glomerular filtration rate (GFR) calculated by the Bedside Schwartz clearance [10] less to 60 ml/min/1.73m<sup>2</sup> for more than 3 months and staging as end-stage kidney failure for a GFR  $< 15$  ml/min/1.73m<sup>2</sup>;
- Renal survival was referred to as the absence of renal impairment at 6 and 12 months.

All participants were treated with steroids according to KDIGO 2021 recom-

recommendations: 4 weeks at full dose followed by 4 weeks on alternate-day glucocorticoid dosing (total 8 weeks) or 6 weeks at full dose followed by 6 weeks of alternate-day dosing (total 12 weeks). The minimal length of follow up was 12 weeks. Patients lost to follow-up before the end of the first year were assessed on the basis of their follow-up at 12 weeks and 6 months.

### **2.3. Data Management and Analysis**

Data were entered and analysed using the Statistical Package for Social Science (SPSS) version 23 and Microsoft Excel 2016. A descriptive analysis of sociodemographic, clinical, biological, histological, therapeutic and evolutionary characteristics of patients was performed. Continuous variables were presented as means and standard deviations for normally distributed data, and medians and interquartile ranges (IQR) for poorly distributed data. Categorical variables were expressed as proportions, frequencies or percentages, and the chi-squared test was used to test associations. The level of statistical significance was set at a p-value < 0.05 with a 95% confidence interval. To identify factors associated with renal survival, we first performed a bivariate analysis between each of the independent variables and the dependent variable (renal survival), with a significance threshold of 5% at this stage. The tests used were either Pearson's chi-squared test or Fisher's exact test (when the theoretical number in any of the categories was less than 5 for qualitative independent variables, or Student's t-test or its non-parametric equivalent (Mann Whitney Wilcoxon) for quantitative independent variables. We then built a multivariate logistic regression model, including only those independent variables that had reached the 20% significance threshold in the bivariate model. Finally, we considered only those variables that had reached a significance level of 5% as associated factors. Renal survival and mortality were estimated by constructing a Kaplan-Meier survival model. Differences were considered statistically significant at a p-value < 0.05 with a 95% confidence interval.

### **3. Ethical Consideration**

The study received administrative approval from the directors of the participating hospitals and ethical approval from the Ethics Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé (Institutional Ethics Committee approval n° 0437).

### **4. Results**

During the study period, 215 cases of nephrotic syndrome (34 secondary NS, 50 incomplete files) were recorded, of which 131 INS cases were included.

#### **4.1. Patient's Characteristics**

The median [IQR] age of participants was 8 [6 - 11] years, with extremes of 2 and 15 years and a sex ratio of 1.38. About 66.4% had no previous episodes of edema. Consultation delay was between one and six months for most patients,

with a median [IQR] of 3 [1 - 4] weeks and 40.5% are coming from rural areas. High blood pressure, hematuria and renal impairment were respectively found in 53.4%, 48.1% and 33.05%. Hypoalbuminemia was reported in 96.5%; the median was 14.9 g/l [10.9 - 18.98] (**Table 1**). Other biological parameters are presented in **Table 2**. All participants have received steroids. The main treatment in the case of SRNS or SDNS was cyclophosphamide (**Table 3**).

## 4.2. Renal Outcome

In all, the response to corticosteroid therapy was assessed at 4 months in 71 patients (54.19% of cases). We noted that 28.17% (n = 20) were steroids sensitive, 64.78% (n = 46) were steroids resistant and 7.04% (n = 5) were steroids dependent (**Figure 1(a)**).

**Table 1.** General characteristic of participants.

Variables	Frequency (N = 131)	Percentage (%)
<b>Age range (years)</b>		
[2 - 6[	26	19.8
[6 - 10[	57	43.5
[10 - 16[	48	36.6
<b>Sexe</b>		
Male	76	58
Female	55	42
<b>Place of stay</b>		
Urban zone	78	59.5
Rural zone	53	40.5
<b>Positive past history of edema</b>	44	33.6
<b>High blood pressure</b>	70	53.4
<b>Hematuria (dip stick)</b>	63	48.1
<b>Hypoalbuminemia</b>	112	96.5
<b>Renal failure</b>	40	33.1
<b>Anemia</b>	83	81.7

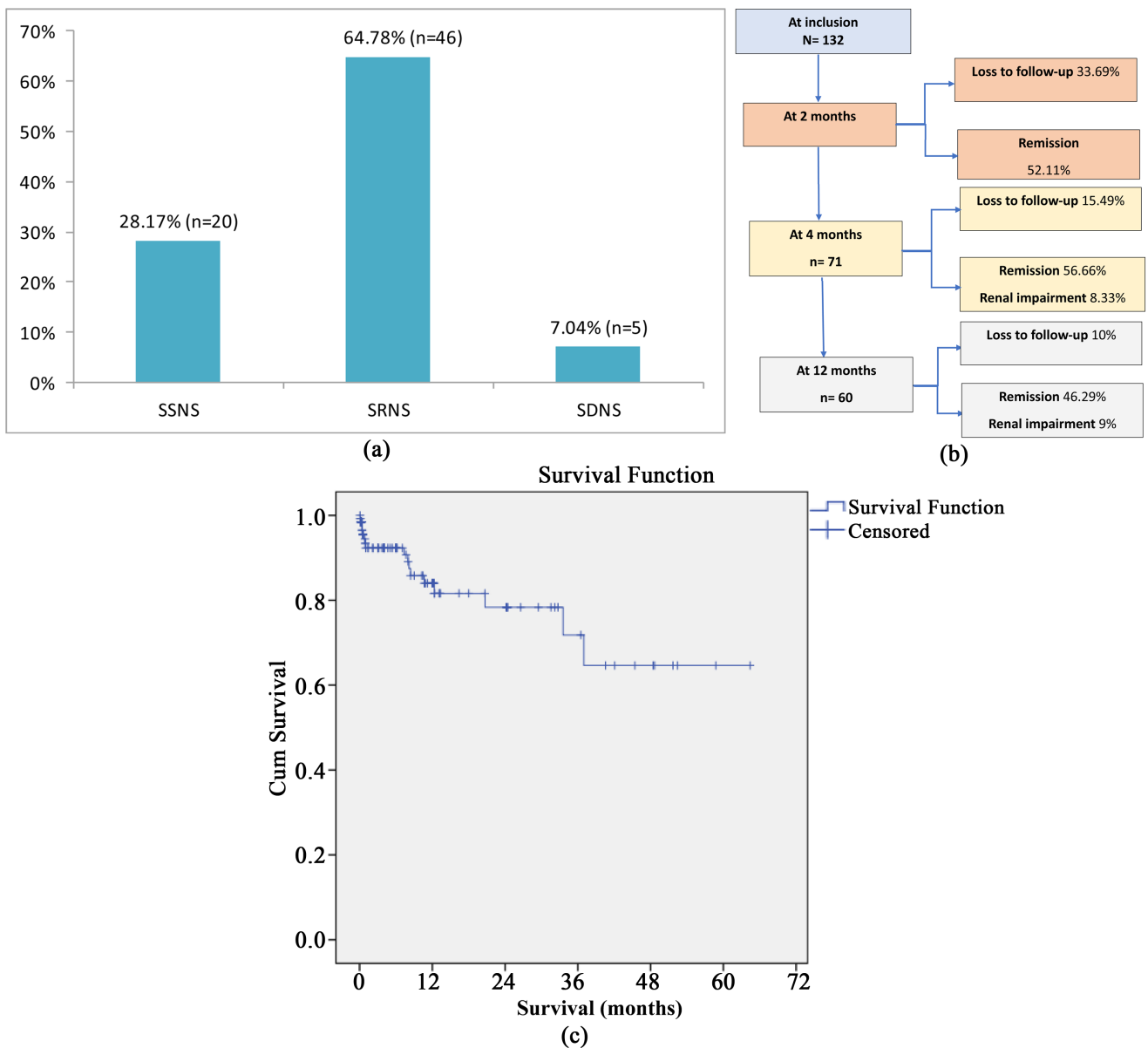
**Table 2.** Biological characteristics at diagnosis.

Variables	Median	IQR*
Proteinuria, g/24h	5	3 - 8.4
Protidemia, g/l	39	[34 - 46]
GRF, ml/min/1.73m <sup>2</sup>	130.36	[68 - 174]
Albuminemia, g/l	14.9	[10.9 - 18.98]

\*Inter quartile range.

**Table 3.** Distribution according to treatment received.

Variables	Frequency (N = 131)	Percentage (%)
Steroids	131	100
Cyclophosphamide	35	26.71
Ciclosporine	8	6.1
Mycophenolate mofetil	3	2.3



SSNS: steroid sensitive nephrotic syndrome; SRNS: steroid resistance nephrotic syndrome; SDNS: steroid dependant nephrotic syndrome.

**Figure 1.** Outcomes. (a) Therapeutic outcome at one year of follow-up; (b) Renal outcome; (c) Global outcome.

Two, four and twelve months outcomes are presented in **Figure 1(b)**. At 2 months of treatment, 39.69% (n = 52) of participants were lost to follow-up and

only 52.11% were in remission. At 4 months after steroids initiation, 11 patients were lost to follow-up and of the 60 patients seen in consultation, remission was observed in 56.66% of cases. Renal function was impaired in 9% at 12 months.

### 4.3. Global Outcome

At the end of a 1-year follow-up, 17 deaths were recorded, representing a mortality rate of 12.97%. **Figure 1(c)** shows that the average survival time of the population was 48.2 [40.9 - 55.5] months. The 1-year crude survival rate was 98.4%.

## 5. Discussion

The aim of our study was to report the prognosis of children with idiopathic nephrotic syndrome from 2018 to 2022 in a cohort of Cameroonian. A total of 131 children were included in this study over a 5-year period. It showed that: 1) Steroid sensitivity was reported in 28.17%; steroid resistance in 64.78%, and steroid dependence in 7.04%. 2) at 8 weeks, remission was obtained in 52.11%. 3) The mortality rate was 12.97%. Survival time averaged 48.2 months, with a crude overall survival rate of 99.2% at 3 and 6 months and 98.4% at 1 year. 4) As for renal survival, renal function was impaired in 8.33% at 6 months and 9% at 12 months.

Keita *et al.* reported steroid sensitivity in 77% of children aged 02-12 admitted to a nephrology unit in Senegal [11]. This proportion was much higher than in the present study. Indeed, 48.1% of patients presented with hematuria and 30.05% with kidney failure at diagnosis, raising questions about the idiopathic nature of INS in our cohort in the absence of biopsy. Also, Esezobor *et al.* in Nigeria in 2020 found steroid sensitivity in 85.9% of cases [5]. However, this trend decreased with age, from 92.6% between 0 and 5 years to 69.2% between 11 and 17 years. It must be said that their population was younger than ours (5 years vs. 8 years). This may partially explain our difference. In our series, evolution under steroid treatment was mainly towards steroid resistance. Rural habitats make access to care difficult, and poor adherence to treatment (29.77% lost to follow-up) and the use of phytotherapy could explain this different response from other series. It is also noteworthy that none of the affected children had a family history of kidney disease, and most were experiencing their first episode (n = 87, 66.4%). This reduces the possibility of potentially steroid resistant familial or genetic NS.

In the Nigerian series by Okoronkwo *et al.*, the trend was towards steroid resistance (69.25%), as in our cohort, with a similar median age at presentation [12]. Asinobi *et al.* described a similar trend towards steroid resistance [13]. In short, steroid resistance in children varies from 16% - 73.5% [14]. Regarding this great variability, he raised the possibility of misclassification due to variable definitions. In our series INS is treated by adult nephrologists as well as nephropediatricians and there is no local consensus.

Steroid therapy is the treatment of choice for INS. This treatment induces remission in around 90% of cases. However, 70% of these patients relapse and of these, 60% have 5 or more relapses [15]. Patients are said to be steroid dependent if a relapse occurs while steroid doses are being reduced or within 3 months of their cessation. Keita *et al.* found steroid dependence in 10% of cases in their study in Senegal and 11% were reported in Bamako by Doumbia *et al.* [11] [16]. This proportion is much higher than in our series (7.04%). Half of all steroid sensitive nephrotic children become steroid dependent or relapse frequently, leading to the need for immunosuppressive drugs (IS). Early prescription of these drugs can reduce disease activity, corticosteroids and their harmful effects [17].

INS is a morbidity and mortality factor in children [1]. As a result, it poses a real problem due to the complications observed and the lack of follow-up in our setting. At the end of a one-year follow-up, we recorded 17 deaths, representing a mortality rate of 12.97%. These results are higher than those reported elsewhere in Africa, with a pooled mortality of 6.3% [1]. In our context, this could be explained firstly by the delay in consultation, with a delay of between 1 and 6 months (55%), and the use of nephrotoxics (44.3%) conducive to the genesis of added renal lesions. This situation is due to cultural beliefs, insufficient economic resources on the part of parents to cover the cost of treatment, and ignorance.

Glomerular nephropathies are one of the main etiologies of chronic kidney disease (CKD), and are 5 to 6 times more frequent in Africa than in Europe [18] [19]. They are responsible for almost half of all end-stage chronic kidney disease (ESKD) [20]. In our series, 8.33% and 20% of our patients developed chronic kidney failure at 6 months and 12 months. Our results are lower than those of Sabi *et al.* in Togo, who found that 33.33% of their patients had progressed to CKD, and higher than those of Carter *et al.* in Canada, who had 1% CKD [21]. This could be explained by the delay in consultation, using nephrotoxic drugs, which further impaired renal function but also by the lack of health insurance.

The mean survival time in our population was 48.2 [40.9 - 55.5] months. The crude survival rate at 3 and 6 months was 99.2% and at one year 98.4%. Our results are similar to those of Olowu *et al.* in Nigeria in 2010, who found a survival rate of 94.1% at 6 months and 83.7% at 12 months [22]. However, the duration of steroid therapy ( $p = 0.007$ ), duration of follow-up ( $p = 0.006$ ) and length of follow-up were factors associated with better survival.

Our results cannot be superimposed on the various African series due to the retrospective design of this study. The large number of patients lost to follow-up reduces the quality of our results. Also, the lack of a consensual case definition, treatment, and follow-up protocol in our setting is a great bias in evaluating the outcome of INS. Renal pathology is not done in Cameroon and must be available for the diagnosis purpose and mainly for treatment guidance.

## 6. Conclusion

The pattern of idiopathic nephrotic syndrome is still a concern in our milieu. Many children are lost to follow-up. For those who are treated for the required duration, adherence and the impact of alternative therapies should be investigated to understand the high occurrence of steroids resistance. Free access to steroids may be able to improve adherence and therapeutic response.

## Availability of Data and Materials

The materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes. The data that support the findings of this study are then available from the corresponding author.

## Authors' Contributions

- Conceptualization: KNPO, KC, KFF
- Formal analysis: MM, GSO, ENJ, KFF. Investigation: DH, GSO, MM.
- Project administration: KNPO, KC, KFF. Supervision: MM, ENJ, KFF, KNPO.
- Validation: MM, KFF, KNPO.
- Writing – review & editing: MM, KFF, KNPO.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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