



# Kidney outcomes in children with primary focal segmental glomerulosclerosis from a low- and middle- income country

Kolluri Priyanka<sup>1</sup> · Bobby Deepthi<sup>1</sup> · Sudarsan Krishnasamy<sup>1</sup> · Rajesh Nachiappa Ganesh<sup>2</sup> · Madhileti Sravani<sup>1</sup> · Sriram Krishnamurthy<sup>1</sup>

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## Abstract

**Background** Limited data exists regarding the clinical course and outcomes of children with primary focal segmental glomerulosclerosis (FSGS) from low- and middle- income countries.

**Methods** Children aged 1–18 years with biopsy-proven primary FSGS followed from January 2010–June 2023 in a tertiary-care center were enrolled and their clinical profile, histological characteristics, kidney outcomes, and predictors of adverse outcomes were determined.

**Results** Over 13 years, 73 (54.8% boys) children with median (IQR) age at FSGS diagnosis 6.7 (3,10) years were recruited and followed up for median 4 (2.5,8) years. FSGS-not otherwise specified (NOS) was the most common histological subtype, in 64 (87.6%) children, followed by collapsing variant in 5 (6.8%) children. At last follow-up, 43 (58.9%), 2 (2.7%) and 28 (38.3%) children were in complete remission (CR), partial remission (PR), and no remission (NR) respectively. Calcineurin inhibitors led to CR or PR in 39 (62%) children. Overall, 21 (28.7%) children progressed to chronic kidney disease (CKD) stage 2–5 (19 from NR vs. 2 from PR group;  $p=0.03$ ); with 41% of those NR at 12 months progressing to CKD 4–5 by last follow-up. On multivariable analysis, collapsing variant [adjusted HR 2.5 (95%CI 1.5, 4.17),  $p=0.001$ ] and segmental sclerosis > 25% [aHR 9.9 (95%CI 2.2, 45.2),  $p=0.003$ ] predicted kidney disease progression.

**Conclusions** In children with FSGS, response to immunosuppression predicts kidney survival as evidenced by nil to lower progression to CKD 2–5 by median follow-up of 4 (2.5,8) years in children with CR and PR, compared to those with no remission at 12 months from diagnosis. Segmental sclerosis > 25% and collapsing variant predicted progression to advanced CKD.

**Keywords** Steroid resistant nephrotic syndrome · Focal segmental glomerulosclerosis · Collapsing FSGS · Kidney survival · CKD progression

## Introduction

Focal segmental glomerulosclerosis (FSGS) is a distinct histopathological entity of glomerular disorders and a leading cause of kidney failure in children [1]. In the pediatric population, this glomerular lesion contributes to 7–20% of idiopathic nephrotic syndrome with an incidence of 0.37 to 0.94

cases per 100,000 children per year [2, 3]. FSGS is essentially a podocytopathy and is either primary (idiopathic) in the absence of any identifiable cause, or secondary to various antecedent causes like reflux nephropathy, genetic disorders, chronic hypertension, morbid obesity etc. The disease has a heterogeneous clinical presentation, with substantial morbidity and variable severity [2]. Therapeutic response to immunosuppressive protocols determines long-term kidney outcomes; with complete remission (CR) conferring excellent kidney survival, and those who fail to attain remission progressing rapidly to kidney failure [1, 2]. However, the implications and prognostic value of partial remission (PR) are not well defined in FSGS. The rate of progression to kidney failure ranges from 6 to 9% at 1 year follow-up, 11 to 25% at 3 years and 37 to 47% at 10 years follow-up [4–10]. Histological variants of FSGS have been described since

✉ Bobby Deepthi  
deepu.reddy222@gmail.com

<sup>1</sup> Pediatric Nephrology Services, Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry 605006, India

<sup>2</sup> Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry 605006, India

2004, however the predictive value of Columbia classification in children is not very clear [5]. Also, limited data exists on the prognostic value of histological variants and predictors of adverse kidney outcomes in children with FSGS from low- or middle-income countries (LMIC) [9–11]. In the scenario of LMIC like India, inadequate healthcare access, poor social and financial support, delayed diagnosis and late referrals are commonly encountered clinical situations, which can potentially lead to outcomes that are different from high-income countries (HIC). Hence, this study was conducted to determine therapeutic response to treatment regimens, kidney outcomes at last follow-up, and identify clinical and histological predictors of these outcomes.

## Methods

### Study participants

The cohort enrolled consecutive children aged 1–18 years with histologically proven primary FSGS from a tertiary care academic centre from January 2010 to June 2023. Children who were diagnosed with FSGS since January 2010 till July 2021 and under follow-up at the Pediatric nephrology clinic or deaths in this period formed the retrospective cohort; while all consecutively presenting children aged 1–18 years who satisfied the definition of primary FSGS from July 2021 onwards, formed the prospective cohort. The records of children who were currently not under follow-up in Pediatric Nephrology clinic or those who died were retrieved from the medical records department. Children with steroid resistant nephrotic syndrome (SRNS), as well as frequently relapsing/steroid dependent nephrotic syndrome (FRNS/SDNS) on calcineurin inhibitors who underwent pre-calcineurin inhibitor (CNI) biopsy were screened and those found to have FSGS based on light microscopy and immunofluorescence were enrolled into the study. Children with clinical evidence of secondary causes of FSGS, and those in whom reliable information could not be retrieved from the medical records, were excluded. Genetic screening was not performed in most patients and restricted only to children with steroid resistant nephrotic syndrome with initial resistance (SRNS-IR) who were also CNI resistant, and those with family history of steroid resistance or extrarenal features, in line with Indian Society of Pediatric Nephrology (ISPN) guidelines [12]. Genetic screening was performed using next generation sequencing (using a clinical exome approach) consisting of the following 61 known FSGS genes: *ACTN4*, *ADCK4*, *ALG1*, *ALMS1*, *ANLN*, *APOL1*, *ARHGAP24*, *ARHGDI1*, *CD151*, *CD2AP*, *CFH*, *COL4A3*, *COL4A4*, *COL4A5*, *COQ2*, *COQ6*, *COQ7*, *COQ9*, *CRB2*, *CUBN*, *DGKE*, *EMP2*, *EXT1*, *FAT1*, *GATA3*, *INF2*, *ITGA3*, *ITGB4*, *KANK1*, *KANK2*, *KANK4*, *KIAA222*, *LAMB2*,

*LMNA*, *LMX1B*, *MAFB*, *MAGI2*, *MEFV*, *MYH9*, *MYO1E*, *NEIL1*, *NEU1*, *NPHS1*, *NPHS2*, *NUP17*, *NUP25*, *NUP93*, *NXF5*, *PAX2*, *PDSS2*, *PLCE1*, *PMM2*, *PTPRO*, *SCARB2*, *SMARCAL1*, *TRPC6*, *TTC21B*, *WDR73*, *WT1*, *XPO5*, *ZMPSTE24*. Children who were steroid sensitive (FRNS/SDNS) and those who responded initially to steroids and were later diagnosed with steroid resistant nephrotic syndrome with late resistance (SRNS-LR) were presumed to be non-genetic in origin and hence genetic screening was not performed in these cases. Children who were diagnosed with monogenic SRNS were excluded. Patients were enrolled in the study after approval from the Institutional Ethics Committee in July 2021 and after obtaining written informed consent from parents/legal guardians and verbal assent from children more than 7 years of age.

### Data collection, recording of outcomes and treatment

All patients were followed up 1–3 monthly in the Pediatric Nephrology clinic and their demographic variables such as age at onset of symptoms, age at diagnosis of FSGS, gender; clinical characteristics such as type of clinical presentation (FRNS/SDNS vs. SRNS), hypertension (defined as systolic and/or diastolic blood pressure > 95th centile for age, height and gender as per the American Academy of Paediatrics guidelines) [13]; and biochemical parameters like serum creatinine, estimated glomerular filtration (eGFR) calculated by modified Schwartz formula, proteinuria, and serum albumin measured 1–3 monthly till last follow-up were collected and noted in a separate predesigned proforma. All patients were initiated on CNI unless they were unable to swallow tacrolimus capsules or afford cyclosporine syrup (intravenous cyclophosphamide (IVCP) pulses were used in these patients) and continued for 2–3 years [12]. Children who had FR/SD course following CNI were maintained on steroids and mycophenolate mofetil (MMF) or rituximab. Children with CNI resistance were offered intravenous cyclophosphamide pulses or rituximab followed by MMF. Immunosuppressive therapy was offered to all patients in our cohort and discontinued only in the following situations as endorsed by the ISPN guidelines [12]: children who progressed to chronic kidney disease (CKD) stage 4 or 5 or children in sustained remission for 2–3 years following therapy with CNI/ IVCP + MMF/ Rituximab + MMF. MMF therapy was continued in those who were in PR until they attained CR or progressed to advanced CKD. Renin–angiotensin–aldosterone system inhibitors (RAASi) were offered to all patients with SRNS. They were transiently discontinued during episodes of diarrhea/AKI and restarted upon resolution of the acute illness. Therapy with RAASi was stopped once patients progressed to advanced CKD or when they developed refractory electrolyte disturbances (chiefly

hyperkalemia). Children with kidney failure were initiated on maintenance hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) as and when indicated [12].

### Definitions used in the study

Standard definitions were used for defining CKD, acute kidney injury (AKI), and nephrotic syndrome [12, 14, 15]. SRNS-IR was defined as failure to achieve CR within 6-weeks of treatment with prednisolone at a dose of 2 mg/kg/day during first episode, while SRNS-LR was defined as being initially steroid sensitive and steroid resistance in a subsequent relapse. Remission status at follow-up was defined as CR (urinary protein:urine creatinine ratio (Up:Uc) < 0.2 and serum albumin > 3 g/dL), PR (Up:Uc 0.2–2 and serum albumin > 3 g/dL) or no remission (NR) (Up:Uc > 2 and serum albumin < 3 g/dL) as per standard guidelines [12]. Good response to treatment was defined as achieving either CR or PR. Primary CNI resistance was defined as no remission despite adequate dose of CNI (monitored by trough levels; 80–120 ng/mL for cyclosporine and 4–8 ng/mL for tacrolimus, respectively) for at least 6 months [12]. Secondary or late CNI resistance was defined as an initial response to CNIs with relapse on withdrawal of therapy and an absent or diminished response on reinitiating the drug (after ensuring compliance to drug therapy, adequate dosage of the drug based on the changes in weight and body surface area, and confirmation that adequate trough levels of the drug were present) [16]. Advanced CKD was defined as progression to CKD stage 4–5 or eGFR < 30 mL/min/1.73 m<sup>2</sup>. Kidney survival time was defined as the time from onset of nephrotic syndrome to progression to CKD stage 4–5. Major adverse kidney events (MAKE) were defined as progression to advanced CKD or mortality.

### Histological characteristics

FSGS was defined as the presence of at least one glomerulus with segmental consolidation (sclerotic or cellular), with or without evidence of hyalinosis [5]. Non-representative FSGS was defined as presence of any evidence of cortical scarring (interstitial fibrosis or tubular atrophy) away from the subcapsular area not attributable to any known insult, in an adequate biopsy sample. Global sclerosis was defined as sclerosis involving 100% of the tuft and segmental sclerosis referred to any sclerosis < 100% of the tuft [17]. The Columbia classification of FSGS namely FSGS-not otherwise specified (NOS), perihilar, cellular, tip and collapsing variant, was applied to all biopsies [5]. Interstitial fibrosis (IF) and tubular atrophy (TA) were defined and reported as per standard guidelines [5]. All histological parameters were defined as per standard guidelines [5, 17].

### Statistical analysis

Data were analysed using SPSS 23.0 software (SPSS Inc. Chicago, Illinois 2015). All categorical and continuous sociodemographic, histological, and clinical variables were summarized and compared using Chi square/Fisher exact test or one way ANOVA or Kruskal–Wallis test as appropriate, after assessing the normality of all continuous variables using Kolmogorov–Smirnov test. Kaplan–Meier survival curve was plotted for the entire cohort of subjects to depict the time to advanced CKD (eGFR < 30 mL/min/1.73 m<sup>2</sup>). Receiver operating characteristic (ROC) curves were used to estimate the discriminative ability of independent risk factors like segmental sclerosis, global sclerosis, IF and TA for predicting kidney survival in primary FSGS. The Youden index was used to determine the best cut-off point for these ROC curves. Factors associated with progression to advanced CKD were analysed by univariate followed by multivariable Cox regression analysis. Two Cox regression predictive models were performed for the cohort: model 1 included clinical characteristics and histo-pathological variables using standard cut-offs, whereas model 2 incorporated the cut-offs based on ROC curve and Youden index for this cohort. In all analyses, a p value < 0.05 was considered statistically significant.

## Results

### Patient characteristics

A total of 102 children with SRNS and 37 with FRNS/SDNS on CNI underwent kidney biopsy during the study period, out of which 80 children had FSGS. Among 80 children screened for eligibility, 25 patients underwent genetic analysis; 4 patients had family history of SRNS (3 of whom were detected to have mutations in *NPHS2* and 1 was negative for any of the known FSGS genes) and 2 patients had microscopic hematuria and sensorineural hearing loss (both were detected to have *COL4A5* mutations). The remaining 19 patients with non-familial and renal restricted manifestations were screened but not detected to have any known genetic abnormality. Two children had secondary FSGS. After excluding 5 monogenic and 2 secondary FSGS, finally 73 children were enrolled, of whom 62 children formed the retrospective cohort, while 11 children were diagnosed and followed prospectively.

The baseline characteristics of these patients are mentioned in Table 1. Twenty children (27.3%) had onset of nephrotic syndrome before 2 years of age, while 13 (17.8%) developed nephrotic syndrome after 8 years of age. Two (2.7%) patients had gross hematuria at diagnosis of FSGS, while 4 (5.4%) had transient microscopic hematuria. Of

**Table 1** Baseline characteristics of children at diagnosis of FSGS ( $n=73$ )

Parameters	Value
Age at onset of Nephrotic Syndrome, years	3 (2, 7)
Age at diagnosis of FSGS, years	6.7 (3,10)
Boys*	40 (54.8)
<i>Clinical Presentation*</i>	
Steroid resistant nephrotic syndrome	60 (82.1)
Frequently relapsing/Steroid dependent nephrotic syndrome	13 (17.8)
<i>Growth parameters as per WHO classification*</i>	
Underweight (weight for age < -2z)	22 (30.1)
Short stature (height for age < -2z)	26 (35.6)
Overweight (weight for age > 1z)	11 (15)
Obese (weight for age > 2z)	3 (4.1)
Serum albumin at diagnosis (g/dL)	1.80 (1.4, 2.4)
Urine protein:urine creatinine ratio (Up:Uc)	4.4 (2.3, 6.8)
Serum cholesterol at diagnosis (mg/dL)	469 (367, 567)
Serum creatinine at diagnosis (mg/dL)	0.50 (0.3, 0.8)

All values are depicted as Median [IQR] or  $n$  (%)\*. FSGS - focal segmental glomerulosclerosis; IQR - interquartile range; eGFR - estimated glomerular filtration rate, eGFR was calculated using modified Schwartz formula ( $0.413 \times \text{height}/\text{serum creatinine}$ )

the 60 (82.1%) patients with SRNS, 31 (42.5%) had initial resistance (SRNS-IR) while 29 (39.7%) had late resistance (SRNS-LR). Twenty-three (31.5%) had hypertension at presentation. The mean (SD) weight, height and BMI z scores of the cohort at initial presentation were  $-1.23$  (1.42),  $-1.46$  (1.37), and  $-0.61$  (1.64) respectively. The baseline eGFR was  $96$  (55,172) ml/min/1.73 m<sup>2</sup>.

### Histological characteristics

As per the Columbia classification, FSGS-NOS was the major histopathological subtype seen in 64 (87.6%) patients, while collapsing, tip, and perihilar variants constituted 5 (6.8%), 3 (4.1%), and 1 (1.36%) respectively. The median number of glomeruli in the kidney biopsy specimens was 24 (16, 32). Global sclerosis was noted in 49 (67.1%) children with a median (IQR) percentage of glomeruli affected by global sclerosis being 12 (5, 26.5)%. Segmental sclerosis was observed in 71 (97.2%) children; median (IQR) percentage of glomeruli with segmental sclerosis was 12 (10, 20)%. While 23 (31.5%) children had no TA, 39 (53.4%) children had < 25% TA, 8 (11%) had 25–50%, and 3 (4.1%) had TA > 50%. Similarly, 41 (56.2%) had no IF, 23 (31.5%) had IF < 25%, 8 (11%) had IF 25–50%, and 1 (1.4%) had IF > 50%. Only 7 children in the cohort had vascular involvement in the form of medial hypertrophy, fibrointimal expansion or thrombotic microangiopathy (2 of these children had collapsing variant). Two major histological subtypes

of FSGS in this cohort (FSGS-NOS and collapsing variant) were compared. Children with collapsing FSGS had a significantly higher median (IQR) percentage of glomeruli affected by TA compared to those with FSGS-NOS [35 (2.5,50)% vs. 5 (4,10)%,  $p=0.007$ ]. A significant proportion (40%) of children with collapsing variant had IF between 25–50%. The median percentage of glomeruli with global and segmental sclerosis was higher in collapsing FSGS compared with FSGS-NOS, though the difference was not statistically significant [12 (4,29)% vs. 5 (0,15)% and 12 (4,30)% vs. 10 (4,16)%, respectively].

### Treatment details

Treatment details of the cohort are summarised in Fig. 1 and Table 2. Sixty-three (86.3%) received calcineurin inhibitors; CNIs led to CR or PR in 39 (62%) children, and there was no difference between those receiving cyclosporine vs. tacrolimus ( $p=0.22$ ). Ten (13.6%) children were administered IVCP as initial therapy due to inappropriate formulation of CNIs, lack of availability of cyclosporine syrup and/or prohibitive cost of therapy, at a dose of 500–750 mg/m<sup>2</sup> as monthly doses for 6 months. At the end of 6 months of IVCP therapy, 1 (10%) achieved CR, 3 (30%) were in PR and 6 (60%) were NR; however, by 12 months, only 2 (20%) were in CR, while the rest were NR. All patients with SRNS also received an angiotensin converting enzyme (ACE) inhibitor. The median dose of enalapril used in SRNS patients was 0.43 mg/kg.

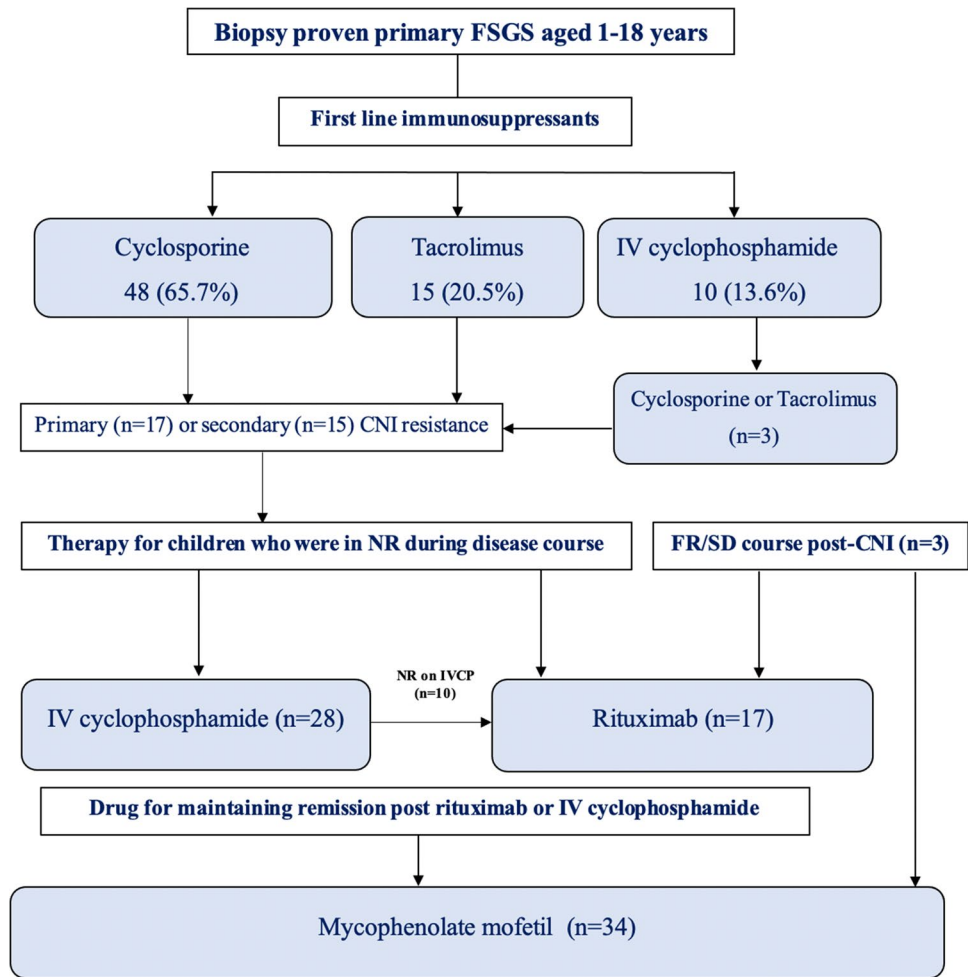
Children who were NR despite adequate dose of CNI for 6 months, those who developed secondary CNI resistance later in the course and had not progressed to CKD stages 3–5 were administered rituximab or IVCP. Children who failed both CNI and IVCP therapy received rituximab (Fig. 1, Table 2). Thirty-four (46.5%) children were then maintained on MMF therapy out of which 15 (20.5%) were in CR/PR at last follow-up.

### Kidney outcomes and predictors of kidney survival

At 12 months follow-up, 30 (41%) children were in CR, 11 (15%) were in PR, and 32 (43.8%) were in NR. At last follow-up (4 (2.5,8)) years, 43 (58.9%) children were in CR, 2 (2.7%) were in PR and 28 (38.3%) were NR (Table 3). Among children who were NR at 12 months ( $n=32$ ), 3 (9.3%) progressed to CKD 2–3 by last follow-up, while 13 (41%) progressed to CKD 4–5 by last follow-up (Fig. 2). There was no statistical difference in kidney outcomes among children with primary FSGS based on their initial steroid responsiveness (SRNS-IR vs. SRNS-LR) ( $p=0.27$ ). Also children with clinical presentation of SRNS were compared with FR/SDNS (steroid sensitive) group and no



**Fig. 1** Flow diagram depicting treatment details of children with primary FSGS



**Table 2** Treatment response to specific immunosuppressants in children with primary FSGS

Drug	n	Median (IQR) dose	Duration of therapy in months; median (IQR)	CR or PR rates; n (%)	Time to CR in months; median (IQR)
Cyclosporine	48	4.25 (3.65, 5) mg/kg	22 (12.5, 27)	31 (64.5%)	4 (2, 8)
Tacrolimus	15	0.15 (0.1, 0.22) mg/kg	14 (4.5, 18)	8 (53.3%)	4 (3, 8)
IV Cyclophosphamide <sup>#</sup>	10	500–750 mg/m <sup>2</sup> × 6 pulses	6 (4, 6)	2 (20%)	4 (4, 6)
IV Cyclophosphamide <sup>*</sup>	28	500–750 mg/m <sup>2</sup> × 6 pulses	6 (3, 6)	11 (39.3%)	4.5 (3, 6)
Rituximab	17	375 mg/m <sup>2</sup> per dose × 3 (2, 6) doses	-	9 (52.9%)	4 (2, 5)
Mycophenolate mofetil	34	900 (820, 1100) mg/m <sup>2</sup>	17 (9, 30)	-	7 (3.2, 16)

<sup>#</sup> IV Cyclophosphamide as initial therapy in CNI-naïve SRNS <sup>\*</sup> IV Cyclophosphamide in CNI-resistant SRNS, CR - complete remission, PR - partial remission

statistical difference was noted in baseline demographic, clinical, histopathological characteristics or long-term outcomes.

Kidney outcomes of the FSGS cohort as per Columbia classification were compared among children with NOS variant versus collapsing variant. Among children with NOS variant, eGFR at last follow-up was relatively preserved, with highest mean kidney survival time of 3.5 (2.5)

years. The lowest eGFR at presentation was noted in collapsing variant, with no significant improvement in eGFR at last follow-up. Three out of five children with collapsing FSGS progressed to kidney failure within 12 months of presentation ( $p = 0.008$  for collapsing vs. NOS) and had significantly lower median kidney survival compared to NOS variant (1.8 years vs. 3.5 years,  $p = 0.05$ ).

**Table 3** Outcomes of the FSGS cohort at last follow-up ( $n=73$ )

Parameters	Value
Duration of last follow-up, years*	4 (2.5, 8)
<i>Growth parameters as per WHO classification</i>	
Underweight (weight for age < -2z)	9 (12.3)
Short stature (height for age < -2z)	38 (52)
Overweight (weight for age > 1z)	5 (6.8)
Obese (weight for age > 2z)	3 (4.1)
Hypertension	61 (83.5)
Serum albumin (g/dL)*	3.2 (1.9, 4.03)
Serum creatinine (mg/dL)*	0.42 (0.30, 1.32)
Estimated GFR (mL/min/1.73 m <sup>2</sup> )*	130 (52.5, 168)
Remission status at last follow up	
Complete remission	43 (58.9)
Partial remission	2 (2.7)
No remission	28 (38.3)
Progression to chronic kidney disease stage 2–5	21 (28.7)
Advanced kidney failure (CKD stage 4–5)	14 (19.1)
Mortality	11 (15)
<i>Complications</i>	
Infections <sup>#</sup>	19 (26)
Hypertension induced concentric LVH	13 (18)
Hypertensive retinopathy	7 (9.5)
Posterior reversible encephalopathy syndrome (PRES)	15 (20.5)
Medication related side effects	
• Cosmetic side effects (gum hypertrophy and hirsutism)	13 (18)
• Dyselectrolyemia	24 (32.8)
• CNI induced acute nephrotoxicity	11 (15)
• Tacrolimus causing hyperglycemia	2 (2.7)
• Tacrolimus induced neurotoxicity	1 (1.3)

All values are depicted as Median [IQR] \* or n (%). *BMI* - Body Mass Index; *eGFR* - Estimated Glomerular Filtration Rate; <sup>#</sup> Infections included spontaneous bacterial peritonitis, pneumonia, varicella, cellulitis, urinary tract infections and tuberculosis; *LVH* - left ventricular hypertrophy

Overall, 21 (28.7%) children progressed to CKD stages 2–5 (19 from NR group, 2 from PR;  $p=0.03$ ); 14 (19.1%) of whom progressed to CKD 4–5 with a median kidney survival time of 18 (8,36) months (Fig. 3). The 4-year kidney survival rate was 100%, 91% and 59.3% for children in CR, PR, and NR at 12 months, respectively, with the median kidney survival time being 36 (24,60) and 24 (13,48) months in children in PR and NR, respectively.

Among the 14 children who progressed to CKD 4–5, 3 had collapsing variant, 10 NOS variant, and one child had perihilar variant ( $p=0.004$ ). Two and four patients each were initiated on CAPD and maintenance HD, respectively, while 8 (57.1%) were not on kidney support therapy. Mortality was noted in 11 (15%) children; 8 were on palliative

care. Both children on CAPD succumbed to septic shock following peritonitis, while one child on maintenance HD expired due to severe varicella infection. The median time to mortality following a diagnosis of FSGS was 18 (8,36) months. At last follow-up, 14 (19.1%) children developed MAKE (including advanced CKD and/or mortality).

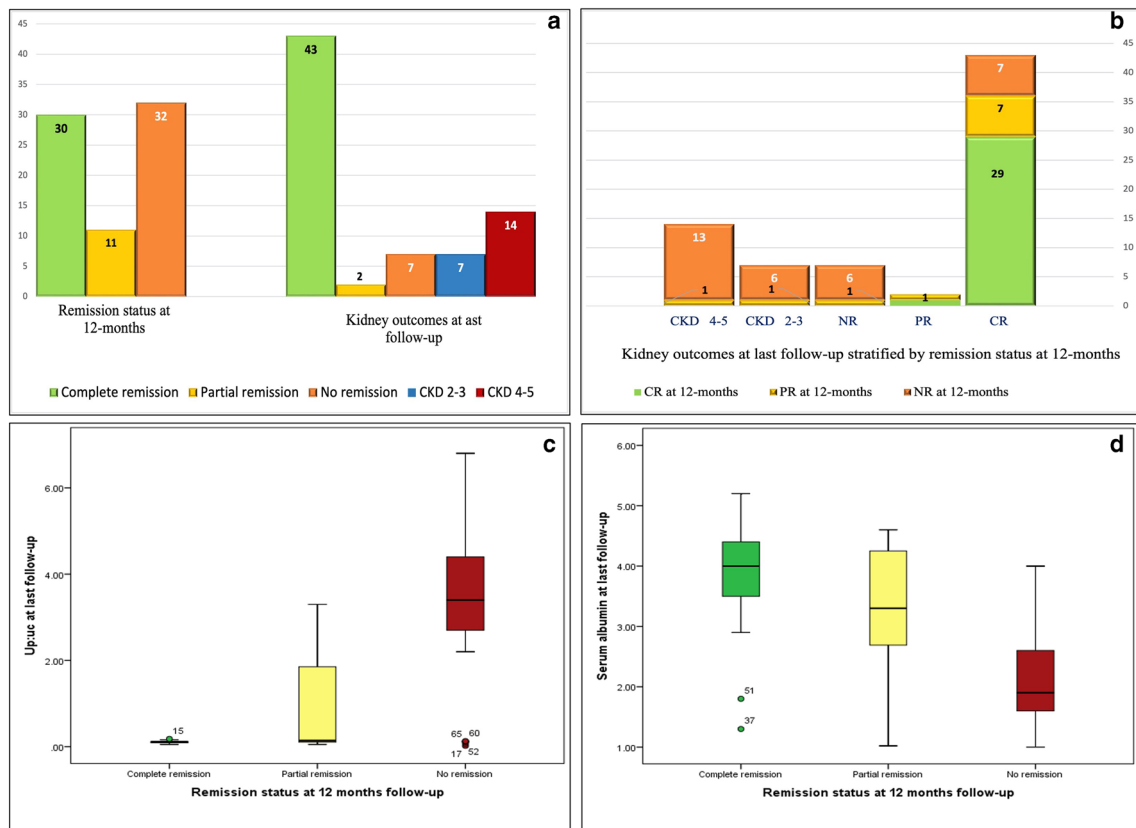
### Predictors of kidney survival

Children in partial remission at 12 months were noted to have significantly lower probability of progression to CKD stage 2–5 than those not in remission ( $p=0.033$ ) by last follow-up. Clinical and histological predictors of progression to CKD 4 and 5 among children with primary FSGS on univariate analysis are depicted in Table 4. On multivariable Cox regression analysis, collapsing variant (adjusted HR 2.5, 95%CI 1.5, 4.17) and segmental sclerosis > 25% (aHR 9.9, 95%CI 2.2, 45.2) were found to predict progression of kidney disease. The ROC curves plotted for diagnostic accuracy of histological parameters in predicting progression to advanced CKD revealed an AUC of 0.86, 0.81, 0.84 and 0.85 for segmental sclerosis, global sclerosis, TA and IF respectively. The optimum cut-off points for these histological parameters (15%, 22%, 7.5% and 7.5% respectively) were chosen based on maximum Youden index (0.55, 0.65, 0.62, and 0.67 respectively). Univariate followed by multivariable Cox regression models using the above histological cut-off points also identified segmental sclerosis and collapsing variant as predictors of progression to advanced CKD.

### Discussion

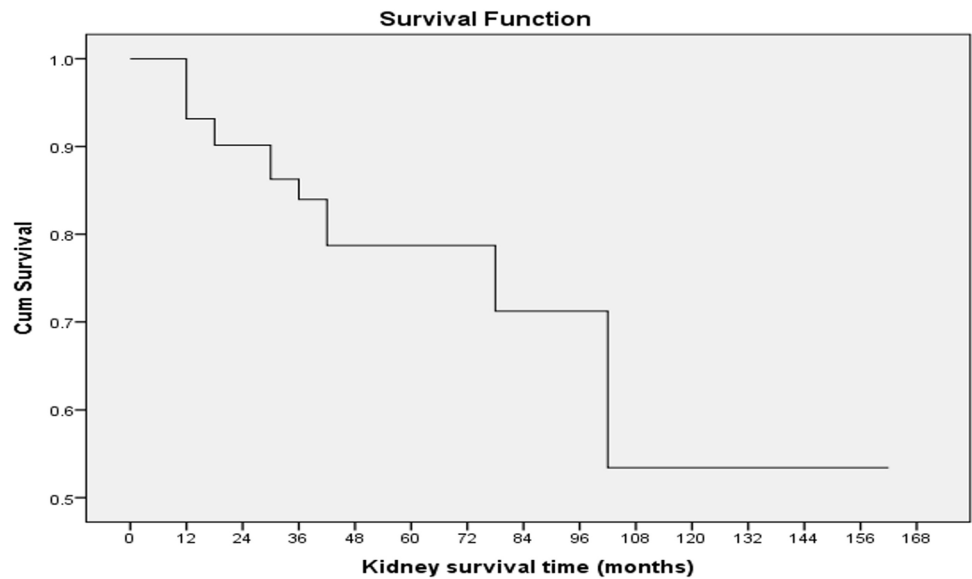
This cohort study examined the clinical and histological characteristics of children with primary FSGS, assessed the therapeutic response to treatment regimens and analysed the risk factors for adverse kidney outcomes. While a sizeable fraction of children in NR (41%) progressed to advanced CKD by last follow-up, a nil to lower progression to CKD 4–5 was noted in children who were CR or PR at 12 months. It is noteworthy that achieving at least partial remission in the first year of FSGS diagnosis is associated with significantly improved kidney outcomes. Collapsing variant and segmental sclerosis > 25% portend a poor prognosis.

In line with the observations from most studies, which reported a median age of 6–8 years at FSGS diagnosis, this cohort also had a median age of 6.7 years [6–10, 18]. CNI was the most common agent used and it led to good response in 62% in this cohort as compared to 40.7–72% in other studies [7, 8, 10, 18–23]. The FSGS-CT trial including both children and young adults demonstrated 46% response rate to CNI therapy (CR or PR) by 1 year [21]. The median time to good response was 4 (2,8) months in our study,



**Fig. 2** Kidney outcomes of children: (a) at 12 months and last follow-up at 4 (2.5,8) years, (b) at last follow-up stratified by their remission status at 12 months from FSGS diagnosis, (c) serum albumin at last follow-up, (d) urine protein to urine creatinine ratio at last follow-up

**Fig. 3** Kidney survival curve of the entire cohort with their remission status throughout the course



Time	12	24	48	72	96	120	144	168
At risk	73	55	41	29	21	15	12	5
CR	30	28	20	14	10	7	6	1
PR	11	7	7	5	2	1	0	0
NR	32	20	14	10	9	7	6	4

**Table 4** Predictors of progression to CKD 4,5 among children with Primary FSGS on univariate and multivariable analysis

Characteristics	HR (95% CI)	P value
<b>Univariate analysis</b>		
Age at onset of NS > 8 years	0.33 (0.11, 1.01)	0.070
Male gender	0.75 (0.26, 2.16)	0.608
SRNS-Initial resistance (vs. SRNS-LR)	1.57 (0.54, 4.5)	0.276
Steroid resistance (vs. steroid sensitive)	0.73 (0.25, 2.09)	0.562
Presence of primary CNI resistance	1.71 (0.46, 6.38)	0.697
eGFR at presentation < 90 mL/min/1.73 m <sup>2</sup>	2.40 (0.74, 7.7)	0.142
<b>Histological sub-types of FSGS</b>		
NOS	1	-
Collapsing	4.89 (1.28, 18.5)	<b>0.020</b>
Tip	3.62	1.0
Perihilar	20.5 (2.2, 188)	<b>0.008</b>
Segmental sclerosis > 25%	11.0 (3.7, 32.1)	<b>0.000</b>
Global sclerosis > 25%	6.28 (2.14, 17.87)	<b>0.001</b>
Interstitial fibrosis > 25%	5.8 (2, 16.9)	<b>0.001</b>
Tubular atrophy > 25%	5.3 (1.85, 15.11)	<b>0.002</b>
Presence of vascular involvement	3.09 (0.95, 9.9)	0.059
<b>Multivariable analysis</b>		
Collapsing variant	2.5 (1.5, 4.17)	<b>0.001</b>
Segmental sclerosis > 25%	9.9 (2.2, 45.2)	<b>0.003</b>

All values are depicted as n (%). NS - Nephrotic syndrome; SRNS - steroid resistant nephrotic syndrome; LR - late resistance; eGFR - estimated glomerular filtration rate; CNI - Calcineurin inhibitor; CKD - chronic kidney disease; NOS - Not otherwise specified; HR - Hazard ratio

which was similar to  $3 \pm 1.8$ ,  $3.5 \pm 1.7$  and 3 (2,4) months as observed in other cohorts [24–26], but better than 6.5 (2.5,7.5) months reported in a Korean cohort [7]. The differences in the response rate and the time to good response could be attributed to the type of CNI used, the dose, underlying histology (MCD vs. FSGS), and concomitant use of ACE inhibitors. Rituximab is commonly employed in children with CNI-resistant SRNS with previous reports showing limited response rates (CR or PR) ranging from 19.5 to 41.5% (Table 5) [27–33]. In the index study, a response rate

of 52.9% was obtained. The possible reason for such higher remission rate in our cohort is due to inclusion of SDNS children with FSGS who accounted for one-fifth of the entire cohort, *vis-a-vis* inclusion of a relatively large number of patients with monogenic SRNS, diffuse mesangial sclerosis and secondary SRNS in the other cohorts [1]. In LMIC, where cost of rituximab may be prohibitive, cyclophosphamide has emerged as a reasonable alternative [34]. We have recently shown that IVCP has led to a response rate of 58.6% (44.8% CR and 13.8% PR) in CNI-resistant SRNS,

**Table 5** Treatment response in CNI-resistant SRNS from published literature

First author, year of publication [R]	n	Drug	Dose	Duration of follow-up; years	Histopathological characteristics MCD/FSGS/DMH	Outcome at last follow-up (CR/PR)
Gulati, 2010 [28]	34	Rituximab	375 mg/m <sup>2</sup> /wk × 4 doses	1.79 ± 0.95	17/16/1	45.4%
Sinha, 2015 [27]	58	Rituximab	375 mg/m <sup>2</sup> /wk × 2–4 doses	2.5 ± 4.4	17/41/0	29.3%
Basu, 2015 [29]	24	Rituximab	375 mg/m <sup>2</sup> /wk × 2–4 doses	2	13/11/0	45.5%
Hoseini, 2018 [30]	30	Rituximab	375 mg/m <sup>2</sup> /wk × 4 doses	2	4/24/2	56.7%
Sinha, 2023 <sup>®</sup> [33]	123	Rituximab	375 mg/m <sup>2</sup> /dose × 3–5 courses	1.8 (1,2.6)	-/38/-	55.3%
Haddad, 2021 [35]	8	IVCP	500 mg/m <sup>2</sup> /mo. × 6 doses	6.5 (0.5–8) <sup>#</sup>	6/2	62.5%
Saiteja, 2023 [34]	29	IVCP	500 mg/m <sup>2</sup> /mo. × 6 doses	4 (2.4,5.2)	5/21/3	58.6%*

MCD - minimal change disease; FSGS - focal segmental glomerulosclerosis; DMH -diffuse mesangial hypercellularity; IVCP -intravenous cyclophosphamide; CR - complete remission; PR - Partial remission; <sup>®</sup> Authors used sequential rituximab regimen at a dosing interval of 7.0 (6.0–9.4) months in CNI-dependent and CNI-refractory SRNS in this study resulting in sustained remission in 55.3% patients. <sup>#</sup> duration in months \*CR/PR rate at 6-months



similar to other studies [34, 35] (Table 5). MMF was used for maintaining remission in our cohort post CNI / rituximab / IVCP, which resulted in remission in an additional 10.9% patients. While previous studies have suggested that initial non-response to steroids is a predictor of kidney failure, our study did not find a significant association between these factors in our specific patient cohort [6].

By last follow-up (median 4 years), two-thirds of patients attained complete or partial remission. The Indian, Turkish and Brazilian cohorts have previously reported comparable remission rates of 72.2%, 69% and 70.2%, respectively [6, 18, 36]; while the Nephrotic Syndrome Rare Disease Clinical Research Network (NEPTUNE) and Jordanian cohorts reported lower remission rates of 55% and 42%, respectively [4, 11]. The discrepancies are probably due to varied clinical presentations, histopathological features, treatment protocols and higher number of familial / monogenic FSGS (Jordan cohort) [11].

The frequency of progression to advanced CKD in children with FSGS varies from 11 to 25% by 3 years [1, 4, 37]. One fifth of children in the index study progressed to kidney failure by last follow-up, as against 13% in the Kidney Research Network (KRN) cohort and 9.1–21.8% in other cohorts [2, 4, 6–8, 17]. As depicted in the Kaplan–Meier kidney survival curves, the kidney survival rates were 90.5% and 80.9%, respectively at 1 year and 4 years. The kidney survival in our study was higher than the Jordanian and Korean cohorts predictably due to higher proportion of familial FSGS and lower rates of response to immunosuppression in the latter studies [7, 11].

The most compelling predictor for FSGS progression remains the response in proteinuria to the immunosuppressive medications administered [1, 6–8]. Partial remission at 12 months from diagnosis was recognised to confer significantly better kidney outcomes compared to those in no remission, reiterating the strongest need to achieve complete or at least partial remission in FSGS to prevent further kidney damage [4, 38]. The FSGS-CT cohort study observed that among 44% children and adolescents in NR at 6 months, there was 22% risk of progression to kidney failure by 3 years [4, 21]. Our study extends these observations, demonstrating that 41% of children in NR progressed to advanced CKD by 4 years.

Our remission rates (CR/PR) were comparable to those reported in FSGS cohorts from other LMICs (67.6% in Turkish cohort, 72.7% in Pakistani children, vs. 61.6% in our cohort) as well as high-income countries (HIC) (70.7% in a cohort from United states and 54.3% in a South Korean cohort) [7, 10, 18, 39]. The kidney failure rates were however much higher in LMICs (19.1% at 4 years in this cohort, 8.9% at 2 years in Pakistani children, 32.4% in Turkish cohort at 4 years vs. 12.2% at 4 years in United States, 20% at 7 years in Brazil, 21.7% at 8 years in a South Korean

cohort) [6, 7, 10, 18, 39], probably due to limited access to specialised care, healthcare affordability and treatment options dictated by financial constraints [10, 18]. Kidney failure requires lifelong dialysis or kidney transplantation, which may be unavailable or unaffordable, and hence significantly reduces patient survival rates in LMICs. A notable proportion of FSGS in kidney failure in our cohort and the Turkish cohort (57.1% and 41.6% respectively) who required kidney support therapy were unable to access it [18].

Like other studies, our study identified FSGS-NOS as the most common histological subtype [3, 7, 8, 23]. In this study, children with collapsing variant experienced the greatest risk of progression to CKD 4–5 (60% within 12 months) as compared to NOS variant (15.6%), which is in line with other previous studies [2, 6, 8, 40]. It is notable that collapsing variant had highest percentage of glomeruli with global and segmental sclerosis and IF between 25–50%, with similar observations in a Chinese cohort [8]. Also, the poor response to immunosuppression (60% in NR by 12 months) in this study, which was also demonstrated in the other studies (46–65% children in NR), could account for faster progression to kidney failure in collapsing variant [7, 41]. While the number of patients in the other variants are small, the Columbia Classification still remains a valid histological predictor of adverse kidney outcomes. Additionally, segmental sclerosis > 25% was significantly associated with MAKE in this cohort, similar to results from a recent study from China which reported that the combination of Columbia classification, chronic tubulointerstitial injury  $\geq$  25% and segmental sclerosis > 26.5% had the best predictive value for kidney outcomes [8].

Our study reports a relatively large cohort of primary FSGS from a single center and systematically studied the prognostic significance of Columbia classification and other histological parameters in these children. The study is, however, limited by the retrospective study design, small number of patients with tip, perihilar and cellular variants, and a relatively short median follow-up period in a disease with potentially long-term consequences. We acknowledge the unavailability of electron microscopy as a limitation.

In conclusion, in children with primary FSGS, response to immunosuppression predicted kidney survival at a median follow-up of 4 years. Attaining even partial remission by 12 months may be an important therapeutic target in FSGS with implications for significantly better kidney survival. Collapsing variant and segmental sclerosis > 25% predicted progression to advanced CKD and defined the group meriting close follow-up.

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**Author's contributions** KP, BD, SK, SuK and MS managed the patients. KP participated in study protocol preparations, recruited

patients, participated in data analysis and drafted the first version of the manuscript. BD and SK conceptualized the study design. BD collected the data, interpreted the data and critically revised the manuscript. SK, SuK and MS participated in recruitment of the patients, data analysis and drafting the manuscript. RNG interpreted the histopathological findings. All authors contributed to protocol preparation, drafting of the manuscript, and approved the final version of the manuscript. BD shall act as the corresponding author. SK shall act as guarantor of the paper.

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**Data availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Code availability** Not applicable. Data subsets are available with the corresponding author.

## Declarations

**Ethics approval** Approved by the Ethics Committee of the institute (IEC/2021/116 dated 19 July, 2021).

**Consent to participate** The authors affirm that human research participants provided informed consent.

**Consent to publish** The authors affirm that human research participants provided informed consent for publication of the images if applicable.

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