# Clinical Course and Long-term Outcome of Adults with Primary Focal Segmental Glomerulosclerosis: A Retrospective Cohort Study

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**Keywords.** adults, focal segmental glomerulosclerosis, nephrotic syndrome, end-stage kidney disease, Pakistan

**Introduction.** Focal segmental glomerulosclerosis (FSGS) is one of the common causes of end-stage kidney disease (ESKD) in adults with primary glomerular diseases. Information on clinical course and long-term renal outcome of primary FSGS in adults are scanty. We aimed to determine the clinical course and long-term outcome of primary FSGS in a large number of adult patients from a tertiary care kidney center in Pakistan.

**Methods.** A retrospective review of the clinical charts of all adults (≥ 16 years) with a biopsy proven diagnosis of FSGS presenting to Sindh Institute of Urology and Transplantation, Karachi, between January 1995 and December 2017 was carried out. Cases with secondary FSGS were excluded. Relevant data items were retrieved both at baseline and on last follow-up.

**Results.** Among 401 adults with primary FSGS, 144 (35.9%) were followed for a mean duration of 66.6 ± 27.4 months, out of which, 129 (89.5%) were treated with steroids and immunosuppressants. Response to steroids was obtained in 62 (48%) patients, while 67 (52%) showed no response. Among responders, 24/62 (38.7%) relapsed after a mean duration of 24.2 ± 23.2 weeks, who were re-treated with same dose of steroids alone or combined with cyclosporine and all achieved remission. The long-term outcomes were significantly different between steroid responsive and non-responsive cohorts. None of the patients in steroid responsive group developed ESKD or died, while 7 (10.4%) patients in non-responsive group developed ESKD and 2 (3%) died.

**Conclusion.** Almost half of adults with primary FSGS achieved sustained remission with steroids and immunosuppressants and consequently exhibited excellent long-term outcome.

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## INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a clinicopathologic entity, associated with variable amounts of proteinuria, usually of nephrotic range, and kidney biopsy findings of focal and segmental sclerosis of glomeruli. The lesion was first described by Rich in 1957 in an autopsy series.[1] FSGS has emerged as one of the most common forms of primary glomerular diseases, particularly in adults.[1,2] Of interest, the incidence of FSGS appears to be increasing in recent years.[3,4] The lesion more commonly affects men and is observed in 20-30% of

patients with nephrotic syndrome (NS). Incidence of FSGS is 3 to 7 times higher in young black men as compared with whites.[5] The typical clinical course of patients with primary FSGS is one of progressive kidney injury culminating in end-stage kidney disease (ESKD) in a significant proportion of cases in more than 10 years. Currently, the disease can only be diagnosed with kidney biopsy.

The management of primary FSGS poses significant challenges because of its highly variable clinical course. The treatment approach is still mostly empirical, and no universally acceptable protocols exist because of the lack of prospective randomized controlled trials. Spontaneous remission occurs in less than 5% of patients. Hence, all eligible patients need to be treated. Corticosteroids remain the frontline therapy for primary FSGS.[6, 7]

Steroid-induced remission of proteinuria in primary FSGS is the most important prognostic factor and is associated with better long-term survival. It is therefore important to be able to predict which patients are more likely to respond to steroid treatment, and use steroids only in those who respond to treatment and save the non-responders from the adverse effects of steroids.[8, 9] We have previously reported the short-term outcomes of steroid therapy in primary FSGS in adult patients with a median follow-up of 16 months at our center.[10] Our results showed that roughly half of adults with primary FSGS showed sustained remission with prolonged steroid therapy. However, data on the long-term outcome is not available in our region. The aim of this study was to determine long-term results of steroid treatment and the renal outcome of adults with primary FSGS at a single large tertiary care renal center in Pakistan.

## MATERIALS AND METHODS

### Patient Selection

A retrospective review of clinical charts of 401 consecutive adults (≥ 16 years) with a biopsy proven diagnosis of FSGS who presented to the adult nephrology clinic of Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan between January 1995 and December 2017 and had regular follow-up, was carried out. Patients with erratic or irregular follow-up or missing information were not included in the study. SIUT has an institution-based renal registry, whereby complete computerized data of all patients are collected. SIUT provides not only free consultation but also free medicines to most patients, which ensure an acceptable degree of compliance. After careful review of clinical records, only cases with idiopathic or primary FSGS were selected, and secondary cases of FSGS were excluded. Clinical charts were reviewed to determine patients' age, sex, level of urinary protein excretion, blood pressure (BP), serum creatinine, estimated glomerular filtration rate (eGFR), serum total protein and albumin and presence of hematuria at the time of presentation and at last follow-up. All patients underwent percutaneous native kidney biopsy, using real-time ultrasound guidance. Kidney biopsy specimens were examined by two experienced nephropathologists and evaluated by light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) as described in detail in our previous study. [10]

### Definitions

Nephrotic syndrome (NS) was diagnosed in accordance with standard criteria. [10] Hypertension was defined as systolic BP exceeding 140 mmHg and diastolic, 90 mmHg on two occasions in supine position, or the need for antihypertensive therapy. Renal insufficiency was defined as eGFR < 60 mL/ min/ 1.73m$^2$ according to MDRD equation, at presentation and on follow-up. FSGS was diagnosed according to standard histopathological criteria. [10] Tubular atrophy on kidney biopsies was semi-quantitatively scored as 0 when it involved 1 to 5% of the area of cortical tubules, 1 when 6 to 25% of area of cortical tubules, 2 when 26 to 50% of area of cortical tubules, and 3 when > 50% of area of cortical tubules.[11]

### Therapeutic Regimens and Outcomes

The therapeutic regimens and response to therapy definitions were used as per our previous study.[10] In brief, patients were treated with prednisone with a dose of 1.0 mg /kg body weight per day for six weeks, followed by 0.75 mg/kg/d for additional six weeks, which was then gradually tapered over 3 months. Response to treatment was categorized into remission, either complete or partial, or no remission. Complete remission (CR) was considered when there was a decline in the amount of proteinuria to ≤ 0.2 g/d. Partial

remission (PR) was defined as a decrease in the amount of proteinuria to between 0.21 and 2 g/d. Time to remission was calculated from the date of initiation of treatment to the date of remission. [10, 12] Relapse was defined as recurrence of the nephrotic-range proteinuria and edema while tapering the dose of steroids or on stopping them. Relapses were treated with a second course of steroids either alone or in combination with cyclosporine. Doubling of serum creatinine from the basal values at presentation, was used as a surrogate marker of progressive renal insufficiency. [10]

The clinical course and outcome of patients were evaluated by recording current medications, BP, serum creatinine and albumin levels, urinalysis and 24h urinary protein excretion on last follow-up.

Statistical Analysis

Data were analyzed by SPSS version 20. Descriptive data were used for expressing the continuous and categorical variables. Continuous variables were presented as mean with standard deviation, or median with interquartile range (IQR), were appropriate. Categorical variables were reported as frequency and percentages. Mean differences for continuous variables and proportion differences for categorical variables between the groups were compared using Chi-square or Fisher's Exact and student's *t*-test. Multivariate analysis for significant factors on univariate analysis was done by logistic regression method, while hazard ratios for risk factors of renal outcome were calculated by using Cox regression model. *P* value ≤ .05 was considered as significant.

## RESULTS

A total of 401 patients were diagnosed with primary FSGS during 22-year study period. Among these, 144 (35.9%) patients had regular follow-up of four or more years, which formed the long-term follow-up cohort of the present study. A comparison of main demographic, clinical, and laboratory characteristics and treatment responses of both cohorts of all patients [n = 401] and patients with long-term follow-up [n = 144], at the time of presentation and last follow-up, is shown in Table 1. As is obvious from the table, both patient cohorts are more or less comparable, except for the mean serum creatinine at the time of presentation,

**Table 1.** Comparison of Main Demographic, Clinical, Laboratory, Treatment and Outcome Parameters Among All and Long-term Follow-up Groups of Primary FSGS Groups (144) at Presentation and at Last Follow-up

| Characteristics | All Patients (n = 401) | Patients with Long-term Follow-up (n = 144) | *P* |
|---|---|---|---|
| Age, y (Mean ± SD) | 29.4 ± 12.3 | 27.2 ± 10.7 | .05 |
| Male to Female Ratio | 2.1:1 | 1.8:1 | > .05 |
| Systolic BP, mmHg (Mean ± SD) | 129.3 ± 18.7 | 127.9 ± 19.9 | > .05 |
| Diastolic BP, mmHg (Mean ± SD) | 85.1 ± 12.7 | 84.3 ± 13.4 | > .05 |
| Initial Proteinuria, mg/24h (Mean ± SD) | 4697.3 ± 3315.8 | 4554.7 ± 2739.1 | > .05 |
| Serum Albumin, g/dL (Mean ± SD) | 2.1 ± 1.2 | 2.2 ± 1.4 | > .05 |
| Serum Creatinine, mg/dL (Mean ± SD) | 1.2 ± 0.9 | 0.9 ± 0.5 | < .05 |
| Renal Insufficiency, n (%) | 98 (24.4) | 27 (18.7) | - |
| Male (eGFR < 60 mL/min/ 1.73m$^2$), n (%) | 70 (17.5) | 16 (11.1) | > .05 |
| Female (eGFR < 60 mL/min/ 1.73m$^2$), n (%) | 28 (7.0) | 11 (7.6) | > .05 |
| Follow-up Duration, mo (Mean ± SD) | 36.3 ± 29.8 | 66.6 ± 27.4 | - |
| NOS, n (%) | 185 (46.1) | 73 (50.7) | > .05 |
| Tip, n (%) | 100 (24.9) | 28 (19.49) | > .05 |
| Cellular, n (%) | 6 (1.5) | 2 (1.4) | > .05 |
| Hilar, n (%) | 3 (0.7) | 1 (0.7) | > .05 |
| Collapsing, n (%) | 58 (14.5) | 25 (17.4) | > .05 |
| Unclassified, n (%) | 49 (12.2) | 15 (10.4) | > .05 |
| Total Steroid Dose, mg, (Mean ± SD) | 4316.7 ± 1922.5 | 4411.8 ± 2342.2 | > .05 |
| Duration of Steroid Treatment, weeks (Mean ± SD) | 22.5 ± 21.9 | 25.0 ± 29.0 | > .05 |
| Complete Remission, n (%) | 86/138 (62.3) | 34/62 (54.8) | > .05 |
| Partial Remission, n (%) | 52/138 (37.7) | 28/62 (45.2) | > .05 |
| Time to Remission, weeks (Mean ± SD) | 12.2 ± 17.5 | 16.3 ± 27.8 | > .05 |

BP, blood pressure; eGFR, estimated glomerular filtration rate

which was significantly lower in the long-term follow-up cohort ($P < .05$). Renal insufficiency at presentation was found in 98 (24.4%) of all patients and 27 (18.7%) in the long-term follow-up group. Of all patients with primary FSGS (n = 401), 337 (84.0%) were treated with steroids according to our institutional treatment protocol. Among these, 138 (40.9%) patients achieved remission with steroids, with 86 (62.3%) CR and 52 (37.6%) PR. The mean time to remission was 12.2 ± 17.5 weeks. It was noted that > 70% of patients showed response to steroids within 12 weeks of treatment (data not shown).

Among 144 patients with long-term follow-up, 129 (89.5%) patients were treated with steroids. These were further analyzed in detail, particularly with regard to treatment responses and outcome. The mean follow-up duration of the long-term follow-up cohort was 66.6 ± 27.4 months. Among them, 62 (48%) patients achieved remission, which was complete in 34 (54.8%) and partial in 28 (45.2%) patients, while 67 (52%) patients did not respond. A comparison of the main demographic, clinical, laboratory, treatment and outcome features of the steroid responsive and non-responsive groups is shown in Table 2. the main clinical and laboratory parameters including eGFR and proteinuria at the time of presentation were similar except for diastolic BP, which was significantly higher in the steroid non-responsive group ($P < .05$). The latter group had significantly poorer outcome on last follow-up as shown by higher serum creatinine ($P < .001$) and lower eGFR ($P < .05$).

A comparison of the main histopathologic findings between the steroid responsive and non-responsive groups is shown in Table 3.

**Table 2.** Comparison of Main Demographic, Clinical, Laboratory, Treatment, and Outcome Parameters Among Steroid-responsive and Non-responsive Primary FSGS Groups at Presentation and at Last Follow-up (n = 129)

| Parameters | Steroid-responsive Group (n = 62) | Steroid Non-responsive Group (n = 67) | *P* |
|---|---|---|---|
| Age, y (Mean ± SD) | 27.8 ± 10.8 | 25.8 ± 10.0 | > .05 |
| Gender (M: F) | 45:17 | 38:29 | > .05 |
| Systolic BP, mmHg (Mean ± SD) | 124.9 ± 15.9 | 130.6 ± 21.9 | > .05 |
| Diastolic BP, mmHg (Mean ± SD) | 81.1 ± 12.3 | 86.8 ± 13.3 | < .05 |
| Initial Proteinuria, mg/24h (Mean ± SD) | 4412.3 ± 2333.0 | 4416.2 ± 2304.8 | > .05 |
| eGFR on Presentation (Mean ± SD) | 101.3 ± 37.4 | 106.5 ± 38.3 | > .05 |
| Renal Insufficiency on Last Follow-up, n (%) | 8 (12.9) | 24 (35.8) | < .001 |
| Doubling of Serum Creatinine, n (%) | 3 (4.8%) | 10 (14.9%) | > .05 |
| eGFR on Last Follow-up (Mean ± SD) | 102.4 ± 39.7 | 84.9 ± 52.6 | < .05 |
| Cumulative Steroid Dose, mg/kg | 28.9 ± 31.3 | 43.5 ± 34.1 | < .05 |
| Total Steroid Duration, weeks (Mean ± SD) | 24.2 ± 23.2 | 25.8 ± 33.7.7 | > .05 |

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate.

**Table 3.** Comparison of Histopathology Findings in Steroid-responsive and Steroid Non-responsive Groups (n = 129)

| Histopathologic Parameters | Steroid-responsive Group (n = 62) | Steroid Non-responsive Group (n = 67) | *P* |
|---|---|---|---|
| No. of Glomeruli (Mean ± SD) | 17.8 ± 9.3 | 15.4 ± 8.1 | > .05 |
| No. of Glomeruli with Global Sclerosis (Mean ± SD) | 2.7 ± 2.2 | 2.7 ± 2.9 | > .05 |
| No. of Glomeruli with Segmental Sclerosis (Mean ± SD) | 2.1 ± 1.6 | 2.9 ± 2.5 | > .05 |
| Tubular Atrophy, n (%) | | | |
| Mild | 43 (95.6) | 32 (80) | < .05 |
| Moderate | 2 (4.4) | 8 (20) | |
| Fibro-intimal Thickening of Arteries, n (%) | | | |
| Mild | 5 (71.4) | 5 (83.3) | > .05 |
| Moderate | 2 (28.6) | 1 (16.7) | |
| FSGS Variants | | | |
| NOS | 30 (48.4) | 38 (56.7) | > .05 |
| Tip | 21 (33.9) | 06 (9.0) | < .001 |
| Collapsing | 9 (14.5) | 14 (20.9) | > .05 |

Note. Tubular atrophy was scored as 0 when it involved 1 to 5% of the area of cortical tubules, 1 (mild) when 6 to 25% of area of cortical tubules, 2 (moderate) when 26 to 50% of area of cortical tubules, and 3 (severe) when > 50% of area of cortical tubules.

As it is evident, moderate tubular atrophy was more prevalent in steroid non-responsive group ($P < .05$). Patients with tip variant lesion achieved CR and PR more frequently (77.7%), as compared with NOS (44.1%) and collapsing variants (39.1%) ($P < .001$, data not shown). On multivariate analysis by logistic regression method on all factors, that had shown significant association on univariate analysis, only tip variant showed significant independent association with steroid responsiveness (OR = 11.361, 95% CI: 1.171 to 110.185, $P < .05$).

Among initial responders in the long-term follow-up cohort, 24/62 (38.7%) patients relapsed after a mean duration of 24.2 ± 23.2 weeks (range: 4 to 139 weeks). These patients were treated with a second course of steroids, either alone (7 patient, 29.16%) or in combination with cyclosporine (17 patients; 70.83%) patients. All of the patients achieved remission of proteinuria and remained in remission, until the end of this study, as shown in Figure 1.

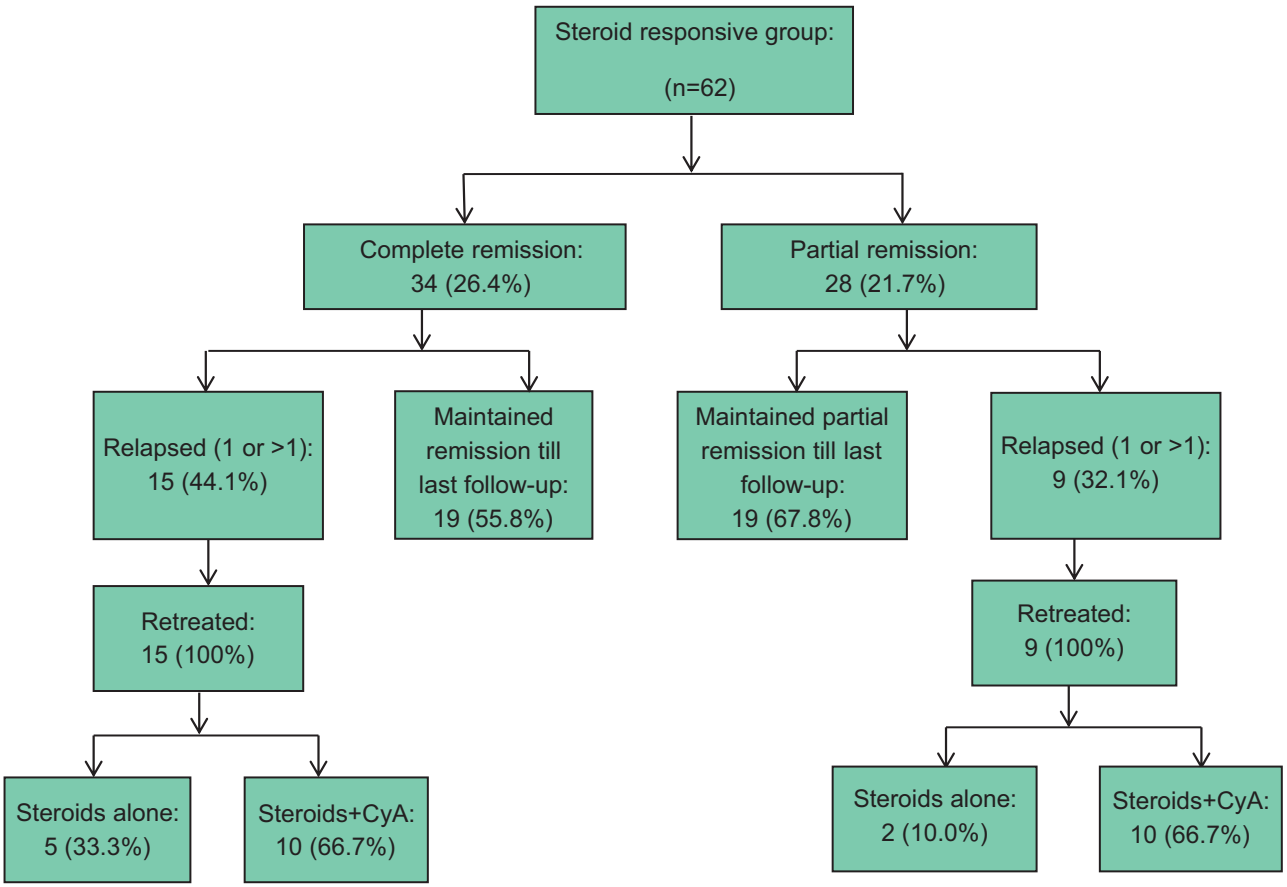
The long-term outcomes were significantly different between the steroid responsive and non-responsive cohorts. None of the patients in steroid responsive group developed ESKD or required dialysis or died. In contrast, in the steroid non-responsive group, 7 patients (10.4%) developed ESKD and 2 (3%) died.

Cox regression analysis did not show any significant effect of diastolic BP, cumulative steroid dose, tubular atrophy, tip variant and eGFR or renal insufficiency at last on the outcome of CKD or ESKD (Table 4).

## DISCUSSION

This is one of the largest studies on the clinical course and long-term outcome of primary FSGS in adults, from a single tertiary care center in Pakistan. In fact, this study is a continuation of our previous study with extended longitudinal data. [10]

The clinical and laboratory features of this overall relatively young adult population of primary FSGS are more or less similar to those of our previous study, at presentation, albeit with improvements




Flow Chart Depicting the Treatment Approach to Patients Who Relapsed After Achieving Remission with Steroids

**Table 4.** Cox Regression Analysis of Hazard Ratios of Various Risk Factors for the Outcome (n = 129)

| Risk Factors | B | *P* | Hazard Ratios (HRs) | 95% CI |
|---|---|---|---|---|
| Diastolic BP | 0.019 | > .05 | 1.019 | 0.968 to 1.073 |
| Cumulative Steroid Dose | -0.003 | > .05 | 0.997 | 0.969 to 1.026 |
| Renal Insufficiency at Last Follow-up | 1.303 | > .05 | 3.679 | 0.122 to 111.195 |
| Tubular Atrophy | 1.208 | > .05 | 3.348 | 0.807 to 13.882 |
| Tip Variant | -10.610 | > .05 | 0.000 | 0.000 |
| eGFR at Last Follow-up | -0.028 | > .05 | 0.972 | 0.936 to 1.010 |

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate.

in a number of parameters. [10] One of the important parameters that showed improvement, compared to our previous study, was the incidence of renal insufficiency at the time of presentation, which was reported in 33.8% of our patients in the previous and, 24.4% of the patients in the current study. This might be due to increased awareness and early referral of patients to specialized centers over recent years. An elevated creatinine and eGFR < 30 mL/ min/ 1.73m$^2$ at presentation is usually considered a poor prognostic marker in terms of subsequent kidney survival but in our earlier study we showed that, this was most probably due to hemodynamic factors and did not adversely affect the outcome. [10, 12] In one study that provided a stratified analysis, remission was achieved in only 5 of 21 (23.8%) patients with a serum creatinine exceeding 1.4 mg/ dl compared to 36 of 60 (60%) with lower serum creatinine concentration.[12,13] We also found that, elevated serum creatinine at presentation was not predictive of steroid responsiveness, similar to our previous study, and we suggest that it should not stop clinicians from starting steroid treatment, especially in subjects with short duration of disease.

In this analysis, a sizeable number of patients (144: 35.9%) had adequately long follow-up, which encouraged us to analyze the clinical course and outcome of this subgroup in detail, and this subgroup is the focus of this study.

We also found that, response rate with steroids was higher (84% overall and 89% in long-term follow-up group), as compared with our previous study (63.7%).[10] This strategy may have been provoked by studies and reviews over the past two to three decades, and our own experience indicates better response to steroids in primary FSGS. [10] However, the overall response rate was lower in this study (40.9%) as compared with our previous study (50.6%). On the other hand, the response rate of the long-term follow-up group was more or less similar (48.1%) to the previous study. This finding is discernible as most of the patients in the latter group were also participants in the previous study. [10] This also implies that we were more careful in prescribing steroids during the early phase of the study. [10]

The proportion of patients with renal insufficiency at presentation in both groups (24.5%) and (18.7%)] was lower as compared with our previous study. [10] Renal insufficiency in these cases is multifactorial and not always due to chronic and irreversible loss of renal function. It may well be a consequence of hemodynamic alterations in acute-onset NS and hence improves with treatment of the underlying glomerulopathy, as proved in our previous study. [10, 12]

Among the long-term follow-up group, the proportion of subjects with renal insufficiency at baseline was marginally higher in the steroid-responsive group. Still, it decreased after achieving remission, and their renal functions improved with stabilization of eGFR. A decline of eGFR was observed in patients belonging to the steroid non-responsive group ($P < .05$).

We also analyzed the main histologic features of FSGS including the histological variants of FSGS and the degree of chronic parenchymal changes, considering steroid responsiveness of the disease. The tip variant showed the highest response rate to steroids and was associated with the best prognosis, both on univariate and multivariate analysis ($P < .05$).

Corticosteroids are the cornerstone of treatment of primary FSGS, and the therapeutic response to steroids appears to be the best predictor of long-term outcome and prognosis. However, the protocols vary considerably regarding the dose and duration of treatment. Even the decision to treat or not to treat varies from physician to physician.[14,15] As stated in our previous study, our

strategy is to treat all eligible adults with primary FSGS with our steroid protocol of, if not otherwise contraindicated. [10] As alluded to earlier, we were more liberal in prescribing steroids in the later part of our study.

The overall remission rate achieved in our steroid-treated cohort with long-term follow-up was 48.1%. The steroid response rates in different studies have varied from 30 to 80%, depending on the dose and duration of steroid treatment.[16-18] Our treatment protocol consisted of daily high-dose steroid treatment for three months followed by tapering over the next 2–3 months regardless of response. We continued treatment with steroid for longer duration in steroid non-responders with the hope to achieve delayed response, which is reflected by a higher total dose of steroids in this group. The mean time to remission was as long as five months in the series by Goumenos *et al*.[19] The mean time to remission in our current study was slightly more than four months, which is similar to the study by Goumenos *et al.* and our previous study.[10,19] Our primary treatment duration is shorter than the current recommendation of high-dose steroid treatment for 4–6 months. A response rate as high as 80% has been reported in some series with protracted steroid treatment.[17, 18] This suggests that use of steroids for a longer period has remission-inducing effects.[19] Steroid dosage in our study was reduced by 50% at the beginning of the fourth month. Further tapering was done fortnightly. The fact that more than half of patients responded after three months also supports the phenomenon of delayed response to prolonged lower dose. This may have important implications for future treatment, as the side effects of high-dose steroids are considerable. If these observations are confirmed in prospectively conducted trials, it may decrease steroid-related toxicity.[20-24]

The cumulative steroid dose and duration in the steroid non-responsive group were higher than the steroid-responsive group, although only the former was statistically significant. This may reflect relatively rapid tapering in subjects responding to steroid treatment after three months of high-dose therapy, as high-dose glucocorticoid therapy is associated with several adverse effects.

We did not find frequent relapses in our adult patients with FSGS and all relapses responded to re-treatment with steroids either alone or in combination with cyclosporine. We did not observe any spontaneous remission in our study, as none of the untreated patients achieved remission.

Response to steroids is associated with long-term preservation of renal function in patients with FSGS.[12, 14, 25-29] This was also proved in our study, as none of the steroid-responsive patients developed CKD or ESKD or died until the last follow-up. In contrast, 35.8% of the patients in the steroid non-responsive group developed CKD, 10.4% of them developed ESKD, and 3% patients died.

Thus, this study supports the positive role of glucocorticoid therapy on kidney survival and improvement of long-term outcomes in adult patients with primary FSGS.

### Limitations of the Study

There are certain limitations in the present study, which include the retrospective and single-center nature of the study, and lack of a control group. The strengths of the study include large sample size, the uniform racial origin of patients, uniform protocols for the diagnosis, and management of FSGS with long-term follow-up. Thus, we believe that the results of our study accurately, represent the clinical course and outcome of primary adult FSGS in this country.

## CONCLUSION

This study shows that, almost half of adult patients with primary FSGS achieved sustained remission with a long course of steroid therapy s and second-line immunosuppressive medications and consequently exhibited an excellent prognosis for long-term outcomes. We suggest that these patients should be treated with steroids and second-line therapy, whenever necessary.

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