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Original Article

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Response to Steroids Is Not Completely Protective Against the Development of Progressive Kidney Disease in Collapsing Focal Segmental Glomerulosclerosis

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ABSTRACT

Objective: Collapsing focal segmental glomerulosclerosis, a recently described condition, has an increased risk of ending up in kidney failure with replacement therapy. Data are limited on clinical presentation, treatment responses, and outcomes. This study sought to elucidate the clinicopathological profile, therapeutic responses, and outcome of idiopathic collapsing focal segmental glomerulosclerosis in adults.

Methods: The study was conducted at the Department of Nephrology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan on patients with biopsy-proven collapsing focal segmental glomerulosclerosis between January 1995 and December 2017. The clinical charts were scrutinized to retrieve relevant data items. Data were entered and analyzed in Statistical Package for the Social Sciences version 20.

Results: Among 401 patients with idiopathic focal segmental glomerulosclerosis, 58 (14.4%) belonged to collapsing focal segmental glomerulosclerosis category; 34 (58.6%) were males and 24 (41.4%) females with a mean age of 30.1 ± 12.4 years. The mean value of 24-hour proteinuria was 3.81 ± 1.85 g/day and the median time to kidney biopsy was 2.5 weeks (interquartile range = 1-5). Among 58, 53 (91.4%) were treated with steroids; 2 (3.8%) achieved complete remission and 11 (20.8%) achieved partial remission. Steroid responsive (n = 13) and non-responsive (n = 40) groups showed no significant differences in all characteristics. Calcineurin inhibitors were also used in 17/53 (32%) patients. Kidney biopsy showed the lesions to be mild in most cases. Overall, progressive kidney failure was observed in 37/53 (69.8%) patients; 27 (50.9%) showed variable degrees of kidney failure, while 10 (18.8%) required replacement therapy (kidney failure with replacement therapy). The median time to kidney failure was 22 months (interquartile range = 6-33). The steroid responsive group also developed progressive kidney failure in 8/13 (61.5%) cases.

Conclusion: The results show that the response to steroids and calcineurin inhibitors is poor in collapsing focal segmental glomerulosclerosis and does not completely protect from progression to kidney failure.

Keywords: Adults, collapsing focal segmental glomerulosclerosis, chronic kidney disease, kidney failure with replacement therapy

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is one of the dominant causes of nephrotic syndrome (NS) in both adults (40%) and children (20%). It has an approximate incidence of 7 patients per million population. It is also the foremost primary glomerular disease leading to kidney failure with replacement therapy (KFRT) in the world.[1]

Collapsing FSGS (cFSGS), a histologic variant of FSGS, is a severe form of kidney injury which has become preeminent as an important cause of kidney failure (KF) with or without kidney replacement therapy throughout the world.[2-7] Some researchers suggest that it is different from FSGS and may be classified as a separate disease in the near future.[8,9] Collapsing focal segmental glomerulosclerosis is a unique pattern of kidney

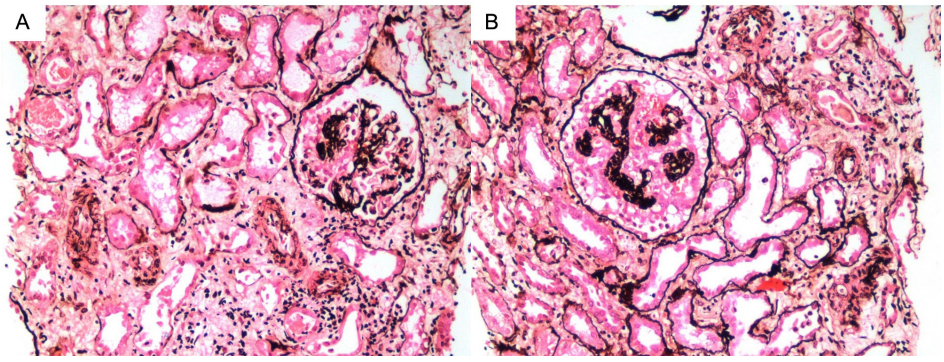

Figure 1. a,b. Histopathology of collapsing FSGS. (A) A glomerulus showing segmental collapse of capillary tufts at 9 o'clock position. There is associated podocyte hyperplasia and hypertrophy. Surrounding parenchyma shows chronic interstitial inflammation and mild tubular atrophy (Jones' Silver stain, ×400). (B) In this biopsy, the glomerulus shows global collapse of capillary tufts with associated florid podocyte hyperplasia and hypertrophy. Surrounding parenchyma shows chronic interstitial inflammation and mild tubular atrophy (Jones' Silver stain, ×400). FSGS, focal segmental glomerulosclerosis.

injury, which is presently at the forefront of research, due to its rising incidence, increasing association with conditions other than the classical risk factors such as human immunodeficiency virus-1 infection and intravenous drug abuse, and its uniformly poor prognosis. It is a heterogeneous group of disorders rather than a single disease entity. Although, at first reported from North America, the disease is actually universal in distribution.[7-13] Its definite diagnosis can only be established by histopathological evaluation of kidney biopsies. The clinical and laboratory features are generally similar to those observed in non-cFSGS but are typically severe. The treatment strategies used at present are also similar to those used for non-cFSGS, based on the use of steroids or immunosuppressive agents.[14] The overall results are generally poor, with reported complete remission rates of <10% and partial remission rates of around 15%.[4]

There is minimal information on the clinicopathological presentation and long-term prognosis of idiopathic cFSGS in adults in low-to-middle-income countries. We previously reported the clinicopathological profile of 10 patients with cFSGS from our center, which showed some differences in clinical and laboratory parameters of the disease in our patients.[15] However, long-term prognosis and outcomes were not analyzed in detail in that study. In this study, we aimed to analyze the clinicopathological profile and outcome of a larger sample of cFSGS in adult patients to better understand its presentation, treatment, and prognosis over a medium-term duration.

MAIN POINTS

- Focal segmental glomerulosclerosis (FSGS) is a heterogeneous clinicopathological entity that leads to kidney failure in a significant number of cases. Collapsing FSGS is one of the variants of FSGS with worst prognosis.
- Treatment of collapsing FSGS is particularly challenging and still empirical.
- Steroids are the mainstay treatment for idiopathic collapsing FSGS; however, the response is uniformly poor.
- Cyclosporine is used as second-line therapy, but evidence is still scarce on its efficacy and safety.
- Response to steroids is not completely protective against progression to kidney failure in collapsing FSGS.

METHODS

The study conducted at the the Department of Nephrology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan was permitted by the institutional ethical review committee (SIUT-ERC-2019-PA-191, dated: November 7, 2019), and it was carried out according to the ethical tenets as envisaged in the Declaration of Helsinki. SIUT has an internal computerized kidney disease database, whereby complete data of all patients are accessible to concerned healthcare persons. Our hospital provides not only free consultation but also free medicines to most patients, which ensure a high rate of compliance and follow-up. Patients diagnosed with idiopathic cFSGS from January 1995 till December 2017 were included. A total of 401 biopsy-proven FSGS patients were identified during the above study duration. Cases of secondary FSGS due to, for example, immunoglobulin A nephropathy, lupus nephritis or other known diseases, were excluded. Idiopathic cFSGS comprised 58/401 (14.4%) cases. This retrospective review was conducted on these 58 consecutive adults (≥19 years) with biopsy-proven cFSGS with at least 2 years of regular follow-up. The clinical records were scrutinized to retrieve the patients' age, gender, and degree of proteinuria, blood pressure (BP), serum creatinine, total protein, and serum albumin. Collapsing focal segmental glomerulosclerosis was diagnosed on histopathologic examination even in the presence of a single glomerulus with segmental or global collapse of tufts as per standard criteria (Figure 1). The clinical course, treatment response, and final outcome of all patients were evaluated by noting down relevant clinical and laboratory parameters at the time of presentation and last follow-up, as appropriate.

The diagnosis of NS was made in accordance with the standard definition.[16] Hypertension was defined as BP readings exceeding 140/90 mmHg for systolic and diastolic BP in the supine position in 2 consecutive measurements or the requirement for antihypertensive therapy. Abnormal kidney function at presentation and on follow-up was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) equation.[17] Standard treatment regimens and response to treatment definitions with slight modifications were used, as in our previous study.[17] Briefly, all eligible patients were treated with prednisone at a dose of 1 mg/kg body weight per day for 6 weeks, tapering to 0.75 mg/kg/day for 6 additional weeks, which was then progressively tapered over >3 months. Complete remission (CR) was defined as a decline in the rate of protein excretion to ≤0.2 g/day, whereas partial remission (PR) was defined as a decline in the rate of urinary protein excretion to 0.21 to 2 g/day. Time to remission was defined as the interval from the date of administration of treatment to the date of first remission. Relapse was defined as a reappearance of edema or nephrotic-range proteinuria during the tapering of the steroids or on cessation of steroid treatment. Relapsers were treated with a second course of steroid treatment in combination with cyclosporine. Chronic kidney disease and KFRT were defined as per standard criteria.[16]

Data were analyzed in Statistical Package for the Social Sciences (SPSS) software 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were used for summarizing the categorical and continuous variables. Continuous variables were summarized as mean and standard deviation and median and interquartile range (IQR) as required. Categorical variables were reported as numbers and percentages. The chi-square test was used to determine the proportion differences between remission and no remission for categorical variables. To compare mean differences between treatment-responsive and treatment-resistant cases for continuous variables, Student's 2 sample '*t*-test' was used. $P \leq .05$ was taken as statistically significant.

RESULTS

Among 401 subjects with biopsy-proven idiopathic FSGS, 58 (14.4%) belonged to the cFSGS category and formed the study population for the present study. Their main demographic, clinical, and pathologic features at the time of presentation and on the last follow-up are depicted in Table 1. Among 58 patients, 34 (58.6%) were males and 24 (41.4%) were females. The male-to-female ratio was 1.4 : 1. The mean age of all patients was 30.1 ± 12.4 years and the range was 19-60 years. Hypertension was noted in 21 (36.2%) patients. The mean systolic BP was 130 ± 18.9 mmHg and mean diastolic BP was 87.6 ± 14.1 mmHg. The mean 24-hour proteinuria was 3.81 ± 1.85 g/day. Among all, 42/58 (72.4%) patients had nephrotic-range proteinuria, with 8/58 (13.7%) having protein excretion of >5 g/day. Proteinuria < 3.5 g/day was found in 16/58 (27.6%) patients. The mean value of serum albumin was 2.1 ± 1.1 g/dL (median: 2.0 g/dL).). The mean eGFR at presentation was 87.8 ± 43.7 mL/min/1.73 m^2. An abnormal kidney function was found at the time of presentation in 19 (32.8%) patients; among these, 12 (20.7%) were males and 7 (12.1%) females. The median time from presentation to kidney biopsy was 2.5 weeks (IQR = 1-5 weeks).

Table 1. The Main Demographic, Clinical, and Laboratory Findings at Presentation in 58 Patients with Primary Collapsing FSGS

Parameters	Results
Age (years), mean ± SD (range)	30.1 ± 12.4 (19-60)
Male to female ratio	1.4 : 1
Systolic blood pressure (mmHg), mean ± SD	130.0 ± 18.9
Diastolic blood pressure (mmHg), mean ± SD	87.6 ± 14.1
Initial proteinuria (g/24 h), mean ± SD	3.81± 1.85
Serum albumin (g/dL), mean ± SD	2.1 ± 1.1
Serum creatinine (mg/dL), mean ± SD	1.4 ± 0.9
eGFR (mL/min/1.73 m^2), mean ± SD	87.8 ± 43.7
Abnormal kidney function, n (%)	19 (32.8)
Males, n (%)	12 (20.7)
Females, n (%)	7 (12.1)

eGFR, estimated glomerular filtration rate; SD, standard deviation.

The total steroid dose, duration of steroid intake, response to steroid therapy, and final outcome of 53 (91.4%) patients who were treated with steroids are given in Table 2. Among these, 2/53 (3.8%) patients achieved CR, while 11/53 (20.8%) showed PR. The mean time to remission was 7.5 ± 5.8 weeks. Among initial responders, 4/13 (30.7%) relapsed. These were re-treated with steroids in combination with Cyclosporine A (CsA). All 4 went into PR. Among the steroids' non-responders, 13/40

Table 2. Treatment Responses and Medium-Term Outcome of 53 Patients of Collapsing FSGS Treated with Steroids

Parameters	Results
Follow-up duration (months), mean ± SD	39.3 ± 26.8
Duration of steroid treatment (weeks), mean ± SD	21.4 ± 17.6
Total steroid dose (mg), mean ± SD	4024.6 ± 1597.6
Remission, n (%)	13 (24.6)
Complete remission, n (%)	2 (15.3)
Partial remission, n (%)	11 (84.6)
Time to remission (weeks), mean ± SD	7.5 ± 5.8
Final proteinuria (g/24 h), mean ± SD	3.35 ± 2.80
Kidney failure, n (%)	27 (50.9)
Kidney failure with replacement therapy, n (%)	10 (18.8)

SD, standard deviation.

Table 3. Comparison of Clinical, Laboratory, Histopathological, and Treatment Parameters Among Steroid-Responsive and Steroid-Non-Responsive Collapsing FSGS Groups at Presentation and Last Follow-Up (n = 53)

Parameters at Presentation	Steroid-Responsive Group (n = 13)	Steroid Non-Responsive Group (n = 40)	*P*
Age (years) (mean ± SD)	27.9 ± 13.6	30.4 ± 11.8	>.05
Gender (M:F)	9 : 4	22 : 18	>.05
Systolic BP (mmHg) (mean ± SD)	127.1 ± 15.8	132.0 ± 20.0	
Diastolic BP (mmHg) (mean ± SD)	84.5 ± 11.9	88.4 ± 14.5	>.05
Initial proteinuria (g/24 h) (mean ± SD)	4.26 ± 2.03	3.67 ± 1.83	>.05
Initial serum creatinine (mg/dL) (mean ± SD)	0.9 ± 0.4	1.3 ± 0.8	>.05
Initial serum albumin (g/dL) (mean ± SD)	1.6 ± 1.0	2.2 ± 1.1	>.05
eGFR, mL/min/1.73 m^2, mean ± SD	96.4 ± 42.2	87.3 ± 45.3	.526
Elevated serum creatinine, n (%)	2 (15.3%)	15 (37.5%)	>.05
Histopathology			
No. of glomeruli, mean ± SD	19.0 ± 8.5	17.9 ± 10.2	>.05
No. of glomeruli with segmental to global collapse, mean ± SD	3.1 ± 2.3	4.3 ± 3.7	>.05
No. of glomeruli with global glomerulosclerosis, mean ± SD	1.9 ± 0.6	2.1 ± 1.2	>.05
Tubular atrophy, n (%)			
Mild, n (%)	9 (75.0)	24 (68.6)	>.05
Moderate, n (%)	3 (25.0)	11 (31.4)	
Fibrointimal thickening of arteries, n (%)	2 (15.4)	2 (5.0)	>.05
At last follow-up			
Duration of follow-up (months) (mean ± SD)	43.9 ± 24.6	34.7 ± 29.0	>.05
eGFR, mL/min/1.73 m^2, mean ± SD	64.9 ± 50.1	62.6 ± 44.8	.879
Total steroid dose (mg) (mean ± SD)	3707.7 ± 1063.3	4341.6 ± 2131.9	>.05
Steroid duration (weeks) (mean ± SD)	19.5 ± 10.9	23.3 ± 24.4	>.05
Kidney failure, n (%)	6 (46.2)	21 (52.5)	>.05
Kidney failure with replacement therapy, n (%)	2 (15.4)	8 (20)	>.05

BP, blood pressure; eGFR, estimated glomerular filtration rate; SD, standard deviation

(32.5%) were treated with steroids in combination with CsA. None of these responded to this combination therapy. Instead, their kidney functions started deteriorating; hence, therapy was discontinued.

Table 3 shows a comparison of important clinical, laboratory, and treatment variables between steroid-responsive and steroid-non-responsive groups at the presentation and on the last follow-up. It is apparent from this table that steroid-responsive and steroid-non-responsive groups have more or less similar parameters ($P > .05$). Pathological findings on kidney biopsies of 53 patients in the 2 groups are also shown in Table 3. This shows that the lesions were mild in most cases of cFSGS. The overall number of glomeruli with collapse was very low in both groups. The disease was, however, comparatively more severe in steroid-non-responsive patients.

Immunofluorescence study of all 58 cases showed segmental positivity of immunoglobulin M in 28 (48.3%) cases, C3 positivity in the same distribution in 21 (36.2%) cases, while the rest of the cases were negative for kidney-panel immune reactants.

Overall, progressive KF was observed in 37/53 (69.8%) patients. Among these, 27 (50.9%) patients developed KF, while 10 (18.8%) required replacement therapy (KFRT) on last follow-up. The median time to development of KF was 22 months (IQR = 6-33 months). Among steroid-responsive group, 8/13 (61.5%) patients developed progressive KF, whereas in steroid-unresponsive group, 29 (72.5%) developed progressive KF. Thus, steroid-responsive group also developed progressive KF in a significant number of cases. There was no statistically significant difference between the rates of progressive KF in both groups. Since none of the

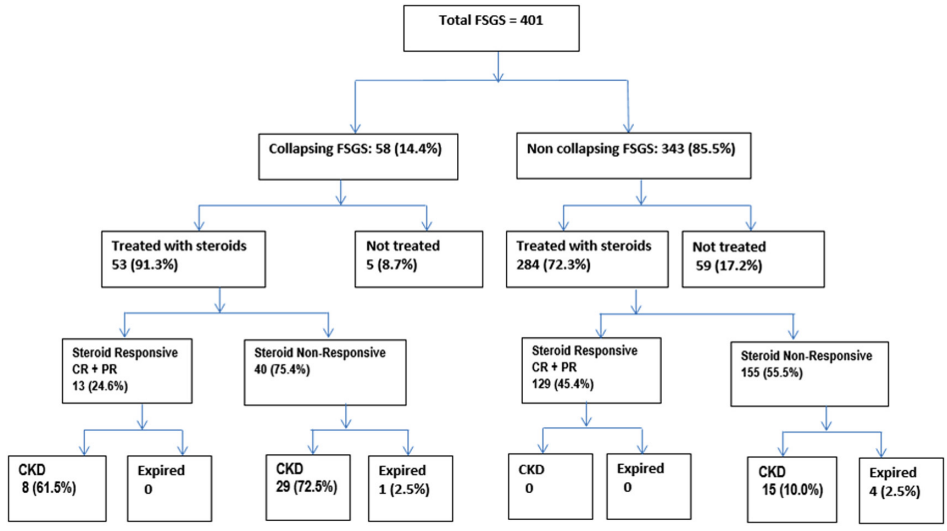

Figure 2. Flowchart showing the clinical course of adults with collapsing and non-collapsing FSGS. FSGS, focal segmental glomerulosclerosis.

parameters was significantly different between the 2 groups, multivariate analysis was not done.

A comparison of treatment responses and outcomes between cFSGS and non-cFSGS cohorts is shown in Figure 2. It is worthy of note that none of the steroid-responsive patients went into KF or KFRT in the non-cFSGS group. Even in steroid non-responders in the non-cFSGS group, the rate of development of progressive KF was 10%, which is markedly low as compared to the cFSGS cohort. Kidney survival rates were significantly poor in cFSGS cohort in comparison with non-cFSGS, as shown in Figure 3.

A comparison of some common clinical, pathological, therapeutic, and outcome parameters between cFSGS and 343 non-cFSGS patients is shown in Table 4. As is seen, among the clinical parameters, only diastolic BP showed a statistically significant difference between the 2 groups ($P = .043$). Among the pathological features, number of glomeruli with global glomerulosclerosis, segmental collapse, and moderate tubular atrophy were significantly more in the cFSGS cohort as compared to the non-cFSGS group ($P < .05$ in all). Similarly, the final outcome parameters were significantly worse in the cFSGS group as compared with the non-cFSGS group ($P < .05$ in all).

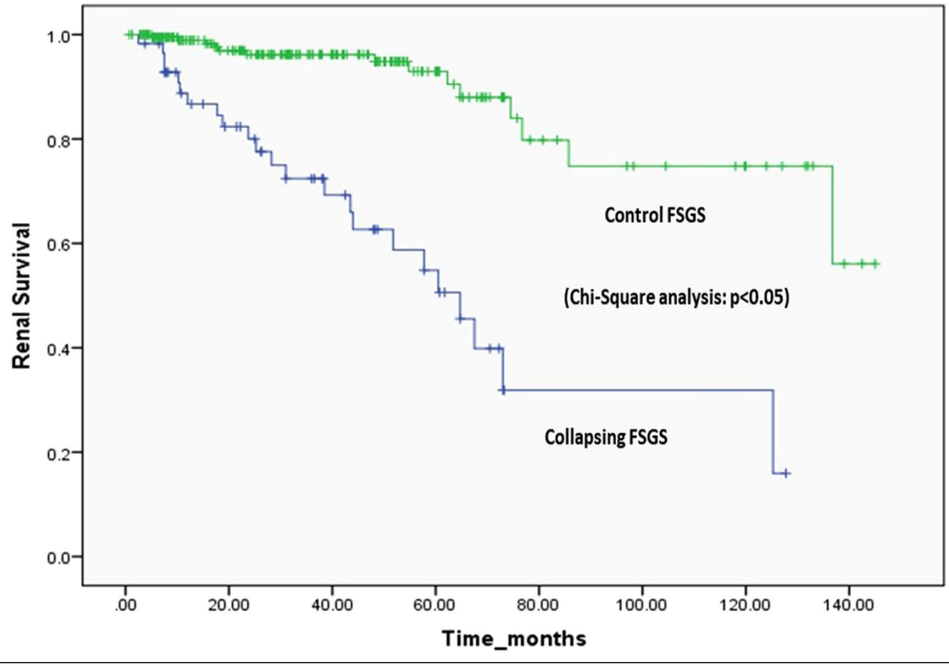

Figure 3. Comparison of kidney survival among collapsing and non-collapsing FSGS. FSGS, focal segmental glomerulosclerosis.

DISCUSSION

The present study is one of the largest longitudinal studies exclusively on cFSGS in the literature. This is, in fact, an extension with a continuing follow-up study of a previous study from our center, which reported preliminary data on medium-term outcomes of cFSGS in 10 patients.[15]

The presenting features of the current study cohort are almost in complete concordance with the results from our previous work and other studies from the region, including India.[15,18-24] Relatively young adult population is affected by this lesion in this region as compared with a mean age of around 44 years in Western studies.[18] The mean age was 26.9 years in an Indian prospective study on cFSGS on 22 patients.[19] The average age was 28 years in a Saudi study including 31 patients with 74% being adults.[20] Gender-wise distribution of the lesion was more or less comparable to previous studies, which is equal or only slightly skewed toward males.[9-14,18,19] Interestingly, in our previous report, only 1 of 10 patients was female.[15] Husain[20] also reported 65% of patients to be males in a Saudi study. The degree of proteinuria is comparatively low and massive proteinuria is very rare as classically reported in studies from the West. Raja et al[19] also found a similar level of proteinuria as in the present study. The reason for this is not completely understood but may be partly due to the poor nutritional status of the majority of our patients.[16] It is also well known that when serum albumin concentration is low, albumin excretion in urine may decline.[16] In addition, there is emerging evidence that a significant portion of filtered albumin is reabsorbed by the proximal tubular epithelial cells and catabolized by these cells; this results in an underestimation of measured urinary protein excretion than the actual leakage.[16] There is, however, a need for further research to determine the true causes of these discrepancies in clinicopathologic presentations of cFSGS in this region.

The other unique feature of this cohort is that the degree of KF at presentation was not severe. This is in contrast to classical studies on cFSGS, which often reported severe KF at the time of presentation.[9-12] Kidney failure was also more severe in the study by Raja et al.[19] However, Husain[20] found elevated serum creatinine in only 1 of 31 patients with cFSGS at the time of presentation. The frequency of KF was slightly higher in cFSGS patients (32.8%) compared to our overall FSGS cohort (24.4%).[17]

Table 4. A Comparison of Some Common Clinical, Pathological, Therapeutic, and Outcome Parameters Between 58 cFSGS and 343 Non-cFSGS Patients

Parameters	Non-cFSGS (n = 343)	cFSGS (n = 58)	*P*
Age (years), mean ± SD	28.9 ± 11.8	30.1 ± 12.4	.485
Systolic BP (mmHg), mean ± SD	128.4 ± 18.0	130.0 ± 18.9	.408
Diastolic BP (mmHg), mean ± SD	83.9 ± 12.1	87.6 ± 14.1	**.043**
Initial proteinuria (mg/24 h), median (IQR)	3700 (2281-6078)	3900 (2216-4800)	.509
Serum albumin (g/dL), mean ± SD	2.0 ± 1.2	2.1 ± 1.1	.648
Serum creatinine (mg/dL), mean ± SD	1.1 ± 0.9	1.4 ± 0.9	.513
Initial eGFR (ml/min/1.73 m^2), median (IQR)	85.4 (59.5-128.9)	69.1 (41.9-127.3)	.179
No. of glomeruli with global sclerosis, mean ± SD	2.1 ± 1.9	3.6 ± 2.5	**.001**
No. of glomeruli with segmental collapse, mean ± SD	2.5 ± 2.2	3.7 ± 3.3	**.031**
Tubular atrophy, mild, n (%)	146 (93.6)	35 (68.6)	**<.001**
Tubular atrophy, moderate, n (%)	10 (6.4)	16 (31.4)	
Follow up duration (months), mean ± SD	36.2 ± 29.2	37.0 ± 27.7	.841
Total steroid dose (mg), mean ± SD	4285.7 ±1933.2	4186.1 ± 1935.3	.733
Duration of steroid treatment (weeks), median (IQR)	18.5 (14-23)	17 (13.5-20.5)	.242
Total cyclosporine dose (mg), mean ± SD	27 998.2 ± 26 763.2	21 549.7 ± 1657.7	.323
Time to remission, median (IQR)	9 (4.3-14.0)	7.5 (2.0-7.5)	.532
Final proteinuria, median (IQR)	1700 (528.8-4425.0)	2590 (814.8-6659.0)	.617
Final eGFR (mL/min/1.73 m^2), median (IQR)	93.4 (60.4-129.3)	53.1 (15.3-93.4)	**<.001**
Kidney failure, n (%)	15 (4.3)	37 (63.7)	**<.001**
Kidney failure with replacement therapy, n (%)	5 (2.4)	13 (22.4)	**<.001**

BP, blood pressure; eGFR, estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range
Bold values indicate significant *P* value.

One possible reason for the milder presentation of the disease in this and other regional studies may be an early biopsy and a mild degree of pathological lesions on kidney biopsy. The median time from presentation to kidney biopsy was 2.5 weeks in this study. The median pre-biopsy duration was 2 months in an Indian study by Ahuja et al[21] Another Indian study by Kanodia et al[22] reported an average pre-biopsy duration of 34 days. Both glomerular and tubulointerstitial lesions were of milder degree and less extensive in this study. Similar to our study, Husain[20] reported milder lesions on pathological evaluation. The author also found serum creatinine to be within normal limits at the time of presentation. The pathological lesions were also milder in Indian studies.[19,21,22]

Regarding response to steroids, it was poor in this study, as reported in almost all previous studies on this disease.[9-12,14,18] Overall, remission was achieved in one-fourth of patients (24%) as compared to around 50% in the overall FSGS group and interestingly, PR was more common than CR. This is reflected in poor medium-term outcomes, which is understandable given the poor response to steroids. Raja et al[19] obtained complete remission in 13.6 % of cases and PR in an additional 4.5% of cases. In contrast, none of 26 patients treated with steroids alone responded in the study by Valeri et al[11] back in mid-90s. No remission was also obtained in a study of 31 patients with cFSGS from Saudi Arabia who received standard treatment with prednisolone.[20] However, on treatment with second-line immunosuppressants, 8 (26%) went into CR, 6 (19%) into PR, and 7 (23%) did not show any significant response.[20] Laurin et al[14] reported a 65.7% remission rate of proteinuria in cFSGS cases, and it was more or less similar to those of non-cFSGS patients. The overall kidney survival of patients with cFSGS was not poorer than that of patients with non-cFSGS in multivariate analyses after adjusting for baseline characteristics and immunotherapy in the later study.

Disease relapse was seen in nearly one-third of cases in the present study. However, these patients responded by PR to re-treatment with steroids in combination with CsA.

One more interesting finding of the present study is that patients showing steroid response also progressed to KF and KFRT, albeit at a lower rate as compared to steroid non-responders. This has important implications for medium- and long-term outcomes of these patients.[21,22] It also signifies that steroid responsiveness does not protect from the development of progressive KF in this disease. One of the possible factors may be an overall poor degree of response to steroids, as majority of responders achieved only PR. Complete remission was very rare in this cohort. More recently, rituximab has been used in cFSGS with favorable outcomes.[23,24]

The median time to progression to KF was 22 months in this study. Hussain[20] reported almost similar time duration (23 months) in 31 cases. This is shorter than time required to KFRT in classic FSGS.

The present study has certain limitations too. These include its retrospective design and single-center origin. We also did not perform genetic analysis in this cohort of patients for certain predisposing genetic variants, e.g., APOL1. We also did not treat our patients with rituximab, which has been shown to be effective in a number of case reports and small case series.

CONCLUSION

The results from this study show that cFSGS has a uniformly poor prognosis in adults despite treatment with steroids and calcineurin inhibitors. Steroid responsiveness does not completely protect from the development of progressive KF.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of SIUT (Approval no: SIUT-ERC-2019-PA-191, Date: November 7, 2019).

Informed Consent: Written informed consent was obtained from the patients/patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.J., F.A., M.M.; Design – N.J., F.A., M.M.; Supervision – F.A., M.M.; Resources – F.A., M.M.; Materials – N.J., A.S.K., F.A., M.M.; Data – N.J., A.S.K., M.M.; Analysis – N.J., F.A., M.M.; Literature search – A.S.K., M.M.; Writing – N.J., A.S.K., M.M.; Critical review – F.A., M.M., N.J., A.S.K.

Declaration of Interests: The authors have no conflict of interest to declare.

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REFERENCES

1. Shabaka A, Tato Ribera A, Fernández-Juárez G. Focal segmental glomerulosclerosis: state-of-the-art and clinical perspective. *Nephron*. 2020;144(9):413-427. [CrossRef]
2. Tsuchimoto A, Matsukuma Y, Ueki K, et al. Utility of Columbia classification in focal segmental glomerulosclerosis: renal prognosis and treatment response among the pathological variants. *Nephrol Dial Transplant*. 2020;35(7):1219-1227. [CrossRef]
3. Morales E, Alonso M, Gutiérrez E. Collapsing glomerulopathy: update. *Med Clin (Barc)*. 2019;152(9):361-367. [CrossRef]
4. Kukull B, Avasare RS, Smith KD, Houghton DC, Troxell ML, Andeen NK. Collapsing glomerulopathy in older adults. *Mod Pathol*. 2019;32(4):532-538. [CrossRef]
5. Buob D, Decambron M, Gnemmi V, et al. Collapsing glomerulopathy is common in the setting of thrombotic microangiopathy of the native kidney. *Kidney Int*. 2016;90(6):1321-1331. [CrossRef]
6. Moktefi A, Audard V, El Karoui K. Infections and collapsing glomerulopathy. *Am J Kidney Dis*. 2020;76(4):600-601. [CrossRef]
7. Chamarthi G, Clapp WL, Gopal S. Collapsing glomerulopathy in a patient with mixed connective tissue disease. *CEN Case Rep*. 2021;10(2):189-193. [CrossRef]
8. Gougeon F, Singh HK, Nickeleit V. Renal comorbidities in collapsing variant focal segmental glomerulosclerosis: more than a coincidence? *Nephrol Dial Transplant*. 2022;37(2):311-317. [CrossRef]

9. Weiss MA, Daquioag E, Margolin EG, Pollak VE. Nephrotic syndrome, progressive irreversible renal failure, and glomerular "collapse": a new clinicopathologic entity? *Am J Kidney Dis*. 1986;7(1):20-28. [CrossRef]
10. Detwiler RK, Falk RJ, Hogan SL, Jennette JC. Collapsing glomerulopathy: a clinically and pathologically distinct variant of focal segmental glomerulosclerosis. *Kidney Int*. 1994;45(5):1416-1424. [CrossRef]
11. Valeri A, Barisoni L, Appel GB, Seigle R, D'Agati V. Idiopathic collapsing focal segmental glomerulosclerosis: a clinicopathologic study. *Kidney Int*. 1996;50(5):1734-1746. [CrossRef]
12. Laurinavicius A, Hurwitz S, Rennke HG. Collapsing glomerulopathy in HIV and non-HIV patients: a clinicopathological and follow-up study. *Kidney Int*. 1999;56(6):2203-2213. [CrossRef]
13. Grcevska L, Polenakovik M. Collapsing glomerulopathy: clinical characteristics and follow-up. *Am J Kidney Dis*. 1999;33(4):652-657. [CrossRef]
14. Laurin LP, Gasim AM, Derebail VK, et al. Renal survival in patients with collapsing compared with not otherwise specified FSGS. *Clin J Am Soc Nephrol*. 2016;11(10):1752-1759. [CrossRef]
15. Mubarak M, Kazi JI. Collapsing FSGS: a clinicopathologic study of 10 cases from Pakistan. *Clin Exp Nephrol*. 2010;14(3):222-227. [CrossRef]
16. Jafry N, Ahmed E, Mubarak M, Kazi J, Akhter F. Raised serum creatinine at presentation does not adversely affect steroid response in primary focal segmental glomerulosclerosis in adults. *Nephrol Dial Transplant*. 2012;27(3):1101-1106. [CrossRef]
17. Jafry N, Mubarak M, Rauf A, Rasheed F, Ahmed E. Clinical course and long-term outcome of adults with primary focal segmental glomerulosclerosis: a retrospective cohort study. *Iran J Kidney Dis*. 2022;16(3):195-202.
18. Nicholas Cossey LN, Larsen CP, Liapis H. Collapsing glomerulopathy: a 30-year perspective and single, large center experience. *Clin Kidney J*. 2017;10(4):443-449. [CrossRef]
19. Raja R, Nada R, Yadav AK, et al. A prospective study of collapsing focal segmental glomerulosclerosis. *Ren Fail*. 2016;38(6):894-898. [CrossRef]
20. Husain S. Collapsing glomerulopathy, the Saudi Arabian scenario. A study of 31 cases and a review of literature. *Saudi Med J*. 2017;38(5):509-516. [CrossRef]
21. Ahuja A, Gupta R, Sharma A, et al. Idiopathic collapsing glomerulopathy: a clinicopathologic analysis of 30 cases. *Indian J Nephrol*. 2014;24(4):239-242. [CrossRef]
22. Kanodia KV, Vanikar AV, Patel RD, et al. Collapsing glomerulopathy: a single centre clinicopathologic study of seven years. *J Clin Diagn Res*. 2016;10(4):EC15-EC17. [CrossRef]
23. Ramachandran R, Rajakumar V, Duseja R, Sakhuja V, Jha V. Successful treatment of adult-onset collapsing focal segmental glomerulosclerosis with rituximab. *Clin Kidney J*. 2013;6(5):500-502. [CrossRef]
24. Girimaji N, Bharati J, Nada R, Rathi M, Kohli HS, Ramachandran R. Rituximab in treatment of collapsing FSGS-A case series. *Nephrology (Carlton)*. 2021;26(2):134-141. [CrossRef]