

Factors predicting for renal survival in primary focal segmental glomerulosclerosis

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SUMMARY

Background: In Peru, the incidence of primary focal segmental glomerulosclerosis (PFSGS) has considerably increased in the last decade and at the present; it is the first cause of primary glomerulonephritis in adults. Because of its prevalence and high probability to progress to end-stage renal disease (ESRD), we searched for factors with prognostic value for renal survival and proteinuria remission.

Subjects and methods: Historical cohort of 44 patients. We studied clinical and histological characteristics at the time of renal biopsy and clinical condition and renal function at the end of follow-up. **Principal outcomes:** renal impairment (increase \geq 50% of basal creatinine levels and/or ESRD), proteinuria remission (partial 0.3-3.49 g/day and complete $<$ 0.3 g/day). Kaplan-Meier's curves and Cox's Multivariate Regression were used.

Results: The 59% of patients were men. The 54.5% had renal failure, 53.5% nephrotic syndrome and 43.2% hypertension or high blood pressure (HBP) at renal biopsy. The frequency of histological variants was: not otherwise specified (NOS) 75%, cellular 13.6%, tip 6.8% and perihilar 4.5%. The 56.8% received steroids for 4.3 ± 4.5 months and 32% of these patients were corticoid-dependent. After a mean follow-up of 21.6 ± 27.8 months, the renal function decreased in 18.2% of patients. The 37.8% and 32.4% of patients reached partial and complete proteinuria remission respectively. Treatment with steroids, antihypertensive therapy and IgM and C3 glomerular deposits were associated with a high renal survival. The treatment with steroids was the only factor that forecasted a high renal survival (hazard ratio or HR: 0.07, 0.01-0.9) and proteinuria remission (HR: 0.2, 0.04-0.9). In general, high blood pressure (HR: 6.2, 1.1-35.2), renal failure (HR: 2.9, 1.1-7.6), cellular variant and interstitial fibrosis (HR: 5.2, 1.02-26.7) were prognostic factors for not achieving proteinuria remission.

Conclusions: In primary focal segmental glomerulosclerosis, treatment with steroids forecasted a high renal survival and proteinuria remission. Renal failure and interstitial fibrosis were prognostic factors for not achieving proteinuria remission.

Key words: Focal segmental glomerulosclerosis. Nephrotic syndrome. Renal failure. Renal survival.

RESUMEN

Introducción: En Perú la incidencia de glomeruloesclerosis focal y segmentaria primaria ha aumentado considerablemente durante la última década y actualmente es la primera causa de glomerulonefritis primaria en adultos. Por su prevalencia y alta probabilidad de progresar a insuficiencia renal crónica terminal, se buscaron factores con valor pronóstico para supervivencia renal y remisión de proteinuria.

Pacientes y métodos: Cohorte histórica de 44 pacientes. Estudiamos las características clínicas e histológicas al momento de la biopsia renal y la función renal al seguimiento. \geq Los desenlaces principales fueron: deterioro renal (incremento de creatinina 50% y/o insuficiencia renal terminal) y remisión de proteinuria (parcial 0,3-3,49 g/día y completa $<$ 0,3 g/día). Se usaron curvas de Kaplan-Meier y regresión multivariable de Cox.

Resultados: El 59% de los pacientes fueron varones. El 54,5% presentó insuficiencia renal, 53,5% síndrome nefrótico y 43,2% hipertensión arterial al momento de la biopsia. Los tipos histológicos fueron: no especificado 75%, celular 13,6%, tip 6,8% e hilar 4,5%. El 56,8% recibió esteroides por $6,2 \pm 4,1$ meses y el 32% fue corticoid-dependiente. La función renal empeoró en el 18,2%. El 37,8% logró remisión parcial y 32,4% remisión completa de proteinuria. El tratamiento con esteroides, con antihipertensivos y los depósitos glomerulares de IgM y C3 se asociaron a mayor supervivencia renal. El tratamiento con esteroides fue el único factor que predijo independientemente, mayor supervivencia renal (hazard ratio o HR: 0,07, 0,01-0,9) y remisión de proteinuria (HR 0,2, 0,04-0,9). La hipertensión arterial (HR: 6,2, 1,1-35,2), la insuficiencia renal (HR: 2,9, 1,1-7,6), la variante celular y la fibrosis intersticial (HR: 5,2, 1,02-26,7) fueron indicadores de pobre remisión de proteinuria.

Conclusiones: En glomeruloesclerosis focal y segmentaria primaria, el tratamiento con esteroides determinó mayor supervivencia renal y mayor probabilidad de remisión de proteinuria. La presencia de insuficiencia renal y fibrosis intersticial determinaron no remisión de proteinuria.

Palabras clave: Glomeruloesclerosis focal y segmentaria. Síndrome nefrótico. Insuficiencia renal. Supervivencia renal.

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a clinical and pathological syndrome characterized by proteinuria and segmental sclerosis of some glomeruli, with fusion of podocyte

Table I. Clinical characteristics at biopsy and follow-up

Baseline characteristics	Mean + SD (range) or % (n)		
Age (years)	37.2 ± 15.8 (15-73)		
Male sex	59.1% (26)		
Disease duration (months)	13.6 ± 35.9 (1-216)		
Follow-up time (months)	21.6 ± 27.8 (1-123)		
Arterial hypertension	43.2% (19)		
Anemia	34.9% (15)		
Hemoglobin (g/dL)	13.3 ± 2.4 (7.7-17.1)		
Hypoalbuminemia	77.3% (34)		
Serum albumin (g/L)	2.1 ± 0.8 (0.9-4.8)		
Hypercholesterolemia	75.0% (33)		
Total cholesterol (mg/dL)	462.3 ± 217.2 (160-1,275)		
Nephrotic syndrome	54.5% (24)		
Creatinine clearance (mL/min/1.73 m ² BSA)	56.1 ± 23.7 (13.2-104.6)		
Renal failure	54.5% (24)		
Casts and/or WBCs in urine without infection	54.5% (24)		
Renal parameters	Renal biopsy	Follow-up	p ¹
Arterial hypertension	43.2% (19)	13.6% (6)	0.002
Systolic blood pressure (mmHg)	123.8 ± 23 (80-200)	115.8 ± 16 (80-150)	> 0.10
Diastolic blood pressure (mmHg)	77.4 ± 13 (60-120)	73.0 ± 12 (40-100)	0.078
Creatinine (mg/dL)	1.8 ± 1.2 (0.6-6.8)	1.7 ± 1.7 (0.6-9.0)	0.025
Proteinuria 24 h (g)	4.8 ± 3.2 (0.2-13.6)	2.0 ± 2.6 (0.03-8.9)	0.001
Nephrotic proteinuria	53.5% (23)	25.0% (11)	0.001
Main clinical outcomes	n (%)		
• <i>Proteinuria remission</i> ²			
– Complete (less than 300 mg/day)	12 (32.4)		
– Partial (300 mg/day - 3.49 g/day)	14 (37.8)		
– No remission (≥ 3.5 g/day)	11 (29.7)		
• <i>Renal impairment</i>	8 (18.2)		
– ESRD ³ no dialysis	7 (15.9)		
– Dialysis	1 (2.3)		

¹Calculated using a non-parametric Wilcoxon test for two related samples.

²The total number of patients analyzed was 37 because 7 patients had no quantitative proteinuria at the end of follow-up.

³ESRD: end-stage renal disease.

processes. Obliteration of glomeruli by cell proliferation or accumulation of extracellular collagen matrix may occur.¹ FSGS is classified as primary in the absence of an underlying disease. Clinical signs of FSGS are variable, but most patients have proteinuria in the nephrotic range, arterial hypertension (AHT), and some grade of kidney function impairment.² Primary FSGS has a variable prognosis depending on the ethnic, clinical, and histopathological characteristics, treatment scheme, treatment response, and the different observation periods. There is however agreement in that patients with the collapsing and cellular histological variants have a poorer prognosis and experience a relatively rapid kidney function impairment.³⁻⁶ Clinically, it is estimated that 50% of patients with persistent proteinuria in the nephrotic range will progress to end-stage renal disease (ESRD) within 5-10 years. Untreated patients have a poor prognosis, reaching the end stage within 3-6 years.^{7,8}

An increasing incidence of primary FSGS has been reported in several countries. In the United States, FSGS is the most common cause of nephrotic syndrome and ESRD in black and white adults with primary glomerulonephritis.⁹⁻¹¹ A similar trend has been noted in Latin America.¹²⁻¹⁴ In Peru, FSGS has displaced membranoproliferative glomerulonephritis as the most common primary glomerulonephritis.^{15,16} Ho-

wever, recent European studies do not show this trend. Thus, in Spain, the glomerulonephritis registry of the SEN¹⁷ showed no changes in incidence between 1994 and 2005. Similarly, Cameron¹⁸ found no differences in London in the 1970-2000, during which the incidence rate remained at 20%. In Italy,¹⁹ incidence changed from 11.7% to 10.4% from 1987 to 1993.

Few studies have been conducted in Peru on primary FSGS, and because of its epidemiological significance and its risk of progressing to ESRD, a search was made for clinical and histological factors having a prognostic value in the evolution of kidney function and that would allow for implementing a rational and appropriate therapeutic approach based on current evidence.

PATIENTS AND METHODS

Study design and population

A longitudinal, retrospective study was conducted on a historical cohort of patients diagnosed with primary FSGS based on a kidney biopsy who attended the department of nephrology of Hospital Nacional Arzobispo Loayza from January 1994 to December 2004. Medical records and pathology reports of patients were reviewed, and their demographic, clinical, labo-

Table II. Histopathological characteristics in 44 patients with primary FSGS

Histological classification	n (%)
– Hilar lesion	2 (4.5)
– Tip lesion	3 (6.8)
– Cellular lesion	6 (13.6)
– Classical lesion (NOS)	33 (75.0)
– Collapsing lesion	0 (0.0)
Glomerular involvement	Mean ± SD (range)
No. of glomeruli per biopsy	23.9 ± 27.9 (8-160)
Percent glomerular sclerosis	23.7 ± 22.3 (1-100)
No. of glomeruli affected per biopsy	4.0 ± 4.3 (1-21)
No. of glomeruli with segmental sclerosis per biopsy	2.5 ± 2.7 (0-17)
No. of glomeruli with global sclerosis per biopsy	1.5 ± 2.7 (0-15)
Mesangial involvement	n (%)
Mesangial hypercellularity	8 (18.2)
Tubulointerstitial involvement	
• <i>Tubular atrophy (TA)</i>	20 (45.5)
– No TA	24 (54.5)
– Mild to moderate TA	16 (36.4)
– Severe TA	4 (9.1)
• <i>Interstitial fibrosis (IF)</i>	7 (15.9)
– No IF	37 (84.1)
– Mild to moderate IF	4 (9.1)
– Severe IF	3 (6.8)
Vascular involvement: Atherosclerosis	7 (15.9)
Immunofluorescence	
– IgG deposits	7 (15.9)
– IgM deposits	25 (56.8)
– IgA deposits	3 (6.8)
– C3 deposits	21 (47.7)

ratory, and histological data were recorded at the time of kidney biopsy. Among 64 patients with a histological diagnosis of FSGS, 51 patients had primary FSGS. Clinical follow-up and home visit were performed in 44 patients (86.3%), while the remaining 7 patients moved and could not be located. These 44 patients formed the final analysis sample. Patients older than 15 years with a diagnosis of primary FSGS, a renal biopsy sample with 8 or more glomeruli, and light microscopy and immunofluorescence studies were enrolled into the study. Patients with concomitant nephropathy, obesity (BMI \geq 30 kg/m², based on dry weight), refusal to participate in the study in the follow-up phase and/or the home visit, incomplete data in medical records, impossibility to review the pathology slide, or admitted to chronic dialysis immediately after the renal biopsy were excluded from the study.

Renal biopsy and classification of primary FSGS

Histological diagnosis of FSGS was done at the department of pathology of Hospital Nacional Guillermo Almenara Irgoyen. Fifty-six biopsies, taken using a percutaneous or surgical procedure, transported on PBS (phosphate buffer solution), and sent to such department were studied. Twelve 3 to 5 μ m-thick sections were obtained on average from each sample and processed using conventional light microscopy and im-

munofluorescence techniques. Stains used included hematoxylin-eosin (H-E), periodic acid-Schiff (PAS), Masson's trichromic, and methenamine silver.

For the immunofluorescence study, the tissue was frozen at -40 °C, cut in 5 μ m sections in a cryostat, and incubated with fluorescein-labelled anti-IgG, anti-IgM, anti-IgA, and anti-C3 antibodies.

Slides were re-evaluated by a pathologist blinded to the clinical history, the initial report of renal biopsy, and the current patient status. Characteristics of the Columbia classification were taken into account.¹

FSGS was defined as a glomerular lesion characterized by sclerotic areas located in glomerular segments and involving less than 50% of all glomeruli, in which IgM and C3 deposits are usually seen by immunofluorescence. *Mesangial hypercellularity* was defined as the presence of 3 or more cells in a mesangial segment. Histological variants were classified as: *hyaline-perihilar variant* if perihilar sclerosis and hyalinosis were found involving more than 50% of glomeruli with segmental sclerosis, excluding the cellular, tip, and collapsing variants; *cellular* if there was at least one glomerulus with endocapillary segmental hypercellularity occluding the lumen, with or without foam cells and karyorrhexis, excluding the tip and collapsing variants; *tip variant* if there was at least one segmental lesion in 25% of the tuft close to the proximal tubule origin, with adhesion or confluence of podocytes with parietal or tubular cells in the tubular lumen or neck, excluding the collapsing variant and any perihilar sclerosis; *collapsing variant* when there was at least one glomerulus with segmental or global collapse and podocyte hypertrophy and hyperplasia; and *classical or not otherwise specified (NOS) variant* if at least one glomerulus had segmental increase in the mesangial matrix obliterating the capillary lumens, excluding all other variants. *Tubular atrophy* was defined as a decreased tubular size with thickening of basement membrane. Atrophy was defined as mild (< 25%), moderate (25%-50%), and severe (> 50%). *Interstitial fibrosis* was defined as the presence of fibroblasts and collagen in interstitium. Fibrosis was defined as mild (< 25%), moderate (25%-50%), and severe (> 50%). *Arteriosclerosis* was defined as the presence of subintimal sclerosis.

Clinical definitions

Disease duration: from the occurrence of symptoms attributable to kidney disease to performance of biopsy. Follow-up time: from renal biopsy to the last control (nephrology outpatient clinic or home visit) AHT: systolic blood pressure \geq 40 mmHg and/or diastolic blood pressure \geq 90 mmHg or use of antihypertensives. Anemia: hemoglobin values less than 12 g/dL. Renal failure: serum creatinine > 1.2 mg/dL in females and > 1.4 mg/dL in males in repeated measurements. Hypoalbuminemia: serum albumin < 3.5 mg/dL. Hypercholesterolemia: serum total cholesterol levels > 200 mg/dL. Twenty-four hour proteinuria was characterized as: non significant < 0.3 g/day, significant from 0.3 and 3.49 g/day, in nephrotic range \geq 3.5 g/day. Nephrotic syndrome: nephrotic persistent proteinuria, hypoalbuminemia, and edema. Primary FSGS: typical lesions of focal segmental glomerulosclerosis in the

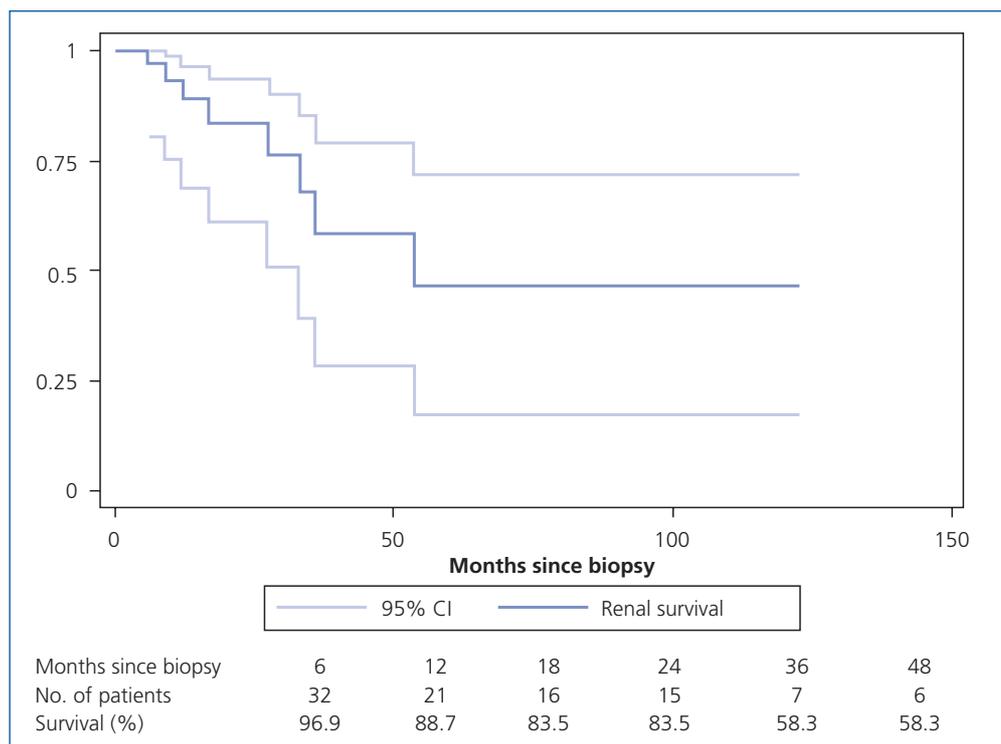


Figure 1. Renal survival in 44 patients with primary FSGS.

absence of known causes (anatomic, obesity, viral, drugs, immune).

Clinical outcomes

Complete proteinuria remission: decrease from baseline proteinuria to less than 0.3 g/day; *partial proteinuria remission:* decrease from baseline proteinuria to values ranging from 0.3 and 3.49 g/day; *renal function impairment:* ≥ 50% increase in baseline creatinine and/or development of ESRD and/or admission to a chronic dialysis program in last check-up; *renal survival:* probability of not experiencing renal function impairment at a given time since renal autopsy (expressed as percentage).

Statistical analysis

Categorical demographic, clinical, and histological variables were given as frequencies or proportions (%) and were evaluated using a Chi-square test or a Fisher’s exact test when required. Continuous variables were described as mean ± standard deviation and were evaluated using a non-parametric Mann-Whitney’s U test or a Wilcoxon test for 2 groups, and with a Kruskal-Wallis test (or a median test as appropriate) for 3 or more groups.

For time-dependent variables and estimates of renal survival and proteinuria remission, Kaplan-Meier curves and the Nelson-Aalen cumulative hazard function were used respectively. A non-parametric log-rank test was used to compared survival curves between the groups in the univariate analysis.

To independently establish the prognostic value in the studied factors and to adjust for study confounding variables, a

Cox multivariate regression was performed among variables with a significant (p < 0.05) or marginal value (0.05 < p < 0.1) in the univariate analysis and/or taking into account variables not having statistical association but having a biological basis or clinical relevance for the tested outcomes. Effect size in the multivariate analysis was measured using the hazard ratio (HR) and its 95% confidence intervals. All values of p < 0.05 were considered statistically significant. Stata version 8 software for Windows (Stata Corporation, Texas-USA; <http://www.stata.com>).

RESULTS

Clinical characteristics at baseline and follow-up

Forty-four patients with primary FSGS were evaluated. Male/female ratio was 1.4. AHT was found in 19 patients (43.2%), and renal failure and nephrotic syndrome in 24 patients (54.5%). These percentages and the mean values of serum creatinine level and 24-hour proteinuria significantly changed at the end of follow-up (see table I).

Histological characteristics

The main characteristics are shown in table II. The most common histological variants were NOS (34 patients, 74.3%) and the cellular variant (6 patients, 13.6%). No patient had the collapsing variant. The cellular (n = 6) and hilar variants showed a greater proportion of sclerotic glomeruli per biopsy (57.1% and 34.7% respectively) and a higher total number of glomeruli involved (6.2 ± 5.7 and 19.0 ± 2.8 respectively), with a statistically significant difference from all other lesions (p < 0.001).

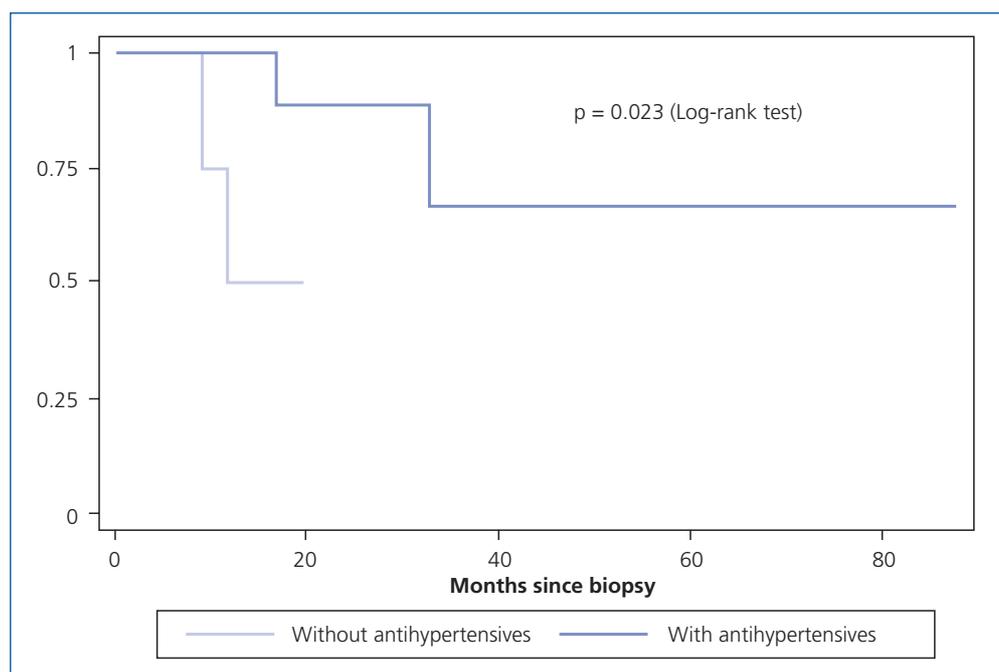


Figure 2. Renal survival by antihypertensive treatment.

Treatment of primary FSGS

Twenty-five patients (56.8%) were treated with steroids at a dose of 1 mg/kg/day for a period of 3-4 months with subsequent tapering. Mean treatment time was 6.2 ± 4.1 months, and 8 (32%) of these patients developed corticosteroid dependence. Six patients (13.6%) were treated with cyclophosphamide. All other patients did not comply with steroid treatment for economic reasons or non-adherence. Adverse effects occurred in 52% of patients. Most common adverse effects included Cushingoid face, pyrosis, and acne.

Twenty-five patients (56.8%) received antihypertensive treatment, 20 of them (80%) angiotensin converting enzyme inhibitors (ACEIs).

Renal prognosis and survival in primary FSGS

After a follow-up time of 21.6 ± 27.8 months, eight patients (18.2%) experienced renal function impairment (table I). Six of these patients (13.6%) died, five from ESRD with no chance of access a chronic dialysis program and one from cirrhosis of the liver.

Renal survival was 96.9% at 6 months, 88.7% at 12 months, and 46.7% at 5 years of follow-up (fig. 1). In the univariate analysis, factors associated to a better renal survival were: classical or NOS lesion ($p = 0.05$), glomerular deposits of IgM ($p = 0.002$) and C3 ($p = 0.01$), antihypertensive treatment ($p = 0.023$, fig. 2), and steroid treatment ($p = 0.004$, fig. 3). The presence of tip lesion ($p = 0.004$) and tubular atrophy ($0.05 < p < 0.1$) resulted in a poorer renal survival. When these variables were analyzed using a Cox multivariate regression including the presence of AHT, renal failure at the time of biopsy, treatment with steroids and antihypertensives, steroid therapy was the only factor with independent prognostic value resulting in an improved renal survival (HR: 0.073, 95% CI:

0.006-0.899, $p = 0.041$) (table IV). The small patient sample did not allow for analyzing renal survival by simultaneously comparing all histological variants, but there a marginal association was seen between frequency of renal impairment and variants (cellular 0.0%, NOS 15.2%, perihilar 50.0%, tip 66.7%, $p = 0.054$ by a Chi-square test).

As regards proteinuria, the cumulative probabilities of partial and/or complete remission were 15.4% at 6 months, 30.8% at 12 months, and 76.7% at 5 years of follow-up. When remission over time was expressed as cumulative risk (remission hazard), this was seen to increase from 0.16 at 6 months to 0.35 at 12 months and 1.37 at 5 years of follow-up (fig. 4). The most marked increase was achieved in the first year, particularly in the first six months of steroid treatment (see table below fig. 4). Patients treated with steroids ($n = 25$) who achieved proteinuria remission ($n = 19$) showed less clinical and histological severity at renal biopsy as compared to the treated group achieving no remission ($n = 6$). They also had lower creatinine levels (non-significant difference) at follow-up (table III). Similar results were seen in the group not treated with steroids ($n = 12$, data not shown). A survival analysis of all patients with primary FSGS showed renal failure ($p = 0.07$) and the cellular histological variant ($p = 0.0099$) to be associated with less proteinuria remission, while steroid treatment ($p = 0.034$) resulted in greater proteinuria remission. When the treated group was analyzed, 76% had achieved remission of proteinuria (partial and/or complete), as compared to 37.5% of untreated patients ($p = 0.044$ by a Chi-square test). In the Cox multivariate regression model, independent factors predicting for no proteinuria remission included AHT ($p = 0.04$) and the cellular histological variant ($p < 0.00001$), while in that same model, the finding of mesangial hyperplasia in the biopsy ($p < 0.0001$) and steroid treatment ($p = 0.035$) predicted for proteinuria remission. Renal

Table III. Clinical characteristics of patients with primary FSGS treated with steroids depending on proteinuria remission

Variable	Total cohort (n = 44)	Steroid-treated group (n = 25)			p
		No remission (n = 6)	Partial remission (n = 11)	Complete remission (n = 8)	
Baseline creatinine (mg/dL) ¹	1.8 ± 1.2	1.9 ± 1.3	1.9 ± 1.1	1.1 ± 0.4	0.050
Creatinine clearance (mL/min) ¹	56.1 ± 23.7	41.0 ± 21.0	49.6 ± 25.3	74.4 ± 23.0	0.028
Renal failure ³	54.5%	66.7%	63.4%	25.0%	>0.10
Baseline proteinuria (g/24 h)	4.8 ± 3.2	4.5 ± 3.2	5.3 ± 2.4	6.8 ± 4.8	> 0.10
No. of glomeruli affected/biopsy ²	4.0 ± 4.3	5.5 ± 5.4	3.9 ± 4.5	3.0 ± 3.0	> 0.10
No. of glomeruli with global sclerosis ²	2.5 ± 2.7	2.7 ± 3.3	0.4 ± 0.5	1.1 ± 1.7	0.044
Glomerular C3 deposit ³	47.7%	16.7%	72.7%	62.5%	0.076
Baseline arterial hypertension ³	43.2%	66.7%	54.5%	37.5%	> 0.10
Final arterial hypertension ³	13.6%	50.0%	9.1%	12.5%	> 0.10
Final systolic pressure ¹	115.8 ± 16.0	133.3 ± 13.7	109.1 ± 13.0	120.6 ± 17.4	0.014
Final creatinine (mg/dL) ¹	1.7 ± 1.7	1.6 ± 0.6	1.5 ± 1.0	1.0 ± 0.4	0.09
Change in proteinuria ¹	-2.7 ± 4.4	+2.5 ± 4.2	-3.8 ± 2.6	-6.7 ± 4.8	0.007

¹A Kruskal-Wallis test was used for K groups with parametric distribution. ²A median test was used for K groups with parametric distribution, marginal significance 0.05 < p < 0.10. ³Calculated by Chi-square test.

failure and interstitial fibrosis were statistically significant poor prognostic factors for complete proteinuria remission (see table IV).

DISCUSSION

Incidence of primary FSGS has substantially increased in Peru in the past decade, and FSGS is currently the leading cause of primary glomerulonephritis in adults.^{15,16} This trend, also reported in the United States and other Latin American countries, has not been seen in Europe, maybe because of ethnic factors (predominance of a white population in Europe).^{12-14,17-19} The clinical relevance and costs for the health system of this condition are significant. A search was therefore made for factors predicting for remission of proteinuria and renal survival in this group of patients. Clinical data such as age, disease duration at the time of biopsy, and high frequency of AHT, renal

failure, and nephrotic syndrome agreed with those reported in other studies.^{4,7,11,12} The most common histological variant was NOS, as reported by D'Agati,¹ and the collapsing variant was not found.

Remission of proteinuria was seen throughout the follow-up period, but was more marked in the first six months, similar to reports in other studies where this outcome was achieved within 6 months of steroid treatment.²⁰ Korbet pointed out that proteinuria remission significantly improves renal survival,¹² but unfortunately, spontaneous decreases in proteinuria are rare in FSGS, and response to immunosuppressive treatment has been historically poor.¹¹ Recent experience with more aggressive immunosuppressive agents has increase the remission rate and is expected to improve prognosis of this glomerular disease.¹³ In this study, arterial hypertension and the cellular variant were found to be poor prognostic factors for remission.

Table IV. Factors with prognostic value in primary FSGS by Cox regression

Main outcome	HR (95% CI)	p
<i>Proteinuria remission (partial and/or complete)</i>		
- Arterial hypertension	6.2 (1.09-35.21)	0.04
- Renal failure	3.0 (0.57-16.39)	0.194
- Mesangial hypercellularity	0.000259 (0.000173-0.000369)	< 0.0001
- Cellular variant	12.964.9 (> 22.026.5)	< 0.00001
- Steroid treatment	0.2 (0.04-0.89)	0.035
- Antihypertensive treatment	0.5 (0.09-2.49)	0.383
<i>Complete proteinuria remission</i>		
- Arterial hypertension	1.9 (0.71-5.04)	0.204
- Renal failure	2.9 (1.07-7.64)	0.037
- Interstitial fibrosis	5.2 (1.02-26.72)	0.048
- Steroid treatment	0.5 (0.16-1.38)	0.170
<i>Renal impairment</i>		
- Renal failure	0.51 (0.01-21.52)	0.725
- Steroid treatment	0.07 (0.01-0.9)	0.041
- Antihypertensive treatment	0.06 (0.001-4.05)	0.193

¹HR: Hazard Ratio, 95% CI: 95% confidence interval. A HR > 1 is a poor prognostic factor and HR < 1 is a good prognostic factor for the outcome assessed.

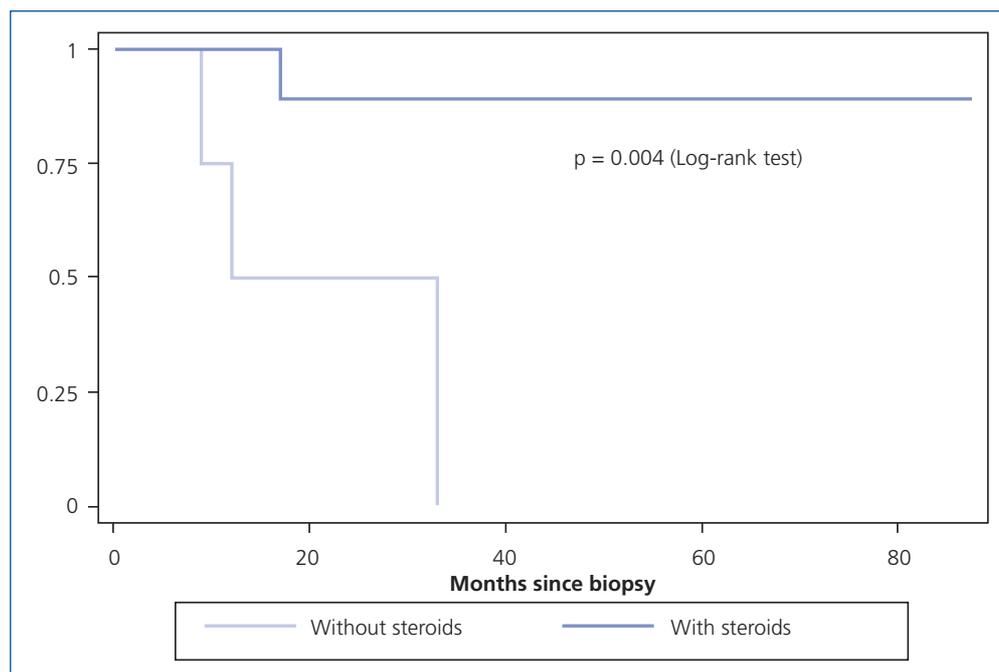


Figure 3. Renal survival by steroid treatment.

Steroid treatment is recommended in this condition as one of the initial measures.^{6-8,20,22-24} As expected, steroid therapy was associated in our series to a greater proteinuria remission, that was more frequent in patients having better baseline kidney function and less AHT. By contrast, renal failure and interstitial fibrosis, indicating more advanced kidney disease, were independent predictors for no remission in proteinuria.

Among our patients, 43.2% did not received steroids for economic reasons and/or early discontinuation of immunosuppressive treatment, but they were given antihypertensive and antiproteinuric treatment with ACEIs. A recently published study by Thomas, conducted on a cohort of 282 patients followed up from 1982 to 2001, found that treatment with ACEIs or angiotensin receptor blockers was not associated with remission of nephrotic syndrome, unlike steroid use, that did result in complete remission in 30% of patients.²⁵

Renal survival 5 years after biopsy was less than 50%, in agreement with reports by Korbet, who stated that nephrotic patients with primary FSGS have a 50% probability of progressing to end-stage renal disease during the first 3 to 8 years,¹¹ similar results are shown by Detwiler⁴ and Valeri.⁵ Renal survival was higher in patients given steroids, and steroid treatment was the only independent factor predicting for higher renal survival. This was also reported by Chun et al in a series of 87 nephrotic patients in which 47% of untreated patients reached the ESRD stage, as compared to 24% of steroid-treated patients.²² This finding was also reported by other authors such as Matalon, Appel, and Korbet.^{23,24} Korbet, Schwartz, and Lewis⁸ reported that nephrotic patients responding to steroids had a better course and did not progress to end-stage renal disease. Eddie also found that the most important prognostic marked in nephrotic syndrome in children was steroid response.²⁶ In the Tho-

mas study, steroid therapy was not associated to an improved renal survival, but this study included Afro-American patients and up to 11% of all patients had the collapsing variety, that marks a poor steroid response from the start.

Antihypertensive treatment was not associated to a higher renal survival. A similar finding was made by Burguess,²⁰ who reported that AHT was not a consistent prognostic marker of renal impairment.

The tip lesion showed a poorer renal survival as compared to all other histological variants together. This is striking because most series consider that this lesion has a more favorable prognosis, similar to minimal change nephropathy.²⁷ This finding is similar to that reported by Thomas, who did not find in his series a better survival for the tip lesion as compared to all other categories evaluated, except for the collapsing variant, which was shown to have a poorer prognosis.²³

Limitations of this study include its retrospective character and the fact that more than 10% of patients with primary FSGS could not be followed up and their outcome was therefore unknown. However, this is the first study conducted in Peru on a cohort of patients at a high risk for progression to ESRD.

In our primary FSGS series, steroid treatment was found to be a prognostic factor for in a higher renal survival and a greater probability of proteinuria remission. High blood pressure, renal failure, cellular variant, and interstitial fibrosis were factors leading to a poor proteinuria remission. These important findings will serve us to conduct adequate follow-up and clinical trials and to better understand the highly variable behavior of this complex disease.

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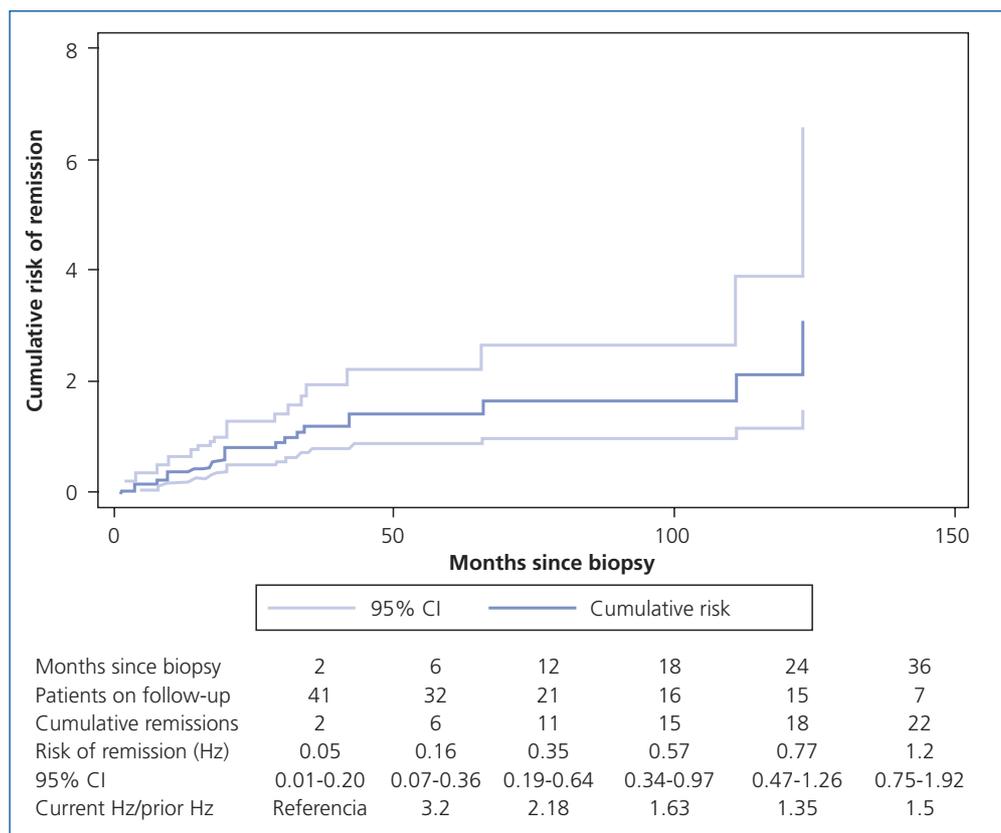


Figure 4. Proteinuria remission in primary FSGS.

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