IJKD KIDNEY DISEASES

Kidney Outcome in Primary Focal Segmental Glomerulosclerosis (FSGS) by Using a Predictive Model

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Original Paper

Introduction. Focal segmental glomerulosclerosis (FSGS) is one of the important causes of end stage kidney disease (ESKD). We evaluated the progression risk factors of primary FSGS to chronic kidney disease (CKD) or ESKD with a predictive model including clinical and histological predictors.

Methods. 201 patients with primary FSGS (59% male, mean age: 38 ± 15 years), were studied. Time-dependent Cox model and C statistics were used for the predictive model. Interaction and correlation between independent variables were estimated.

Results. During 55 ± 27 months of follow-up, 82 patients (41%) developed CKD (46) or ESKD (36) patients. In adjusted model, 1 unit of higher serum creatinine (SCr) at baseline (HR = 1.39, 95% CI: 1.15 to 1.70) and 1% increase in glomeruli with segmental glomerulosclerosis (SGS) (HR = 1.03, 95% CI: 1.02 to 1.04) or interstitial fibrosis/tubular atrophy (IF/TA) (HR = 1.03, 95% CI: 1.01 to 1.05) increased the risk of CKD/ESKD. In adjusted model, higher baseline proteinuria and collapsing variant were not associated with risk of CKD/ESKD. By adding SGS and IF/TA scores to baseline SCr in the model, discrimination by C statistics was 0.83 (95% CI: 0.77 to 0.90). Median renal survival was 3.1 years (95% CI: 2.2 to 4.1 years) in patients with highest risk score (baseline eGFR < 25 mL/min/1.73m^2 + IF/TA/SGS > 50%), and 8.1 years (95% CI: 7.7 to 8.6 years).in those with lowest score (baseline eGFR > 75 mL/min/1.73m^2 + IF/TA/SGS < 5%).

Conclusion. In primary FSGS, higher baseline SCr, increased SGS and IF/TA, but not baseline proteinuria and collapsing pathology, were the predictors for CKD/ESKD. These findings indicated the importance of timely detection and referral in prognosis of primary FSGS.

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INTRODUCTION

Idiopathic or primary focal segmental glomerulosclerosis (FSGS) is a syndrome with proteinuria, mostly nephrotic range, focal and segmental glomerular sclerosis lesions and foot process effacement.[1-4] FSGS is known as a one of the leading glomerular causes of end stage kidney disease (ESKD) in most parts of the world.[5-7] In a recent report by our group the prevalence of FSGS rose to second rank among primary glomerular diseases.[8] However, in reports from many countries FSGS is the most common glomerulopathy

diagnosed by kidney biopsy.[9,10] In patients with primary FSGS response to treatment or progression to chronic kidney disease (CKD) are very diverse and it has been reported that more than half of the patients progressed to ESKD after 10 years of follow-up.[7]

Columbia morphologic classification, which was defined in 2004, is the most popular method of classification of FSGS, and classifies FSGS to five pathologic variants including collapsing, cellular, tip lesion, perihilar and not otherwise specified (NOS).[1] It has been suggested that the histologic subtypes of FSGS correlate with remission and renal outcome.[11,12]

Identifying the risk factors that predict the progression of primary FSGS to CKD/ESKD could enable appropriate patient care and improved individualized decision-making. The aim of this study was to develop a model of prediction of CKD/ ESKD (dialysis or kidney transplantation) in patients with primary FSGS by baseline clinical, laboratory and pathological findings as predictors.

MATERIALS AND METHODS

In this retrospective cohort study, the baseline clinical and laboratory data and the last proteinuria and serum creatinine of 356 patients with FSGS, who had been biopsied between 2005 and 2014 was extracted from the glomerulonephritis database of our hospital. The mean follow-up was 55 ± 27 months. The exclusion criteria were urinary reflux, single kidney, substance abuse, HIV disease, sickle cell anemia, morbid obesity and other serious systemic diseases that would have caused secondary FSGS and age of less than 16 years old at the time of disease onset. Of 356 patients with diagnosis of FSGS, 78 patients were excluded from the study because of secondary disease, 77 were excluded because of information deficit and finally 201 patients were enrolled.

Definitions

Clinical Definitions. Demographic data at admission included age, sex, weight and clinical symptoms (hypertension and edema) and the result of laboratory parameters [serum creatinine (SCr), estimated GFR (eGFR), albumin, cholesterol and 24-hour urine protein]. The final SCr and 24 hours urine protein were recorded from outpatient charts and the outcome of treatment was defined according to the results of these parameters.

Complete Remission. Final proteinuria < 300 mg/d and SCr < 1.4 mg/dL.

Partial Remission. Final proteinuria between 300 and to1999 mg/d and < 50% of baseline and SCr < 1.4 mg/dL.

No Remission. Final proteinuria ≥ 2000 mg/d and/or reduction of < 50% or SCr ≥ 1.4 mg/dL.

Chronic kidney disease (CKD) at admission. eGFR < 60 mL/min/1.73m^2 according to MDRD equation and SCr ≥ 1.4 mg/dL for ≥ 3 months before admission.

Progressive CKD, as the kidney outcome. eGFR < 60 mL/min/1.73m^2 according to MDRD equation and ≥ 50% decrease of eGFR from baseline and SCr ≥ 1.4 mg/dL and increase of SCr ≥ 50% of the baseline.

ESKD or death due to kidney disease, as the kidney outcome. ESKD was defined as the patient on maintenance dialysis or kidney transplant. Death due to kidney disease was defined as death on maintenance dialysis or kidney transplant due to the complications of either modality.

Arterial hypertension. It was defined as systolic B*P* ≥ 140 mmHg and/or diastolic B*P* ≥ 90 mmHg.

Renal function was expressed as estimated GFR (eGFR) (mL/min/1.73m^2) and was calculated by using the Modification of Diet in Renal Disease study equation (MDRD). Estimated GFR at baseline was categorized to four groups: > 75 mL/min/1.73m^2) [normal (score = 0)], between 50 to 75 mL/min/1.73m^2 [mild azotemia (score = 1)], 25 to 49 mL/min/1.73m^2 [moderate azotemia (score = 2)], < 25 mL/min/1.73m^2 [severe azotemia (score = 3)].

Pathological findings definitions. The criteria for enrollment were at least 5 glomeruli in light microscopic field, at least 1 segmentally sclerotic glomerulus.

The biopsy result included the number of glomeruli in biopsy specimens, the percentage of segmental glomerulosclerosis (SGS) (number of glomeruli with segmental sclerosis/all glomeruli ×100) and percent of interstitial fibrosis/ tubular atrophy (IF/TA) of the cortical area. FSGS variants based on Columbia classification were extracted from the patients' files.

Perihilar leions was defined as the presence of hyalinosis or sclerosis at glomerular hilum. The diagnosis of tip lesion was based on the presence

of at least one segmental lesion at tip domain or outer part of glomeruli close to proximal tubule. Cellular lesion was defined as occlusion of capillary lumina by segmental endocapillary hypercellularity. Collapsing variant was defined as segmental or global glomerular capillary wall collapse in association with extracapillary epithelial cell hypertrophy or proliferation. The lesion without perihilar, tip lesion, cellular or collapsing features was defined as non otherwise specified (NOS).

The pathology slides were re-evaluated and reported in case of previously unclassified FSGS report.

Both SGS and IF/TA percentages were classified as 1 to 5% [normal (score = 0)], 6 to 25% [mild (score = 1)], 26 to 50% [moderate (score = 2)], and > 50% [severe (score = 3)].

Statistical Analyses and Development of Risk Prediction Model

Categorical data were presented as numbers and percentages, and continuous data as mean ± SD. To compare the different clinical and laboratory characteristics of FSGS variants we used the Chi-2, one-way ANOVA and Post hoc Bonferoni tests, where appropriate. The correlation between SGS and IF/TA and laboratory findings were evaluated by Pearson test.

Continuous and categorical prognostic factors were analyzed by Cox regression model to estimate the risk of CKD/ESKD. Hazard Ratio (HR) with 95% confidence interval (CI) was estimated by univariate and multivariate analyses. Possible interactions between significant variables were tested. A significant interaction was found between SGS and IF/TA percentages ($P < .05$) and also baseline SCr and IF/TA percentage ($P = .05$) (trend). As a result, we calculated the product of two independent variables in model by using centered interaction.

Supplementary Table 2. Risk Stratification According to Baseline eGFR (MDRD) and Percentages of Interstitial Fibrosis / Tubular Atrophy and Segmental Glomerulosclerosis

Total Score	0 to 3	4 to 6	7 to 9
Risk Definition	Low Risk	Moderate Risk	High Risk

According to the sum of the baseline scores of eGFR, SGS and IF/TA, the patients were classified into three groups of low risk (total score 0 to 3), medium risk (total score: 4 to 6) and high risk (total score: 7 to 9). Finally, Kaplan–Meier and the log-rank methods were used to estimate renal survival in each group (Supplementary Table 1 and 2).

In prognostic model, discrimination was evaluated using the C-statistic, which represents the area under the receiver operating characteristic curve (ROC) curve. Accuracy of the test was described as area under the ROC curve (AUC). An area of 1.0 reflects perfect discrimination (sensitivity and specificity both 100%) and C-Statistic less than 0.5 is equivalent to random guessing.

In Multivariate analyses each main independent variable was adjusted for other variables. In addition, due to significant interaction between IF/TA percentages and SGS and IF/TA and SCr at baseline, we added the main effect of their products in the model, as explained in methodology.

RESULTS

Baseline Characteristics

Baseline characteristics of 201 patients and histological variants are shown in Table 1. The prevalence of FSGS variants by kidney biopsy was as follows: NOS (68%), tip lesion (22%), perihilar (6%), collapsing (3%), and cellular (1%).

Clinical and Laboratory Findings at Baseline

In 201 patients, the mean age was 38 ± 15 years and 119 were male (59%). Eighty patients (40%) were hypertensive at admission, however 70% of the patients with collapsing variant were hypertensive.

Supplementary Table 1. Scoring of Baseline eGFR (mL/min/1.73m^2) (MDRD), Interstitial Fibrosis / Tubular Atrophy (IF/TA), and Segmental Glomerulosclerosis (SGS)

	Score 0	Score 1	Score 2	Score 3
eGFR (mL/min/1.73 m^2)	eGFR ≥ 75 (Normal)	50 ≤ eGFR < 75 (Mild Azotemia)	25 ≤ eGFR < 50 (Moderate Azotemia)	eGFR < 25 (Sever Azotemia)
IF/TA (%)	0 to 5 (Normal)	6 to 25 (Mild)	26 to 50 (Modrate)	> 50 (Severe)
SGS (%)	0 to 5 (Normal)	6 to 25 (Mild)	26 to 50 (Modrate)	> 50 (Severe)

Table 1. Baseline Characteristics in All Patients and Histological Variants According to Columbia Morphologic Classification

	Total	Perhilar	Cellular	Tip lesion	Collapsing	NOS	*P*
N (%)	201	11 (5.5)	2 (1)	44 (21.9)	7 (3.5)	137 (68.2)	-
Age at biopsy, y	38 ± 15	44 ± 11	33 ± 15	36 ± 15	36 ± 7	38 ± 16	> .05
Sex (Female, %)	41	27	50	56	49	37	> .05
Weight, kg	72 ± 15	75 ± 17	75 ± 26	70 ± 7	74 ± 21	72 ± 14	.001
Serum albumin, g/dL	3.2 ± 0.8	3.1 ± 0.6	3.0 ± 0.3	2.6 ± 0.7	3.1 ± 0.6	3.4 ± 0.7	.001
Serum Creatinine, mg/dL	1.89 ± 1,63	1.29 ± 0.6	0.8 ± 0.1	1.44 ± 1.2	4.0 ± 3.2	2.0 ± 1.6	.001
eGFR, mL/min/1.73 m^2	65 ± 38	81 ± 38	115 ± 30	82 ± 42	27 ± 19	60 ± 35	.001
Urine Protein g /24h	4.6 ± 3.6	5.3 ± .4.0	5.2 ± 0.3	7.4 ± 4.6	4.7 ± 4.7	3.6 ± 2.6	.001
Hypertension (%)	40	27	50	29	71	42	> .05
SGS Score (%)	Normal (4) Mild (72) Moderate (17) Severe (7)	Normal (0) Mild (90) Moderate (10) Severe (0)	Normal (50) Mild (0) Moderate (50) Severe (0)	Normal (10) Mild (86) Moderate (4) Severe (0)	Normal (0) Mild (60) Moderate (20) Severe (20)	Normal (2) Mild (70) Moderate (20) Severe (8)	.001
IF/TA Score (%)	Normal (6) Mild (65) Moderate (24) Severe (5)	Normal (19) Mild (79) Moderate (2) Severe (0)	Normal (0) Mild (50) Moderate (50) Severe (0)	Normal (16) Mild (84) Moderate (0) Severe (0)	Normal (0) Mild (20) Moderate (70) Severe (10)	Normal (4) Mild (64) Moderate (25) Severe (7)	.001

Data are means ± SD or frequencies (%).
Definition of segmental glomerular sclerosis and IF/TA scores (%): Normal: 0 to 5%, Mild: 6 to 25%, Moderate: 26 to 50%, Severe > 50%.
eGFR: according to MDRD, Hypertension: systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, SGS: segmental glomerular sclerosis, IF/TA: interstitial fibrosis and Tubular atrophy.

The mean SCr at baseline was 1.89 ± 1.63 mg/dL, the mean eGFR at baseline was 65 ± 38 (60 ± 34) mL/min/1.73m^2 and 94 patients (47%) had SCr > 1.4 mg/dL and 111 patients (55%) had eGFR < 60 mL/min/1.73m^2. In collapsing lesion 88% of the patients had SCr > 1.4 mg/dL, their baseline SCr was significantly higher (4.0 ± 3.2 mg/dL, $P < .001$), and eGFR was significantly lower (27 ± 19 mL/min/1.73m^2, $P < .001$) than others (Table 1).

Mean serum albumin was 3.2 ± 0.8 g/dL and 24-hour urine protein was 4.6 ± 3.6 g/24h in all patients. Patients with tip lesion had the lowest serum albumin (2.6 ± 0.7 g/dL) and the highest amount of proteinuria (4.0 ± 4.6 g/24h) at baseline.

Histological Findings

The average number of glomeruli per one biopsy specimen was 19.8 ± 9.8. Most of the patients (72%) had normal (0 to 5%) to mild (6 to 25%) SGS or IF/TA. SGS and IF/TA > 50% were only observed with collapsing and NOS variants.

Development of CKD, ESKD and Non-response

In this cohort of FSGS patients with a mean follow- up of 55 ± 27 months, 82 (41%) patients developed CKD [46 patients (23%)] or ESKD [36 patients (18%)]. Ninety patients (44%) did not respond to treatment and among them only 8 patients (9%) did not develop CKD/ESKD. At the end of the study the patients had a mean SCr of 1.87 ± 1.89 mg/dL and proteinuria of 0.76 ± 0.96 g/24h.

Risk Factors Associated with Renal Outcome

Association between continuous and categorical independent variables and the risk of development of CKD/ESKD are shown in Table 2.

Univariate Analyses

In univariate analyses with continuous variables, higher SCr at baseline, higher percentage of glomeruli with SGS and higher IF/TA percentages were associated with increased risk of CDK/ESKD. Higher albuminuria at baseline was associated with slight increase of risk. In categorical variables hypertension was associated with increased risk of CKD/ESKD.

Multivariate Analyses

In multivariate analysis, Scr at baseline and percentages of SGS and IF/TA were still significantly associated with development of CKD/ESKD.

Histological Variants and the Risk of Non-response and CKD/ESKD with Primary FSGS

Among 137 patients with NOS variant, 80 (58%) were defined as non-responders and 71 cases

Table 2. Univariate and Multivariate Analyses of Baseline Clinical and Laboratory Predictors of CKD/ESKD

	Univariate Analysis (HR, 95% CI)	*P*	Multivariate Analysis (HR, 95% CI)	*P*
Age, y	1.00 (0.98 to 1.01)	> .05	1.00 (0.98 to 1.02)	> .05
Sex (Female)	1.56 (0.98 to 2.49)	.056	0.743 (0.40 to 1.38)	> .05
Weight, kg	1.00 (0.98 to 1.01)	> .05	0.99 (0.97 to 1.01)	> .05
Serum Albumin, g/dL	1.10 (0.82 to 1.47)	> .05	1.07 (0.74 to 1.56)	> .05
LDL-Cholesterol, mg/dL	0.996 (0.99 to 1.00)	0.01	0.99 (0.98 to 1.01)	> .05
Serum Creatinine, mg/dL	1.61 (1.45 to 1.80)	< .0001	1.63 (1.12 to 2.37)	.01
Urine protein, g/24h	1.00 (1.00 to 1.00)	.047	1.00 (1.00 to 1.00)	.070
Hypertension	1.81 (1.17 to 2.82)	.008	1.69 (0.94 to 3.06)	.082
SGS (%)	1.03 (1.02 to 1.04)	< .0001	1.04 (1.01 to 1.08)	.05
IF/TA (%)	1.05 (1.03 to 1.07)	< .0001	1.06 (1.03 to 1.09)	< .0001

All variables are at baseline.
HR: hazard ratio with 95% confidence interval (CI).
SGS: segmental glomerular sclerosis
IF/TA: interstitial fibrosis and tubular atrophy
In multivariate analyses the main variable was adjusted for all other variables in addition to SGS(%) × IF/TA (%) and baseline serum creatinine × IF/TA (%).

(52%) developed CKD/ESKD. In 11 patients with perihilar lesion, two (18%) progressed to CKD/ESKD and did not respond to treatment. From 44 patients with tip lesion variant, only two (5%) developed CKD/ESKD and both were defined as non-responders. The two cases with cellular variant achieved complete remission. None of the 7 cases with collapsing lesion (100%) responded to treatment and all progressed to CKD/ESKD.

The risk of CKD/ESKD with histological variants of primary FSGS is given in Table 3. In univariate analyses, with the NOS type defined as the reference group, the collapsing type was significantly associated with increased risk of developing CDK/ESKD (HR = 5.24, 95% CI: 2.38 to 11.36, $P < .001$). However, in multivariate model, when adjusted for pathological findings of SGS and IF/TA percentages, the risk of developing CDK/ESKD with collapsing lesion was not significant (HR = 2.31, 95% CI: 0.73 to 7.30; $P > .05$).

Table 3. Univariate and Multivariate Analyses of Predictors for CKD/ESKD with Each Histological Variant of FSGS

FSGS Variants	Univariate Analysis (HR, 95% CI)	*P*	Multivariate Analysis (HR, 95% CI)	*P*
Perihilar	0.17 (0.42 to 0.71)	.016	0.280 (0.06-1.25)	> .05
NOS	1	-	1	-
Tip lesion	0.04 (0.01 to 0.26)	.05	0.15 (0.02-1.15)	> .05
Collapsing	5.24 (2.38 to 11.36)	< .0001	2.31 (0.73-7.30)	> .05
Cellular	-a	-a	-a	-a

All variables are at baseline.
HR: hazard ratio with 95% confidence interval (CI).
SGS: segmental glomerular sclerosis
IF/TA: interstitial fibrosis and tubular atrophy
In multivariate analysis the main variable was adjusted for all other variables in addition to SGS (%) × IF/TA (%) and baseline serum creatinine × IF/TA (%).

Risk Category and Renal Survival

As mentioned before, the prognostic risk score was calculated according to the sum of the baseline scores of eGFR, SGS, IF/TA, and divided into three categories of low risk (≤ 3), medium risk (4 to 6 points), and high risk (7 to 9 points). 92 (46%) were classified as low risk, 83 (41%) as medium risk, and 26 (13%) as high risk. Renal survival by risk category is shown in Figure 1. The median renal survival was calculated at 6.7 years for all patients (95% CI: 6.1 to 7.2 years), 8.1 years for low risk patients (95% CI: 7.7 to 8.6), 5.8 years for medium-risk patients (95% CI: 5.1 to 6.5 years), and 3.3 years for high-risk patients (95% CI: 2.3 to 4.2 years; $P < .001$).

Five Years Prediction of CKD/ESKD

The five years prediction of CKD/ESKD is given in Figure 2. Receiver-operating characteristic curves (ROC-curve) with C-Statistic were used to estimate discrimination of the risk predictors.

Serum Cr at baseline and SGS and IF/TA percentages had C-Statistic of 0.83 (95% CI: 0.77 to 0.89), 0.82 (95% CI: 0.75 to 0.88) and 0.88, (95% CI: 0.83 to 0.94). Prediction of risk by using all three variables in prognostic risk score resulted in C-Statistic of 0.83 (95% CI: 0.77 to 0.90).

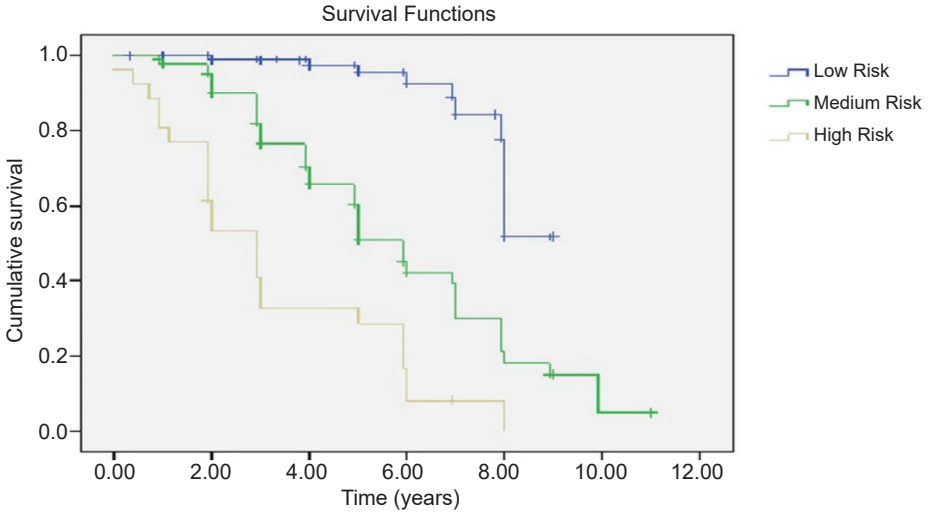
Baseline proteinuria as a predictor had C-Statistic less than 0.5 (0.40, 95% CI: 0.35 to 0.50) (Figure 2).

DISCUSSION

FSGS is caused by podocyte loss and is mostly a progressive glomerular disease.[13,14] Renal outcome is very diverse and progression to advanced kidney failure is common.[15,16]

In the present study we assessed the predictors of CKD/ESKD in patients with primary FSGS. Forty- five percent of our patients did not respond to treatment and 41% developed CKD or ESKD. The link between remission and renal survival was very high and 90% of patients without remission developed CKD/ESKD. In a study by Chun *et al.* the 10 years' kidney survival rate of patients with FSGS was 92% in patients with remission compared to 33% in those without remission.[2]

Despite including 6 patients younger than 18 years, the demographics of our patients are almost similar to other studies of adult FSGS, with a mean age of 38 ± 15 years in our study and an age at diagnose of 35 to 50 years old in other studies.[11,15] The prevalence of idiopathic FSGS was somewhat more in men in our study similar to others.[14,17]



	Numbers of patients at risk						
Time, y	0	2	4	6	8	10	12
Low risk	92	77	65	30	8	1	-
Medium risk	82	69	43	15	6	0	-
High risk	26	14	8	3	0	0	-

Figure 1. Kaplan–Meier curves showing the lower probability of renal survival in high risk patients compared with others (Log Rank < 0.001).

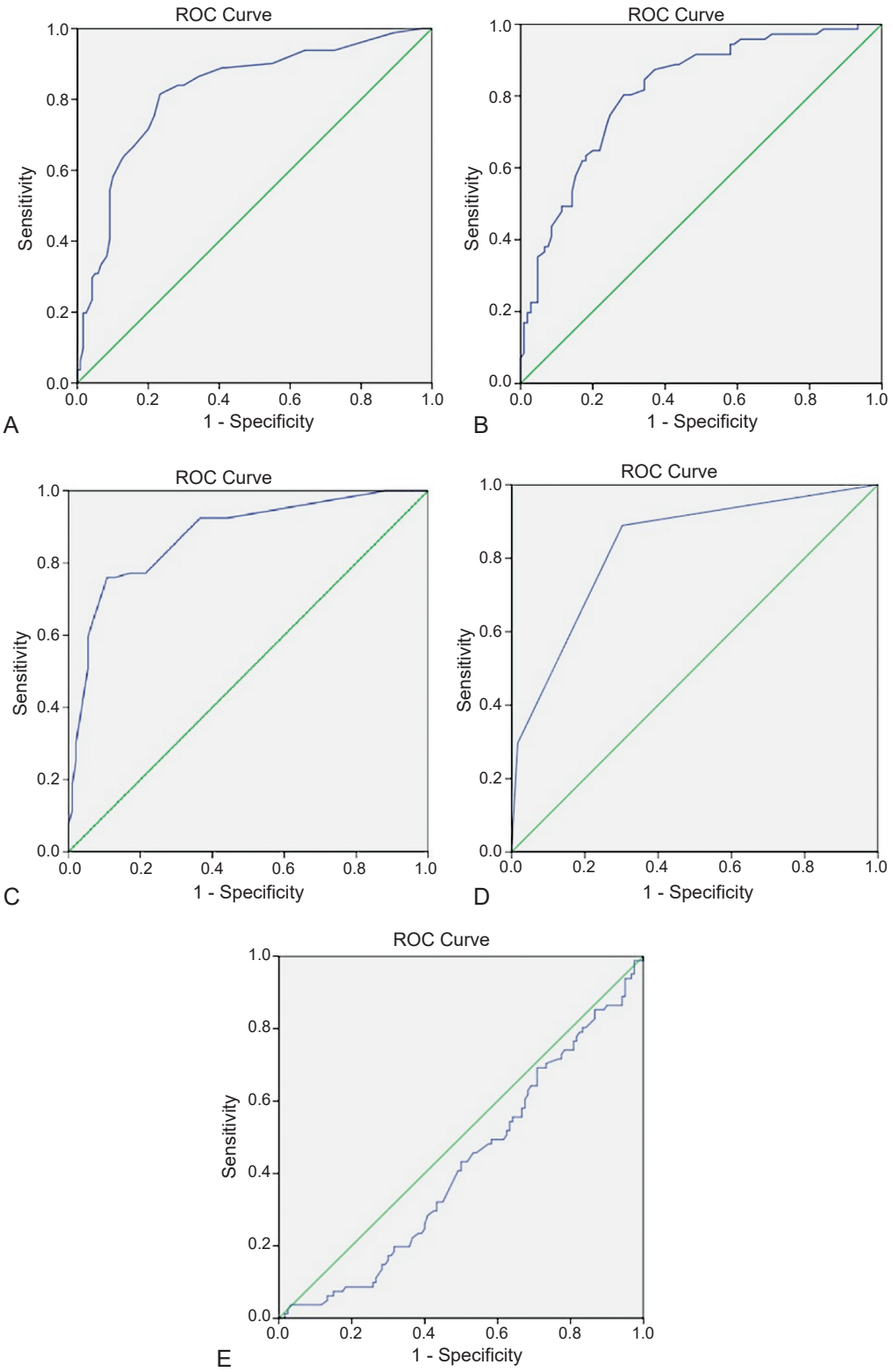


Figure 2. Receiver-operating characteristic curves estimated for evaluating the capacity of discrimination of the risk score to predict CKD/ESKD for five years. A, Baseline serum creatinine C-Statistic: 0.83 (95% CI: 0.77 to 0.89). B, Segmental glomerular sclerosis (%) C-Statistic: 0.82 (95% CI: 0.75 to 0.88). C, Interstitial fibrosis/ tubular atrophy (%) C-Statistic: 0.88 (95% CI: 0.82 to 0.93). D, Accuracy of the score applied to the sample C-Statistic: 0.83 (95% CI: 0.77 to 0.90). E, Proteinuria at baseline C-Statistic: 0.40 (95% CI: 0.35 to 0.50).

Most of the patients in this study had mild renal impairment at baseline (MDRD eGFR: 65 ± 38 mL/min/1.73m^2). Renal function at admission is very diverse in adult primary FSGS but it is mostly reported as mild to moderate renal dysfunction at admission. [18,19] Our findings, like others showed that higher renal function at admission was positively related to better renal outcome. [2,20]

In our study the most prevalent variant of FSGS was NOS (68%), followed by tip lesion (22%), perihilar (6%), collapsing (3%), and cellular types (1%). Demographic features are different between various histologic subtypes of FSGS. Collapsing lesion has been reported with a higher prevalence in Afro-American patients and both tip lesion and collapsing variants have been more common in teenagers and adults compared to children.[11,12,21]

Most studies have reported NOS variant as the most prevalent type of FSGS which is similar to our study.[12, 21] However it is suggested that longer duration of FSGS may be correlated with NOS variant, probably due to evolution of segmental sclerosing lesions from tip lesion over time, as a part of chronicity process.[22]

Regarding renal outcome, collapsing lesion has been associated with worst renal outcome and more common in non-responders.[23] In our study all of the seven patients with collapsing lesion developed CKD/ESKD, including the two patients who ended in dialysis.

Tip lesion variant has been associated with a significantly better kidney survival.[24,25] Among 44 patients with tip lesion, only two did not attain complete or partial remission and developed CKD. In the current study 58% of patients with NOS did not respond to treatment and more than half (52%) developed CKD/ESRD, which shows a worse prognosis in our NOS patients compared to other studies.[11,21,26] This may have been the center effect and due to referral of more complicated patients to our kidney hospital, the effect of later referral compared to the mentioned studies or a basically different epidemiology of the disease in our country, which needs further investigation. Of the eleven patients with perihilar lesion, two progressed to CKD (18%) and were defined as non-responders. In the study by Thomas *et al* the patients with perihilar variant had good renal survival at 1 year (89%) and 3 years (75%).[21]

In our study the only two cases of cellular variant attained complete remission. In other studies, cellular variant shows an intermediate prognosis between the two variants of collapsing and tip lesion.[21] The low number of patients with cellular lesion in the present study does not let us to reach any hard conclusions.

We showed that in the collapsing variant the risk of CKD/ESKD is significantly high in univariate analyses, however after adding IF/TA score in the adjusted multivariate model, this risk was no longer significant. So, the high frequency of bad outcome in collapsing FSGS may be due to higher chronicity at diagnosis and this should be noticed and examined in other series.

There are some limitations in using Columbia classification as a predictor of clinical outcome. Different location of segmental lesions makes overlapping and heterogeneity between variants, which can lead to misdiagnosis by kidney biopsy.[27-29] The accuracy of diagnosis highly depends on the number of glomeruli and sample size in biopsy.[30,31]

We showed that high IF/TA score at diagnosis strongly predicted the risk of CKD/ESKD in primary FSGS. The term interstitial fibrosis/tubular atrophy was first introduced in kidney allograft biopsy.[32,33] However today it is used as a predictor for progression of kidney failure, regardless of the type of the glomerular disease and interstitial fibrosis and tubular atrophy are well identified hallmarks for development of CKD.[34-36]

The presence of global and segmental sclerosis in kidney biopsy indicates worse prognosis in kidney survival.[4,34] Global sclerosis is highly age-related and segmental sclerosis is the most important pathological finding in the typical FSGS.[35] In this study we used the percentage of segmental sclerosis in the biopsy specimen as a predictor. Our finding showed that the higher number of glomeruli with segmental sclerosis on biopsy highly predicts the risk of CKD/ESKD.

In this study baseline proteinuria was not associated with increase in the risk of CDK/ESKD. This finding is contrary to the previous finding of proteinuria as an important risk factor for development of renal failure.[36,37] On the other hand in a very recent study on 466 patients with primary FSGS and proteinuria, followed for 1,4 and 8 months, by using a novel definition of remission, reduction of proteinuria was associated

with better long-term renal outcomes.[38] In a sub-analysis in our patients (not shown), greater decrease of proteinuria between baseline and last proteinuria was associated with decreased risk of CKD/ESRD [multivariate analysis (HR = 0.92, 95% CI: 0.86 to 0.97)].

This study has several limitations. Since this is an observational study, a cause–effect relationship cannot be established. The patients were treated by different physicians and treatment protocols or follow-up time may have had an influence on outcome. Interval from early clinical manifestations and renal biopsy is diverse and this can lead to time bias. Laboratory data were reported by different laboratories which may have slightly affected the accuracy of the data.

However, the major strengths of this cohort study are adequate number of patients with primary FSGS, good number of events, very few missing data and examination of all kidney biopsy samples by one expert pathologist.

CONCLUSION

Our study showed that regardless of the histologic variant, kidney function at admission and percentages of glomeruli with segmental sclerosis and the degree of interstitial fibrosis and tubular atrophy at kidney biopsy have high sensitivity and specificity to predict the kidney outcome. This is a retrospective observational study and these findings need to be examined by further prospective studies, which should consider the effect of therapeutic regimens.

ABBREVIATIONS

FSGS: Focal segmental glomerulosclerosis
ESKD: End stage kidney disease
CKD: Chronic kidney disease
NOS: Not otherwise specified
SCr: Serum creatinine
eGFR: Estimated glomerular filtration rate
SGS: Segmental glomerulosclerosis
IF/TA: Interstitial fibrosis/ tubular atrophy
HR: Hazard Ratio
CI: Confidence interval
ROC: Receiver operating characteristic curve
AUC: Area under curve

DECLARATIONS

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Code of ethics: 94/D/105/198

Ethics Committee of Iran University of Medical Sciences

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from

the corresponding author on reasonable request.

FUNDING

Not applicable.

AUTHORS' CONTRIBUTIONS

SO has designed study and wrote the manuscript. SO, MY, MA and HA analyzed data, and participated in writing the manuscript. HA performed statistical analyses. MY and HB collected data. MA preformed renal pathological analysis. SO supervised the project. All of the authors read and approved the manuscript.

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DISCLOSURE STATEMENT

The authors have no competing interests.

We can provide our data and material in a SPSS chart if needed.

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