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# Recurrence of FSGS after Kidney Transplantation in Adults

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## Abstract

**Background and objectives** FSGS recurrence after kidney transplantation is a major risk factor for graft loss. However, the natural history, clinical predictors, and response to treatment remain unclear because of small sample sizes and poor generalizability of single-center studies, and disease misclassification in registry-based studies. We therefore aimed to determine the incidence, predictors, and treatment response of recurrent FSGS in a large cohort of kidney transplant recipients.

**Design, setting, participants, & measurements** The Post-Transplant Glomerular Disease (TANGO) project is an observational, multicenter, international cohort study that aims to investigate glomerular disease recurrence post-transplantation. Transplant recipients were screened for the diagnosis of idiopathic FSGS between 2005 and 2015 and details were recorded about the transplant, clinical outcomes, treatments, and other risk factors.

**Results** Among 11,742 kidney transplant recipients screened for FSGS, 176 had a diagnosis of idiopathic FSGS and were included. FSGS recurred in 57 patients (32%; 95% confidence interval [95% CI], 25% to 39%) and 39% of them lost their graft over a median of 5 (interquartile range, 3.0–8.1) years. Multivariable Cox regression revealed a higher risk for recurrence with older age at native kidney disease onset (hazard ratio [HR], 1.37 per decade; 95% CI, 1.09 to 1.56). Other predictors were white race (HR, 2.14; 95% CI, 1.08 to 4.22), body mass index at transplant (HR, 0.89 per kg/m<sup>2</sup>; 95% CI, 0.83 to 0.95), and native kidney nephrectomies (HR, 2.76; 95% CI, 1.16 to 6.57). Plasmapheresis and rituximab were the most frequent treatments (81%). Partial or complete remission occurred in 57% of patients and was associated with better graft survival.

**Conclusions** Idiopathic FSGS recurs post-transplant in one third of cases and is associated with a five-fold higher risk of graft loss. Response to treatment is associated with significantly better outcomes but is achieved in only half of the cases.

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## Introduction

FSGS is one of the leading glomerular causes of kidney failure in adults (1). When no secondary cause (genetic, viral, drug-associated, or adaptive [2]) can be identified and the patient presents with a clinical history of nephrotic syndrome, FSGS is termed primary or idiopathic. The accurate distinction between idiopathic and secondary causes, however, remains challenging, particularly if ultrastructural evaluation of the kidney biopsy or genetic testing are missing (3).

Distinguishing between idiopathic and secondary FSGS is especially important in patients being considered for kidney transplantation because idiopathic forms frequently recur in the graft with a substantial rate of subsequent graft loss. Reported rates of recurrence are wide, ranging from 17% to 55% (4–23) in

smaller studies and from 9% to 15% (24–27) in registry-based studies. Because FSGS is rare, most published studies are limited by small sample size and thus insufficient power to precisely determine incidence, predictors, and outcomes of FSGS recurrence. Administrative registries with large sample sizes, such as the US Renal Data System, are limited by missing data, misclassification of glomerular disease diagnoses (28), and failure to capture cases of FSGS recurrence that do not lead to graft loss, rendering data unreliable for drawing robust conclusions (29). The same limitations are present in prior studies that aimed to identify predictors of recurrence, in which most proposed predictors were identified by univariable analysis without adjustment for relevant confounding factors (Supplemental Table 1).

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To combine the strengths of a large registry, with the detailed and accurate nature of single-center studies, we established the Post-Transplant Glomerular Disease (TANGO) study (30). This international network of centers, located in three different continents, studies the recurrence of glomerular disease after kidney transplantation, using a standardized approach to data and biosample collection. Herein, we examine retrospectively collected data of patients with biopsy-proven native kidney FSGS from 15 centers and report FSGS recurrence rates, risk factors for recurrence, and responses to therapy. To our knowledge, this is the largest nonregistry-based cohort ever created to study this patient population.

## Materials and Methods

### Study Design, Objectives, and Predictors

We performed a multicenter, retrospective study in patients from 15 kidney transplant centers participating in the TANGO study in Europe, Brazil, and the United States. Our primary objective was to determine the incidence of FSGS recurrence after kidney transplantation in patients with idiopathic FSGS. We also aimed to identify risk factors for FSGS recurrence, to compare clinical outcomes of patients with and without recurrent FSGS, and to evaluate the effect of different treatments on recurrent FSGS outcomes. A more detailed description of used methods can be found in Supplemental Appendix 1.

### Patient Selection and Data Collection

All adults (aged  $\geq 16$  years) who received a kidney transplant between January 2005 and December 2015 were reviewed by TANGO investigators in the 15 collaborating centers. Patients with a biopsy-proven native kidney diagnosis of idiopathic FSGS were included. Patients with secondary causes of FSGS, as determined by kidney biopsy (*e.g.*, only mild effacement of foot processes, glomerular hypertrophy) and/or by clinical features (*e.g.*, absent nephrotic syndrome at disease onset or a clear secondary cause, including infections, drugs, reduced kidney mass, long-standing diabetes, or morbid obesity) were excluded. Electron microscopy evaluation of the kidney biopsy was performed and available for 36 patients. From all patients who were included in the study, data were extracted from their medical records. Two patients with less than half a year of follow-up were excluded from analysis. Ten other patients who were lost to follow-up (median time to lost to follow-up, 5.7 years; interquartile range [IQR], 1.84–7.36) were censored at time of loss to follow-up in the Cox proportional hazards analysis.

### Statistical Analyses

Data are shown as frequencies (percentages) for categorical variables, and as medians (IQR) or means  $\pm$  SD for continuous variables. Statistical analysis of Table 1 was done by complete case analysis. Continuous variables were analyzed by *t* test, and binary and categorical variables by chi-squared or Fisher exact test, as appropriate. Confidence intervals around proportions were calculated by Wald testing.

Cumulative incidence, Kaplan–Meier curves, and 95% confidence intervals (95% CIs) around curves were graphed

by Prism 5.0b software (GraphPad). Predictors were selected informed by prior literature and clinical practice (4–22,24–27,31). Univariable Cox proportional hazards regression was performed by complete case analysis. Missing data per predictor is shown in Supplemental Table 2. Because of the large amount of missing data in the predictor “time to ESKD” (40 missing values, 23%), this predictor was not imputed and was removed from the multivariable model. STATA’s multiple imputation by chained equations (MICE) procedure was used to impute missing data (described in more detail in Supplemental Appendix 1). Cox proportional hazards regression was performed, with categorical variables entered as binary variables, analyzed as largest group versus other groups (*e.g.*, white race versus other races). Backward selection was used to remove collinear variables and select a final model from previously defined predictors with both stay and entry criteria of  $P=0.05$ . Schoenfeld residuals were evaluated to assess for violation of the proportional-hazard assumption. Deviance residuals were used to examine model accuracy and outliers, after which time on dialysis was log-transformed to improve random scatter of residuals. Longitudinal data were collected yearly after transplantation and means of groups were graphed over time. For eGFR, in case an in between year of follow-up was missing, the value was imputed using interpolation by STATA. An eGFR value of 5 was imputed for patients after experiencing graft loss. Other longitudinal data were not imputed. A two-sided *P* value of  $<0.05$  was deemed significant in all used tests. Statistical analyses were performed using Prism 5.0b software (GraphPad) and STATA version 15.1 (StataCorp.).

## Results

### Cohort Demographics

A total of 11,742 patients who received a kidney transplant between 2005 and 2015 were screened for FSGS in four European centers, five Brazilian centers, and five United States centers; 253 patients with idiopathic FSGS were included in our online database. Fifty nine patients did not meet inclusion criteria and were excluded from analysis (Supplemental Figure 1). Twenty-two of these patients were excluded because their primary kidney disease did not manifest with nephrotic syndrome (none of these patients experienced recurrence of FSGS). Finally, 176 patients with biopsy-proven primary FSGS were included for analysis. Patient and donor characteristics of all patients, as well as by recurrence status (recurrent/nonrecurrent FSGS), are shown in Table 1.

### Recurrence of FSGS

Fifty-seven patients experienced a recurrence of FSGS post-transplant (32%; 95% CI, 25% to 39%). Most recurrences occurred early after transplant (Figure 1A), with a median time to recurrence of 1.5 months (IQR, 0–11 months). The incidence of recurrent FSGS differed across geographical regions (Figure 1B). A higher percentage of patients in the recurrence group (9%) had received two prior transplants compared with nonrecurrent patients ( $P=0.003$ ). Body mass index (BMI) of patients with a recurrence was lower than of patients without a recurrence ( $24 \pm 5$  kg/m<sup>2</sup> versus  $26 \pm 5$  kg/m<sup>2</sup>, respectively;  $P=0.02$ ).

**Table 1. Baseline recipient and donor characteristics in all patients and according to FSGS recurrence**

Baseline Characteristic	Overall Cohort (n=176)	No Recurrence (n=119)	Recurrence (n=57)
Follow-up, yr	5.2 [3.0–8.1]	6.2 [3.9–8.4]	3.3 [1.6–5.9]
Age at transplantation, yr	38 [29–47]	38 [30–46]	39 [28–49]
Age at diagnosis, yr	27 [17–40]	27 [17–36]	29 [17–43]
Male sex	106 (60)	72 (61)	34 (60)
<b>Race/ethnicity</b>			
White	98 (56)	63 (53)	35 (61)
Black	19 (11)	13 (11)	6 (11)
Hispanic	8 (5)	6 (5)	2 (4)
Asian	8 (5)	8 (7)	0 (0)
Mixed	18 (10)	14 (12)	4 (7)
Other/unknown	25 (14)	15 (13)	10 (18)
BMI at transplantation	25±5	26±5	24±5
<b>Manifestation of FSGS in native kidney</b>			
Nephrotic syndrome	122 (69)	78 (66)	44 (77)
Unknown	54 (31)	41 (34)	13 (23)
Time from diagnosis to ESKD, mo	38 [14–75]	40 [12–83]	32 [15–62]
Time on dialysis, mo	29 [11–57]	29 [11–60]	32 [12–51]
<b>Type of dialysis</b>			
Hemodialysis	127 (73)	84 (71)	43 (77)
Peritoneal dialysis	21 (12)	13 (11)	8 (14)
Both	15 (9)	12 (10)	3 (5)
Pre-emptive transplant	12 (7)	10 (8)	2 (4)
Nephrectomy of native kidneys	12 (7)	4 (3)	8 (14)
Prior transplant loss due to FSGS	16 (9)	6 (5)	10 (18)
<b>Number of prior transplants</b>			
None	132 (75)	89 (75)	44 (75)
1	39 (22)	30 (25)	9 (16)
2	5 (3)	0 (0)	5 (9)
PRA>50%	28 (18)	20 (18)	8 (17)
DSA at transplantation	14 (9)	10 (9)	4 (8)
<b>Deceased donor</b>	118 (67)	82 (69)	36 (63)
Extended criteria donor (KDPI>85%)	16 (14)	12 (15)	4 (12)
Cold ischemia time, h	19±7.0	18.6±6.9	20.1±7.2
<b>Living donor</b>	58 (33)	37 (31)	21 (37)
Living related donor	39 (67)	22 (59)	17 (81)
Donor age, yr	40±14	40±15	40±14
HLA-A/B/DR mismatch	3.2±1.6	3.3±1.6	2.9±1.6
<b>Induction therapy</b>			
None	22 (13)	15 (13)	7 (12)
Anti-thymocyte globulin	72 (42)	46 (40)	26 (46)
Basiliximab	73 (42)	51 (44)	22 (39)
Daclizumab	6 (3)	4 (3)	2 (4)
<b>Immunosuppressive regimen</b>			
Tacrolimus + MMF + steroids	126 (72)	85 (72)	41 (72)
Cyclosporine + MMF + steroids	29 (17)	21 (18)	8 (14)
Tacrolimus + MMF	9 (5)	5 (4)	4 (7)
Other	11 (6)	7 (6)	4 (7)
Prophylactic plasmapheresis	22 (13)	13 (11)	9 (16)

Values represent frequency (percentage), mean±SD, or median [interquartile range]. BMI, body mass index; PRA, panel reactive antibody; DSA, donor-specific antibody; KDPI, kidney donor profile index; MMF, mycophenolate mofetil.

More patients with a recurrence had a prior nephrectomy of native kidneys (14% versus 3%, respectively;  $P=0.02$ ). Other parameters did not differ between patients with and without recurrent FSGS (Table 1).

### FSGS Recurrence and Graft Survival

Graft failure occurred in 18 patients (15%) without recurrence and in 22 patients with recurrence (39%) (Figure 2A). After adjusting for important confounders such as HLA mismatch, pretransplant donor-specific antibody, donor type and age, and post-transplant rejection, Cox regression revealed a hazard ratio (HR) for graft loss of 4.80 (95% CI, 2.85 to 12.16;  $P<0.001$ ) in patients with

versus without recurrence. Graft loss was mainly confined to patients who failed to enter remission (20 out of 31 patients, 65%), with a median time from recurrence to graft loss of 7 months (IQR, 2–18 months) (Figure 2B). Two out of 16 patients (13%) with partial remission experienced graft loss after 3.2 and 6.4 years after recurrence, whereas ten patients with complete remission did not experience graft loss. Overall, FSGS recurrence was associated with a five-fold higher risk of graft loss, mainly because of the high rate of graft loss in the patients without response to treatment of recurrent FSGS. Ten patients died during the follow-up time: seven patients in the nonrecurrence group (6%) versus three patients (5%) who experienced FSGS recurrence.

**Table 2. Univariable and multivariable Cox-hazard analysis in patients without FSGS recurrence compared with patients with FSGS recurrence**

Predictors	Missing Values, n (%)	Univariable Analysis	Univariable Analysis	Multivariable Analysis	Multivariable Analysis	Model Selection
		HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI), P Value
<b>Geographic location of center</b>						
United States	0 (0)	Ref		Ref		Ref
Brazil	0 (0)	1.42 (0.77–2.62)	0.27	0.45 (0.21 to 0.98)	0.05	0.46 (0.24 to 0.90), 0.02
Europe	0 (0)	1.11 (0.57 to 2.17)	0.74	0.39 (0.18 to 0.87)	0.02	0.39 (0.19 to 0.79), 0.009
Age at diagnosis FSGS, per 10 yr	4 (2)	1.14 (0.96 to 1.37)	0.12	1.37 (1.12 to 1.68)	0.002	1.31 (1.09 to 1.56), 0.003
White race	19 (11) <sup>a</sup>	1.80 (0.95 to 3.41)	0.07	2.39 (1.16 to 4.96)	0.02	2.14 (1.08 to 4.22), 0.03
BMI, per 1 kg/m <sup>2</sup>	1 (1)	0.94 (0.89 to 0.99)	0.03	0.89 (0.83 to 0.96)	0.002	0.89 (0.83 to 0.95), 0.001
Time on dialysis, per mo (log)	2 (1)	1.04 (0.86 to 1.27)	0.69	1.10 (0.85 to 1.42)	0.49	NS
Native nephrectomy	1 (1)	2.56 (1.21 to 5.41)	0.01	2.89 (1.09 to 7.66)	0.03	2.76 (1.16 to 6.57), 0.02
Living donor	0 (0)	1.23 (0.72 to 2.11)	0.45	1.55 (0.76 to 3.16)	0.23	NS
Age donor, per 10 yr	14 (8)	0.99 (0.82 to 1.19)	0.90	0.84 (0.66 to 1.06)	0.14	NS
HLA mismatch >3	10 (6)	0.65 (0.37 to 1.14)	0.14	0.71 (0.39 to 1.31)	0.27	NS
Presence of DSA	15 (9)	0.98 (0.35 to 2.72)	0.97	0.83 (0.25 to 2.79)	0.76	NS
Use of induction	3 (2)	1.12 (0.51 to 2.47)	0.79	1.23 (0.53 to 2.89)	0.63	NS
Plasmapheresis pretransplant	0 (0)	1.28 (0.63 to 2.61)	0.50	1.27 (0.54 to 2.97)	0.58	NS
Immunosuppression with tacrolimus + MMF + steroids	1 (1)	1.01 (0.57 to 1.81)	0.96	0.88 (0.46 to 1.66)	0.69	NS
Time to ESKD, per mo	40 (23)	1.00 (0.99 to 1.00)	0.26			

HR, hazard ratio; 95% CI, 95% confidence interval; Ref, reference; BMI, body mass index; NS, not significant; DSA, donor-specific antibody; MMF, mycophenolate mofetil.

<sup>a</sup>Most patients with missing race come from France, where race/ethnicity is not allowed to be reported.

### Predictors of FSGS Recurrence

Univariable Cox regression revealed associations between FSGS recurrence and BMI at transplant as well as history of native kidney nephrectomies (Table 2). After multivariable analysis and backward selection of variables in the model, age at diagnosis (HR, 1.31; 95% CI, 1.09 to 1.56 per decade;  $P=0.003$ ), white race (HR, 2.14; 95% CI, 1.08 to 4.22;  $P=0.03$ ), BMI (HR, 0.89; 95% CI, 0.83 to 0.95 per 1 kg/m<sup>2</sup>;  $P=0.001$ ), and native nephrectomy (HR, 2.76; 95% CI, 1.16 to 6.57;  $P=0.02$ ) remained significant variables. The geographical region was also of importance in multivariable analysis, with centers in Brazil and Europe having lower recurrence rates than in the United States (HR, 0.46; 95% CI, 0.24 to 0.90;  $P=0.02$  and HR, 0.39; 95% CI, 0.19 to 0.79;  $P=0.009$ , respectively). Time from native kidney FSGS onset to ESKD was not included in the multivariable model because of 23% of missing data. A univariable complete case analysis did not reveal an association between time to ESKD and recurrent FSGS (HR, 1.00; 95% CI, 0.99 to 1.00;  $P=0.26$ ).

### Previous Allografts and Recurrent FSGS

Previous allograft loss owing to FSGS has been described as a risk factor for recurrent FSGS in subsequent allografts. In our cohort, 45% and 100% of patients who had lost one or two prior allografts, respectively, because of recurrent FSGS experienced another recurrence (Supplemental Figure 2). Patients who lost a previous graft because of reasons other than recurrent FSGS were associated with a lower incidence of FSGS recurrence in the new allograft (14%).

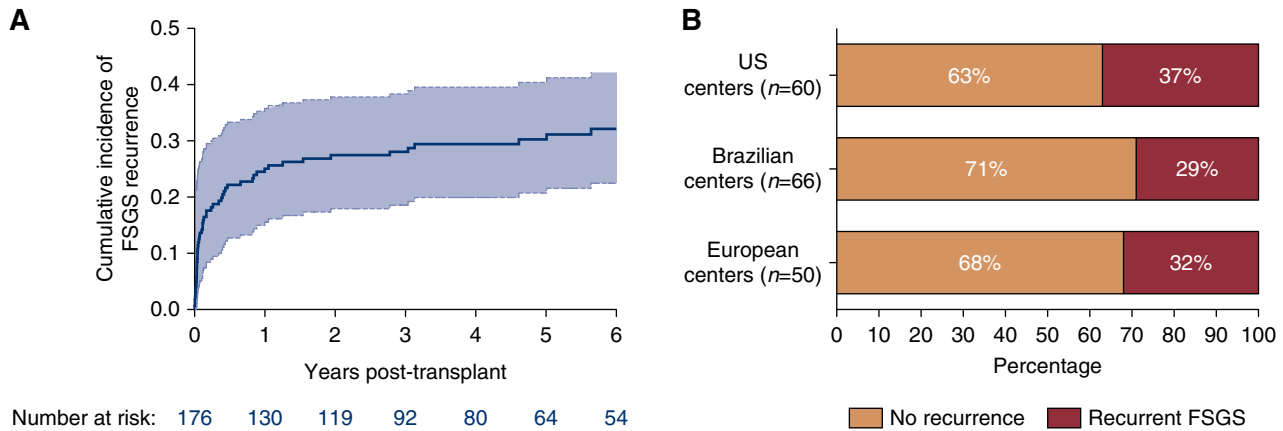
### Response to Treatment of Recurrent FSGS

We evaluated treatment response in 75 patients with FSGS recurrence: 57 patients from the primary cohort and an additional 18 from two centers that did not have native biopsy results available (see Supplemental Appendix 1). Immunosuppressive treatments varied across the cohort and included steroids, cyclosporine, plasmapheresis, rituximab, cyclophosphamide, and immunoabsorption (Table 3). Five patients did not receive any further immunosuppressive treatment because of active infection or advanced scarring on kidney biopsy. Plasmapheresis with or without rituximab was the most frequent treatment (61 patients, 81%) and the only one inducing complete remission. Frequency of plasmapheresis varied from one to three sessions a week, with duration ranging from 2 weeks to a year. The median number of rituximab doses was two (IQR, 1–3).

Plasmapheresis with or without rituximab was associated with complete remission in 13 patients (21%), partial remission in 22 patients (36%), and no response in 26 patients (43%) (Figure 3A). Thirty-two patients received both plasma exchange and rituximab, 25 received only plasmapheresis, and three only received rituximab (Figure 3B). Two patients with a complete remission experienced a relapse that responded to repeated treatments.

Univariable logistic regression analysis in patients treated with plasmapheresis with or without rituximab did not show an association between early FSGS recurrence (within 6 months) and response to treatment





**Figure 1. | FSGS recurs in one third of kidney transplant recipients.** (A) Cumulative incidence curve of FSGS recurrence in kidney transplant recipients with biopsy-proven idiopathic FSGS. Overall recurrence of FSGS was 32%, with median time to recurrence of 1.5 months. Shaded area around the curve represents the 95% confidence interval. (B) Recurrence rates per geographical location of the centers.

(odds ratio [OR], 0.83; 95% CI, 0.24 to 2.85;  $P=0.77$ ) (Supplemental Table 3). Younger age at transplantation (OR, 0.97; 95% CI, 0.93 to 1.01;  $P=0.10$ ) and female sex (OR, 2.38; 95% CI, 0.82 to 6.91;  $P=0.11$ ) showed a trend for a higher chance of responding to treatment, but we could not assess this in a multivariable model because of the small group sizes.

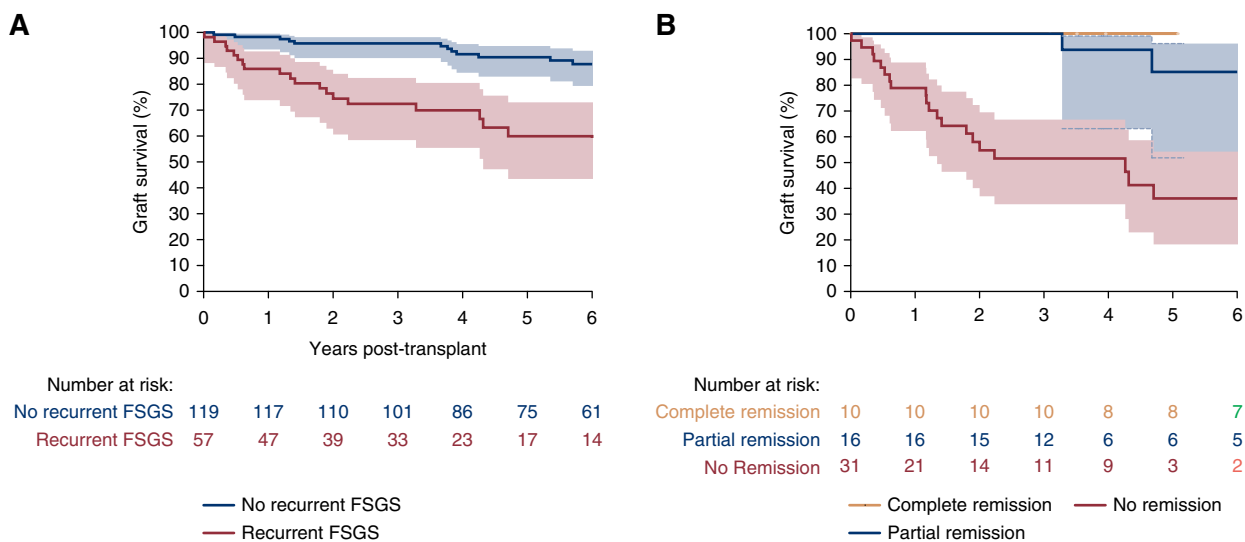
**FSGS Recurrence and Post-Transplant Complications**

Increased intensity of immunosuppression in patients with recurrent FSGS may lead to a higher risk of infectious complications such as BK virus and cytomegalovirus reactivation. Using Cox regression and adjusting for confounders, we did not find differences in incidence of BK or cytomegalovirus viremia, acute rejection rates, or cancer between patients with or without a recurrence (Table 4),

nor did we find differences in delayed graft function or diabetes using logistic regression.

**Graft Function**

As predicted, proteinuria in patients with partial or no remission was higher than in patients with complete remission (Figure 4A). eGFRs of patients with complete remission were comparable to those of patients who did not experience recurrent FSGS (Figure 4B). For patients with a partial or no remission, eGFR was lower and progressively declined, especially in patients without remission. Other clinical parameters, such as BP and serum calcium, phosphate, and total cholesterol, are shown in Supplemental Figure 3, illustrating that patients with partial or complete remission, in most parameters, cluster with patients who did not experience a recurrence, whereas the mean



**Figure 2. | Recurrence of FSGS is associated with reduced graft survival, especially in patients with no response to treatment.** (A) Kaplan–Meier graft survival curve comparing patients with and without recurrent FSGS after kidney transplantation. (B) Kaplan–Meier graft survival curve comparing only patients with recurrent FSGS stratified by their treatment response. Areas around the curve represent the 95% confidence intervals.

Treatment	No Remission	Partial Remission	Complete Remission	Total
Plasmapheresis	7 (28)	11 (44)	7 (28)	25
Plasmapheresis + rituximab	16 (53)	9 (30)	5 (17)	30
Immunoadsorption <sup>a</sup>	2 (67)	1 (33)		3
Rituximab only		1 (50)	1 (50)	2
Plasmapheresis + cyclophosphamide	1 (100)			1
Steroids only	5 (83)	1 (17)		6
Cyclosporine <sup>b</sup>	2 (67)	1 (33)		3
No treatment	5 (100)			5
Total	38 (51)	24 (32)	13 (17)	75

<sup>a</sup>Two patients dependent on immunoadsorption had received plasmapheresis and rituximab treatment without remission; one patient had received only rituximab and immunoadsorption.  
<sup>b</sup>Patients were switched from oral tacrolimus to oral cyclosporine. Treatment was not given intravenously.

values of patients with recurrence and no response were often abnormal.

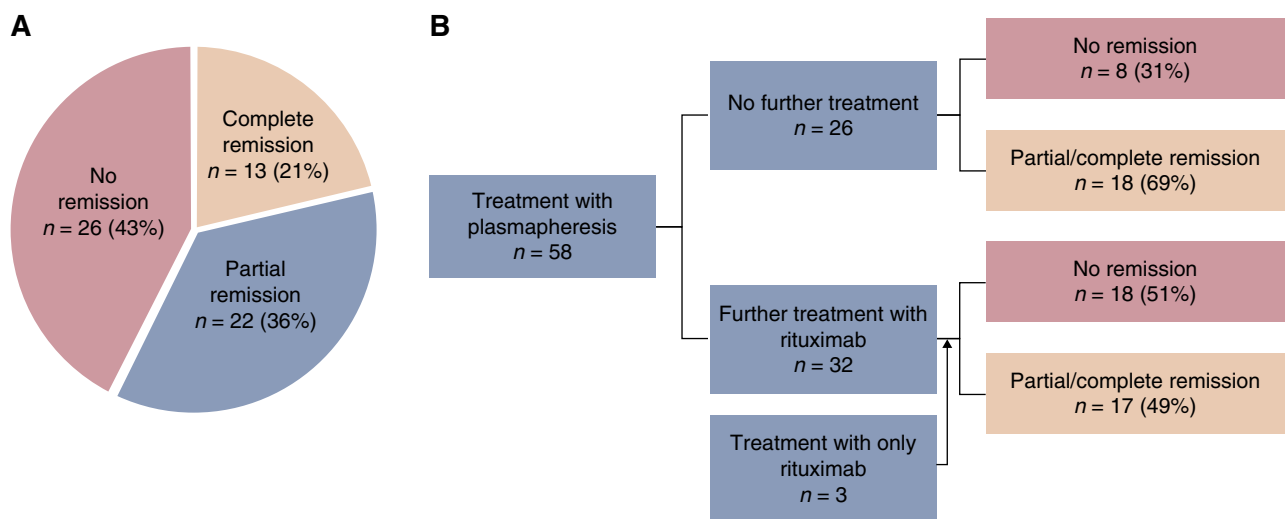
### Discussion

In this large, multicenter, international cohort of adults with idiopathic FSGS, we observed that FSGS recurred in 32% of patients, with subsequent graft loss in 39%. Multivariable analysis revealed older age at primary disease onset, native kidney nephrectomies, white race, and lower BMI at transplant to be associated with a higher risk for recurrence. Recurrent FSGS was most often treated with plasmapheresis with or without rituximab, and this regimen resulted in partial or complete remission in 57% of patients.

Previous studies on recurrent FSGS have reported a wide range of recurrence rates and potential predictors (Supplemental Table 1) (4–22). However, most of these studies have major limitations, including small sample size in single-center studies and poor data quality in registry-based analyses. A small sample size lowers the precision

of incidence estimates and results in broad confidence intervals (Supplemental Table 1). Furthermore, studies with modest sample sizes are not only underpowered to detect predictors (32), but also inflate effect sizes because of wider sample distributions (33,34), thus reducing the likelihood that a statistically significant result reflects a true effect. Lastly, small studies are limited in multivariable analysis in which adjustment of confounders can be performed. Registry studies have larger sample sizes, but suffer from potential FSGS misclassification and failure to capture cases of FSGS recurrence that do not lead to allograft loss (28), as suggested by the generally lower reported recurrence rates (24–27,31). Another source of bias is the inclusion of multiple transplants per patient (Supplemental Table 1) because it creates correlation within the data set and makes use of standard statistical tests and related *P* values invalid.

The analyses of our large data set showed that only a few of the previously described predictors of recurrence were independently associated with risk for FSGS recurrence. Contrary to the previously reported association between



**Figure 3. | Treatment of recurrent FSGS with plasmapheresis with or without rituximab leads to complete remission in only a minority of patients.** (A) Overall effect of treatment in patients treated with plasmapheresis and/or rituximab. (B) Flow chart of treatment outcome per treatment modality. One patient treated with plasmapheresis was also treated with cyclophosphamide, without remission.

**Table 4. Complications post-transplantation in all patients and according to FSGS recurrence**

Variable	Overall Cohort (n=176)	No Recurrence (n=119)	Recurrence (n=57)	Hazard Ratio (95% CI)	P Value
<b>Acute rejection</b>	29 (16)	23 (19)	6 (11)	0.63 (0.25 to 1.56) <sup>a</sup>	0.31
Cellular mediated	18 (62)	15 (65)	3 (50)		
Antibody mediated	11 (38)	8 (35)	3 (50)		
CMV	20 (11)	18 (14)	3 (5)	0.34 (0.09 to 1.15) <sup>b</sup>	0.08
BK viremia	10 (6)	5 (4)	5 (9)	2.69 (0.77 to 9.36)	0.12
Cancer	9 (5)	7 (6)	2 (4)	1.07 (0.22 to 5.17)	0.91
New-onset DM	21 (12)	13 (11)	8 (14)	NA	0.55
Delayed graft function	64 (38)	42 (36)	22 (41)	NA	0.26 <sup>c</sup>

Acute rejection, CMV, BK viremia, and cancer were assessed by Cox hazard regression. New-onset DM and delayed graft function were analyzed by logistic regression. 95% CI, 95% confidence interval; CMV, cytomegalovirus; DM, diabetes mellitus; NA, not applicable.

<sup>a</sup>Hazard ratio and P value are corrected for pretransplant HLA mismatch and pretransplant donor-specific antibody, by adding those variables to the regression model.

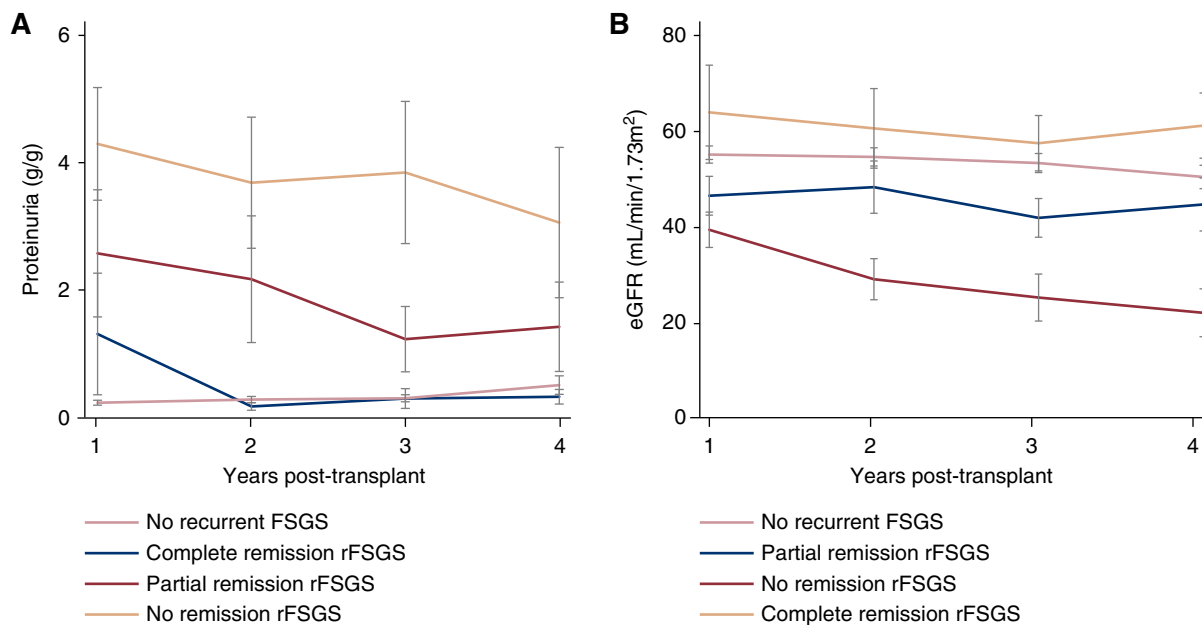
<sup>b</sup>Hazard ratio and P value are corrected for pretransplant recipient/donor CMV IgG status.

<sup>c</sup>P value is corrected for donor type and age.

younger age at disease onset and higher risk of recurrence (4,6,14,15,17,22,26,27), patients in our cohort with older age at disease onset had a higher HR of recurrence. This conflicting finding could be due to our different study population (adults with mixed race/ethnicities), our stringent exclusion of secondary FSGS that is more common at older age, or our ability to perform multivariable analyses. On the other hand, only few of the patients in our cohort were tested for genetic causes of FSGS. The fact that older age at onset was a predictor of recurrence may capture the fact that some cases diagnosed at younger age were, in fact, genetic and less likely to recur (35–37). Therefore, our

result regarding age at diagnosis should be considered with caution.

A higher rate of FSGS recurrence in white recipients has previously been reported in United States studies (11,27,38), whereas data from New-Zealand and Australia showed a higher risk in nonwhite recipients (26). There is no consensus on how ethnicity affects recurrent FSGS. Black (or mixed race) patients, the second-largest race group in our cohort, have a higher prevalence of *APOL1* high-risk alleles that are associated primarily with FSGS (39). Because *APOL1*-related FSGS is not associated with greater risk of recurrence post-transplantation (due to the



**Figure 4. | Clinical outcomes of patients who achieve complete remission of rFSGS are comparable with patients who did not experience recurrence.** Comparison of levels of (A) proteinuria and (B) eGFR calculated by Modification of Diet in Renal Disease Study (MDRD) in patients without recurrence with patients with recurrent FSGS (rFSGS) stratified by their response to treatment. eGFR after graft loss was imputed with a value of 5 ml/min per 1.73 m<sup>2</sup>. Error bars represent SEMs.



effect of *APOL1* alleles in the kidney itself [36,37,40]), this could contribute to our observed difference.

In agreement with our results, nephrectomy of native kidneys has been associated with a higher risk for recurrence (10,17). One of the hypotheses is that the native kidneys left *in situ* may act as a “sponge” to absorb the potential pathogenic circulating factor, leading to reduction of the free circulating factor that may injure the transplanted kidney (41). Nonetheless, the incidence of nephrectomy of native kidneys is low (7% in our cohort) and it is usually only performed in severe disease, which could both bias outcomes.

We found that patients with a recurrence had, on average, a lower BMI at time of transplant. Despite our careful selection of our cohort, it is possible that some patients with obesity-induced FSGS were misdiagnosed as primary FSGS, explaining this finding. Obesity is known to cause secondary FSGS through increased mechanical and metabolic stress on glomeruli, although some of these patients are difficult to differentiate from primary FSGS because obesity-induced FSGS can manifest with nephrotic-range or even massive proteinuria (42,43). Regardless, patients with high BMI are not exempted from recurrence as six patients in our cohort with BMI >30 kg/m<sup>2</sup> at transplantation experienced recurrent FSGS.

Our data reflect the lack of official guidelines on the treatment of recurrent FSGS. Although most centers used plasmapheresis with or without rituximab, treatment intensity and duration varied considerably. This nonstandardized treatment approach could explain the lower rate of treatment response (57%) compared with previous literature, especially regarding the achievement of complete remission (44–46). An alternative hypothesis is that prior reports have a publication bias, which highlights the importance of systematic, unbiased, multicenter approaches to data collection, such as TANGO. Interestingly, although prior literature suggested the use of high-dose intravenous cyclosporine to treat FSGS recurrence (44,47,48), none of our included patients received this treatment, possibly because of concern for nephrotoxicity and/or logistical challenges with continuous intravenous infusion (49). Irrespective of the regimen, response to treatment was associated with graft survival, as graft loss mainly occurred in patients who failed to enter remission.

Our study has some limitations, including its retrospective design, which could have resulted in selection bias. Further, adjustment for all potential confounders was not possible. Selection of patients with FSGS by history and pathology was performed by clinicians in the participating centers and was not centralized. Although detailed history on secondary causes and biopsy reports were obtained to minimize variation, differences across center may still be present. We were not able to correct our analyses for center variation because the number of patients per center was low and we had a high number of participating centers. Instead, we adjusted for the continent of residence. Another limitation is the lack of genetic testing in most patients, which might create bias as genetic FSGS usually does not recur after transplantation (35–37).

Herein, we demonstrate that international, multicenter collaborations as in the TANGO study are logistically possible and scientifically pivotal to better understand the

natural history of rare diseases such as FSGS recurrence. Besides clinical information, a large number of biologic samples from patients with FSGS are currently being collected as part of the TANGO study, which will allow further investigation into the pathophysiologic mechanisms underlying recurrent FSGS, including validation of prior biomarkers and expansion of the biologic understanding of this challenging disease.

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#### Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.08970719/-/DCSupplemental>.

Supplemental Table 1. Published studies on incidence of recurrent FSGS since 1990, including >20 participants.

Supplemental Table 2. Missing data in predictors for patients without and with recurrent FSGS.

Supplemental Table 3. Univariable logistic regression for any response to treatment.

Supplemental Figure 1. Flow chart of the study population.

Supplemental Figure 2. Prior graft loss owing to FSGS recurrence and risk of recurrence in subsequent graft.

Supplemental Figure 3. Clinical outcomes post-transplantation in patients with a functioning allograft.

Supplemental Appendix 1. Supplemental methods.

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## **Supplemental Material – Table of Contents**

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**Supplemental Methods**

**Supplemental Table 1. Published studies on incidence of recurrent FSGS since 1990 including > 20 subjects.**

Year	Population	Total n	Incidence	95% CI	Multiple Tx	Analysis	Ethnicity	Risk factors
1990 <sup>4</sup>	Children + Adults	59	22%	11-33	Yes	Univariable	Unknown	Younger age onset FSGS, Mesangial prominence
1990 <sup>5</sup>	Children + Adults	25	48%	28-68	Yes	Univariable	Unknown	
1991 <sup>6</sup>	Children	40	15%	4-26	Yes	Univariable	Mixed	Younger age onset FSGS
1991 <sup>7</sup>	Adults	47	30%	17-43	Yes	Univariable	Unknown	Shorter duration of kidney disease
1992 <sup>9</sup>	Children	132	21%	14-27	Yes	Univariable	Mixed	Rapid progression to ESKD
1992 <sup>11</sup>	Children + Adults	78	25%	22-42	Yes	Univariable	Mixed	Rapid progression to ESKD, white ethnicity
1996 <sup>10</sup>	Children + Adults	114	20%	13-28	Yes	Multivariable	Mixed	Nephrectomy native kidneys
1999 <sup>8</sup>	Children	29	52%	34-70	No	Univariable	Unknown	Older age onset FSGS, rapid progression to ESKD*
2001 <sup>12</sup>	Adults	27	48%	29-67	No	Multivariable	Asian	Higher donor age
2006 <sup>13</sup>	Adults	35	34%	19-50	Yes	Univariable	Unknown	Higher donor age
2008 <sup>16</sup>	Children	37	43%	27-59	No	Univariable	Mixed	
2009 <sup>14</sup>	Children + Adults	30	47%	29-65	No	Univariable	Mixed	Younger age at transplant, lower number HLA mismatches, living-related donor, higher pre-transplant peak proteinuria, treatment with Cyclosporine before transplant.
2009 <sup>17</sup>	Adults	22	23%	5-40	No	Univariable	Unknown	Younger age onset FSGS, rapid progression to ESKD, living donor, nephrectomy native kidneys, higher pre-transplant peak proteinuria, female gender
2010 <sup>15</sup>	Adults	52	23%	12-34	Yes	Univariable	Unknown	Younger age onset FSGS, male gender, duration of dialysis
2010 <sup>18</sup>	Adults	66	23%	13-33	No	Univariable	Mixed	
2010 <sup>19</sup>	Children + Adults	77	55%	43-66	No	Univariable	Unknown	
2011 <sup>22</sup>	Children + Adults	131	17%	10-23	Yes	Univariable	Mixed	Younger age at transplant
2012 <sup>23</sup>	Children + Adults	107	28%	20-37	No	Univariable	Asian	
2013 <sup>20</sup>	Children + Adults	66	42%	31-54	No	Multivariable	Mainly white	Lower serum albumin at diagnosis
2018 <sup>21</sup>	Children	158	41%	33-48	No	Multivariable	Mixed	Histology of minimal change disease compared to FSGS

CI, confidence interval; FSGS, focal segmental glomerulosclerosis; Tx, transplants.

\*The abstract of this article has different outcomes than reported in the text. Risk factors are selected from the main text of the article.

**Supplemental Table 2. Missing data in predictors for patients without and with recurrent FSGS**

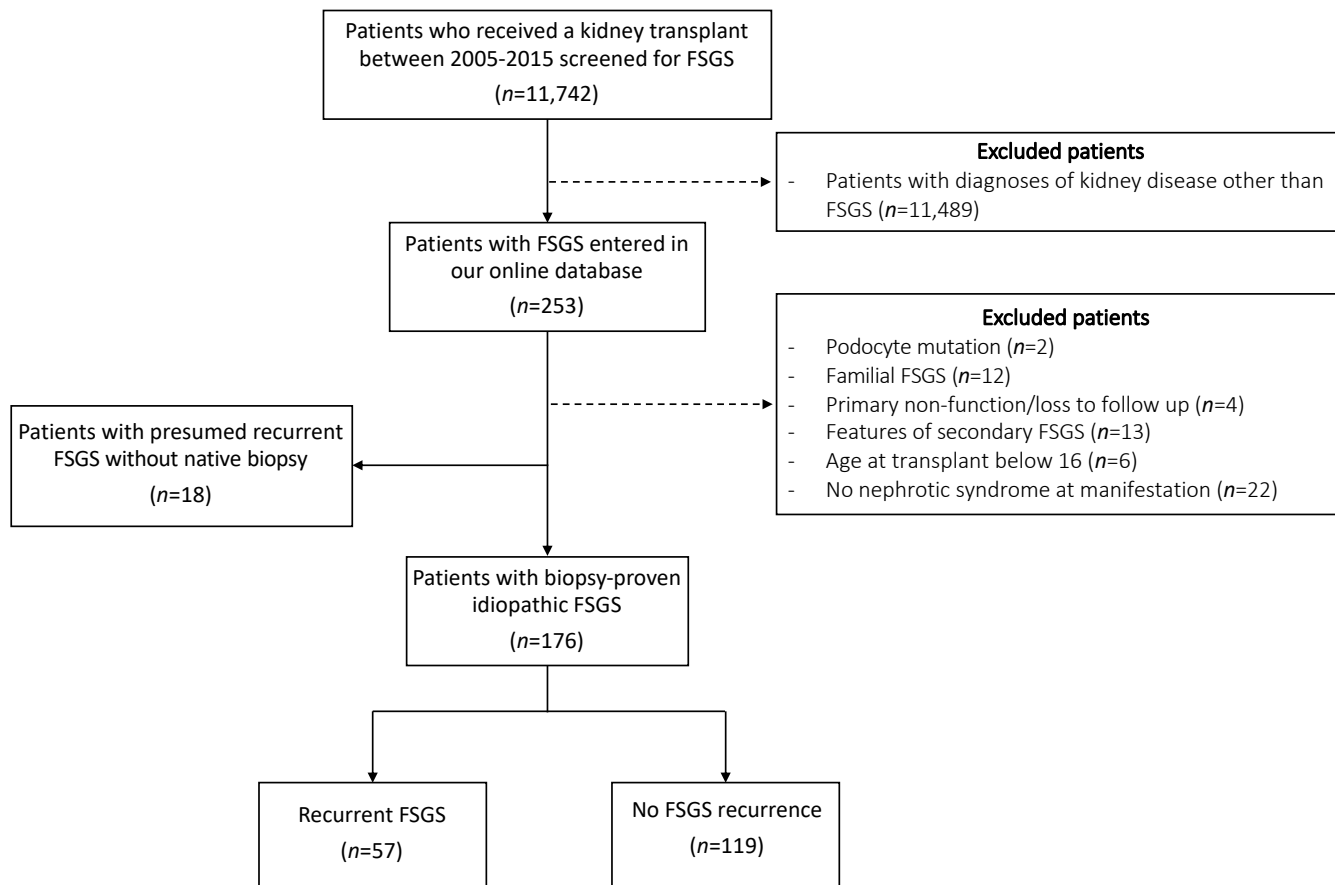
Variable	No recurrence (n=119)	Recurrence (n=57)	P-value
Age at diagnosis	2 (2)	2 (4)	0.596
White race	10 (8)	9 (16)	0.193
BMI	0 (0)	1 (2)	0.324
Time on dialysis	0 (0)	2 (4)	0.104
Nephrectomy of native kidneys	1 (1)	0 (0)	1.000
Age donor	11 (9)	3 (5)	0.553
HLA-mismatch	7 (6)	3 (5)	1.000
DSA at transplant	10 (8)	5 (9)	1.000
Use of induction	3 (3)	0 (0)	0.552
Immunosuppressive regimen	1 (1)	0 (0)	1.000
Continent	0 (0)	0 (0)	NA
Type of transplant	0 (0)	0 (0)	NA
Prophylactic plasmapheresis	0 (0)	0 (0)	NA
<b>Total missing values (% of all data)</b>	<b>45 (3)</b>	<b>25 (3)</b>	

**Supplemental Table 3. Univariable logistic regression for any response to treatment.**

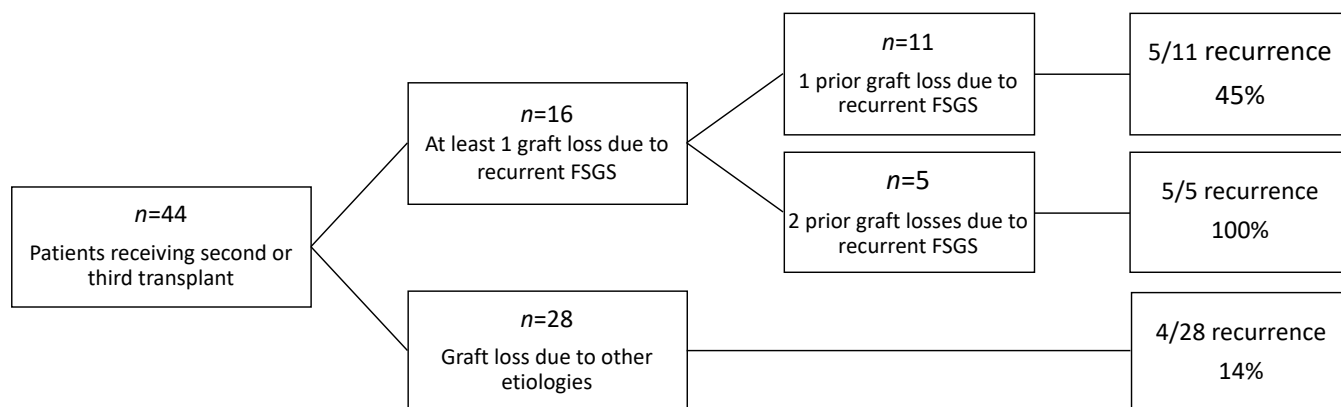
Variable	No response to treatment (n=26)	Any response to treatment (n=35)	Odds ratio (95% CI)	P-value
Recurrence within 6 months	20 (77)	28 (80)	0.83 (0.24-2.86)	0.772
Age at transplantation, <i>per year</i>	41 (28-56)	33 (27-44)	0.97 (0.93-1.01)	0.104
Female gender	8 (31)	18 (51)	2.38 (0.82-6.91)	0.110
White race	15 (68)	19 (59)	0.68 (0.22-2.14)	0.511
Geographical location				
USA	7 (27)	13 (37)	Ref	Ref
Brazil	10 (38)	16 (46)	0.86 (0.26-2.89)	0.810
Europe	9 (35)	6 (17)	0.36 (0.09-1.43)	0.146



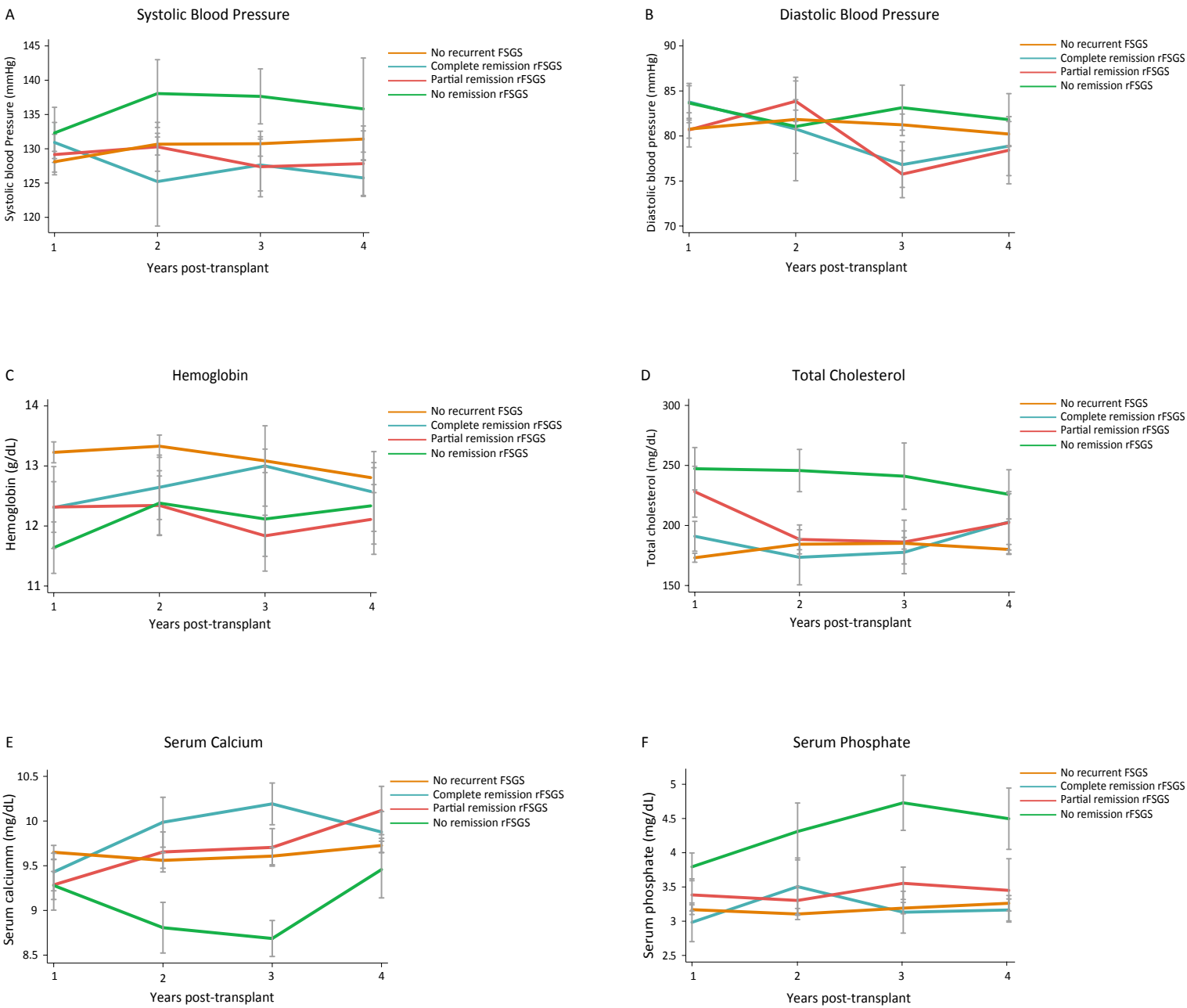
**Supplemental Figure 1. Flowchart of the study population.**



**Supplemental Figure 2. Prior graft loss due to recurrent FSGS and risk of recurrence in subsequent allografts.**



**Supplemental Figure 3. Clinical outcomes post-transplantation in patients with a functioning allograft.** Comparison of levels of (A) systolic- and (B) diastolic blood pressure, (C) Hemoglobin, (D) cholesterol, (E) calcium and (F) phosphate levels in patients without recurrence with patients with recurrent FSGS stratified by their response to treatment of recurrent FSGS. Error bars represent standard errors. FSGS, focal segmental glomerulosclerosis; rFSGS, recurrent focal segmental glomerulosclerosis.



## Supplemental Methods

### Collected data

Collected data comprised patient demographics, medical history, information on native biopsy, transplantation characteristics, immunosuppressive regimen and data collected at annual post-transplant visits including clinical parameters, rejection, FSGS recurrences and other complications. Patients were censored at the first of graft loss, patient death, loss to follow-up, or in January 2019.

### Patient selection (continued)

In two participating centers, Hospital do Rim and Cajuru University Hospital, both in Brazil, native kidney biopsies were not available for all patients. Therefore, these two centers were excluded from the primary analysis on incidence and predictive factors of FSGS. However, most of their patients with a pretransplant kidney disease history highly suspicious of FSGS (*e.g.*, sudden onset of nephrotic syndrome) and who had nephrotic-range proteinuria post-transplant, underwent an allograft biopsy for diagnosis. If this post-transplant biopsy showed FSGS features, the patient was included in analyses on treatment efficacy of recurrent FSGS.

### Predictor selection

Informed by prior literature and clinical practice,<sup>4-22,24-27,34</sup> we selected and collected data on the following potential predictors of recurrent FSGS: age at disease onset, race/ethnicity, BMI at time of transplantation, time to ESKD, dialysis vintage, nephrectomy of native kidneys, type of donor (living vs. deceased), age of the donor, HLA mismatch, donor-specific antibodies (DSA) prior to transplant, use of induction therapy, pretransplant prophylactic plasmapheresis and initial immunosuppressive regimen. To account for the different geographical regions in which the patients were followed-up, continent of residence was also added as a predictor.

### Data storage

All data was stored in an online database that was designed for TANGO-study, using REDCap™ (Research Electronic Data Capture): a secure, HIPAA-compliant web-based application<sup>48</sup> hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure and Services (ERIS) group.

Investigators received access to the secured website to enter patient data online, and/or to access data only from their center. Upon downloading of the dataset, event dates were date-shifted to further de-identify the dataset to ensure confidentiality of participants.

### Definitions

Recurrent FSGS was detected by nephrotic-range proteinuria post-transplant and was confirmed by kidney biopsy showing either FSGS lesions by light microscopy or diffuse foot process effacement by electron microscopy. In 9 cases, FSGS was not biopsy-confirmed but was immediately treated with plasmapheresis or immunosuppression, due to the high clinical suspicion for recurrent FSGS. These patients were considered to have recurrent FSGS. Three patients developed proteinuria while being on mTOR inhibitors, and proteinuria decreased after switching to another immunosuppressant agent (tacrolimus). These three patients were not considered to have recurrent FSGS.

Treatment response of recurrent FSGS was divided into complete, partial, or no remission. Complete remission was defined as a reduction of proteinuria below 0.3 g/24h (or 0.3 g/g of urinary creatinine) with stable eGFR (*e.g.*, maximum decline of 15%). Partial remission was defined as a reduction of proteinuria below 2.0 g/24h (or 2.0 g/g), or a reduction of proteinuria of at least 50% of the highest value to a level below 3.5g/24h (or 3.5 g/g), both with stable eGFR. eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) Study equation.<sup>49</sup>

Delayed graft function was defined as the need for hemodialysis within the first week post-transplant. Acute antibody- or cellular-mediated rejection was recorded if confirmed on kidney biopsy by the pathologist of the corresponding center. Borderline rejection was not considered acute rejection. New onset diabetes was defined as a new and persistent elevation of blood glucose levels post-transplantation requiring glucose-lowering medication.

### Potential sources of Bias

We implemented the following strategies to avoid potential sources of bias: Centers were instructed to chronologically add patients according to their date of transplant, to avoid selection bias towards patients who had a recurrence. We recorded detailed medical histories to be able to make a proper evaluation for secondary causes of FSGS. Review of histories and biopsies of patients included in our database was done in a blinded fashion for the primary outcome of post-transplant FSGS recurrence. Each case of post-transplant recurrence was reviewed and when questions were raised (*e.g.*, no treatment was given, recurrence occurred very late after transplant), clarification was asked from the specific center to verify it was a true recurrence. Clarification of centers on specific patients was also asked when yearly post-transplant proteinuria values suddenly increased and persisted without clear cause, but no recurrent FSGS was recorded. Analyses to graft failure and complications post-transplant were corrected for the most important confounders known from literature. The multi-center setup of this study over multiple continents was done to make sure many ethnical groups were present to avoid population bias. Unfortunately, some ethnical groups (especially patients with an Asian background) were still underrepresented. An analysis plan with clearly defined outcome and predictors (selected from literature) was made before the start of data-analysis and was followed throughout the analysis of data.



## Imputation

Little's missing completely at random (MCAR) test was performed on all predictors and outcome to investigate randomness of missing data, and resulted in a significant outcome ( $p=0.0068$ ), which implies that the pattern of missing data was not completely at random. However, detailed analysis of missing data showed a low frequency of missing data (overall 3%) and Fisher's exact test showed no difference per predictor between recurrence groups (Supplemental Table 2), after which we proceeded with imputation. STATA's multiple imputation by chained equations (MICE) procedure was used to impute missing categorical, ordinal, normal continuous and non-normal continuous variables by logistic regression, ordinal regression, linear regression and predictive mean matching, respectively. Imputations were made using all predefined predictors, including recurrence and graft failure. For each missing value, 100 values were imputed. In case of perfect prediction, augmentation was performed to avoid bias in imputations. Imputations were graphically assessed on outliers and variances and coefficients were checked on agreement.

## Sensitivity analyses

Because missing data was imputed by MICE, we performed a sensitivity analysis to determine the impact of the chosen method for handling missing data. Complete case analysis on the final model (geographic location of center, age at diagnosis FSGS, white race, BMI and nephrectomy of native kidneys) resulted in an analysis of 151 patients. Similar to the imputed model, significant  $p$ -values for all variables were observed, except for nephrectomy of native kidneys (95% CI: 0.62-5.85). An explanation for the difference in outcome between complete case and imputed model was found in the pattern of missing data: in 25 patients who were excluded from the complete case multivariable analysis due to missing in one of the parameters, 5 patients had a nephrectomy of native kidneys (in the total cohort, 12

patients had a nephrectomy). Therefore, analysis of imputed data for this variable seems more reliable than complete case multivariable analysis.

In our analysis plan, we had planned to perform a sensitivity analysis on the multivariable model, by performing the final multivariable model on the patients of each possible combination of two continents, to see whether significance of variables would hold. When we executed this method, most significant parameters held, except nephrectomy when patients from Europe or the United States were removed, and race when patients of the USA were removed. The explanation for this can be found in the numbers of nephrectomies done, as there were none performed in Brazil. When removing United States or Europe, the total number of patients with a nephrectomy got too low (5 or 7) for analysis. Regarding race, most non-white patients were included in the USA, while only one non-white person was included from Europe. Therefore, when USA patients were removed from the total sample size, significance for white race did not hold.

#### Ethical considerations

The overall protocol of TANGO-study was submitted and approved by the ethical committee of the Partners Human Research Committee (PHRC) at the Brigham and Women's hospital in Boston (protocol number: 2015P000993), and at each participating center. In one participating center, the University Medical Center Groningen, ethical approval was waived by the Medical Ethics review Board (METC UMCG). All protocols are in accordance with International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.