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Risk factors associated with allograft failure in pediatric kidney transplant recipients with focal segmental glomerulosclerosis

Lee Jin Koh[1,2] | Karen Martz[3] | Tom David Blydt-Hansen[4] | on behalf of the NAPRTCS Registry Investigators

[1]Paediatric Nephrology, National University Hospital System, Singapore, Singapore

[2]Pediatric Nephrology, BC Children's Hospital, Vancouver British Columbia, Canada

[3]EMMES Corporation, Rockville, Maryland United States of America

[4]Multi Organ Transplant Program, BC Children's Hospital, Vancouver British Columbia, Canada

Correspondence
Tom David Blydt-Hansen, Division of Paediatric Nephrology, British Columbia Children's Hospital, University of British Columbia, Room K4-149, Ambulatory Care Building, Vancouver, BC, CAN V6H3V4, Canada.
Email: tom.blydthansen@cw.bc.ca

Abstract

Background: With improved outcomes for children transplanted with FSGS since previous NAPRTCS registry reports, this study re-evaluates the association of living donation, immunosuppression, and DGF on graft survival.

Setting: Patients transplanted between 2002 and 2016, comparing FSGS diagnosis vs other glomerular diseases.

Methods: Primary outcomes were allograft survival and FSGS recurrent-free graft survival. Potential risk factors were obtained at the time of transplant and up to 30 days post-transplantation. Analysis considered a priori that DGF may be a proxy for severe FSGS recurrence. Multivariable survival models for outcome were tested for sensitivity without/with DGF to determine features independent of recurrence.

Results: From the larger cohort of 3010 patients, 5-year graft survival in children with FSGS (n = 455) was worse (74.3%) compared with other glomerular diseases (87.1%, n = 690) (HR 1.45, $P = 0.033$). Modeling all glomerular diseases, survival risk was associated with deceased donor (HR 1.83, $P = 0.002$), re-transplantation (HR 1.58, $P = 0.013$), and recipient age (HR 1.06/y, $P = 0.002$). The living donor advantage was not confirmed in a FSGS model (HR 1.51 for deceased, $P = 0.12$). DGF was highly associated with graft failure (HR 4.39, $P < 0.001$) and independent of re-transplant history but not FSGS diagnosis. Induction agents or primary immunosuppression choices were not associated with survival.

Conclusion: Graft survival rates have improved since the previous report. Living donor did not predict graft failure, but there remains no survival advantage. DGF was the primary independent predictor for graft loss secondary to FSGS recurrence, consistent with DGF being a proxy for severe recurrent disease.

KEYWORDS

focal segmental glomerulosclerosis, FSGS, pediatric kidney transplant, recurrence of original disease

Abbreviations: ALG, antilymphocyte globulin; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; ATG, antithymocyte globulin; CI, confidence interval; DGF, delayed graft function; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio; ILR2B, interleukin receptor 2 blocker; NAPRTCS, North American Pediatric Renal Trials and Collaborative Studies; non-GN, non-glomerular kidney diseases; Other GN, non-FSGS glomerulonephropathies; SID, systemic inflammatory disease; UNOS, United Network for Organ Sharing; USRDS, United States Renal Data System.

1 | INTRODUCTION

Recurrence of FSGS is an important cause of graft failure in children post–kidney transplantation. Prior reports from international transplant registries indicate recurrence rates of 15%-36%,[1-3] with higher rates of recurrence noted in children with idiopathic FSGS. The PodoNet Registry cohort reported a post-transplant disease recurrence rate of 25.8% in patients without a confirmed genetic disorder compared to 4.5% in patients with a genetic diagnosis.[4]

Analysis of the NAPRTCS registry of children with FSGS who were transplanted between 1987 and 2000 revealed a loss of survival advantage in transplants from living kidney donors, compared with transplants from deceased donors.[5] More recent reports have indicated that FSGS recurrence may be more common in transplants using live donor kidneys, but despite this, graft survival was improved.[3] This may reflect changes in the landscape of immunosuppression induction and maintenance therapy over the last 15 years. Whether improved survival is due to changes in recurrence risk is unclear. Overall, outcomes from pediatric kidney transplantation have improved significantly since the original 2001 report by Baum, et al, and evaluation of contemporary risk factors that may predict allograft outcome in this population has not been recently reported.

Using the NAPRTCS registry data, this study proposes to re-assess the association of potential risk factors for adverse outcome in children with FSGS who have been transplanted since 2001. In particular, we will examine the impact of living donor source, primary immunosuppression, and DGF on overall survival and FSGS recurrence-free graft survival.

2 | METHODS

2.1 | Study population

Since 1987, the NAPRTCS registry has maintained a voluntary registry that includes kidney transplant recipients from North America, including 145 transplant centers in the United States, Canada, Mexico, and Costa Rica. Kidney transplant centers are eligible for participation with >4 pediatric patients receiving renal allografts annually and maintain local research ethics approval. Since the last NAPRTCS report on FSGS outcomes included patients transplanted before 2000, we identified patients for a contemporary analysis who were transplanted between January 1, 2002, and December 31, 2016, over a similar period of time.

Data are collected 1-month post-transplant and at 6-month intervals, and these data include transplant characteristics, immunosuppression regimen, graft rejection episodes, graft failure, and patient death. Outcomes for FSGS patients were compared to patients with Other GN and non-GN. Kidney diseases coded under Other GN were as follows: familial nephritis Alports syndrome, congenital nephrotic syndrome, membranoproliferative GN type 1, membranoproliferative GN type 2, membranous nephropathy, idiopathic crescentic GN, chronic GN, SID w/SLE nephritis, SID w/Henoch-Schonlein purpura nephritis, SID w/Bergers nephritis, SID w/Wegener's granulomatosis, diabetic glomerulonephritis, sickle cell nephropathy, Drash syndrome. All other diagnoses were coded as non-GN. NAPRTCS does not record genetic testing results; hence, we were not able to differentiate between idiopathic and genetic forms of FSGS.

2.2 | Analysis

The primary outcome of the analysis was allograft survival (including death with function), and secondary outcomes included patient survival and acute rejection. NAPRTCS does not currently capture data to confirm the presence of early disease recurrence (eg, proteinuria), but identifies primary disease recurrence among potential causes at the time of allograft failure. Allograft failure attributed directly to recurrent FSGS was examined by censoring for allograft failure from other causes. Graft survival was defined as time from transplantation to end of the study period, time of alternative renal replacement therapy, death with function or at the time of last follow-up with transfer to a non-participating center.

Potential risk factors associated with allograft survival were captured from data obtained at the time of transplant and up to 30 days post-transplantation. Data analysis was performed using standard univariate and multivariable statistical methods. Kaplan-Meier estimates of graft survival, acute rejection, and patient survival were constructed. Potential risk factors identified on univariate testing ($P < 0.1$) were included in multivariable analysis. Cox proportional hazards regression models were used to describe relative risks of allograft failure in patients with a glomerular disease diagnosis only (ie, excluding non-GN diagnosis) and were adjusted for various baseline and transplant characteristics. We included DGF as a post-transplant covariate, with the a priori assumption that DGF may be a surrogate indicator for early severe recurrent disease. DGF was defined as requirement for dialysis in the first month after transplant. Modeling was first completed with baseline and transplant characteristics, and then, the sensitivity of features was tested for independence by adding DGF to the model. Features confounded by addition of DGF were considered as potentially specific to risk from severe recurrence. Data were analyzed using SAS System for Windows, v 9.3 (SAS Institute), with P values < 0.05 considered statistically significant.

3 | RESULTS

3.1 | Patient and transplant characteristics

There were 3010 incident transplants recorded during the study period, of which 455 had FSGS, 690 had Other GN, and 1865 had non-GN as the primary diagnosis. Median follow-up time for the cohort was 2.5 years (0.0-14.3 years). Cohort characteristics are summarized in Table 1.

Patients with FSGS most resembled Other GN patients demographically. They had older age at transplantation (median age 14.8 and 14.4 years, vs. 11.7 years for non-GN, $P < 0.001$) and

TABLE 1 Baseline demographics, n = 3010

Demographics	FSGS, n = 455	Other GN, n = 690	Non-GN, n = 1865
Male sex (%)	256 (56.3)	317 (45.9)	1187 (63.6)
Race (%)			
White	176 (38.7)	322 (46.7)	1174 (62.9)
African American	152 (33.4)	140 (20.3)	279 (15)
Other	127 (28.0)	228 (33.0)	412 (22.1)
Age at first transplant (min, max)	14.8 (1.1, 22.4)	14.4 (0.0, 27.5)	11.7 (0.2, 23.4)
Native nephrectomy (%)	137 (30.1)	182 (26.4)	376 (20.2)
Preemptive transplant (%)	39 (8.6)	61 (8.8)	496 (26.6)
Transplant year (%)			
2002-2006	251 (15.2)	358 (21.6)	1042 (63.1)
2007-2011	150 (15.9)	221 (23.4)	571 (60.6)
2012-2016	54 (12.9)	111 (26.6)	252 (60.4)
Donor source (%)			
Living donor/parent	111 (24.4)	216 (31.3)	698 (37.4)
Living donor/sibling	11 (2.4)	13 (1.9)	55 (2.9)
Living donor/other related	24 (5.3)	40 (5.8)	124 (6.6)
Living donor/unrelated	18 (4)	39 (5.7)	119 (6.4)
Deceased donor	287 (63.1)	370 (53.6)	852 (45.7)

increased proportion of native nephrectomies (30.1% and 26.4% vs 20.2%; $P < 0.001$). There was a larger proportion of patients of African American race in the FSGS group (33.4%) compared to the Other GN (20.3%) and non-GN groups (15%). Mean height and weight *Z* scores were significantly lower in children with a non-GN diagnosis (−1.47; −0.70) compared to a GN (−0.89; −0.49) or FSGS diagnosis (−1.03; −0.41) ($P < 0.001$; $P < 0.001$ for height and weight, respectively).

Children with a non-GN diagnosis were more likely to have received a preemptive transplant (26.6%) compared to Other GN or FSGS diagnosis (8.8 and 8.6%, respectively; $P < 0.001$). A greater proportion of children with FSGS as the primary diagnosis were transplanted with a deceased donor kidney (63.1%), compared with Other GN and non-GN (53.6% vs 45.7%, respectively; $P < 0.001$). Choice of induction immunosuppression and primary maintenance immunosuppression was not markedly different in children with FSGS compared to children who had Other GN (Table 2). A significantly higher proportion of FSGS patients were reported having DGF during weeks 1-4, compared to Other GN patients (14.1% vs 8.3%, $P < 0.001$).

3.2 | Patient and allograft survival

There was no significant difference in patient survival comparing the FSGS group, the Other GN, and non-GN groups ($P = 0.358$) (Figure 1). Pairwise comparison between FSGS and Other GN patients identified significantly worse graft survival after living donor transplantation, with 5-year graft survival of 74.3% for FSGS patients of vs 87.1% for Other GN ($P = 0.006$). This difference in 5-year graft survival was not statistically significant in the case of deceased donor transplants (73.6%, vs 77.2% for FSGS, Other GN, respectively; $P = 0.212$, Figure 2). Freedom from acute rejection (Figure 3)

TABLE 2 Post-transplant characteristics of children with FSGS and Other GN, n = 1145

Demographics	FSGS n = 455(%)	Other GN n = 690 (%)	*P*
Induction immunosuppression			
None	172 (37.8)	302 (43.8)	0.057
ATG/ALG	88 (19.3)	118 (17.1)	0.125
ILR2B	155 (34.1)	202 (29.3)	0.382
Other induction	22 (4.8)	52 (7.5)	0.155
More than 1 type	14 (3.1)	12 (1.7)	0.079
Missing	4 (0.9)	4 (0.6)	0.553
Primary immunosuppression			
Tacrolimus	309 (67.9)	484 (70.1)	0.060
Cyclosporine	37 (8.1)	40 (5.8)	0.657
Sirolimus	4 (0.9)	8 (1.2)	0.136
More than 1 type	48 (10.5)	48 (7.0)	0.650
None of the above	57 (12.5)	110 (15.9)	0.040
Dialysis during weeks 1-4			
Yes	64 (14.1)	57 (8.3)	<0.001
No	373 (82)	591 (85.7)	
Missing	18 (4.0)	42 (6.1)	

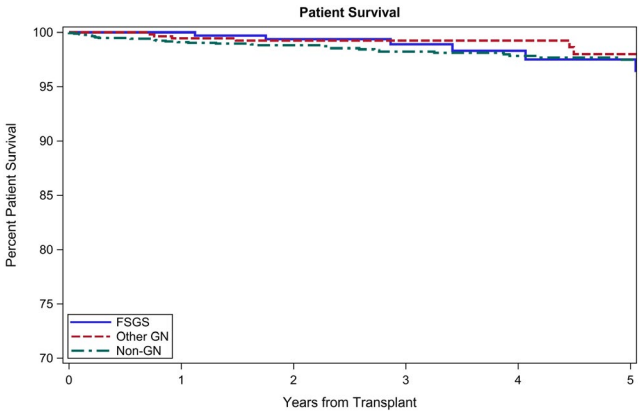

FIGURE 1 Kaplan-Meier patient survival curves from time of transplant, comparing FSGS, Other GN and non-GN patients, up to 5 years post-transplant. Survival curves show no significant differences in patient survival in the first 5 years post-transplant

was also similar between FSGS and Other GN and was superior in the non-GN transplant recipients by comparison ($P = 0.007$).

Table 3 summarizes the causes of graft failure in the three groups. In the FSGS patients, graft failure due to recurrence of the original disease was substantially more common than in Other GN or non-GN diagnosis (42.9%, vs 6.9% and 1%, $P < 0.001$). In a subset of 12 FSGS patients who were re-transplanted following graft failure (seven from recurrent FSGS), 2 (16.7%) have reported graft failure, with a median follow-up time of 29.5 months. In these cases, graft failure was attributed to chronic rejection after patient discontinued medication and ATN/unknown. Rejection was an important cause of graft failure in both populations, more so in Other GN patients (54.2%) than FSGS (33.8%), although not significantly different ($P = 0.132$; $P = 0.339$ for chronic and acute rejection, respectively).

Graft survival was modeled by Cox proportional hazards, for patients with FSGS and Other GN diagnosis. Univariate analysis identified worse graft survival in FSGS patients compared with Other GN (HR 1.76, $P < 0.01$), which remained significant after adjusting for additional baseline and transplant characteristics but not including DGF post-transplant (HR 1.45, CI 1.03-2.03, $P = 0.033$) (Table 4). This adjusted model shows worse graft survival associated with older age (HR 1.06 per year, $P = 0.002$), deceased donor (HR 1.83, $P = 0.002$), and history of prior transplantation (HR 1.58, $P = 0.013$). The addition of post-transplant DGF to the multivariable model identifies an interaction with the diagnosis of FSGS. In the model that includes DGF, the reduced graft survival in patients with FSGS is not confirmed (HR 1.12, $P = 0.564$), indicating the FSGS diagnosis is not independent from DGF. Prior independent association of age, donor source and prior transplant were maintained, and DGF was an additional risk for graft loss (HR 4.44, $P < 0.001$). Neither of the models including or excluding DGF showed a significant association for race, either type of induction agent or baseline initial immunosuppression.

We then modeled graft survival only in patients with FSGS diagnosis (Table 5), without and with DGF. A significant survival advantage was not confirmed for living donor transplants (HR 1.51 for deceased donor, $P = 0.118$). Worse graft survival was only significantly associated with prior transplantation (HR 1.68, $P = 0.045$). Addition of DGF did not reveal any further interactions in the model. Prior transplantation remained significantly associated with graft survival (HR 1.94, $P = 0.014$), as was DGF (HR 4.39, $P < 0.001$). Recipient age and donor source were not associated with increased risk of graft failure in FSGS only patients. There continued to be no association with graft survival and race, type of induction agent or choice of primary immunosuppression.

We further tested whether baseline or transplant characteristics were specifically associated with graft loss from recurrent disease (n = 33 events), using a restricted definition of graft loss from recurrent disease by censoring for graft failure from other causes (Table S1). DGF was the only significant risk factor and was highly associated with graft failure from recurrent FSGS (HR 7.33, CI 3.23-16.62, $P < 0.01$; Table S1). Neither donor source, race, retransplant, type of induction agent, nor choice of primary immunosuppression was significantly associated with graft failure from recurrent FSGS.

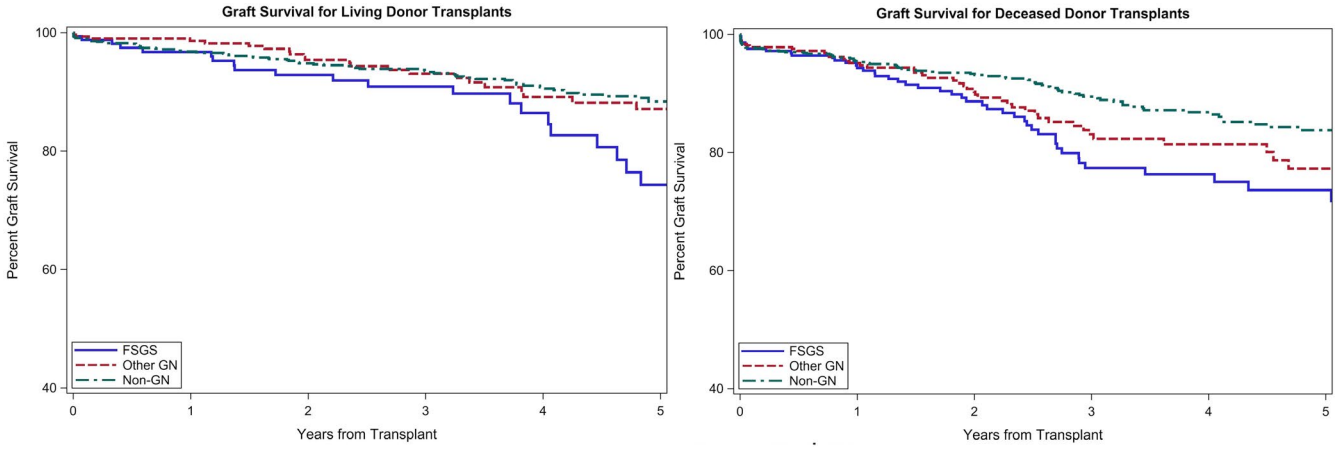

FIGURE 2 Kaplan-Meier graft survival curves from time of transplant, comparing FSGS, Other GN and non-GN patients, separated by living donor and deceased donor transplants, up to 5 years post-transplant. Allograft survival curves for LD transplants of FSGS patients deviate from that of Other GN and non-GN patients, and approximate that of DD transplants of FSGS patients

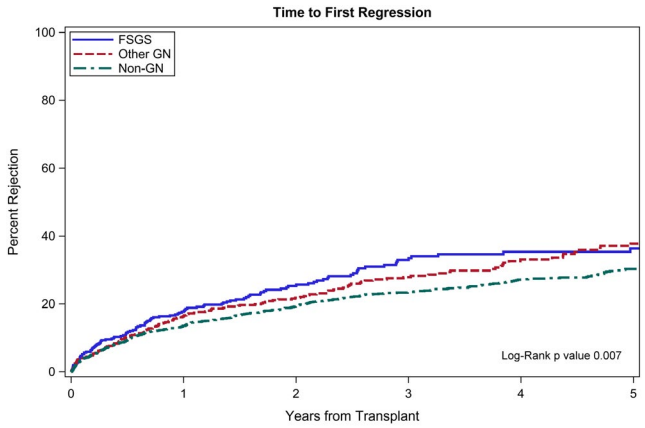

FIGURE 3 Kaplan-Meier graft survival curves demonstrating time to first allograft rejection, comparing FSGS, Other Gn and non-GN patients. Survival curves demonstrate significant difference in time to first allograft rejection, with curves separating for non-GN patients, compared to Other GN and FSGS

TABLE 3 Causes of graft failure, comparing FSGS with Other GN, n = 149

	FSGS n = 77 (%)	Other GN n = 72 (%)	*P*
Death with functioning graft	2 (2.6)	4 (5.6)	0.369
Primary non-function	2 (2.6)	3 (4.2)	0.601
Vascular thrombosis	2 (2.6)	4 (5.6)	0.369
Other technical	0 (0)	1 (1.4)	0.301
Hyperacute rejection	0 (0)	1 (1.4)	0.301
Acute rejection	11 (14.3)	15 (20.8)	0.339
Chronic rejection	15 (19.5)	23 (31.9)	0.132
Recurrence of original disease	33 (42.9)	5 (6.9)	<0.001
Bacterial/viral infection	2 (2.6)	0 (0)	0.171
De novo kidney disease	1 (1.3)	0 (0)	0.334
Patient discontinued medication	3 (3.9)	3 (4.2)	0.934
Other	6 (7.8)	13 (18.1)	0.080

4 | DISCUSSION

This report provides a contemporary update of graft outcome of kidney transplant recipients with a primary diagnosis of FSGS, contrasted to children transplanted with Other GN as the primary comparator group. While overall graft survival rates have improved since the initial NAPRTCS report over 16 years ago by Baum et al,[5] we find that the survival advantage that is associated with living donor transplantation in other primary kidney failure diagnoses, continues to be lacking in children transplanted for FSGS. And although improved overall allograft survival may well be attributable to advances in the types of induction and immunosuppressant medications currently available, we could find no significant impact on the risk of graft failure related to the differences in treatment protocols in this cohort.

Reported 5-year graft survival in patients with the primary diagnosis of FSGS ranges from 60% to 81%,[3,5,6] with worse graft survival among children compared to adults.[3] The graft survival rates in this cohort are consistent with these other reports and are similar between transplants from living donors (74.3%) and deceased donors (73.6%). This represents a substantial improvement in outcome compared to the previous report, where 5-year graft survival is reported at 69% and 60% for living and deceased donor transplants, respectively.[5]

Rates of preemptive transplant in children with FSGS are low (8.6%) compared to children with non-glomerular disease, but similar to children with primary glomerular diseases in the NAPRTCS cohort. These findings are similar to a USRDS cohort of pediatric patients transplanted between 2000 and 2012, where only 77 of 937 (8.2%) of FSGS patients received preemptive transplants.[7] In the ESPN registry, patients with FSGS were also less likely to receive a transplant preemptively when compared with receiving a transplant while being on dialysis for more than a year (OR 0.26, CI 0.18-0.39).[6]

Deceased donor kidney transplants are more common in FSGS patients in the NAPRTCS registry, and the proportion of deceased donors has increased since 2001 (63.1% vs 55.7%).[5] This rate of deceased donation mirrors the rate reported in the ESPN registry (70.7%).[6] This is in contrast to the ANZDATA cohort, where living donor rates for pediatric recipients with the primary diagnosis of FSGS were comparable to that of recipients with the primary diagnosis of other diseases (64% vs 63%, respectively).[3] The ANZDATA cohort observed improved living donor graft survival of 14.8 years vs 12.1 years (*P* = <0.01). Our data suggest similar graft survival between living donor and deceased donor transplants.

A NAPRTCS special study in 1992 reported 27 of 132 (20.5%) of allografts in pediatric patients with FSGS developed recurrence of disease post-transplant.[2] The PodoNet Registry cohort reported a proteinuria recurrence rate of 25.8% in children with non-genetic FSGS.[4] However, in this cohort we were unable to identify which patients had recurrence of proteinuria post-transplant and rather had to rely on attribution of recurrence as a cause of graft failure. This is likely to underestimate the true recurrence risk, but identified recurrent FSGS overwhelmingly as the most important cause of graft failure (43%), more than all types of acute or chronic rejection combined.

There was no significant association between living donor transplant and disease recurrence in the UNOS cohort (1988-2008, OR 1.22, CI 0.96 to 1.55).[1] Francis et al[3] did identify a risk associated with living donor transplant for disease recurrence (HR 2.04 *P* = 0.02), although not in the pediatric subgroup. Interestingly, the rates of recurrence were similar in both living and deceased donor pediatric kidney transplants (LD 33%, DD 40%, *P* = 0.78). Subgroup analysis in the ANZDATA cohort according to era of immunosuppression showed a lower risk of recurrence after introduction of mycophenolate and tacrolimus. In this cohort, the odds ratio for recurrence comparing the two seven-year eras after 1998 are 0.48

TABLE 4 Multivariable analysis of FSGS and GN patients for all-cause graft failure, n = 1121

Baseline factor	Comparison group	Reference group	HR, no DGF (95% CI)	*P*	HR with DGF (95% CI)	*P*
Primary diagnosis	FSGS	Other GN	1.45 (1.03-2.03)	0.033	1.12 (0.76-1.67)	0.564
Recipient age	Continuous variable		1.06 (1.01-1.11)	0.002	1.06 (1.01-1.11)	0.018
Recipient race	African American	White	1.23 (0.82-1.83)	0.316	1.37 (0.86-2.19)	0.188
	Hispanic		0.76 (0.46-1.25)	0.279	0.97 (0.54-1.76)	0.928
Donor source	Deceased donor	Live donor	1.83 (1.25-2.66)	0.002	1.71 (1.11-2.63)	0.016
Transplant history	Prior transplants	Primary	1.58 (1.10-2.27)	0.013	1.79 (1.17-2.72)	0.007
Primary immunosuppression	Cyclosporine	Tacrolimus	1.22 (0.68-2.19)	0.515	1.26 (0.64-2.49)	0.51
	Sirolimus		1.39 (0.32-6.00)	0.658	0.5 (0.06-3.92)	0.506
	More than 1 type		0.88 (0.44-1.78)	0.724	0.64 (0.29-1.44)	0.282
	None of the above		1.53 (0.94-2.50)	0.087	1.69 (0.90-3.17)	0.103
Induction therapy	None	IL2RB	0.90 (0.60-1.35)	0.611	0.76 (0.48-1.21)	0.244
	ATG/ALG		0.65 (0.38-1.12)	0.119	0.61 (0.34-1.08)	0.091
	Other type		0.59 (0.23-1.51)	0.267	0.39 (0.14-1.13)	0.083
	More than 1 type		1.25 (0.48-3.28)	0.649	0.52 (0.17-1.58)	0.245
DGF	Yes	No	–	–	4.44 (2.75-5.72)	<0.001

and 0.54 (*P* = 0.02 and 0.06, respectively). Analysis of the USRDS database showed no association between living donor transplant and graft loss from recurrent disease on multivariate analysis.[8] Our data also found no association between living donor transplant and graft loss from recurrent disease.

DGF occurred more often in this cohort in FSGS patients compared to GN patients. DGF was found to be an independent predictor of graft failure from all causes and in particular with graft failure from recurrence of disease. These findings are consistent with a previous NAPRTCS report.[9] DGF was considered as a potential proxy of severe early recurrent FSGS,[9] since FSGS typically recurs within 24-48 hours after transplant.[10] Disease recurrence was found to predict graft outcomes in some studies[3,10,11] but not in other studies.[12] The difference in graft outcomes in later studies may reflect better treatment strategies used in the last decade. In this cohort, DGF was identified in 14.1% of patients and was strongly associated with poor graft survival, especially when the outcome was restricted to graft failure with recurrent FSGS. In the analysis of all GN patients together, FSGS diagnosis was a significant risk for graft failure only without DGF in the model, which indicates that FSGS diagnosis and early, severe DGF are not independent. In addition, it suggests that for children who do not develop DGF

TABLE 5 Multivariable analysis of graft failure from all causes in only FSGS patients, n = 447

Baseline factor	Comparison group	Reference group	HR, no DGF (95% CI)	*P*	HR with DGF (95% CI)	*P*
Recipient age	Continuous variable		1.05 (0.99-1.11)	0.101	1.04 (0.98-1.10)	0.234
Recipient race	African American	White	0.86 (0.5-1.49)	0.586	0.82 (0.46-1.45)	0.491
	Hispanic		0.52 (0.24-1.14)	0.104	0.64 (0.29-1.42)	0.277
	Other		0.57 (0.17-1.92)	0.365	0.53 (0.12-2.27)	0.391
Donor source	Deceased donor	Live donor	1.51 (0.90-2.52)	0.118	1.46 (0.86-2.46)	0.161
Transplant history	Prior transplants	Primary transplant	1.68 (1.01-2.78)	0.045	1.94 (1.15-3.28)	0.014
Primary immunosuppression	Cyclosporine	Tacrolimus	1.12 (0.52-2.38)	0.776	1.01 (0.46-2.21)	0.984
	Sirolimus		2.00 (0.26-15.68)	0.510	2.42 (0.31-18.75)	0.396
	More than 1 type		0.43 (0.13-1.42)	0.169	0.35 (0.10-1.16)	0.086
	None of the above		1.41 (0.67-2.94)	0.363	1.28 (0.59-2.79)	0.536
Induction therapy	None	IL2RB	1.07 (0.60-1.91)	0.832	0.92 (0.51-1.67)	0.787
	ATG/ALG		1.04 (0.51-2.12)	0.921	0.92 (0.44-1.91)	0.823
	Other		NR	0.984	NR	0.982
	More than 1 type		2.11 (0.71-6.27)	0.180	0.84 (0.26-2.65)	0.761
DGF	Dialysis	No dialysis	–	–	4.39 (2.53-7.61)	<0.001

post-transplantation, graft survival is similar for patients with FSGS and Other GN diagnoses.

Second transplant after loss from FSGS recurrence in the first transplant has been previously reported as a risk factor associated with increased risk of recurrence.[13,14] It has also been reported that there is an increased risk of graft failure in adolescents compared to younger children.[15] In a Korean cohort, Hwang et al[16] found that there was no significant difference in recurrence rates or overall graft survival between adult FSGS recipients and children <15 years. The USRDS data reported increased risk of graft loss associated with a younger recipient age.[8] We did see an association with re-transplantation and older age in the adjusted analysis including all GN patients, but the finding in the FSGS only cohort was only confirmed for re-transplantation.

Treatment for FSGS recurrence post-transplant has been reported in mostly small retrospective studies with short term follow-up.[3,10,17,18] Complete or partial remission has been reportedly achieved with plasmapheresis (63%-70%),[18,19] high dose cyclosporine (77%-90%),[17] or rituximab (69%).[20,21] Preemptive plasmapheresis has been reported for prevention of recurrence with mixed results. One study identified a benefit to plasmapheresis alone,[22] another found a benefit only in combination with rituximab[10] and a third found no benefit to plasmapheresis.[23] We were unable to review treatment with plasma exchange or rituximab, but besides these we did not identify any benefit among different preferences for induction agents or initial maintenance immunosuppression.

Retrospective cohort reviews are prone to confounding bias. Transplants reported in the registry for FSGS patients have decreased in number, which resulted in a reduced number of outcomes and reduced power to identify associations that are small in their effect. In particular, the analysis of graft loss due to FSGS recurrence was underpowered to confirm a lack of association with some baseline and transplant characteristics. Missing data in some categories, for example, pertaining to HLA matching, limited the types of adjustments possible for the analysis. The NAPRTCS registry does not collect data with regard to FSGS recurrence and so we were restricted to using DGF as a proxy for severe, early recurrence in the analysis. Since the registry does not identify FSGS recurrence that responds to treatment or is less severe (ie, does not cause DGF), it cannot be used to evaluate which therapies may be more effective to manage recurrence and will underestimate the total recurrence rates. Nonetheless, this study represents one of the largest contemporary pediatric cohorts reported with FSGS and provides a valuable insight into factors that are associated with graft failure from FSGS recurrence and evolution of FSGS management in North America.

5 | CONCLUSION

We have re-affirmed that graft survival in children with FSGS is similar when the donor is living or deceased and that the survival advantage normally associated with living donation is not seen in children with FSGS. Graft failure risk is increased in FSGS compared with other types of glomerular disease, which seems to be associated with significantly more frequent rates of DGF in FSGS patients. Indeed, our data are consistent with treatment of DGF as a proxy for severe early recurrent disease. These data do not support a preference for induction agent or primary immunosuppressant in FSGS patients. In the future, revision to NAPRTCS reporting will be enhanced to capture detailed information on recurrence rates and severity and use of different treatment modalities for management of early recurrent disease.

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AUTHORS' CONTRIBUTIONS

Lee Jin Koh: Designed the study questions, and contributed to 50% of the final manuscript; Karen Martz: Conducted the statistical analysis and provided figures and tables for the manuscript; Tom David Blydt-Hansen supervised Lee Jin Koh in the design of the study questions and contributed to 50% of the final manuscript; NAPRTCS investigators have continued to diligently collect and enter longitudinal patient data into the registry, without which this research reporting is not possible.

ORCID

Lee Jin Koh https://orcid.org/0000-0002-2161-2845

Tom David Blydt-Hansen https://orcid.org/0000-0002-8864-0197

REFERENCES

1. Nehus EJ, Goebel JW, Succop PS, Abraham EC. Focal segmental glomerulosclerosis in children: multivariate analysis indicates that donor type does not alter recurrence risk. *Transplantation*. 2013;96(6):550-554.
2. McEnery PT, Stablein DM, Arbus G, Tejani A. Renal Transplantation in Children: a report of the North American Pediatric Renal Transplant Cooperative Study. *New Engl J Med*. 1992;326(26):1727-1732.
3. Francis A, Trnka P, McTaggart SJ. Long-term outcome of kidney transplantation in recipients with focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2016;11(11):2041-2046.
4. Trautmann A, Bodria M, Ozaltin F, et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. *Clin J Am Soc Nephrol*. 2015;10(4):592-600.
5. Baum MA, Stablein DM, Panzarino VM, Tejani A, Harmon WE, Alexander SR. Loss of living donor renal allograft survival advantage in children with focal segmental glomerulosclerosis. *Kidney Int*. 2001;59(1):328-333.
6. Van Stralen KJ, Verrina E, Belingheri M, et al. Impact of graft loss among kidney diseases with a high risk of post-transplant recurrence in the paediatric population. *Nephrol Dial Transplant*. 2013;28(4):1031-1038.

7. Amaral S, Sayed BA, Kutner N, Patzer RE. Preemptive kidney transplantation is associated with survival benefits among pediatric patients with end-stage renal disease. *Kidney Int*. 2016;90(5):1100-1108.
8. Abbott KC, Sawyers ES, Oliver JD, et al. Graft loss due to recurrent focal segmental glomerulosclerosis in renal transplant recipients in the United States. *Am J Kidney Dis*. 2001;37(2):366-373.
9. Baum MA. Outcomes after renal transplantation for FSGS in children. *Pediatr Transplant*. 2004;8:329-333.
10. Hickson LJ, Gera M, Amer H, et al. Kidney transplantation for primary focal segmental glomerulosclerosis: outcomes and response to therapy for recurrence. *Transplantation*. 2009;87(8):1232-1239.
11. Guan I, Singer P, Frank R, Chorny N, Infante L, Sethna CB. Role of race in kidney transplant outcomes in children with focal segmental glomerulosclerosis. *Pediatr Transplant*. 2016;20(6):790-797.
12. Wang CS, Gander J, Patzer RE, Greenbaum LA. Mortality and allograft loss trends among us pediatric kidney transplant recipients with and without focal segmental glomerulosclerosis. *Am J Kidney Dis*. 2018;71(3):392-398.
13. Moroni G, Gallelli B, Quaglini S, Banfi G, Montagnino G, Messa P. Long-term outcome of renal transplantation in adults with focal segmental glomerulosclerosis. *Transpl Int*. 2010;23(2):208-216.
14. Cormican S, Kennedy C, O'Kelly P, et al. Renal transplant outcomes in primary FSGS compared with other recipients and risk factors for recurrence: a national review of the Irish Transplant Registry. *Clin Transplant*. 2018;32(1): e13152.
15. Baum MA, Ho M, Stablein D, Alexander SR, Study NAPRTC. Outcome of renal transplantation in adolescents with focal segmental glomerulosclerosis. *Pediatr Transplant*. 2002;6(6):488-492.
16. Hwang JH, Han SS, Huh W, et al. Outcome of kidney allograft in patients with adulthood-onset focal segmental glomerulosclerosis: comparison with childhood-onset FSGS. *Nephrol Dial Transplant*. 2012;27(6):2559-2565.
17. Cravedi P, Kopp JB, Remuzzi G. Recent progress in the pathophysiology and treatment of FSGS recurrence. *Am J Transplant*. 2013;13(2):266-274.
18. Ponticelli C. Recurrence of focal segmental glomerular sclerosis (FSGS) after renal transplantation. *Nephrol Dial Transplant*. 2010;25(1):25-31.
19. Kashgary A, Sontrop JM, Li L, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: a systematic review and meta-analysis of 77 case-reports and case-series. *BMC Nephrol*. 2016;17(1):1-8.
20. Araya CE, Dharnidharka VR. The factors that may predict response to rituximab therapy in recurrent focal segmental glomerulosclerosis: a systematic review. *J Transplant*. 2011. [Epub ahead of print]. https://doi.org/10.1155/2011/374213.
21. Strologo LD, Guzzo I, Laurenzi C, et al. Use of rituximab in focal glomerulosclerosis relapses after renal transplantation. *Transplantation*. 2009;88(3):417-420.
22. Gohh RY, Yango AF, Morrissey PE, et al. Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. *Am J Transplant*. 2005;5(12):2907-2912.
23. Verghese PS, Rheault MN, Jackson S, Matas AJ, Chinnakotla S, Chavers B. The effect of peri-transplant plasmapheresis in the prevention of recurrent FSGS. *Pediatr Transplant*. 2018;22(3):e13154.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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