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ORIGINAL ARTICLE

Clinical characteristics and favorable treatment responses of recurrent focal segmental glomerulosclerosis or steroid-resistant nephrotic syndrome in children after kidney transplantation

Vikas R. Dharnidharka[1] · Rebecca R. Scobell[2] · Mahmoud Kallash[3] · Amy J. Goodwin Davies[2] · Nicole Marchesani[2] · Mitchell G. Maltenfort[2] · Leslie Walther[1] · Megan Kelton[4] · Margret Bock[5] · Eliza Blanchette[5] · Hillarey K. Stone[6] · Caroline Gluck[7] · Frank Hullekes[8] · Leonardo V. Riella[8] · William E. Smoyer[3] · Mark Mitsnefes[6] · Bradley P. Dixon[5] · Joseph T. Flynn[4] · Michael J. G. Somers[9] · Christopher B. Forrest[2] · Susan Furth[2] · Michelle R. Denburg[2,10]

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Abstract

Background Recurrence of focal segmental glomerulosclerosis (FSGS) or steroid-resistant nephrotic syndrome (SRNS) after kidney transplant leads to significant morbidity and potentially earlier allograft loss. To date however, reported rates, risk factors and treatment outcomes have varied widely.

Methods We applied computational phenotypes to a multicenter aggregation of electronic health records data from 7 large pediatric health systems in the USA, to identify recurrence rates, risk factors, and treatment outcomes. We refined the data collection by chart review.

Results From > 7 million patients, we compared children with primary FSGS/SRNS who received a kidney transplant between 2009 and 2020 and who either developed recurrence ($n = 67/165$; 40.6%) or did not ($n = 98/165$). Serum albumin level at time of transplant was significantly lower and recipient HLA DR7 presence was significantly higher in the recurrence group. By 36 months post-transplant, complete remission occurred in 58.2% and partial remission in 17.9%. Through 6 years post-transplant, no remission after recurrence was associated with an increased risk of allograft loss over time ($p < 0.0001$), but any remission showed similar allograft survival and function decline to those with no recurrence. Since treatments were used in non-random fashion, using spline curves and multivariable non-linear analyses, complete + partial remission chance was significantly higher with greater plasmapheresis sessions, CTLA4-Ig doses or LDL-apheresis sessions. Only treatment with anti-CD20, CTLA4-Ig agents, or LDL-apheresis sessions were associated with complete remission. Excluding 25 patients with mutations did not significantly change our results.

Conclusions Our contemporary high-risk cohort had higher favorable response rates than most prior reports, from combinations of agents.

Keywords Focal segmental glomerulosclerosis · Steroid-resistant nephrotic syndrome · Kidney transplant · Pediatrics · Recurrent disease

✉ Vikas R. Dharnidharka
vikasD@wustl.edu

[1] Washington University School of Medicine and St. Louis Children's Hospital, Room NWT 10-119, CB 8116, 660 South Euclid Avenue, St. Louis, MO 63110, USA

[2] Children's Hospital of Philadelphia, Philadelphia, PA, USA

[3] Department of Pediatrics, The Research Institute at Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA

[4] Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA

[5] Renal Section, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA

[6] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[7] Nemours Children's Health, Jacksonville, FL, USA

[8] Massachusetts General Hospital, Boston, MA, USA

[9] Boston Children's Hospital, Boston, MA, USA

[10] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

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Abbreviations

ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
FSGS	Focal segmental glomerulosclerosis
HR	Hazard ratio
IQR	Interquartile range
KTx	Kidney transplant
LDL-A	Low-density lipoprotein apheresis
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
rFSGS	Recurrent focal segmental glomerulosclerosis
SD	Standard deviation
TANGO	Post-TrANsplant GlOmerular Consortium
TPE	Therapeutic plasma exchange, also known as plasmapheresis
USRDS	United States Renal Data System
SRNS	Steroid-resistant nephrotic syndrome

Introduction

Primary and idiopathic (gene mutation negative) focal segmental glomerulosclerosis (FSGS) is an uncommon but devastating disease, seen in approximately 20% of nephrotic syndrome cases in children and 40% of such cases in adults, with an estimated incidence of 7 per 1 million individuals in the United States (US) and accounting for 10–15% of kidney failure in children [1–3]. One of the devastating features of primary idiopathic FSGS is its recurrence after kidney transplantation, with reported rates of recurrent FSGS (rFSGS) ranging from 17 to 60% in smaller studies of 1–3 centers and from 9 to 64% in national registry-based or international collaborative studies [4–6]. Because rFSGS is relatively uncommon, most published studies are limited by small sample sizes and thus have insufficient power to precisely determine treatment efficacy and outcomes of rFSGS. Commonly utilized databases such as ANZDATA, NAPRTCS, or USRDS have a large degree of missing data and often misclassify patients with diagnoses of glomerular diseases. Moreover, some of these databases fail to capture cases of rFSGS that do not lead to kidney allograft loss, rendering these data unreliable for drawing robust conclusions about long-term outcomes.

Further, the management of rFSGS following kidney transplantation remains extremely challenging for a variety of reasons. The rarity of the event has made it very difficult to conduct randomized trials, such that treatment recommendations are based on small study cohorts, case series, and case reports. Interpretation of the published literature is hindered by the heterogeneity of definitions for primary FSGS, disease recurrence, and remission [7]. There is no established standard for the treatment of rFSGS post-transplant [8]. Instead, various therapeutic regimens are applied, with wide variability in timing of initiation of treatment, number of sessions if apheresis is used, timing/dosing of depleting antibodies, and concomitant immunosuppressive regimens [7, 9]. Many of these therapies are tried together or in random sequence. As in primary FSGS affecting native kidneys, response to therapy for post-transplant rFSGS is often poor, with only 40–60% of patients achieving any response, and these responses are often incomplete and not sustained [10]. FSGS recurrence portends a negative impact on graft survival [11, 12].

To better address these barriers to studying rFSGS, it is necessary to utilize an interconnected, multicenter, longitudinal infrastructure to capture adequate numbers of affected children, and provide the scope and granularity of information necessary to characterize response to treatments. PEDSnet, a national research pediatric network that has now aggregated electronic health record (EHR) data from inpatient and outpatient settings for millions of patients, provides a unique opportunity to study rare childhood diseases such as rFSGS at scale. In the present study, we sought to characterize risk factors, treatment practices, and outcomes for rFSGS by utilizing PEDSnet to identify a contemporary cohort of children who underwent kidney transplant for FSGS/SRNS. We hypothesized that use of this large and granular EHR aggregated database would enable better identification and confirmation of current treatment approaches and outcomes.

Methods

Study setting and data sources

This study used data from PEDSnet, a clinical research network that has aggregated EHR data from several large children's healthcare systems under IRB protocol #14–011242 [13]. PEDSnet standardizes EHR data across institutions to a common data model, which is based on the Observational Medical Outcomes Partnership (OMOP) common data model version 5 [14]. For this study, we used the PEDSnet database version 4.0, which included data from January 2009–December 2020. Data was extracted in December 2020 and came from 7 centers: Children's Hospital of Philadelphia; Children's Hospital Colorado; Cincinnati Children's Hospital Medical Center; Nationwide Children's Hospital; Nemours Children's Health System (a Delaware and Florida health system); Seattle Children's Hospital; and St. Louis Children's Hospital/Washington University. This analysis and chart review was approved by the Children's Hospital of Philadelphia Institutional Review Board protocol #

16–012878 as part of the PEDSnet Master Protocol, which is accepted by all participating PEDSnet sites.

Chart review data were collected and managed using Research Electronic Data Capture (REDCap) hosted at Children's Hospital of Philadelphia [15, 16]. REDCap (https://www.project-redcap.org) is a secure, web-based software platform designed to support data capture for research studies.

Cohort identification

We first used our published computable phenotype to identify patients who had at least 3 visits to a nephrology provider and who had nephrotic syndrome [17]. We excluded patients whose primary glomerular disease was lupus nephritis, as analyses indicated that among glomerular diseases, lupus is frequently misclassified as nephrotic rather than nephritic using this nephrotic syndrome algorithm. We then refined that algorithm to identify patients with evidence of a kidney transplant between January 1, 2009, to December 31, 2020 (Fig. 1). To maximize capture of cases, we supplemented the PEDSnet query with lists of FSGS patients maintained locally by centers. At some centers, local lists identified eligible patients who were not identified by the computational phenotype. We then used a standardized chart review for investigators at all 7 sites to confirm the diagnosis of primary FSGS or steroid-resistant nephrotic syndrome (SRNS), and to collect data on HLA alleles of donor and recipient. To identify rFSGS, we used a urine protein/creatinine ratio of > 2.0 mg/mg at any time within the first 2 years post-transplant, similar to Verghese et al. [18]. Where patients had multiple kidney transplants within the study period, chart review was restricted to the first transplant. The chart review was also used to confirm treatment for recurrence of FSGS and collect data on treatments used, their time course, and kidney allograft outcomes. Medication doses were considered only if after the transplant date and prior to allograft loss date, if applicable. Site investigators made the final attributions of complete and partial remission in the chart reviews, where patients had at least one the following criteria [4, 19, 20]: (a) complete remission: urine protein < 100 mg/m^2/24 h, OR < 0.2 mg/mg urine protein-to-creatinine ratio (for children less than 2 years old < 0.5 mg/mg), OR negative urine dipstick, OR serum albumin > 30 g/L combined with trace urine dipstick; (b) partial remission: 24 h protein > 100 mg/m^2 but < 1 g/m^2, OR urine protein-to-creatinine ratio of 0.2–2 mg/mg (for children less than 2 years old 0.5–2 mg/mg), OR urine dipstick 1 + proteinuria in combination with serum albumin > 30 g/L, OR urine dipstick trace in combination with serum albumin < 30 g/L. Data extracted from the EHRs in the central database included patient demographics and pre-transplant lab values, pre-transplant risk factor covariates, serial height and weight, serial serum creatinine, serum albumin, urine protein or albumin, and urine creatinine. Aggregated EHR data allowed us to assess pre-transplant risk factors, calculate the serial eGFRs, confirm the rFSGS treatment number and timing, confirm the remission timing, and develop the spline models. All data entries were subject to field validation checks and queries for unexpected values [21, 22].

Statistical analyses

Data are presented as frequencies (percentages) for categorical variables, and as means and standard deviations (SD) for continuous variables if following a Gaussian distribution and as medians (interquartile range [IQR]) if not. Continuous variables were analyzed by *t*-test or Mann–Whitney *U* test, and binary and categorical variables by chi-square or Fisher's exact test, as appropriate. We constructed Kaplan–Meier time to event analyses for recurrence, remission, and allograft loss. Multivariable Cox proportional hazards regression was used to compute the relative hazard for complete remission or complete + partial remission (complete + partial), with the therapies as time-dependent covariates, modeled with penalized splines (2 degrees of freedom) for serum albumin, CTLA4-Igs (abatacept or belatacept), anti-CD20 agents, and the number of low-density lipoprotein apheresis sessions, to account for fluctuating response rates with increasing doses of a treatment. The slopes of eGFR decline were calculated over the study period using linear mixed-effects modeling. eGFR was calculated using the CKiD age- and sex-dependent serum creatinine clinical equation [23].

The R statistical environment (version 3.5, R Core Team 2022, Vienna, Austria) was used to perform all statistical analyses [24]. Cox modeling was performed using R's *survival* package [25] and mixed modeling using the *lme4* package [26].

Results

From the PEDSnet cohort of more than 7.2 million children across 7 centers, we identified a subset of almost 41,000 children with at least 3 visits to a nephrology provider (Fig. 1) between January 1, 2009, to December 31, 2020. Using our previously published algorithm, 2265 children met criteria for nephrotic syndrome, excluding lupus nephritis. Of these 2265 patients, 295 were identified as kidney transplant recipients via procedure or diagnosis codes. To maximize capture, patients identified via application of the computational phenotype were augmented by registry lists maintained locally by the site investigators, resulting in identification of an additional 52 patients. Many of these patients were not identified in the nephrotic syndrome cohort because the FSGS diagnoses they received in the institution's source

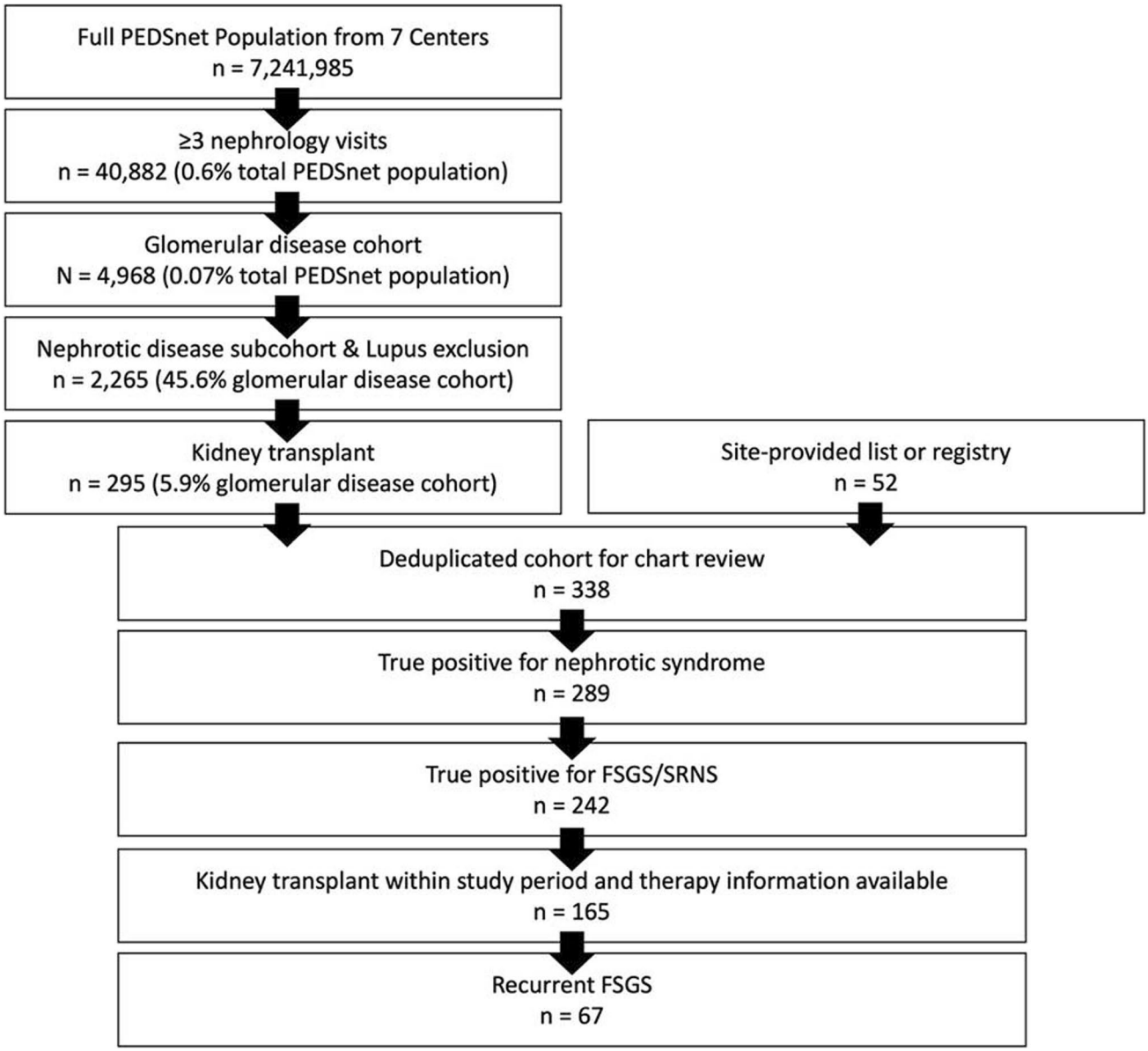


Fig. 1 Sequential derivation of the cohort, starting from all PEDSnet encounters (step 1), then limited by those with 3 or more nephrology visits (step 2), those identified with glomerular disease (step 3) and a nephrotic condition, after exclusion of lupus (step 4), and those who received a kidney transplant between January 2009–December 2020 (step 5). The 295 patients were then combined with 52 patients provided by sites. After deduplication, the cohort for chart review was 338. Through the chart review, we determined that the final cohort of FSGS patients who received a kidney transplant in the eligible period was 165, of whom 67 were treated for recurrence

data were mapped to nephritic syndrome standard concepts in the PEDSnet EHR data (N05.1 "Unspecified nephritic syndrome, focal and segmental glomerular lesions" mapping to 7724006 "Nephritic syndrome"). Further, some patients on the registry lists may not have been identified due to kidney transplants that were performed outside the PEDSnet network or outside the study date range. After deduplicating patients using sex and date of birth, a total of 338 patients were identified for chart review. The accuracy of our computable phenotype algorithm was 84%.

Using this approach, 289 (85%) of these 338 patients were confirmed to have nephrotic syndrome, and 242 (74%) specifically had FSGS or SRNS as their primary diagnosis. Of these 242, a total of 165 received a kidney transplant between January 1, 2009, and December 31, 2020, and had information about therapies available in their charts. The vast majority of the 77 excluded at this stage were due to the date of the kidney transplant being outside the study date range. Of these 165 patients, 67 (40.6%) were identified by the chart reviewer as experiencing recurrent FSGS.

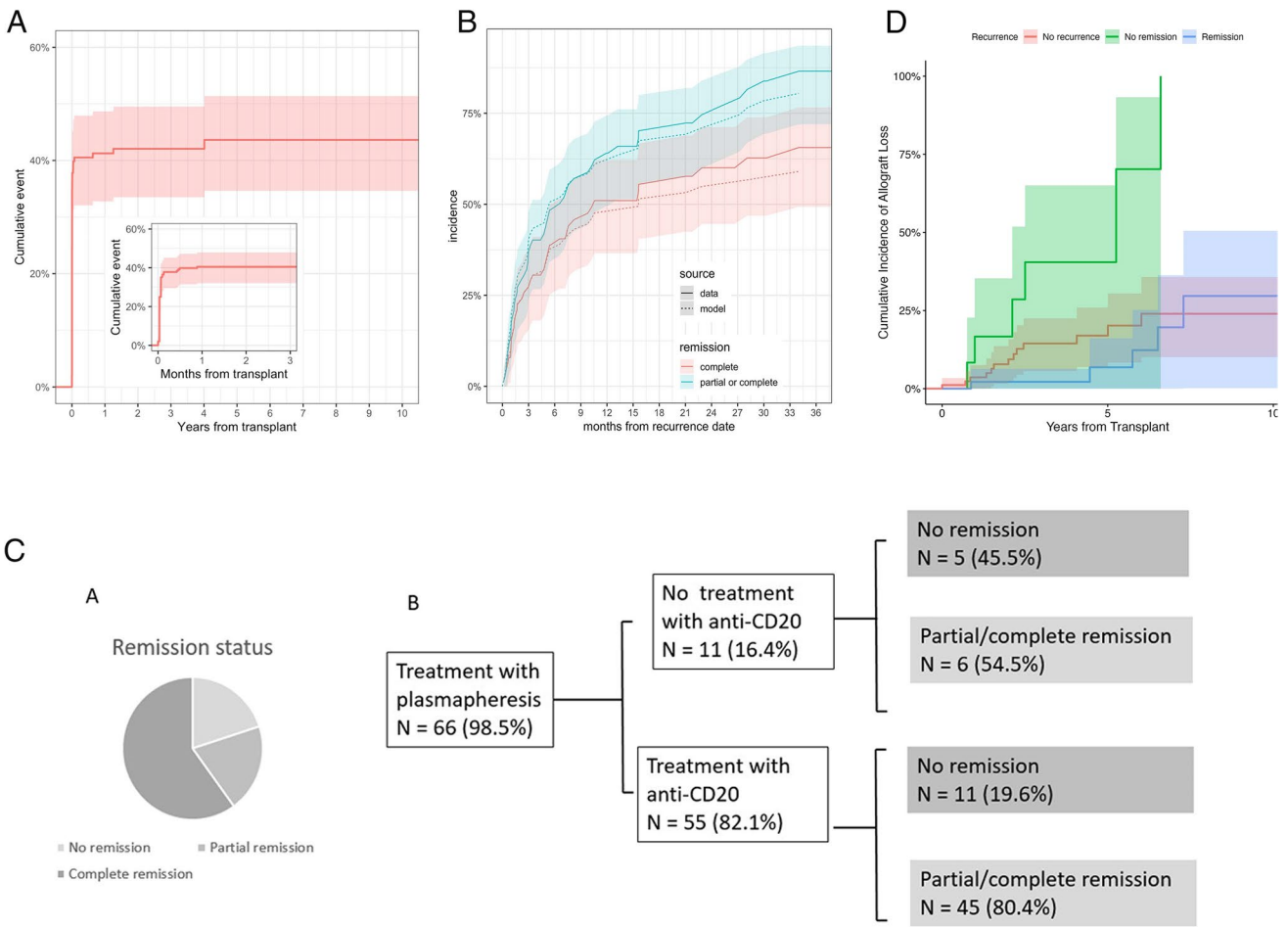


Fig. 2 Clinical outcomes after rFSGS: **A** Panel **A** shows the time to recurrence by year after transplant on x axis. Inset graph shows the x axis from month 0 to 3 post-transplant. **B** Panel **B** shows the proportion achieving complete remission (pink solid line) or complete + partial remission (complete + partial remission; blue solid line) by months post-transplant. The shaded areas represent the 95th percentile confidence intervals. **C** Panel **C** shows the proportions in No remission, partial remission, or complete remission, stratified by use of TPE or antibodies to CD20. **D** Panel **D** depicts the cumulative incidence of kidney allograft loss by year post-transplant, stratified by no recurrence of FSGS (solid pink line), recurrence with either complete, or partial remission (solid blue line) or recurrence without any remission (solid green line; $p < 0.0001$). The shaded areas represent the 95th percentile confidence intervals

Recurrence occurred within the first month post-transplant in 64/67 (Fig. 2A). The median time to recurrence (from day of transplant to the day of recurrent FSGS diagnosis) was 1 day (IQR 1–2 days). A few very late recurrences meant that the mean and SD were larger (mean 36.6 days, SD 194 days).

Table 1 shows the characteristics of the 67 patients with rFSGS and the 98 patients with FSGS without post-transplant recurrence. Both groups were nearly identical in age at transplant and duration of follow-up, as well as in proportions of female sex, living-related allograft source, and pre-transplant native nephrectomy. The group that experienced recurrence had a statistically significantly lower median serum albumin level of 3.65 g/dL closest before transplant versus 3.85 g/dL in the group without recurrence ($p = 0.002$). The presence of the known risk factor HLA DR7 allele in the recipient was significantly more frequent in the rFSGS group (26.8%) versus in those without recurrence (11.2%, $p = 0.012$). The other reported HLA allele-risk factors were present in too few participants to allow for meaningful comparisons. Prior diagnoses of atopy did not associate with recurrence.

Patients received a variety of therapies, including therapeutic plasma exchange (TPE, also known as plasmapheresis); antibodies directed at the CD20 receptor (most commonly rituximab, rarely ofatumumab); low-density lipoprotein (LDL) apheresis, intravenous immunoglobulin (IVIG), fusion proteins directed at the CTLA4 receptor (CTLA4-Igs), and adrenocorticotropic hormone gel. The number of patients who received these respective therapies is shown in Table 2, with TPE in combination with an anti-CD20 agent being the most common, and

Table 1 Demographic and clinical characteristics of the recurrent and non-recurrent FSGS cohorts

FSGS and kidney transplant	No recurrence	Recurrence	All FSGS
N (%)	98 (59.4%)	67 (40.6%)	165
Mean age at transplant in years (SD)	12.5 (6.2)	12.4 (4.4)	12.4 (5.5)
Female sex %	47	46	47
Race/ethnicity			
African ancestry %	20.4	20.9	20.6
Non-African %	67.4	70.1	68.4
> 1 atopy diagnosis (%)	23.5	25.4	24.2
Donor source living related %	29	27	28
Pre-transplant native nephrectomy, yes %	13	16	15
Mean follow-up in years (SD)	7.4 (3.6)	7.4 (3.7)	7.4 (3.7)
Serum albumin (g/dL) at transplant	3.85 (2.70–5.30)	3.65 (1.50–4.50)	3.80 (1.50–5.30)
HLA DR7 allele presence in recipient %	11.2	26.8	17.5

Of the above characteristics, serum albumin at transplant (median; IQR) was significantly lower in the recurrence group versus the No recurrence group, $p = 0.00251$ by the Mann–Whitney test. The HLA DR7 allele was present in significantly higher proportion in those with recurrence versus no recurrence, $p = 0.01236$ by the chi-square test. Race/ethnicity data was unavailable or unknown in 10.9%. HLA DR7 allele data was unavailable or unknown in 50.9%

Table 2 The most common treatments used for recurrent FSGS. These groups are not mutually exclusive and many patients received 3 or more therapies. Per PedsNet policies, cell counts < 11 cannot be reported without explicit permission of all centers

Treatment type	Number of patients who received	Onset of initiation (median post-transplant days (IQR)
TPE + antibody to CD20	55	
Low-density lipoprotein apheresis	17	214 (126–284)
TPE without antibody to CD20	11	
Intravenous immunoglobulin	< 11	373 (55–1184)
Fusion immunoglobulins directed at CTLA4	< 11	97 (69–163)

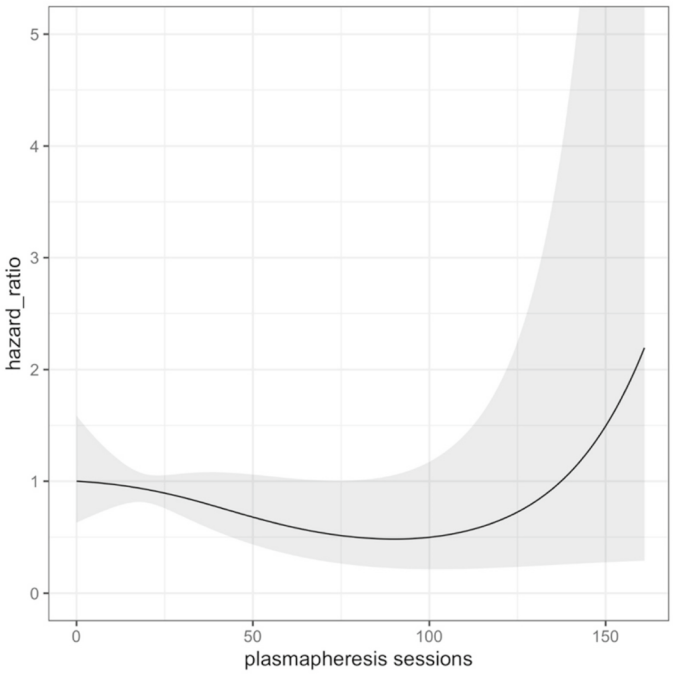
TPE was initiated at a median of 3 days post-transplant (IQR 2–6). Anti-CD20 agents were initiated at a median of 7 days post-transplant (IQR 4.5–18). Due to cell sizes < 11 in the groups, we could not compare treatment responses between specific regimen sequences

TPE, therapeutic plasma exchange

TPE alone being the third most common. Table 2 also shows the time of initiation for each therapy, with TPE being started the earliest, followed by anti-CD20 agents, while LDL-apheresis or CTLA4Igs were initiated at much later time points. Complete remission of recurrence was achieved in 39/67 (58.2%), and an additional 12/67 (17.9%) experienced partial remission (Fig. 2B), such that complete + partial remission was seen in 76.1%. The proportions of those achieving complete and partial remission both increased gradually over the first 36 months post-transplant (Fig. 2B). The mean time to complete remission was 207 days, SD 249 days. For either complete or partial remission, whichever came first, the mean time was 106 days, SD 274 days. In the 18 transplant recipients known to be positive for HLA DR7, complete remission occurred in a slightly higher proportion of 72%, at a median time of 145 days (IQR 63–362 days). A subsequent relapse was seen in 23% of those with complete remission, at a median of 1226 days, while relapse occurred in 41.7% of those with partial remission, at a median of 586 days. Of those who received only TPE, 54.5% achieved a complete or partial remission (Fig. 2C). In comparison, of those who received a combination of plasmapheresis and anti-CD20 therapy, 82.1% achieved a complete or partial remission (Fig. 2C).

Allograft loss by 6 years post-transplant was not significantly different between the groups with no recurrence of FSGS versus recurrent FSGS with any remission (Fig. 2D; 20.2% for no recurrence, 21.8% for recurrence with any remission). However, the group with no remission after recurrent FSGS had significantly worse allograft survival ($p < 0.0001$). To assess if proteinuria reduction was due to reduced GFR, we assessed eGFR declines in both groups. For the patients without recurrence, the median eGFR decline per year was − 0.93, (IQR − 5.83 to + 4.00; min − 29.9, max + 32.4). For patients with rFSGS, the median decline was − 1.56, (IQR − 6.93 to + 2.66; min − 53.5, max + 37.0; Supplementary Fig. 1). These declines were not significantly different (Mann–Whitney *U* test, $p = 0.44$).

A: Hazard Ratio for complete + partial remission by the n umber of plasmapheresis sessions received



Hazard Ratio (HR) and 95% confidence interval (CI) for Complete + partial remission for the cumulative number of plasmapheresis sessions

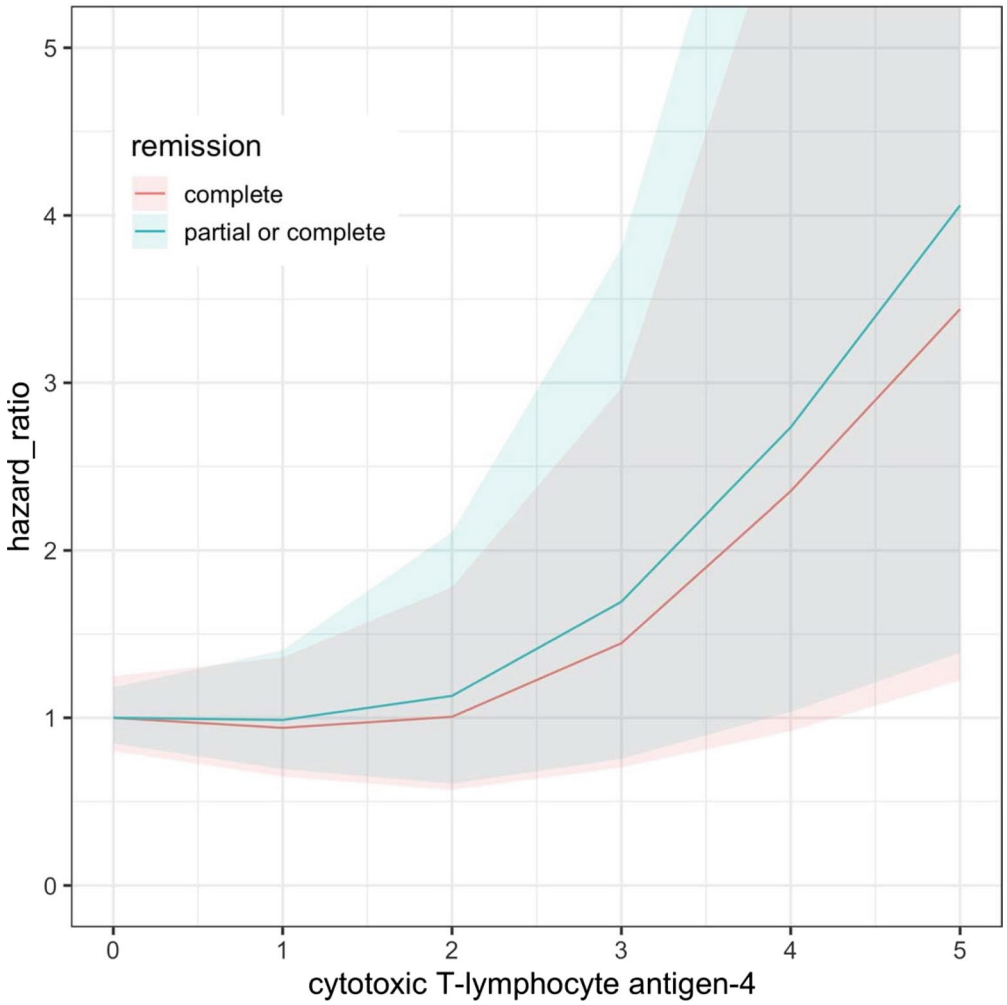
TPE sessions	HR for Complete + Partial Remission	95% CI
0	1.00	0.63–1.59
10	0.97	0.76–1.24
20	0.93	0.81–1.06
40	0.77	0.55–1.08
60	0.60	0.35–1.03
80	0.50	0.24–1.01
100	0.50	0.21–1.17
TPE sessions	**HR for Complete + Partial Remission**	**95% CI**
120	0.65	0.23–1.88
140	1.08	0.26–4.54
160	2.12	0.29–15.65

Fig. 3 Spline fitted models of hazard ratios for remission outcomes after rFSGS treatments. The hazard ratio was set at 1.0 at the time point of zero treatments. Note that the confidence intervals are wide. Because of the observational nature of this study, we cannot be sure if this result presents evidence against stopping treatments prematurely or if it reflects clinicians tending to discontinue treatments early for other reasons. **A** Panel **A** depicts the hazard ratio for complete + partial remission by number of plasmapheresis (TPE) sessions. **B** Panel **B** shows that the hazard ratio for complete + partial or complete remission increased after more doses of fusion proteins to CTLA4. **C** Panel **C** depicts that the hazard ratio for complete + partial remission increased steadily with increasing sessions of low-density lipoprotein apheresis, though the hazard ratio for complete remission was not higher. **D** Panel **D** shows that the hazard ratio for complete remission to anti-CD20 agents was biphasic—a higher likelihood of complete remission with 5 doses or less, and the hazard ratio dropping to negative if no response occurred by 6 doses

We also explored the responses to individual treatments, which were used in varying non-randomized sequences. We saw variable response rates with the number of sessions or doses; hence, spline models and both linear and non-linear Cox proportional hazards models were fitted. Schoenfield tests confirmed the proportional hazards assumptions in all models. From these spline and Cox models, we found that patients had a significantly higher chance of achieving *complete + partial* remission with a greater number of TPE sessions. Figure 3 A shows the spline model with a rising hazard ratio after a high number of sessions. Table 3 shows the significant non-linear Cox model AHR, while the linear AHR was not significant. CTLA-4 Igs were significantly associated with both complete or complete + partial remission in non-linear Cox models (Table 3). The spline curve in Fig. 3B shows the hazard ratios rise above 1 with greater

Fig. 3 (continued)

B: Hazard ratio for complete and complete + partial remission by the number of doses received of fusion proteins to CTLA4

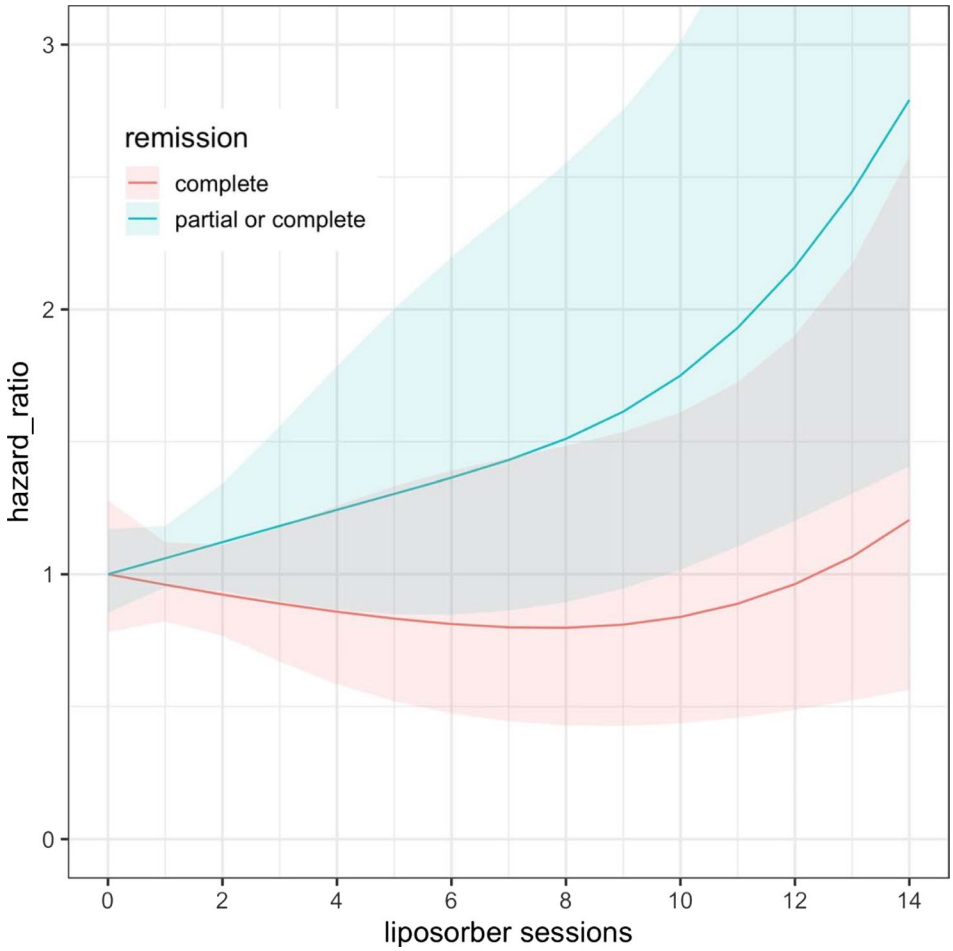


Hazard Ratio and 95% CI for Complete + partial and Complete remission for the cumulative number of doses received of fusion proteins to CTLA4

CTA4 - lgs	HR for Complete + Partial Remission	95% CI	HR for Complete Remission	95% CI
0	1.00	0.85–1.18	1.00	0.80–1.25
1	0.99	0.69–1.40	0.94	0.65–1.36
2	1.13	0.61–2.11	1.01	0.57–1.78
3	1.69	0.75–3.80	1.45	0.70–2.97
4	2.73	1.04–7.22	2.35	0.92–6.01
5	4.06	1.39–11.87	3.44	1.22–9.66

Fig. 3 (continued)

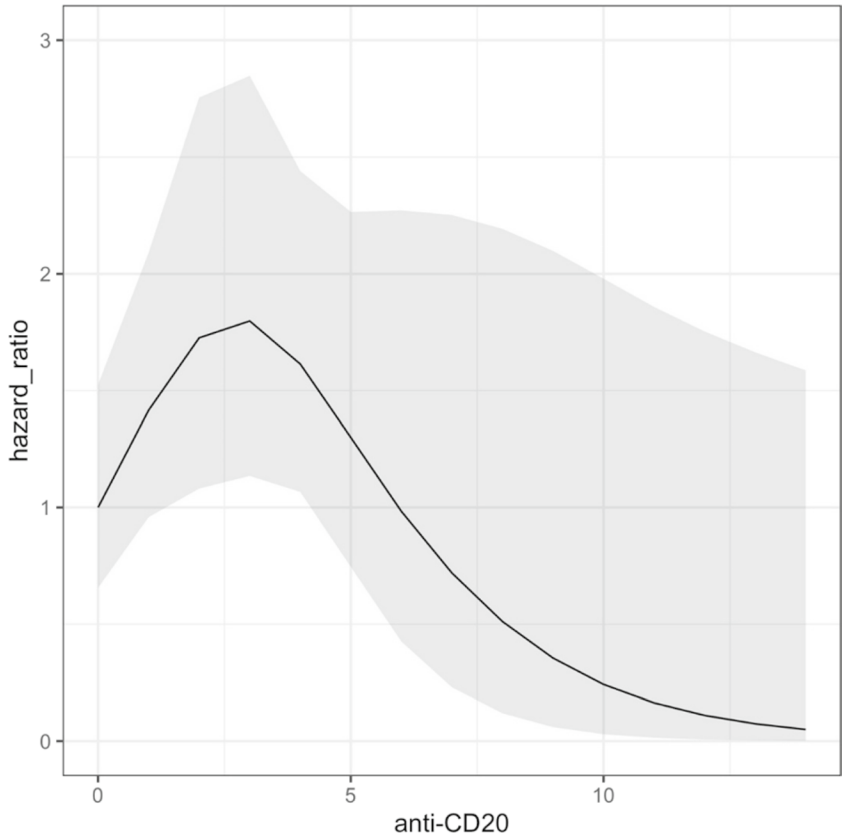
C: Hazard ratio for complete and complete + partial remission by the number of low density lipoprotein apheresis (Liposorber) sessions



Hazard Ratio and 95% CI for Complete + partial and Complete remission for the cumulative number of low density lipoprotein apheresis sessions

LDL - apheresis	HR for Complete + Partial Remission	95% CI	HR for Complete Remission	95% CI
0	1.00	0.85–1.17	1.00	0.78–1.28
2	1.12	0.94–1.34	0.92	0.77–1.11
4	1.24	0.87–1.79	0.86	0.58–1.26
LDL - apheresis	**HR for Complete + Partial Remission**	**95% CI**	**HR for Complete Remission**	**95% CI**
6	1.36	0.85–2.20	0.81	0.47–1.39
8	1.51	0.89–2.55	0.80	0.43–1.48
10	1.75	1.02–3.01	0.84	0.44–1.61
12	2.16	1.20–3.88	0.96	0.49–1.90
14	2.79	1.41–5.54	1.21	0.56–2.58

Fig. 3 (continued) D: Hazard Ratio for complete remission by the number of doses received of an anti-CD20 agent



Hazard Ratio and 95% CI for Complete remission for the cumulative number of doses received of an anti-CD20 agent

Anti-CD20 agent	HR for Complete Remission	95% CI
0	1.00	0.66–1.52
2	1.73	1.08–2.75
4	1.61	1.07–2.44
6	0.98	0.43–2.27
8	0.51	0.12–2.19
10	0.24	0.03–1.98
12	0.11	0.01–1.75
14	0.05	0.00–1.59

CTLA4-Ig doses. Similarly, LDL-apheresis was significantly associated with both complete or complete + partial remission in non-linear Cox models (Table 3). The spline curve in Fig. 3C shows the hazard ratio rise above 1 with increasing number of LDL-apheresis sessions. However, the anti-CD20 agents were associated only with a significantly higher likelihood of achieving only *complete* remission in the non-linear model only (Table 3). In Fig. 3D, the spline curve showed a biphasic pattern, with a hazard ratio above 1 at a lower number of doses, then dropping below 1 at 6 doses or more. The Supplementary Fig. 2 depicts the cumulative percentages of the cohort that received different numbers

Table 3 *p*-values for significance from the linear and non-linear multivariate models for the different treatments used and serum albumin at transplant, by complete + partial or complete remission. TPE and serum albumin at transplant were associated only with complete + partial (complete + partial) remission, while anti-CD20 agents were associated only with complete remission. Separate *p*-values are given for linear and non-linear components

	Complete + partial remission		Complete remission	
	p value (linear)	*p* value (non-linear)	*p* value (linear)	*p* value (non-linear)
Serum albumin	0.10	< 0.001	NA	NA
TPE	0.861	< 0.001	NA	NA
CTLA4-Igs	0.061	0.011	0.065	0.049
LDL-apheresis sessions	0.189	0.002	0.607	0.002
Anti-CD20 agent	NA	NA	0.191	< 0.001

TPE, therapeutic plasma exchange, also known as plasmapheresis; *CLTA4-Igs*, abatacept or belatacept; *LDL*, low-density lipoprotein; *NA*, not available as the multivariate model did not retain this treatment among the significant predictors

of doses/sessions of anti-CD20 agents, CTLA4-Igs, LDL-apheresis, or TPE, respectively.

As our chart review did not specifically exclude cases with gene mutations that were potentially causative for FSGS, we repeated all the analyses after excluding from the cohort of 165 those 25 cases with chart reviewer reported FSGS mutations (> 20 patients in the no recurrence group, < 5 in the recurrence group). The recurrence rate increased from 40.6 to a range between 45 and 47.14%, upper bound within the 47–64% range described in a prior meta-analysis [5]. We cannot report an exact percentage as one group had mutations in < 5 patients, prohibited to report exact numbers by PedsNet policies. The risk factors for recurrent FSGS remained the same, with no major change in risk magnitude or in directionality (Supplemental Table 1). None of the spline curves had any major changes either (data not shown). The 9 gene categories in which mutations were reported by the chart reviewers in the 25 patients are listed in Supplemental Table 2.

Discussion

Using a computable phenotype algorithm, in combination with local registry lists, we were able to successfully identify a contemporary cohort of patients with the very uncommon disease rFSGS. Via combined EHR data extraction and chart review, we collected robust clinical information on this pediatric cohort to assess prior reported risk factors and compare clinical efficacy of treatments and outcomes. Our key findings were a complete + partial recurrence rate of 40.6%, almost all occurring in the first month after kidney transplantation, but high rates of complete (58.2%) or complete + partial remission (76.1%) by 36 months post-transplant. We were also able to replicate that recipients with a HLA DR7 allele or lower serum albumin level at transplant had a higher risk of recurrence [12, 27], but we did not find an association of atopy to higher risk for recurrence [12]. Higher chances for *complete + partial* response were seen with increasing plasmapheresis or LDL-apheresis sessions or increasing doses of CTLA4 fusion antibodies. CTLA4-Igs and LDL-apheresis were also significantly associated with higher chance of complete remission. In contrast, anti-CD20 agents associated only with complete remission, in a biphasic pattern, where the best chance for complete remission was with 2–5 doses, and a drop in remission likelihood to negative with further doses.

Small single center studies quote recurrence rates of FSGS as high as 40–60% following the first kidney transplant [4]. Larger international collaborative efforts such as the TANGO Consortium of 15 centers across 3 continents have published a slightly lower rate of 32% recurrence in adult patients [4]. Among large national registries, the Australia/New Zealand Data Registry (ANZDATA) reported only 8% recurrence in adults, but 36% in children [28]. Nehus et al. reported a 15% recurrence rate in children from the United Network of Organ Sharing in the USA [29]. When separating out 101 children in Italy with non-genetic primary SRNS ($n = 60$) who received a kidney transplant between 2005–2017, Morello et al. reported a 53.3% recurrence rate [6]. In their subsequent meta-analysis of 8 studies and 581 children between 2014 and 2022, Morello et al. reported a 61% recurrence rate in 129 children with SRNS with no genetic mutations identified [5]. In contrast, neither Morello et al. or Mason et al. found any post-transplant recurrence if a pathogenic mutation considered causative for FSGS was found [5, 6, 30]. Our series has a slightly lower recurrence rate of 40.6%, which may relate in part to the possible inclusion of patients with monogenic and secondary causes of FSGS in the cohort.

Baum et al. reported a loss of the living donor survival advantage of kidney transplants in FSGS recipients [31]. From ANZDATA, Francis et al. showed a 5-year allograft survival of only 52% in recipients with rFSGS versus 83%

in those without [28]. We were able to separate out allograft survival in recurrent FSGS patients based on response to therapy and demonstrate that allograft survival was worse only in those who did not achieve any partial or complete remission. In those recurrent FSGS patients with either partial or complete response, we did not see an increased risk of allograft loss up to 6 years post-transplant with recurrence of FSGS. This association between partial remission and prolongation of allograft survival has not previously been reported in the literature.

Many different therapies have been attempted to treat rFSGS. Application of therapeutic plasma exchange (TPE), also known as plasmapheresis, as an approach to rFSGS was first described by Zimmerman in 1985 [32]. Its rationale is based on the rapidity of recurrence and on animal experiments that suggested a circulating permeability factor. In a meta-analysis of 423 patients, Kashgary et al. found a complete + partial remission rate of 71% with plasmapheresis, identical in adults and children, with higher chance of complete remission in males or those who started plasmapheresis within 2 weeks of recurrence [33]. In the TANGO study, Uffing et al. found that complete remission occurred only in those who received plasmapheresis [4]. In their follow-up study, 23/27 (85%) of those who received long-term apheresis for at least 6 months achieved a complete or partial remission [34].

Rituximab is a chimeric human-murine monoclonal antibody to CD20, expressed on pre-B cells, which can deplete B cells and reduce circulating antibody levels [35]. Rituximab was first reported to induce rFSGS remission in patients who received it for treatment of other disorders, such as idiopathic thrombocytopenic purpura or post-transplant lymphoproliferative disorder [36, 37]. We have previously published that response to rituximab was better in patients of male gender or normal serum albumin at time of recurrence [38]. Ofatumumab is a newer, fully human anti-CD20 antibody, with greater affinity to the ligand and higher complement-mediated cytotoxicity. There has been anecdotal success of ofatumumab in cases resistant to other treatments [39, 40], though a more recent case series of 6 patients showed only partial remission in 3 patients and several side effects [41]. For the biphasic pattern that we saw, we speculate that podocyte cytoskeleton responses to anti-CD20 agents occur early, and if not enough to induce remission, then further doses are not of benefit.

Fusion immunoglobulin products of the CTLA4 molecule that block the CD28-B7 costimulatory pathway between antigen presenting cells and T cells have been administered in native primary FSGS and rFSGS, based on the potential role of this pathway in podocyte injury [42]. However, evidence for efficacy remains inconclusive and may be tissue B7-1 expression dependent [43], with at least one report by Delville et al. demonstrating no benefit in 9 consecutive patients with rFSGS [44]. Other therapies such as adrenocorticotropic hormone [45, 46] or the Liposorber® device to perform LDL-apheresis have similarly had mixed success [47]. When administered pre- or peri-transplant to prevent recurrence, rituximab and plasmapheresis have not shown a reduction in rates of rFSGS [18, 19]. Our results suggest that higher number of doses of CTLA4-Igs or greater number of LDL-apheresis sessions may offer benefit. The wider confidence intervals with greater dosages could be explained by either the limited sample size or by greater variability of treatment, which are not mutually exclusive.

The strengths of our study included the high level of granular detail that could be extracted from the EHR across a multicenter population of a very uncommon disease. Our data are extracted from a contemporary era and a large representative source population, allowing for greater generalizability. Limitations of our study include its retrospective nature, the inability to assess for initial steroid responsiveness at native kidney disease presentation as a risk factor for post-transplant recurrence [48, 49], potential inclusion of patients with monogenic and secondary causes of FSGS, and the individualized treatments used at each center, often in greater combinations of agents for those who did not respond early. Further, the evaluation of treatment response is limited by the extensive use of TPE in almost all patients and by the small number of cases treated with CTLA4 agents. We did not attempt to collect adverse effects of the therapies used. We have adjusted for these clinical variations pragmatically in assessing responses to agents. Furthermore, in our regression analyses, it is assumed that the outcome follows the treatment choice and not vice versa. But in these patients, the number of administrations and combinations can increase until the patient responds, so the treatment here is a consequence of whether and how early the patient responds. Our application of time-varying predictor methods for censored time-to-event data addresses this to some extent. We also note the limitations associated with the secondary use of EHR data for research, such as non-random missingness and data quality issues [50].

In summary, using real-world multicenter data, we identified a contemporary targeted high-risk cohort of children with rFSGS after kidney transplant and present novel data on treatment responses. Recurrence occurred in 40.6% (45–47.14% if mutational FSGS excluded), and complete + partial outcomes were favorable in our cohort, without increased risk of renal allograft loss if either partial or complete remission was achieved. In our cohort, the combination of TPE and rituximab resulted in partial or complete remission in a majority of patients, and we identified a potential role for LDL-apheresis and CTLA4-Igs, perhaps at earlier stages than used in these patients. These data can inform the design and focus of future prospective randomized clinical trials for rFSGS.

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Data availability Per PedsNet governance policies, data cannot be shared.

Declarations

Competing interests Dharnidharka: Research grants: CareDx, NIAID, NCI, NIDDK; Denburg: Research grant: Mallinckrodt; Dixon: Consultancy – Apellis Pharmaceuticals, Alexion, Astra Zeneca Rare Disease, Novartis Pharmaceuticals; Smoyer: Consultancy – USC CTSI External Advisory Board, UCLA CCTS External Advisory Board, NephCure Kidney International Board; Funding – NIDDK; Riella: Investigator-initiated research from BMS, CareDx, Visterra; Federal funding from NIH and DOD; Industry-sponsored research Natera; Funding by Wellcome Leap. All other authors have no conflicts of interest to disclose.

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