Recurrence of nephrotic syndrome following kidney transplantation is associated with initial native kidney biopsy findings

Jonathan H. Pelletier[1] · Karan R. Kumar[1] · Rachel Engen[2] · Adam Bensimhon[1] · Jennifer D. Varner[1] · Michelle N. Rheault[3] · Tarak Srivastava[4] · Caroline Straatmann[5] · Cynthia Silva[6] · T. Keefe Davis[7] · Scott E. Wenderfer[8] · Keisha Gibson[9] · David Selewski[10] · John Barcia[11] · Patricia Weng[12] · Christoph Licht[13] · Natasha Jawa[13] · Mahmoud Kallash[14] · John W. Foreman[1] · Delbert R. Wigfall[1] · Annabelle N. Chua[1] · Eileen Chambers[1] · Christoph P. Hornik[1] · Eileen D. Brewer[8] · Shashi K. Nagaraj[1] · Larry A. Greenbaum[15] · Rasheed A. Gbadegesin[1]

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Abstract

Background and objectives Steroid-resistant nephrotic syndrome (SRNS) due to focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) is a leading cause of end-stage kidney disease in children. Recurrence of primary disease following transplantation is a major cause of allograft loss. The clinical determinants of disease recurrence are not completely known. Our objectives were to determine risk factors for recurrence of FSGS/MCD following kidney transplantation and factors that predict response to immunosuppression following recurrence.

Methods Multicenter study of pediatric patients with kidney transplants performed for ESKD due to SRNS between 1/2006 and 12/2015. Demographics, clinical course, and biopsy data were collected. Patients with primary-SRNS (PSRNS) were defined as those initially resistant to corticosteroid therapy at diagnosis, and patients with late-SRNS (LSRNS) as those initially responsive to steroids who subsequently developed steroid resistance. We performed logistic regression to determine risk factors associated with nephrotic syndrome (NS) recurrence.

Results We analyzed 158 patients; 64 (41%) had recurrence of NS in their renal allograft. Disease recurrence occurred in 78% of patients with LSRNS compared to 39% of those with PSRNS. Patients with MCD on initial native kidney biopsy had a 76% recurrence rate compared with a 40% recurrence rate in those with FSGS. Multivariable analysis showed that MCD histology (OR; 95% CI 5.6; 1.3–23.7) compared to FSGS predicted disease recurrence.

Jonathan H. Pelletier, Karan R. Kumar and Rachel Engen contributed equally to this work.

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✉ Rasheed A. Gbadegesin
rasheed.gbadegesin@duke.edu

[1] Department of Pediatrics, Divisions of Nephrology and Critical Care, Duke University Medical Center, Durham, NC 27710, USA

[2] Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois and Children's Hospital Seattle, Washington, USA

[3] University of Minnesota Masonic Children's Hospitals, Minneapolis, MN, USA

[4] Children's Mercy Hospital, Kansas City, MO, USA

[5] Louisiana State University Children's Hospital, New Orleans, Louisiana, USA

[6] Connecticut Children's Medical Center, Hartford, CT, USA

[7] St. Louis Children's Hospital, St Louis, MO, USA

[8] Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

[9] North Carolina Children's Hospital, Chapel Hill, NC, USA

[10] C.S. Mott Children's Hospital, Ann Arbor, MI, USA

[11] University of Virginia Children's Hospital, Charlottesville, Virginia, USA

[12] Mattel Children's Hospital University of California, California, Los Angeles, USA

[13] The Hospital for Sick Children, Toronto, ON, Canada

[14] Nationwide Children's Hospital, Columbus, OH, USA

[15] Emory University and Children's Healthcare of Atlanta, Atlanta, GA, USA

Conclusions Pediatric patients with MCD and LSRNS are at higher risk of disease recurrence following kidney transplantation. These findings may be useful for designing studies to test strategies for preventing recurrence.

Keywords Nephrotic syndrome · Transplantation · Immunosuppression · Lipoid · Nephrosis · Focal segmental glomerulosclerosis

Introduction

Steroid-resistant nephrotic syndrome (SRNS) is a leading cause of end-stage kidney disease (ESKD) in children [1, 2]. The predominant histopathologic pattern associated with SRNS in pediatric patients is focal segmental glomerulosclerosis (FSGS). In the majority of patients with FSGS, the etiology is unknown. However, FSGS is believed to be associated with circulating factors that have not been well characterized [3–7]. In addition, a small percentage of FSGS may be due to mutations in one of over 50 genes that have been identified in patients with familial and sporadic FSGS [3–6]. Most of these genes are localized to the podocyte [8].

Focal segmental glomerulosclerosis and other histopathologic causes of SRNS are characterized by a progressive disease course and development of ESKD within 5 to 10 years of diagnosis in many patients [9, 10]. Recurrence of primary kidney disease is the most important cause of graft loss in patients with SRNS. Previous authors have reported recurrence following kidney transplantation in up to 50% of cases [11–15]. The risk factors for recurrence have not been well established. Small, single-center series have identified Caucasian race, rapid progression to ESKD within 3 years, mesangial hypercellularity on primary biopsy, and living donor transplant as risk factors for FSGS recurrence [16, 17]. However, these findings are inconsistent across studies. Furthermore, patients with genetic SRNS are known to have a low risk of recurrence [18].

A recent study from Europe reported that initial steroid sensitivity followed by steroid resistance in the native kidneys might predict nephrotic syndrome (NS) recurrence after kidney transplantation. In this study, the authors describe a recurrence risk of 93% in patients who were initially steroid-sensitive before developing secondary steroid resistance (late steroid resistance: LSRNS) and ESKD compared with 30% in those with primary SRNS (PSRNS) [19]. These findings suggest that initial steroid response in native kidney may be a potent predictor of NS recurrence following kidney transplant, and this sub-group of patients may therefore be targeted for early intervention and aggressive plasmapheresis and immunosuppression post-transplant [19]. In a follow-up study, the same group confirmed their findings in a National Cohort from the UK [20]. Given the racial heterogeneity of the US population, it is unclear if the same factors can predict risk of recurrence with such high sensitivity. In addition, there is limited information on clinical characteristics that predict the likelihood of response to intensive immunosuppression following recurrence. The objective of this study is to identify pre-transplant factors that predict the risk of recurrence following kidney transplantation and response to treatment following recurrence. Identification of such factors may guide the design of personalized immunosuppression protocols pre and post kidney transplant and ultimately improve survival after kidney transplant.

Materials and methods

Study design and objectives

We performed a multicenter retrospective observational cohort study. Our objectives were to (1) determine risk factors for recurrence of MCD/FSGS within renal allografts and (2) determine factors that predict response to intensive immunosuppression following recurrence. Study participants were retrospectively recruited from major academic medical centers in the Midwest Pediatric Nephrology Consortium (MWPNC). Data were collected and managed using Research Electronic Data Capture tools hosted at Duke University [21].

Setting and participants

Patients aged 0–21 years at the time of diagnosis were eligible for inclusion if they had a diagnosis of SRNS or congenital nephrotic syndrome (CNS), a native kidney biopsy showing minimal change disease (MCD), FSGS, or other histologic variants associated with CNS, and underwent initial kidney transplantation from January 2006 to December 2015. Patients were excluded from the study if they had a diagnosis of SRNS secondary to another cause (such as membranoproliferative glomerulonephritis or membranous nephropathy).

Definitions

Remission of SRNS was defined as a urine protein:creatinine ratio of ≤ 0.2 mg/mg following 8 to 12 weeks of corticosteroid (daily corticosteroid at 2 mg/kg or 60 mg/m^2 per day for 4 to 6 weeks followed by 2/3 of the daily dose on alternate days for

another 4 to 6 weeks). Patients were defined as having PSRNS if they did not achieve remission following 6 weeks of daily corticosteroid. Patients were defined as having LSRNS if they initially achieved remission, and then subsequently developed steroid resistance (defined as failure to sustain remission despite ongoing steroid therapy and subsequent development of ESKD). Recurrence of NS following renal transplantation was defined as development of nephrotic range proteinuria (urine protein:creatinine ratio > 2.0 mg/mg) due to no other apparent cause following kidney transplantation and/or transplant biopsy showing podocyte foot process effacement on electron microscopy.

Predictors

Patients age at NS diagnosis, sex, race/ethnicity, biopsy histology, type of SRNS (PSRNS, LSRNS, or CNS), age at ESKD, time from diagnosis to ESKD, age at transplantation, and transplant type (living or deceased donor) were collected as potential predictors of recurrence of SRNS.

Outcomes

The primary outcome of the study was recurrence of NS following renal transplantation. The secondary outcomes of the study were renal allograft function at 6-month follow-up and response to post-transplantation immunosuppression in those patients who had recurrence of NS, defined as remission of nephrotic range proteinuria at 6-month follow-up.

Analytical approach

We used frequencies (with percentages) and medians (with 25th and 75th percentiles) or means (with standard deviations) to describe categorical and continuous variables, respectively. We compared the distribution of demographics, clinical characteristics, and biopsy findings by disease recurrence using the chi-squared test or Wilcoxon rank sum test, where appropriate. To determine the risk factors associated with NS recurrence, we constructed both unadjusted (univariable) and adjusted (multivariable) logistic regression models with random effects for site. Based on prior literature review, we a priori selected sex, race, initial histology, SRNS type, time to ESKD, and transplant type for inclusion in the multivariate logistic regression model. We used standard graphical and statistical methods to test all model assumptions. These included Pearson standardized residual plots, deviance residual plots, and Pregibon leverage plots to test for influential outliers; the Hosmer-Lemeshow and link tests to evaluate for model fit and specification errors; variance inflation factor (VIF); and tolerance to test for multicollinearity. We report odds ratios (OR) with 95% confidence intervals. We defined statistical significance as a p value < 0.05. We performed all statistical analyses using Stata 15.1 (College Station, Texas).

Results

We identified 201 patients from 16 participating pediatric nephrology centers. Participating centers are listed in Online Resource Table 1. Of these, 43/201 patients (21%) were excluded from the analysis, as shown in Fig. 1. Patients were excluded for the following reasons: 34 were missing information regarding initial response to steroids, 5 were missing information regarding SRNS recurrence after transplantation, 2 were patients who had received a prior kidney transplant, and 2 had no biopsy information available. Thus, the final cohort for analysis included 158 patients.

Cohort demographics are summarized in Table 1. Briefly, 55% of patients were male, 28% of patients were black, 42% were white, 22% were Hispanic, and 8% other race. The median age at diagnosis was 5.0 years (25th and 75th percentiles 2.0 and 10.0 years, respectively). The median time from SRNS diagnosis to ESRD was 1.9 years (25th and 75th percentiles 0.8 and 3.5 years, respectively). Initial histology was FSGS in 77% and MCD in 11% of patients. The remainder had initial biopsies consistent with histological patterns such as diffuse mesangial sclerosis that are typically associated with congenital nephrotic syndrome. Regarding initial steroid response, 69% patients had PSRNS, 17% had LSRNS, and 14% had monogenic SRNS. Genetic mutations reported in some of the patients with monogenic SRNS are shown in Online Resource Table 2. Deceased donor transplantation (58%) was more common than living donor transplantation (42%).

Risk factors associated with recurrence of SRNS

Post-transplantation recurrence of NS occurred in 41% of patients. The median time to recurrence was 2.0 days following transplantation (25th and 75th percentiles 1.0 and 3.8 days, respectively). As shown in Fig. 2, disease recurrence occurred in 78% of patients with LSRNS compared to 39% of those with PSRNS. Patients with MCD on initial native kidney biopsy had a 76% recurrence rate compared with a 40% recurrence rate in those with FSGS and 0% in patients with monogenic NS. Recurrence was diagnosed by kidney biopsy in 56% of patients; the remainder were diagnosed based on the presence of nephrotic range proteinuria.

Unadjusted (univariable) logistic regression of factors associated with recurrence is shown in Table 2. Initial histology (MCD vs. FSGS), initial steroid responsiveness (LSRNS vs. PSRNS), and increasing time to ESKD were associated with increased odds of recurrence in this analysis. Adjusted (multivariable) logistic regression of factors associated with

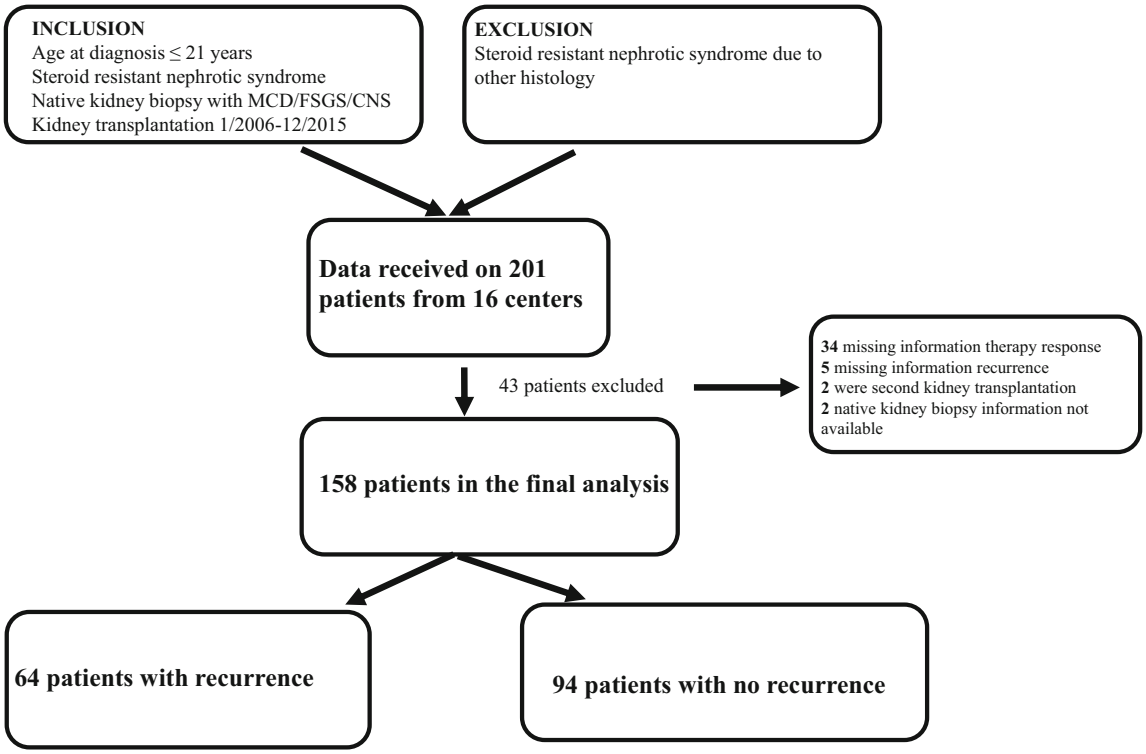

Fig. 1 Flow diagram describing inclusion and exclusion criteria

recurrence is shown in Table 3. Initial histology of MCD was associated with increased odds of NS recurrence following kidney transplantation compared to FSGS histology (OR 5.61, 95% CI 1.33–23.69, $p = 0.02$). There was a trend towards increased odds of NS recurrence in children with LSRNS compared to PSRNS (OR 3.15, 95% CI 0.96–10.34, $p = 0.06$).

Response to immunosuppression in patients with recurrence

Remission data was available for 49/64 (77%) of patients with recurrence at 6-month follow-up. The overall remission rate at 6-month follow up was 14/49 (29%). Remission was not associated with native kidney histology or initial steroid responsiveness. In patients with recurrence of disease following transplantation, 3/13 (23%) patients with initial MCD histology had remission, compared with 11/48 (23%) patients with initial FSGS histology. 4/21 (19%) patients with LSRNS experienced remission, compared with 10/43 (23%) patients with PSRNS.

Renal allograft function in patients with and without recurrence

Data on allograft function for patients with and without recurrence was available for 60/64 (94%) and 90/94 (96%) of patients at 6-month follow-up, respectively. Patients with recurrence were more likely to have ESKD and require dialysis at 6 months (8/60 vs. 3/90, $p = 0.02$). Only one patient with monogenic SRNS developed ESKD requiring dialysis at 6 months; this patient did not have recurrence of NS.

Discussion

End-stage kidney disease secondary to nephrotic syndrome (NS) is the cause of more than 11.5% of pediatric kidney transplants in the USA [22], and recurrent NS post-transplant nearly doubles the risk of graft loss [19]. In this multicenter retrospective study of children undergoing kidney transplantation secondary to NS, we demonstrate a 41% incidence of disease recurrence in the transplanted kidney. Recurrence was associated with minimal change disease histology (MCD) on initial diagnostic native kidney biopsy and late steroid resistance (LSRNS) in univariable analysis. In an analysis adjusting for sex, race, pattern of steroid resistance, time to ESKD, and transplant donor type, an initial histology of MCD continued to be strongly associated with NS recurrence.

The 41% incidence of recurrence in our study is similar to previous reports. In Europe, Ding et al. reported that nephrotic syndrome recurred in 38% of children transplanted for steroid resistant nephrotic syndrome [19], while a 36% incidence of recurrence was reported by Francis et al. in a cohort of 70 children in Australia and New Zealand transplanted for FSGS [15]. These rates are significantly higher than those

Table 1 Demographics of the study population

Characteristic	All, *n* (%)	Recurrence, *n* (%)	
		No	Yes
	(*n* = 158)	(*n* = 94)	(*n* = 64)
Diagnosis age			
< 5 years	78 (50)	40 (43)	38 (59)
5 to < 10 years	37 (23)	19 (20)	18 (28)
10+ years	43 (27)	35 (37)	8 (13)
Sex			
Female	71 (45)	43 (46)	28 (44)
Male	87 (55)	51 (54)	36 (56)
Race			
Black	45 (28)	28 (30)	17 (26)
White	66 (42)	38 (41)	28 (44)
Hispanic	34 (22)	22 (23)	12 (19)
Other	13 (8)	6 (6)	7 (11)
Initial histology			
FSGS	122 (79)	74 (80)	48 (79)
MCD	17 (11)	4 (4)	13 (21)
CNS	15 (10)	15 (16)	0 (0)
SRNS type			
Primary	109 (69)	66 (70)	43 (67)
Late	27 (17)	6 (6)	21 (33)
Genetic	22 (14)	22 (24)	0 (0)
ESKD age			
< 5 years	31 (20)	23 (25)	8 (13)
5 to < 10 years	40 (26)	16 (17)	24 (38)
10+ years	85 (54)	54 (58)	31 (49)
Time to ESKD			
< 1 year	30 (19)	25 (27)	5 (8)
1 to < 5 years	84 (54)	48 (51)	36 (57)
5+ years	42 (27)	20 (22)	22 (35)
Transplant age			
< 5 years	21 (13)	17 (18)	4 (6)
5 to < 10 years	34 (22)	12 (13)	22 (35)
10+ years	103 (65)	65 (69)	38 (59)
Transplant type			
Deceased donor	92 (58)	52 (55)	40 (63)
Living donor	66 (42)	42 (45)	24 (37)

CNS congenital nephrotic syndrome, *ESKD* end-stage kidney disease, *FSGS* focal segmental glomerulosclerosis, *MCD* minimal change disease, *SRNS* steroid-resistant nephrotic syndrome

previously reported using NAPRTCS (20% recurrence) [23] and UNOS data (15% recurrence) [17], possibly because both of those cohorts extended further into the past, when transplant indications may have differed. Notably, fewer patients in our study were of Caucasian race (42%) compared to the European or Australian studies (84 and 89% Caucasian, respectively) [15, 19].

Late steroid resistance NS was associated with a 78% incidence of recurrence in this study, twice the incidence seen in those with PSRNS. While this finding was no longer statistically significant after controlling for sex, race, histology, time to ESKD, and transplant type, the strength of the association and spacing of the 95% confidence interval suggest potential clinical significance, especially as LSRNS has also been associated with NS recurrence in two European studies, (Online Resource Table 3) [19, 20]. Ding et al. showed that children with late steroid resistance were 3.1 times more likely to have post-transplant disease recurrence, while Bierzynska et al. showed a 1.6 times increased risk of recurrence [19, 20].

Primary NS pathophysiology is not fully understood, but disease is thought to have two main causes. The first is a variety of genetically based abnormalities in the function of the glomerular filtration barrier [20]. The second is immune dysregulation, with increased type 2 helper T cells and a presumed circulating factor (or absence of a factor that should be present), leading to podocyte effacement and nephrosis [24]. As genetic testing modalities improve, the number of genes associated with steroid-resistant nephrotic syndrome has continued to rise [5, 25]. We can posit that the lower incidence of recurrence among those with PSRNS is because many of these patients may have a yet to be identified structural defects in the glomerular filtration barrier; these patients never responded to steroids because the etiology of their nephrotic syndrome was not immune-mediated. On the other hand, patients with LSRNS may, hypothetically, have initially responded to steroids because their disease was primarily an immune dysregulation. This group may have a higher incidence of recurrence post-transplant because the underlying immune dysregulation or circulating factor persists. This simple dichotomy, however, would not explain the 39% of patients with PSRNS who did recur, or the 22% of patients with LSRNS who did not. More research is needed to better characterize the pathophysiology underlying these subsets of nephrotic syndrome.

In the present study we show, for the first time, that an initial biopsy finding of MCD in native kidney is associated with post-transplant recurrence; 76% of patients with MCD had recurrence compared to 39% of those with FSGS and 0% of those with monogenic nephrotic syndrome. Interpretation of this finding is challenging because the association between NS histology and pathophysiology is poorly understood. In SRNS, it is not known if MCD histology represents a separate clinical entity, FSGS that is not detected due to sampling error, or the first step in a disease process that will progress to FSGS. The latter possibility is suggested, though by no means confirmed, by the finding that early renal biopsies of FSGS recurrence post-transplant show only foot-process effacement, while later biopsies may show FSGS [26, 27]. If this is true, then the finding of MCD on initial diagnostic biopsy may indicate a more indolent pre-diagnosis course. If, instead, MCD indicates a separate clinical entity, it would suggest a

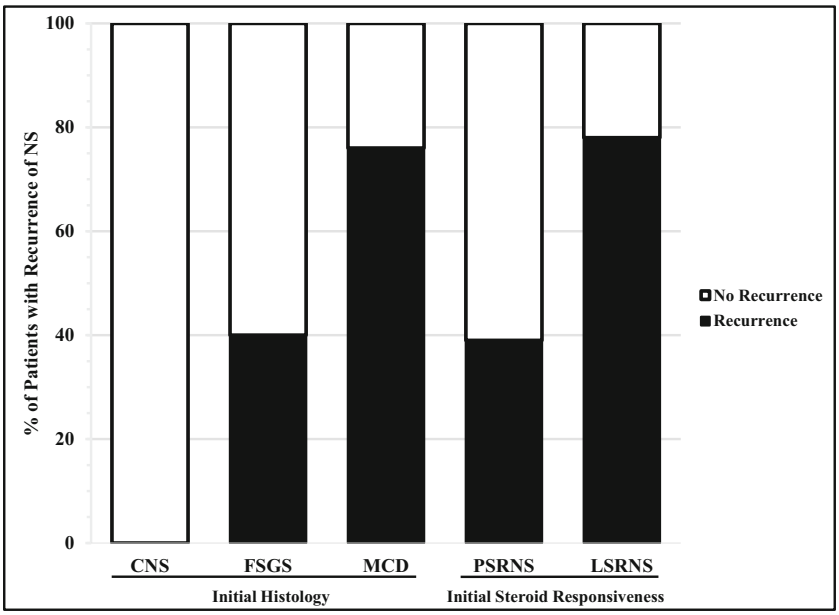

Fig. 2 Proportion of patients with recurrence of nephrotic syndrome after kidney transplantation grouped by initial histology and initial steroid responsiveness. *CNS* congenital nephrotic syndrome, *FSGS* focal segmental glomerulosclerosis, *MCD* minimal change disease, *PSRNS* primary steroid-resistant nephrotic syndrome, *LSRNS* late steroid-resistant nephrotic syndrome. Note that all CNS were due to single gene mutation (monogenic NS)

similarity to steroid-sensitive NS, which is thought to have an immune dysregulation etiology [28–30]. Nevertheless, based on the present findings, it is possible to use genetic findings, native kidney biopsy findings, and pattern of therapy response

Table 2 Unadjusted (univariable) analysis of risk factors for recurrence of nephrotic syndrome following kidney transplantation

Risk factor	OR (95% CI)
Sex	
Female	Reference
Male	1.12 (0.57, 2.19)
Race	
Black	Reference
White	1.19 (0.53, 2.68)
Hispanic	1.01 (0.36, 2.82)
Other	1.91 (0.52, 7.05)
Initial histology	
FSGS	Reference
MCD	5.10 (1.51, 17.28)
CNS	No recurrence
SRNS type	
Primary	Reference
Late	6.50 (2.20, 19.18)
Genetic	No recurrence
Time to ESKD	
< 1 year	Reference
1 to < 5 year	3.73 (1.30, 10.74)
5+ year	5.41 (1.71, 17.13)
Transplant type	
Deceased donor	Reference
Living donor	0.73 (0.37, 1.45)

CNS congenital nephrotic syndrome, *ESKD* end-stage kidney disease, *FSGS* focal segmental glomerulosclerosis, *MCD* minimal change disease, *SRNS* steroid-resistant nephrotic syndrome

Table 3 Adjusted (multivariable) analysis of risk factors for recurrence of nephrotic syndrome following kidney transplantation

Risk factor	OR (95% CI)	*p* value
Sex		
Female	Reference	
Male	0.72 (0.32, 1.63)	0.42
Race		
Black	Reference	
White	2.24 (0.75, 6.70)	0.15
Hispanic	2.04 (0.59, 7.02)	0.26
Other	1.83 (0.34, 9.92)	0.48
Initial histology		
FSGS	Reference	
MCD	5.61 (1.33, 23.69)	0.02
CNS	No recurrence	
SRNS type		
Primary	Reference	
Late	3.15 (0.96, 10.34)	0.06
Genetic	Reference	
Time to ESKD		
< 1 year	Reference	
1 to < 5 years	1.86 (0.54, 6.40)	0.33
5+ years	2.75 (0.67, 11.17)	0.16
Transplant type		
Deceased donor	Reference	
Living donor	0.70 (0.28, 1.76)	0.45

CNS congenital nephrotic syndrome, *ESKD* end-stage kidney disease, *FSGS* focal segmental glomerulosclerosis *MCD* minimal change disease, *SRNS* steroid-resistant nephrotic syndrome

prior to kidney transplant to stratify patients with SRNS undergoing renal transplant into a low-risk group (monogenic NS), a medium-risk group (FSGS on native kidney biopsy and PSRNS), and a high-risk group (MCD on native kidney biopsy and/or LSRNS). The recurrence risk in these proposed groups is illustrated in Online Resource Table 4.

Living donor transplant has been reported to be associated with NS recurrence [19] and to not be associated with recurrence [17]. Non-white race has been associated with recurrence in Australia and New Zealand [15], while being African American was found to be protective in the USA[23]. Rapid progression to ESKD has been associated with disease recurrence in some studies [23] but not in others [19]. None of these factors were found to be significant in our study, likely, due to variations in patient population, definitions of variables, and statistical power.

The chief strength of this study is its relatively large sample size, drawing from 16 different children's hospitals across the USA and Canada to create a diverse cohort. This diversity, however, also prevented us from fully exploring the response to intensive immunosuppression following recurrence of NS post-transplant due to heterogeneity in treatment methods. Similarly, clinical reports of biopsy results from each institution were used to classify histology, so subtle findings, such as mesangial hypercellularity, could not be evaluated due to differences in institutional reporting styles. Lastly, the exact timing of biopsy was not known for each individual patient. As a result, our results may underrepresent the effect size of the initial biopsy finding of MCD in predicting recurrence.

In conclusion, pediatric patients with native kidney MCD histology on initial biopsy and LSRNS show an increased risk for disease recurrence following kidney transplantation. Disease recurrence has a major impact on graft outcomes for this population, and accurate identification of patients at high risk will aid in counseling patients on their risk, creating individualized treatment protocols pre- and post-transplant, and designing clinical trials to prevent and treat nephrotic syndrome recurrence post-transplant.

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Compliance with ethical standards

Each center completed a local institutional review board approval and data usage agreements with the coordinating center at Duke University. Individual centers independently performed chart review to identify eligible patients as determined by the inclusion and exclusion criteria.

Conflict of interest The authors declare that they have no conflict of interest.

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