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Graft Loss Due to Recurrent Disease in Pediatric Kidney Transplant Recipients on a Rapid Prednisone Discontinuation Protocol

Blanche M. Chavers^{1,2}, Michelle N. Rheault¹, Kristen J. Gillingham², and Arthur J. Matas²

¹Department of Pediatrics, University of Minnesota Medical School, 2450 Riverside Avenue, East Building, 6th Floor, Minneapolis, MN 55454

²Department of Surgery, University of Minnesota Medical School, MMC 195, 420 Delaware Street S.E., Minneapolis, MN 55455

Abstract

Recurrent disease is the 4th most common cause of graft loss (GL) in pediatric kidney transplant (KTx) recipients. We studied the incidence of recurrent disease and GL due to recurrent disease in pediatric KTx recipients on a rapid discontinuation of prednisone (RDP) protocol.

Between 2002 and 2010 we performed 74 KTxs in patients age 5–18 years using a RDP protocol, 25 (34%) were at risk for recurrence of primary disease. Outcomes were compared to 69 historical controls (18 [26%] at risk for recurrence), KTx between 1996–2000. Follow up period was 39 ± 25 months in RDP and 124 ± 38 months in controls.

The incidence of recurrent disease at 3 years post KTx was 16% in RDP and 28% in controls ($p=NS$). Mean time to recurrent disease was 22 ± 26 months in RDP and 46 ± 48 months in controls ($p=0.54$). Nine (12%) grafts were lost in the RDP group (1-recurrence) and 32 (46%) in the control group (4-recurrence). Time to GL was 85 months in the RDP recipient and 46 ± 21 months in controls.

A RDP protocol in pediatric KTx recipients may not be associated with increased risk of graft loss due to recurrent disease.

Keywords

Graft loss; pediatric kidney transplantation; rapid discontinuation of prednisone; disease recurrence

Address for correspondence: Blanche M. Chavers, MD, Department of Pediatrics, Division of Nephrology, 2450 Riverside Avenue, East Building, 6th Floor, Minneapolis, MN 55454, Phone: 612-626-2922, Fax: 612-626-2791, chave001@umn.edu.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Blanche Chavers: concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article; Michelle Rheault: data analysis/interpretation, drafting article, critical revision of article, approval of article; Kristen Gillingham: statistics, data analysis/interpretation, drafting article, critical revision of article, approval of article; Arthur Matas: concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article.

INTRODUCTION

Steroid avoidance, minimization and early discontinuance protocols are being used more frequently in pediatric kidney transplant (KTx) recipients. To date, there has not been evidence of increased risk of acute rejection in the early posttransplant period up to 2 years. However, it is unknown whether these protocols are associated with increased risk of graft loss due to disease recurrence in pediatric KTx recipients. Disease recurrence in the allograft has a greater prevalence in children than in adults (1). Overall, recurrence of disease accounts for 7–8% of graft losses in pediatric KTx recipients and is the fourth most common cause of graft loss after chronic rejection, acute rejection, and death with a functioning graft (1). Recurrent diseases leading to graft loss are primarily glomerulonephritides (70–80%) and inherited metabolic diseases. Glomerulonephritides at risk of recurrence with graft loss include focal segmental glomerulosclerosis (FSGS), typical and atypical hemolytic uremic syndrome (HUS), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, Henoch-Schönlein Purpura (HSP) nephritis, systemic lupus erythematosus (SLE) nephritis, membranous nephropathy, anti glomerular basement membrane (GBM) antibody associated GN, and anti-neutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis (1,2). We have previously reported causes of graft loss in our pediatric KTx population receiving steroid based immunosuppression (3). The impact of rapid discontinuation of prednisone on the risk of graft loss due to recurrence of disease in children is unknown. Therefore, we compared graft losses in pediatric KTx recipients on a rapid discontinuation of prednisone (RDP) protocol and with glomerular diseases at risk of recurrence to a historical control group of recipients at risk of graft loss due to disease recurrence but were maintained on a steroid based immunosuppression protocol.

PATIENTS AND METHODS

Approvals

The Institutional Review Board of the University of Minnesota approved our study (Study Number: 0704M05324).

Patient characteristics

Using our database and medical records, we retrospectively reviewed the records of 74 pediatric patients (<19 years) who underwent a KTx at the University of Minnesota from 5/2002 through 8/2010 using a RDP immunosuppression protocol (4). Of the 74 recipients, 25 (34%) were at risk of recurrence of GN. Controls (n=69) were transplanted between 1/1996 and 12/2000 using a protocol incorporating long-term steroids and were matched for age with the RDP group (5). Of these, 18 (26%) were at risk of recurrence of GN. The glomerulonephritides included in this study that have been known to recur in the transplanted kidney include FSGS, IgA nephropathy, HSP GN, MPGN, anti GBM antibody associated GN, HUS, and ANCA associated vasculitis/GN. Diagnoses of anti GBM antibody associated GN, and ANCA + vasculitis were confirmed by serology. Mean follow-up was 39 ± 25 months (range, 1 to 100) for RDP recipients and 124 ± 38 months (range, 0.3 to 176) for control recipients.

Immunosuppression

Our immunosuppressive protocols have been previously described (4,5). Briefly, Thymoglobulin was given at 1.5 mg/kg intravenously (IV) per day for 5–7 days in the RDP recipients. Control recipients received either antithymocyte globulin (ATGAM, 20 mg/kg/day for the first 14 days posttransplant) or Thymoglobulin (1.5 mg/kg/day for the first 10 days posttransplant). For RDP recipients, prednisone was given as follows: 10 mg/kg IV intraoperatively, 1 mg/kg IV on day 1, 0.5 mg/kg IV days 2 and 3, 0.25 mg/kg IV days 4 and

5, and 0 mg/kg on day 6. Mycophenolate mofetil was given at 600 mg/m²/dose twice a day. The first dose was given IV intraoperatively. Cyclosporine A (Neoral) was begun orally on day 1 and dosed to achieve target levels in both groups as follows: zero to three months: 175–200 ng/mL; four to six months: 150–175 ng/mL, seven to nine months: 125–150 ng/mL, nine months to one year: 100–125 ng/mL. For controls, prednisone was started at 2 mg/kg/day orally, then tapered to 0.45 mg/kg/day at 1 month post-transplant, and then to 0.25 to 0.3 mg/kg/day at 1 year. Azathioprine was started at 5 mg/kg/day orally on the day of the KTx, and then tapered to 2 to 2.5 mg/kg/day over the 1st week posttransplant.

Preemptive Plasmapheresis Protocol for Patients with FSGS

Beginning in 2006, patients with FSGS received preemptive plasmapheresis. Living donor recipients received 3 single volume exchanges pretransplant and 5 exchanges posttransplant. Deceased donor recipients received a single plasma volume exchange pretransplant and 5 exchanges posttransplant. Fresh frozen plasma was used for the exchanges immediately pre and the first three posttransplant instead of albumin.

Antimicrobial, antifungal and antiviral prophylaxis

Oral trimethoprim-sulfamethoxazole was given daily to all recipients as prophylaxis against urinary tract infection (UTI) and *Pneumocystis carinii* infection (5). Fungal prophylaxis was provided with oral nystatin for 6 months posttransplant. All recipients received prophylactic acyclovir, gancyclovir, or valgancyclovir for 3 months posttransplant. Recipients with quantitative polymerase chain reaction tests positive for Epstein Barr virus were maintained on valgancyclovir beyond 3 months.

Rejection and disease recurrence

Recipients with a ≥25% increase in serum creatinine above baseline or new onset of proteinuria underwent diagnostic percutaneous kidney biopsy. A renal pathologist at our center read all biopsies. Rejection was characterized as acute or chronic, tubulointerstitial (TI), and/or vascular by established criteria (4,6). Acute rejection episodes were treated with steroids for mild cases. Steroid resistant or more severe acute rejection episodes were also treated with antibody therapy. Recurrence of primary disease was confirmed by kidney biopsy.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) and range. Statistical analyses were performed using the Wilcoxon rank-sum test, chi-square test, Log-rank test, Fisher exact test, and Kruskal-Wallis test. Actuarial graft and patient survival rates, as well as graft loss rates to specific causes were calculated using Kaplan-Meier survival methods. Disease recurrence was confirmed by histological diagnosis. Time to recurrence and time to graft loss due to recurrence were also calculated and compared between groups. Graft loss was defined as return to chronic dialysis, transplant nephrectomy, retransplantation, or patient death. Graft and patient survival rates and the incidence of recurrence and graft loss due to recurrence up to 3 years posttransplant are shown because of small numbers in the RDP group beyond 3 years. A P value ≤0.05 was considered statistically significant.

RESULTS

Demographic data and the primary causes of end stage renal disease (ESRD) are shown in Table 1.

Patient and graft survival and rejection

The mean age at the time of transplant was 13 ± 4 years for RDP recipients and 12 ± 4 years for control recipients ($P=NS$). The majority of the transplants were primary for both groups. Donor source included 70% living donors for RDP recipients and 71% living donors for control recipients ($P=NS$). The cause of primary ESRD was not significantly different between groups.

Patient and graft survival rates at 1, 2, and 3 years posttransplant did not significantly differ between the two groups ($P=NS$). Graft survival rates were 94%, 94%, and 94% at 1, 2, and 3 years for RDP recipients; 96%, 91%, and 88% for control recipients ($P=NS$). Graft survival rates after censoring for death with a functioning graft were 97%, 97%, and 97%, at 1, 2, and 3 years for RDP recipients; 96%, 91%, and 88% for control recipients ($P=NS$, Figure 1). The incidence of acute rejection at 1, 2, and 3 years posttransplant was 23%, 28%, and 33% for RDP recipients and 35%, 39%, and 45% for control recipients. The difference in incidence between the two groups was not statistically significant ($p=0.15$). Sixty percent of RDP recipients at risk for disease recurrence were steroid free at follow up.

Disease recurrence

Overall, biopsy proven disease recurrence was documented in 4 (16%) of RDP recipients and 5 (28%) of control recipients. A log-rank test and Kaplan-Meier estimates revealed there was no significant difference in disease recurrence rates between the two groups, with recurrent disease rates of 8%, 8%, and 15% at 1, 2, and 3 years for RDP recipients; 11%, 11%, and 11% at 1, 2, and 3 years for control recipients ($p=0.42$, Figure 2). Mean time to biopsy diagnosis of recurrent disease was 22 ± 26 months in RDP recipients and 46 ± 48 months in control recipients ($p=0.54$). Disease recurrence is shown in Tables 2 and 3. The cases of recurrence in the RDP group were IgA nephropathy ($n=2$), FSGS ($n=1$), and MPGN ($n=1$). The causes of recurrent disease in the control group were FSGS ($n=2$), HUS ($n=1$), and ANCA positive vasculitis ($n=1$). The incidence of recurrent IgA nephropathy was 100% in the RDP recipients. There were no cases of IgA nephropathy as the primary cause of ESRD in the control recipients. The incidence of recurrent FSGS was 9% in the RDP recipients and 33% in the control recipients. HUS recurred in none of the RDP recipients and in 50% of the control recipients. A single case of ANCA positive vasculitis (Wegener's) recurred in a control recipient.

Causes of graft failure

Overall, grafts were lost in 9 (12%) RDP recipients and 32 (46%) control recipients. The causes of graft failure in RDP recipients were chronic rejection ($n=1$), vascular thrombosis ($n=1$), non-adherence ($n=3$), recurrent disease ($n=1$), chronic allograft nephropathy ($n=1$), and death with graft function ($n=2$). The causes of graft failure in control recipients were acute rejection ($n=6$), chronic rejection ($n=4$), non-adherence ($n=8$), recurrent disease ($n=4$), technical ($n=3$), chronic allograft nephropathy ($n=4$), unknown ($n=1$), and death with graft function ($n=2$). There was no significant difference in the incidence of graft loss due to recurrent disease between the two groups at risk for recurrence, with 0%, 0%, and 15% at 1, 5, and 8 years in RDP recipients; 0%, 17%, and 24% at 1, 5, and 8 years in control recipients ($P=0.54$, log-rank test). The cause of graft loss due to disease recurrence in the single RDP recipient was IgA nephropathy. The causes of graft loss due to disease recurrence in control recipients were FSGS ($n=2$), HUS ($n=2$). Mean time to graft loss due to disease recurrence was 85 months in RDP recipients and 46 ± 21 months in control recipients ($P=NS$).

DISCUSSION

Several studies have shown good outcomes in pediatric KTx recipients on steroid avoidance and early steroid withdrawal protocols (4,7–11). This study extends the prior reports and shows comparable patient and graft survival rates at 3 years posttransplant in pediatric patients on a rapid discontinuation of prednisone protocol compared to steroid based immunosuppression. This is, to our knowledge, the first pediatric study to compare recurrent disease incidence in KTx recipients who received maintenance immunosuppressive therapy with and without steroids. Our results compare to the Stanford experience where 6 out of 17 (35.3%) pediatric KTx recipients failing steroid free immunosuppression at 5 years did so due to recurrent disease, however, a control group was not included (12). Unlike our pediatric study, a recent study of adult KTx recipients at our center demonstrated a significant increase in recurrent disease at 1 year (6.7% vs. 2.4%), 5 years (13.7% vs. 3.8%) and 7 years (19.2% vs. 5.3%) with rapid discontinuation of steroids protocols vs. steroid maintenance, respectively (13). Despite the increased recurrent disease however, there was no difference in graft or patient survival (13). This increased risk of recurrent disease may represent a different mix of primary glomerulonephritides in adults (more IgA nephropathy and membranous nephropathy) vs. pediatric recipients.

All forms of primary GN may recur in the renal transplant. The incidence varies by the type of GN and most data come from studies in adults (1,2, 14–16). There are few reports of primary disease recurrence in children after KTx (1,16–20). An overview of disease recurrence in pediatric KTx recipients was recently reported by Cochat *et al* (1). The review emphasizes that the overall risk of graft loss due to disease recurrence (7–8%) is quite similar to the risk of graft loss due to acute rejection in children (8–9%). Therefore, recurrence of primary disease is an important issue for pediatric KTx recipients as it is associated with approximately twice the risk of graft failure compared to KTx recipients in whom the primary disease did not recur (1). No studies in children have reviewed immunosuppression protocol as a risk factor for recurrence of primary disease.

There are several limitations of this retrospective study. First, it was not a randomized, prospective trial of rapid prednisone discontinuation. Prednisone was not the only difference in immunosuppression between the groups. The RDP received Mycophenolate mofetil while the historical group received azathioprine maintenance immunosuppression. Mycophenolate mofetil acts similar to azathioprine in that they both inhibit de novo purine biosynthesis. However, MMF, unlike azathioprine, inhibits both B- and T-cell proliferation. While widely used to prevent allograft rejection, it has also been used to treat various forms of primary glomerulonephritis in adults and children such as SLE, IgA nephropathy, MPGN, membranous GN, and ANCA+ vasculitis (21–24). It is possible that the use of MMF in the study population was associated with a reduced incidence of recurrence of primary glomerular disease and improved results compared to the use of azathioprine. It is also possible that steroids + MMF + CSA may still be better in terms of lower recurrence rate than steroid discontinuation + MMF + CSA. This comparison cannot be provided due to the retrospective nature of this study.

Second, the number of patients in each group is small and the primary kidney diseases are not uniform in both groups. We had no pediatric patients undergoing KTx for lupus nephritis or membranous nephropathy. The patient numbers are too small to definitely assess the risk of recurrent disease with RDP and collaborative studies are needed. Third, the periods of follow up differed for the two groups and likely led to the appearance of greater allograft loss in the control group. Use of the log-rank analysis and Kaplan-Meier estimates adjusted for the differences in follow up period between the groups and gave equal weight to all events during the follow up period. Using these methods we found no significant difference

in disease recurrence rates or graft loss between the groups. Still, the follow up period for the RDP group is relatively short and longer follow up is required.

Primary focal segmental glomerulosclerosis is the third most common cause of ESRD in pediatric patients after aplastic/hypoplastic/dysplastic kidneys and obstructive uropathy (1,16,25). It is the most common cause of acquired ESRD. The rate of recurrence after KTx in children varies from 14–50% and is associated with 40–60% incidence of graft loss due to disease recurrence (1,16). In our study, the rate of recurrence in historical controls is comparable to published reports. Our rate of recurrence in RDP recipients is low at 9%. The reduced incidence of recurrence in RDP recipients may be related to the use of preemptive plasmapheresis in 7 (64%) of the 11 recipients as reported in adults by Gohh *et al* (26) but in none (0) of the 6 historical controls. This limits our ability to make comparisons between the two groups with FSGS. These living donor recipients received three pretransplant plasmapheresis treatments followed by five posttransplant plasmapheresis treatments. The one RDP recipient with recurrence received preemptive plasmapheresis and continues to have a functioning graft. Our numbers are too small to draw conclusions regarding the efficacy of this protocol. Risk of recurrence is also reduced in patients with underlying mutations in the podocin gene NPHS2 as the cause of their FSGS. In a recent international study of 83 KTx recipients with primary FSGS, the recurrence rate was 45% in patients without NPHS2 mutations compared to no recurrence in recipients with homozygous or compound heterozygous NPHS2 mutations (27). Our FSGS KTx recipients were not consistently evaluated for NPHS2 mutations. None of the controls were tested for mutations such as NPHS2 compared to 7 of 11 RDP recipients. No recipient was found to have a mutation. Similar to reports in the literature, our rate of graft loss due to recurrent FSGS was 100% in control recipients. However, the one recipient with recurrent FSGS in the RDP group still has a functioning graft 34 months posttransplant.

Hemolytic uremic syndrome recurred in half of the control recipients with HUS as their primary cause of ESRD and in none of the RDP recipients. The risk of recurrence after KTx in children with diarrhea positive HUS is low at 0–1% whereas the risk is 20–80% for those with non-diarrhea associated HUS (1,16,17). Recurrence after KTx in children was recently reviewed by Loirat and Fremeaux-Bacchi (17). Because approximately 60% – 70% of patients with non-diarrhea associated HUS have mutations in the genes of 5 proteins that regulate the complement alternative pathway (complement factor H, membrane cofactor protein, factor B, factor I, C3) or have antibodies to complement factor H, these authors recommend complement analysis, screening for complement factor antibodies, and genotyping before KTx in patients with non-diarrhea associated HUS (17). None of the HUS patients in this study underwent genetic testing. Both control recipients with recurrent HUS had loss of their grafts due to recurrence. Both recipients had atypical HUS.

We had no control recipients with IgA nephropathy as the cause of ESRD but both RDP recipients with IgA nephropathy had recurrence of disease. One graft was lost due to disease recurrence 28 months after recurrence. The reported recurrence rate for IgA post KTx ranges from 7–60% (1,16). The recurrence rate is not well documented in children. Graft loss due to recurrence of IgA is reported to range from 7–10%. Larger studies are required to determine if the risk of recurrence of IgA nephropathy is increased with rapid discontinuation or prednisone or steroid avoidance protocols in children. We experienced no recurrence of disease in either RDP or control recipients with HSP as the primary cause of ESRD. Reported rates of recurrence range from 31–100% (1,16). Little has been reported on HSP recurrence in children. In a report from Belgium, 14 transplants were performed in 10 patients with HSP as the cause of ESRD; 8 of 10 patients reported were less than 18 years of age (28). Clinical recurrence of the disease occurred in 2 recipients and an additional recipient had histologic recurrence. In a study from Japan, 17 KTx were performed in 15

children with HSP as their primary cause of ESRD (29). Seven recipients had clinical recurrence and 9 (53%) had histologic recurrence (29). Graft loss due to recurrence was 22% in this series, and range from 8–33% in the literature (1,28,29).

One recipient with ANCA positive vasculitis as the primary cause of ESRD had recurrence of disease and continues with a functioning graft 144 months posttransplant. We were unable to find a pediatric series relative to recurrence after KTx. Recurrence is reportedly rare (1). However, in a report in adults from Italy, vasculitis recurred after KTx in 7 (37%) of 19 recipients but was not the cause of graft loss (30). The rate of graft loss due to recurrence of ANCA positive vasculitis in adults is reported to range between 0% and 6% (1). We have either too few or no patients with MPGN, SLE, anti GBM antibody disease, and membranous nephropathy to comment on their recurrence after KTx in children using either immunosuppression protocol.

In conclusion, in our single-center pediatric study, rapid discontinuation of prednisone was associated with excellent patient and graft survival rates in pediatric patients undergoing kidney transplantation with glomerulonephritis as the primary cause of ESRD. Recurrence of disease is an important problem for pediatric KTx recipients. Our experience suggests that use of a rapid discontinuation of prednisone immunosuppression protocol may not be associated with increased risk of graft loss due to recurrent disease. A multicenter study is needed to confirm our preliminary findings.

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Figure 1. Actuarial uncensored and censored graft survival rates by type of steroid protocol. RDP, rapid discontinuation of prednisone; rates were censored for death with a functioning graft. P= NS, uncensored and censored graft survival (Log rank test).

Figure 2. Actuarial recurrent disease free survival rates by type of steroid protocol. RDP, rapid discontinuation of prednisone. $P=0.42$ (Log rank test).

Table 1

Patient Characteristics, by Steroid Protocol

Characteristic	RDP	Steroid Based	P value
Age (yr, mean $\pm$ SD) (range)	13 $\pm$ 4 (4–18)	12 $\pm$ 4 (5–18)	NS
Race N(%)			NS
White	63 (85)	58 (84)	
Nonwhite	11 (15)	11 (16)	
Gender N(%)			NS
Female	25 (34)	28 (41)	
Male	49 (66)	41 (59)	
Transplanttype N (%)			NS
Deceased donor	22 (30)	20 (29)	
Living donor	52 (70)	49 (71)	
Transplant number N (%)			0.005*
Primary	71 (96)	56 (81)	
Retransplant	3 (4)	13 (19)	
Cause of ESR DN (%)			NS
Congenital anomalies	20 (27)	14 (20)	
Obstructive or refluxuopathy	16 (22)	16 (23)	
Glomerulonephritis	25 (34)	20 (29)	
Other	13 (17)	19 (28)	
Immunosuppression N (%)			
CsA + P + Aza	0 (0)	56 (81)	
CsA + MMF	74 (100)	0 (0)	
CsA + P + MMF	0 (0)	13 (19)	

RDP, rapid discontinuation of prednisone; SD, Standard deviation; ESRD, End-stage renal disease; CsA, Cyclosporine A; P, Prednisone; Aza, Azathioprine; MMF, Mycophenolate mofetil; NS, not significant

* Chi-square test

Table 2

Types of Glomerulonephritis at Risk of Recurrence and Incidence of Recurrence, by Steroid Protocol

Type	RDP		Steroid Based	
	Total N	# Recurred	Total N	# Recurred
IgA nephropathy	2	2	0	0
HSP glomerulonephritis	2	0	1	0
FSGS	11	1	6	2
MPGN	1	1	0	
Anti GBM antibody disease	1	0	0	
ANCA + vasculitis	4	0	7	1
Hemolytic uremic syndrome	4	0	4	2

RDP, rapid discontinuation of prednisone; IgA, immunoglobulin A; HSP, Henoch Schoenlein Purpura; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; GBM, glomerular basement membrane; ANCA, anti neutrophil cytoplasmic antibody

Table 3
Patients with Recurrent Disease

Patient Group	Tx Age	Primary Disease	Donor Source	Tx Number	Time to Recurrence	Outcome
RDP	16	IgA	DD	1	56 months	GL due to recurrence
RDP	15	IgA	DD	1	27 months	GL due to non-adherence
RDP	13	FSGS	LRD	1	27 days	eGFR 35
RDP	17	MPGN	DD	1	3 months	GL due to rejection
Control	9	HUS	LRD	1	50 months	GL due to recurrence
Control	16	FSGS	LRD	1	1 month	GL due to recurrence
Control	14	ANCA + vasculitis	DD	1	117 months	eGFR 37
Control	10	HUS	DD	2	2 months	GL due to recurrence
Control	10	FSGS	DD	2	59 months	GL due to recurrence

Tx, transplant; RDP, rapid discontinuation of prednisone; IgA, immunoglobulin A; DD, deceased donor; GL, graft loss; FSGS, focal segmental glomerulosclerosis; LRD, living related donor; eGFR, estimated glomerular filtration rate using the Schwartz formula (height [cm] $\times$ 0.41/serum creatinine); MPGN, membranoproliferative glomerulonephritis; ANCA, anti-neutrophil cytoplasmic antibody; HUS, hemolytic uremic syndrome