Clinical Kidney Journal, 2023, vol. 16, no. 10, 1644–1655

https://doi.org/10.1093/ckj/sfad077
Advance Access Publication Date: 12 April 2023
Original Article

ORIGINAL ARTICLE

High exposure to tacrolimus is associated with spontaneous remission of recurrent membranous nephropathy after kidney transplantation

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ABSTRACT

Introduction. We aimed to characterize the incidence and clinical presentation of membranous nephropathy (MN) after kidney transplantation (KT), and to assess allograft outcomes according to proteinuria rates and immunosuppression management.

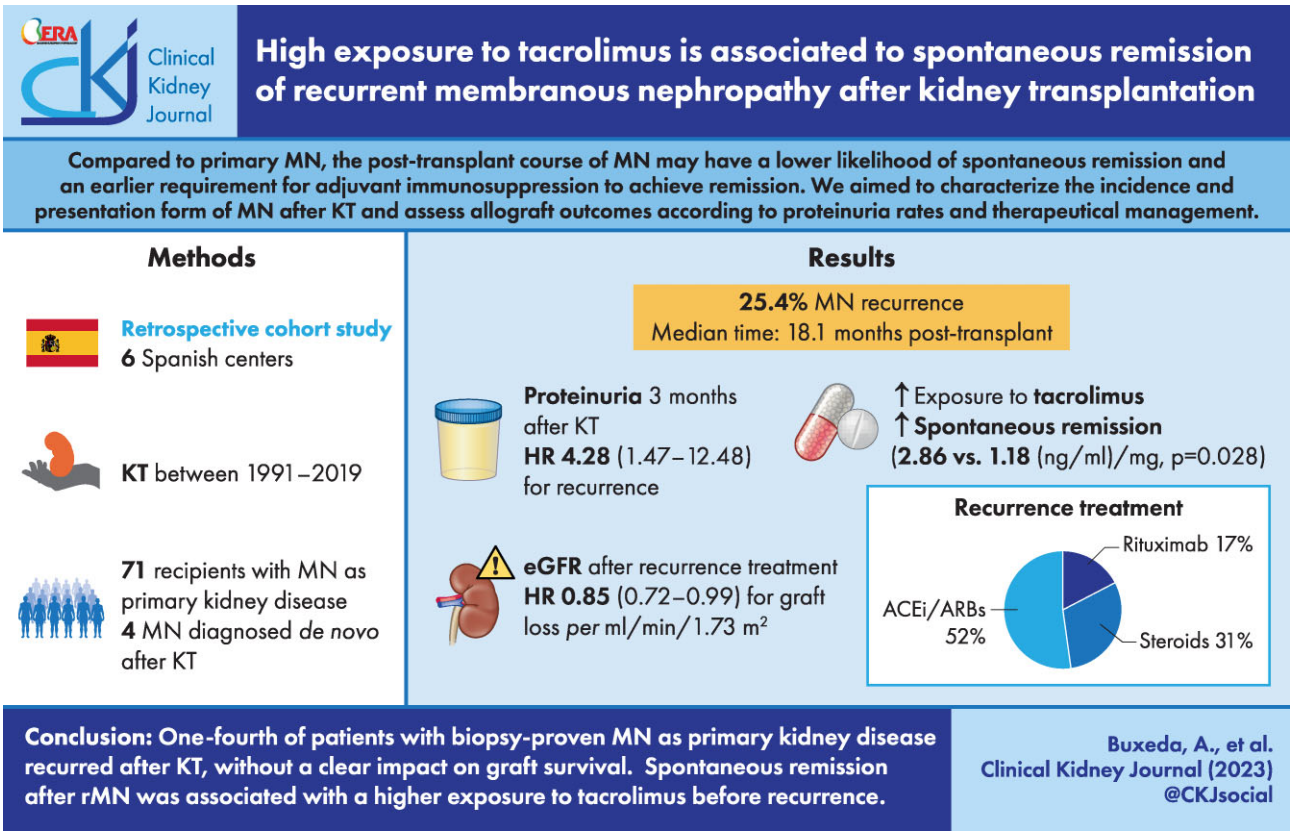
Methods. Multicenter retrospective cohort study including patients from six Spanish centers who received a KT between 1991–2019. Demographic, clinical, and histological data were collected from recipients with biopsy-proven MN as primary kidney disease ($n = 71$) or MN diagnosed *de novo* after KT ($n = 4$).

Results. Up to 25.4% of patients with biopsy-proven MN as primary kidney disease recurred after a median time of 18.1 months posttransplant, without a clear impact on graft survival. Proteinuria at 3-months post-KT was a predictor for MN recurrence (rMN, HR 4.28; $P = 0.008$). Patients who lost their grafts had higher proteinuria during follow-up [1.0 (0.5–2.5) vs 0.3 (0.1–0.5) g/24 h], but only eGFR after recurrence treatment predicted poorer graft survival (eGFR < 30 ml/min: RR = 6.8). We did not observe an association between maintenance immunosuppression and recurrence diagnosis. Spontaneous remission after rMN was associated with a higher exposure to tacrolimus before recurrence (trough concentration/dose ratio: 2.86 vs 1.18; $P = 0.028$). Up to 94.4% of KT recipients received one or several

Received: 25.1.2023; Editorial decision: 21.3.2023

treatments after recurrence onset: 22.2% rituximab, 38.9% increased corticosteroid dose, and 66.7% ACEi/ARBs. Only 21 patients had proper antiPLA2R immunological monitoring.
Conclusions. One-fourth of patients with biopsy-proven MN as primary kidney disease recurred after KT, without a clear impact on graft survival. Spontaneous remission after rMN was associated with a higher exposure to tacrolimus before recurrence.

GRAPHICAL ABSTRACT



Keywords: kidney transplantation, membranous nephropathy, proteinuria, recurrence, tacrolimus

INTRODUCTION

Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults [1], This immune complex-mediated glomerular disease is histologically characterized by the accumulation of electron-dense subepithelial deposits consisting of immunoglobulin G, antigens, and complement components [2]. The immunological injury displays glomerular filtration barrier disruption and the subsequent loss of a large amount of proteinuria [3, 4]. In ∼80% of cases, MN has no underlying cause and is considered a primary disease. M-type phospholipase A2 receptor 1 (PLA2R, ∼70%–80% of primary cases) [5] and thrombospondin type 1 domain-containing 7A (THSD7A, ∼2%–5% of primary cases) [6] were the first target antigens described, confirming the disease's autoimmune nature in humans. Despite diagnostic advances and an improved treatment landscape, ∼10–30% of patients with primary MN will develop end-stage kidney disease and may be suitable candidates for kidney transplantation (KT) [7–9].

When occurring after KT, MN may present either as recurrent (rMN) or *de novo* disease (dnMN) [10–13]. Overall clinical recurrence rates range from 18% to 57% of primary MN cases, depending on surveillance biopsy policies [12, 14–20]. As in native kidneys, the pathophysiology of rMN generally relates to anti-PLA2R antibodies, which have shown a high positive predictive value for recurrence, especially at high pretransplant titers [16–18, 21]. Nonetheless, the posttransplant course of PLA2R-associated rMN may have some distinct characteristics compared with primary MN, including a lower likelihood of spontaneous remission, an earlier requirement for adjuvant immunosuppression to achieve remission or persistent histological activity in both treated and untreated patients [14, 22–24]. These features lead to consider rMN as a progressive disease if proteinuria persists over 1 g/day [25, 26]. Treatment with rituximab may be beneficial if proteinuria is >1 g/24 h [26], but management and outcomes in patients with subnephrotic proteinuria have been scarcely studied and need further assessment [23]. The role of maintenance immunosuppression and recurrence

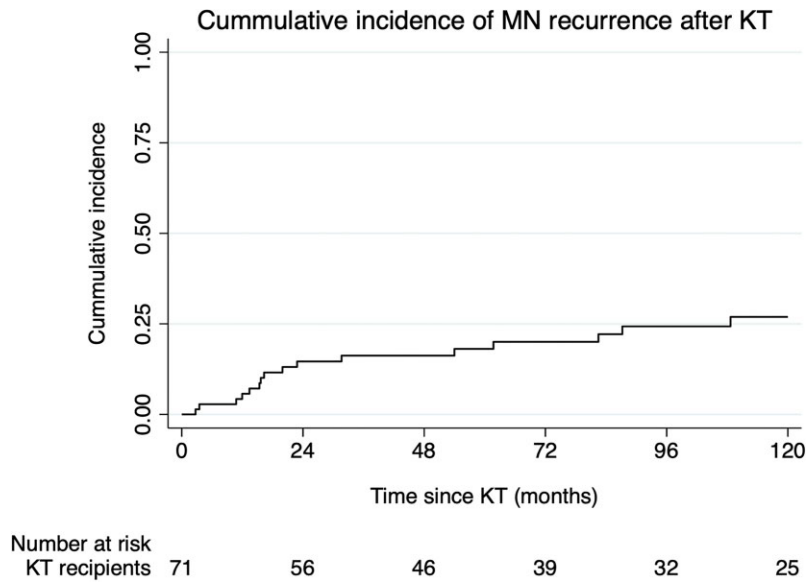


Figure 1: Cumulative incidence of MN recurrence after KT.

development and outcomes is at issue. One study demonstrated that no specific drug was associated with graft failure due to recurrence [27].

Analogously, the outcomes and posttransplant management of dnMN remain elusive due to its low incidence (0.7%–9.3%) and poorly understood pathophysiology [28, 29]. The diagnosis of dnMN is usually hampered by the absence of native kidney biopsy [30], making it difficult to differentiate from recurrence. Consequently, most cases remain unclassified and unstudied.

This multicenter study aimed to characterize the incidence and presentation form of MN after KT in a Spanish cohort and assess allograft outcomes according to proteinuria rates and therapeutical management.

MATERIALS AND METHODS

Study design and patients

Multicenter retrospective cohort study performed in six nephrology departments belonging to the Spanish Transplant Study Group (SENTRA) and the Spanish Glomerular Study Group (GLOSEN). Data from KT recipients aged >18 years old and transplanted between 1991 and 2019 with biopsy-proven MN as primary kidney disease or diagnosed *de novo* after transplantation, were collected. Patient identification was performed by reviewing histopathological charts and clinical histories. The median follow-up time since KT to graft loss or end of follow-up was 8.1 years (4.1–12.8 years), and the median follow-up time since MN diagnosis after KT ($n = 22$) was 1.3 years (IQR, 0.9–4.5 years). The study was approved by the Ethical Committee at the study coordinating center, Hospital del Mar, Barcelona, Spain, and conducted according to the guidelines as dictated by the Declaration of Helsinki. All data were recorded anonymously.

Data collection and definitions

Recorded baseline and follow-up data included: recipient characteristics and comorbidities, cause of renal failure, clinical presentation in native kidneys, time to kidney failure, and time on dialysis before transplantation, type of replacement therapy, type of donor, transplant-related factors such as HLA mismatch, cold ischemia time (CIT), immunosuppressive therapy and dose, and MN treatment after KT. Laboratory parameters analyzed using routine laboratory methods included serum creatinine, estimated glomerular filtration (eGFR) using the CKD-EPI equation [31], proteinuria, serum albumin, *de novo* HLA donor-specific antibodies (HLA-DSA), anti-PLA2R, and anti-THSD7A. Clinical events, such as delayed graft function (DGF), the development of rejection episodes and recurrence, nephrotic syndrome, nephritic syndrome, complete remission, partial remission, graft loss, and patient death, were recorded.

DGF was defined as the need for dialysis during the first week after KT followed by recovery of allograft function. Nephrotic syndrome was defined as proteinuria of >3.5 g/day plus serum albumin <3 g/dl. Complete remission (CR) was defined as proteinuria <0.3 g/day accompanied by normal serum albumin concentration and recovery of baseline kidney function. Partial remission (PR) was defined as urinary protein excretion between 0.3 and 3.5 g/day plus ≥50% reduction from its peak value at recurrence, along with normal albumin and stable renal function (maximum increase of serum creatinine <30% of baseline value). Spontaneous remission (SR) was defined as CR or PR in the absence of specific targeted immunosuppressive therapy.

Histopathologic data at the time of recurrence

Kidney biopsy specimens of patients with recurrent or *de novo* MN were examined in the pathology departments of participating hospitals. The following histopathological data were collected if available: percentage of sclerosed glomeruli, degree of interstitial fibrosis/tubular atrophy (IFTA), glomerulitis, peritubular capillaritis, tubulitis, interstitial inflammation, endarteritis, and C4d deposition in peritubular capillaries, transplant glomerulopathy, arteriosclerosis, mesangial expansion, PLA2R deposition, THSD7A deposition, IgG deposition and subtype, and Ehrenreich Churg category [32].

Outcomes

The main outcomes were: the development of biopsy-proven MN after KT; disease remission after recurrence or *de novo* disease; death-censored graft failure, defined as eGFR <15 ml/min per 1.73 m^2 or the need for maintenance dialysis, and all-cause mortality.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical data are expressed as counts (%) according to their distribution. Comparison of continuous variables was performed by *t*-test or ANOVA for parametric data and Mann–Whitney *U*-test or Kruskal–Wallis test for nonparametric distributions. Nominal variables were compared using the chi-squared test or Fisher exact test, where appropriate. The predictors of recurrence and allograft failure were determined using Cox regression analysis. Predictors were selected as informed by prior literature and clinical practice. Those variables with $P < 0.05$ in the univariate Cox model were included in the multivariate analysis. Recurrence cumulative incidence and survival analyses were plotted using the Kaplan–Meier survival curves, applying the log-rank test and competing risks. Statistical significance was considered at $P < 0.05$. We used Stata/BE (v.17.0, StataCorp LLC, USA) for statistical analysis and GraphPad Prism software (v.9.3.1; GraphPad Software, San Diego, CA, USA) for graphical presentation.

RESULTS

Cohort demographics

Seventy-five patients fulfilled the inclusion criteria and were enrolled in the study (Fig. S1, see online supplementary material for a color version of this figure). Of them, 71 patients had biopsy-proven MN as primary kidney disease and 18 (25.4%) recurred after KT, within a median time of 18.1 (12.0–61.7) months (Fig. 1). Additionally, four MN cases were diagnosed *de novo* or unclassified after KT.

Table 1 displays the demographic and clinical characteristics of patients with MN in their native kidneys according to the recurrence of the disease. No significant differences were observed with regard to age at diagnosis of the primary disease, clinical presentation form, or time to kidney failure. Five patients from the nonrecurrent group had a prior KT, one of which developed a recurrence. The recipient and donor's characteristics were similar. Moreover, most patients received a maintenance immunosuppression regimen based on corticosteroids, calcineurin inhibitors, and mycophenolate mofetil. The percentage of early steroid withdrawal only reached 8.5% of KT recipients. We found no differences in DGF or rejection episodes between groups.

Clinical presentation, histology, and treatment

Table 2 shows the clinical presentation, histology, and treatment of rMN according to graft outcomes. KT recipients with and without allograft failure recurred within a median time of 17.8 and 24 months, respectively (n.s.). Only 16.7% of recurrences presented with nephrotic syndrome. Nonetheless, 83.4% of patients with graft loss developed nephrotic-range proteinuria compared to 33.4% of those with a nonnephrotic range ($P = 0.098$). Therefore, isolated nonnephrotic proteinuria was the predominant clinical presentation in KT recipients with recurrence and functioning graft at the end of follow-up. Median proteinuria rates reached 3.2 (1.4–15.6) vs. 2.2 (1.6–4.3) g/24 h in recipients with and without allograft failure ($P = 0.030$). Likewise, those with death-censored graft loss had worse creatinine values at recurrence (2.3 ± 1.1 vs. 1.7 ± 0.3; $P = 0.014$) that persisted after receiving recurrence treatment 2.4 ± 0.8 vs. 1.7 ± 0.3; $P = 0.030$).

Regarding histology features, no differences were found within the number of globally sclerotic glomeruli, IFTA scores, or other chronic and active lesions. Ehrenreich Churg's classification stage was similar between groups. Of note, a high percentage of cases (61%–100%) did not have PLA2R stain, THSD7A stain, or IgG subtype performed.

We observed no statistically significant differences in disease remission (complete, partial, and spontaneous) between groups. However, no recipients with CR lost their allograft during follow-up.

We next studied the possible effect of maintenance immunosuppression on recurrence development. Tacrolimus, mycophenolate, and corticosteroids levels and doses were similar between groups during the study period (Fig. S2, see online supplementary material for a color version of this figure). Likewise, disease remission was not associated with the mean levels of maintenance immunosuppression before recurrence. But, interestingly, patients with SR had higher trough concentration/dose (C_0/D) ratio of tacrolimus before recurrence [2.86 (1.81–2.87) vs. 1.18 (0.96–1.48) (ng/ml)/mg, respectively; $P = 0.028$] (Fig. 2). Clinical and histological characteristics of patients with MN recurrence according to SR are displayed in Table S1 (see online supplementary material for a color version of this figure). We found no statistically significant differences in clinical presentation, proteinuria, or eGFR between groups. Most histological features were similar. However, patients with SR presented an increased percentage of globally sclerotic glomeruli (9.2% vs. 0%, $P = 0.039$).

Concerning recurrence management, up to 94.4% of KT recipients received one or several treatments after recurrence onset: 22.2% rituximab, 38.9% increased corticosteroid dose, and 66.7% ACEi/ARBs. Of note, rituximab was only administered in patients with proteinuria ≥3 g/24 h (50% vs. 0%, respectively; $P = 0.023$; Table S2, see online supplementary material for a color version of this figure).

Kidney and patient outcomes

Average eGFR was plotted over time in patients with and without recurrence, indicating a similar eGFR in patients with rMN after 5 years of follow-up (Fig. 3A). Conversely, KT recipients with recurrence displayed greater proteinuria values at 3 months post-KT [0.5 (0.3–0.8) vs. 0.2 (0.1–0.4), $P < 0.001$] and in all the subsequent follow-up periods (Fig. 3B).

Although graft losses were more numerous in the recurrence group (33.3% vs. 15.1%), no significant differences in death-censored graft survival were evident (log rank = 0.081; Fig. 4A). We next studied the cumulative incidence of death-censored graft failure according to recurrence after accounting for death as a competing event. Similar to Kaplan–Meier curve results, competing risk analysis showed no significant differences between groups ($P = 0.059$; Fig. S2, see online supplementary material for a color version of this figure). Of note, KT recipients with rMN lost their grafts due to recurrence ($n = 5$) and non-biopsied chronic injury ($n = 1$). In patients without recurrence, graft failure was attributed to urologic cause ($n = 1$), chronic rejection ($n = 3$), and non-biopsied chronic injury ($n = 4$). Regarding

Table 1: Demographic and clinicopathological characteristics of patients with MN as primary kidney disease according to recurrence.

	Overall cohort ($n = 71$)	Recurrence ($n = 18$)	No recurrence ($n = 53$)	P value
Native kidney disease				
Age at diagnosis, years, mean ± SD	42.2 ± 15.9	46.7 ± 14.5	40.6 ± 16.2	0.163
Female sex, *n* (%)	19 (26.8)	3 (16.6)	16 (30.2)	0.362
Clinical presentation, [a] *n* (%)				
Isolated nonnephrotic proteinuria	1 (1.8)	0 (0)	5 (12.8)	0.662
Nephrotic proteinuria	8 (14.3)	3 (17.7)	5 (12.8)	
Nephrotic syndrome	43 (86.8)	14 (82.4)	29 (74.4)	
Nephritic syndrome	4 (7.1)	0 (0)	4 (10.3)	
Considered primary MN at diagnosis, *n* (%)	61 (93.9)	14 (93.3)	47 (94)	1
Creatinine at diagnosis, mg/dl, mean ± SD	1.8 ± 1.2	1.7 ± 1.7	1.8 ± 0.9	0.736
Proteinuria at diagnosis, g/24 h, median (IQR)	6.4 [4.3–8.5]	7 [4–10.6]	6.1 [4.5–8.5]	0.581
Immunosuppression treatment				
None, *n* (%)	4 (6.5)	0 (0)	4 (8.9)	0.568
Corticosteroids, *n* (%)	19 (31.7)	3 (18.8)	16 (36.4)	0.228
Tacrolimus, *n* (%)	28 (46.7)	9 (52.9)	19 (44.2)	0.578
Cyclophosphamide, *n* (%)	12 (20)	3 (17.7)	9 (20.9)	1
Rituximab, *n* (%)	6 (10)	3 (17.7)	3 (7.0)	0.338
Other, *n* (%)	15 (25)	3 (17.7)	12 (27.9)	0.520
Time to kidney failure, months, median (IQR)	70.1 (46–115.4)	54.6 (34.1–99.2)	72.4 (48–119.9)	0.146
Type of RRT, *n* (%)				
Hemodialysis	42 (60)	12 (66.7)	30 (57.7)	0.771
Peritoneal dialysis	21 (30)	4 (22.2)	17 (32.7)	
None (pre-emptive transplant)	7 (10	2 (11.1)	5 (9.6)	
Time on RRT, months, median (IQR)	21.5 (7.8–43.4)	9 (7.5–37.8)	21.9 (9–43.4)	0.441
Recipient characteristics				
Age at transplantation, years, mean ± SD	52.3 ± 13.9	54.8 ± 13.8	51.4 ± 13.9	0.374
Hypertension, *n* (%)	57 (80.3)	17 (94.4)	40 (75.5)	0.098
Diabetes mellitus, *n* (%)	10 (14)	3 (16.7)	7 (13.2)	0.706
Cardiovascular disease, *n* (%)	7 (9.9)	3 (16.7)	4 (7.6)	0.359
History of cancer, *n* (%)	3 (4.2)	1 (5.6)	2 (3.8)	1
HCV, *n* (%)	1 (1.4)	0 (0)	1 (1.9)	1
HBV, *n* (%)	1 (1.4)	1 (5.6)	0 (0)	0.254
HIV, *n* (%)	1 (1.4)	0 (0)	1 (1.9)	1
Prior kidney transplants, *n* (%)	5 (7.3)	0 (0)	5 (9.8)	0.316
MN recurrence in prior kidney transplants, *n* (%) ($n = 5$)	1 (20)	0 (0)	1 (20.0)	-
Kidney transplantation				
Donor age, years, mean ± SD	53.2 ± 14.5	54.2 ± 13.5	52.9 ± 15	0.725
Type of donor, *n* (%)				
Living donor	10 (14.3)	3 (16.7)	7 (13.5)	1
Living related donor ($n = 10$)	8 (80)	2 (66.7)	6 (85.7)	
DBD	50 (71.4)	13 (72.2)	37 (71.2)	
DCD	10 (14.3)	2 (11.1)	8 (15.4)	
Expanded criteria donor, *n* (%)	24 (34.8)	6 (33.3)	18 (35.6)	1
KT decade				
1991–2000	11 (15.5)	3 (16.7)	8 (15.1)	
2001–2010	27 (38)	7 (38.9)	20 (37.4)	**0.048**
2011–2020	33 (46.5)	8 (44.4)	25 (47.2)	
HLA-A/B/DR mismatch, mean ± SD	3.9 ± 1.5	3.6 ± 1.8	4.1 ± 1.4	0.262
CIT, hours, mean ± SD	16 ± 7.8	17.1 ± 7.9	15.6 ± 7.8	0.528
DGF, *n* (%)	24 (35.3)	6 (35.3)	18 (35.3)	1
Baseline immunosuppression				
Induction therapy, *n* (%)				
None	17 (24.3)	6 (33.3)	11 (21.2)	0.246
Antithymocyte globulin	17 (24.3)	2 (11.1)	15 (28.9)	
ALG/ATGAM	3 (4.3)	0 (0)	3 (5.8)	
Basiliximab	29 (41.3)	10 (55.6)	19 (36.5)	
Daclizumab	4 (5.7)	0 (0)	4 (7.7)	
Maintenance immunosuppression				
Corticosteroids, *n* (%)	69 (98.6)	18 (100)	51 (98.1)	1
Early steroid withdrawal, *n* (%)	10 (15.2)	3 (16.7)	7 (14.5)	1
Tacrolimus, *n* (%)	64 (90.14)	15 (83.3)	49 (92.5)	0.359
Cyclosporine, *n* (%)	7 (9.86)	3 (16.7)	4 (7.6)	0.359
Mycophenolate mofetil, *n* (%)	68 (95.8)	17 (94.4)	71 (96.2)	1
De novo mTOR inhibitors, *n* (%)*	2 (2.9)	1 (5.9)	1 (1.9)	0.429
Azathioprine, *n* (%)	1 (1.45)	0 (0)	1 (1.9)	1
Kidney function and outcomes				
Mean eGFR during follow-up, mg/dl, mean ± SD	46.6 ± 17.7	41.6 ± 14.5	48.3 ± 18.5	0.165
Mean Proteinuria during follow-up, g/24 h, median (IQR)	0.4 (0.2–0.7)	1.2 (0.6–1.9)	0.3 (0.1–0.4)	**<0.001**
DGF, *n* (%)	24 (35.3)	6 (35.3)	18 (35.3)	1
Acute rejection, *n* (%)	15 (21.1)	5 (27.8)	10 (18.9)	0.507
Time to recurrence, months, median (IQR)	-	18.1 (12–61.7)	-	
Follow-up time, years, median (IQR)	8.5 (4.2–12.8)	7.7 (4.4–11.4)	8.8 (3.9–13.0)	0.833
Death-censored graft failure, *n* (%)	14 (19.7)	6 (33.3)	8 (15.1)	0.166
Mortality, *n* (%)	5 (7.0)	0 (0)	5 (9.4)	0.320

[a] Data available in 56 patients (78.9%): 1 (5.6%) in the group with recurrent disease versus 14 (26.4%) in the group without recurrence.

* 5 more patients were converted to mTORi during follow-up.

Table 2: Clinical presentation, histology, and treatment of MN recurrence according to death-censored graft loss.

	Overall cohort ($n = 18$)	Graft loss ($n = 6$)	.No graft loss ($n = 12$)	*P* value
Clinical presentation				
Time to recurrence, months	18.1 (12–61.7)	17.8 (13.4–22.8)	24 (11.4–84.9)	0.512
Clinical presentation, *n* (%)				
Isolated nonnephrotic proteinuria	9 (50)	1 (16.67)	8 (66.7)	0.098
Isolated nephrotic proteinuria	6 (33.3)	4 (66.7)	2 (16.7)	
Nephrotic syndrome	3 (16.7)	1 (16.7)	2 (16.7)	
Serum albumin at recurrence, g/dl, mean ± SD	3.5 ± 0.8	3.6 ± 0.7	3.6 ± 0.8	0.796
eGFR at recurrence, per ml/min/1.73 m^2, mean ± SD	39.59 ± 11.87	33.45 ± 12.40	42.15 ± 11.18	0.177
Proteinuria at recurrence, g/24, median (IQR)	2.7 (1.6–4.6)	3.2 (1.4–15.6)	2.2 (1.6–4.3)	**0.030**
eGFR after treatment, per ml/min/1.73 m^2, mean ± SD	38.59 ± 12.85	29.86 ± 10.35	43.36 ± 11.83	**0.033**
Proteinuria after treatment, g/24, median (IQR)	0.6 (0.4–1)	4.3 (0.6–10.5)	0.5 (0.3–0.6)	0.275
Mean eGFR during follow-up, per ml/min/1.73 m^2, mean ± SD	41.6 ± 14.5	32.9 ± 13	46 ± 13.6	0.075
Mean Proteinuria during follow-up, g/24 h, median (IQR)	1.2 (0.6–1.9)	3.2 (1.3–7.2)	0.9 (0.5–1.4)	**0.039**
Kidney biopsy at recurrence				
Globally sclerotic glomeruli, %, median (IQR) ($n = 16$)	2.56 (0–14.3)	0 (0–7.1)	3.85 (0–18.2)	0.271
IFTA, *n* (%) ($n = 16$)				
≤20%	13 (81.3)	2 (50)	11 (91.7)	0.136
20–50%	3 (18.8)	2 (50)	1 (8.3)	
>50%	0 (0)	0 (0)	0 (0)	
Arterio- and arteriolosclerosis, *n* (%) ($n = 16$)				
≤20%	13 (81.3)	2 (50)	11 (91.7)	
20–50%	3 (18.8)	2 (50)	1 (8.3)	0.136
>50%	0 (0)	0 (0)	0 (0)	
Transplant glomerulopathy, *n* (%)	1 (5.9)	0 (0)	1 (8.3)	1
C4d deposition in peritubular capillaries, *n* (%) ($n = 16$)	5 (31.25)	3 (60)	2 (18.18)	0.245
Ehreinreich Churg classification, *n* (%) ($n = 16$)				
Stage 1	10 (62.5)	3 (50)	7 (70)	0.790
Stage 2	4 (25)	2 (33.3)	2 (20)	
Stage 3	2 (12.5)	1 (10)	1 (16.7)	
PLA2R staining				
Negative	2 (11.1)	0 (0)	2 (16.7)	0.342
Positive	5 (27.8)	3 (50)	2 (16.7)	
Not performed	11 (61.1)	3 (50)	8 (66.7)	
THSD7A staining				
Not performed	18 (100)	6 (100)	12 (100)	1
IgG type				
IgG4	3 (16.7)	1 (16.7)	2 (16.7)	1
Not performed	15 (83.3)	5 (83.3)	10 (83.3)	
Concomitant rejection, *n* (%)				
No	16 (88.9)	6 (100)	10 (83.3)	1
ABMR	1 (5.6)	0 (0)	1 (8.3)	
TCMR	1 (5.6)	0 (0)	1 (8.3)	
Management of recurrence				
None	1 (5.56)	0 (0)	1 (8.3)	1
ACEi/ARBs[a], *n* (%)	12 (66.7)	3 (50)	9 (75)	0.344
Steroids[a], *n* (%)	7 (38.9)	1 (16.7)	6 (50)	0.316
Tacrolimus dose increase[a], *n* (%)	0 (0)	0 (0)	0 (0)	n.a.
Rituximab[a], *n* (%)	4 (22.2)	3 (50)	1 (8.3)	0.083
Outcomes				
CR, *n* (%)	4 (23.5)	0 (0)	4 (36.4)	0.237
PR[b], *n* (%)	9 (50)	3 (50)	6 (50)	1
SR, *n* (%)	5 (27.78)	2 (33.3)	3 (25)	1
Delta proteinuria 1 (proteinuria at 3 months post-KT vs. proteinuria at recurrence)	2.2 (0.8–4.4)	2.6 (1.1–14.4)	1.9 (0.4–4.0)	0.399
Delta proteinuria 2 (proteinuria at recurrence vs. proteinuria after treatment)	2.2 (1.1–3.5)	2.1 (0.9–2.8)	2.2 (1.1–3.6)	0.546

[a]Alone or in combination.

[b] Includes patients without recurrence treatment or ACEi/ARBs alone.

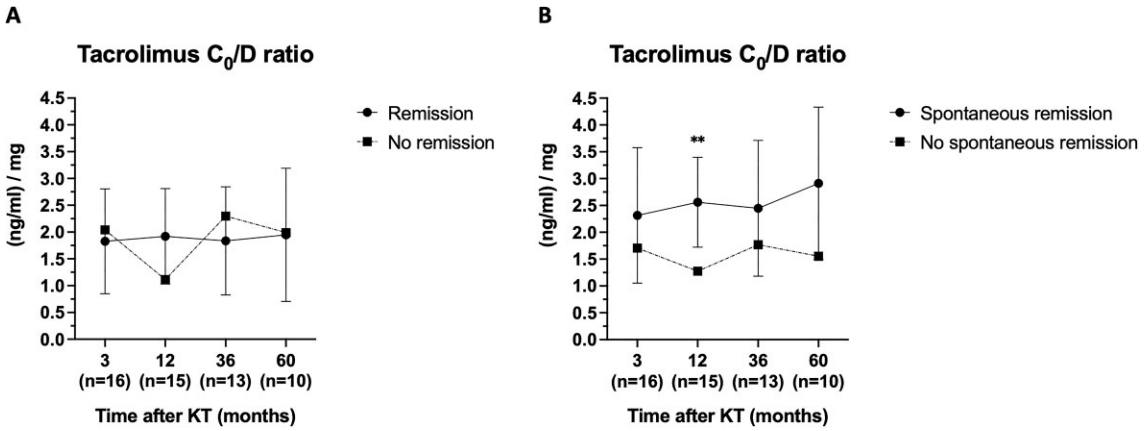


Figure 2: Tacrolimus C_0/D ratio according to remission. (A) Complete or PR and (B) SR.

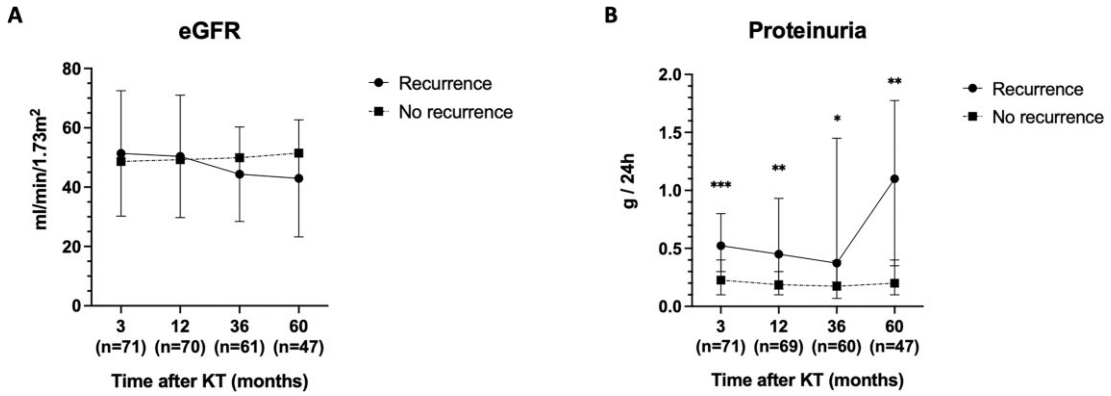


Figure 3: Kidney function during the subsequent follow-up periods after KT (3, 12, 36, and 60 months) according to recurrence. (A) Average eGFR and (B) median proteinuria values.

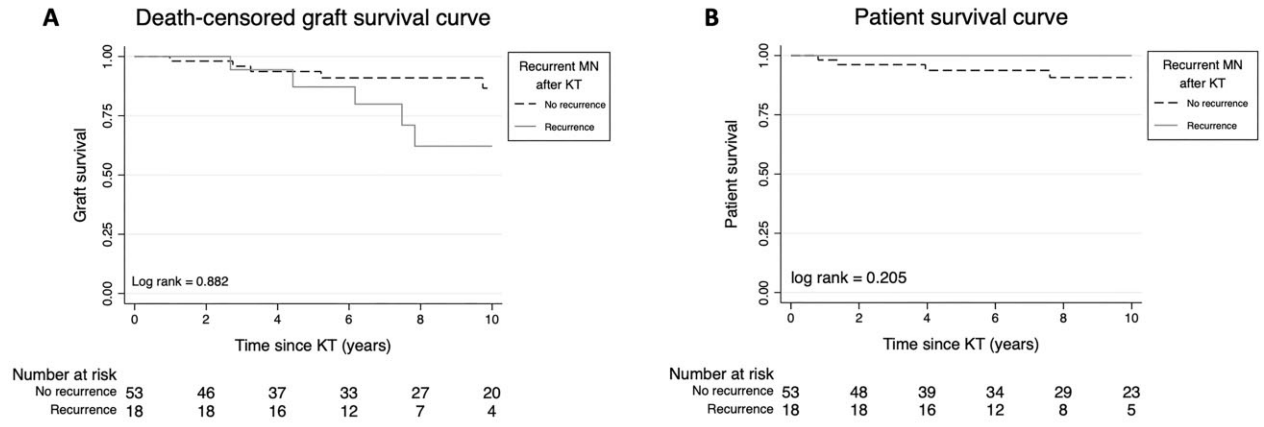


Figure 4: Kaplan–Meier survival curves. (A) Death-censored graft survival according to recurrence. (B) Patient survival according to recurrence.

patient survival, Kaplan–Meier curves showed similar outcomes 5 years after transplantation in those recipients with and without recurrence (100% vs. 93.8%, respectively; log rank = 0.205; Fig. 4B).

Demographic and clinical characteristics of patients according to death-censored graft loss are summarized in Table S3 (see online supplementary material for a color version of this figure) and Fig. 5A and B. Recipients who lost their grafts presented

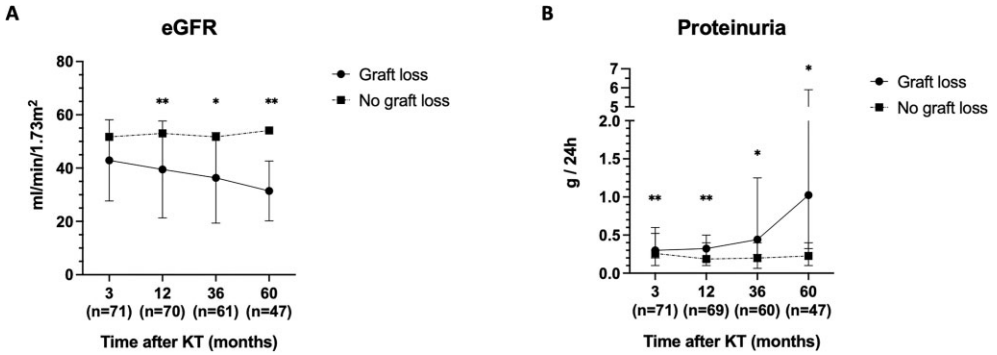


Figure 5: Kidney function during the subsequent follow-up periods after KT (3, 12, 36, and 60 months) according to kidney outcome. (**A**) Average eGFR and (**B**) median proteinuria values.

worse eGFR after one year of follow-up ($P = 0.007$, $P = 0.013$, and $P = 0.005$ at 1, 3, and 5 years post-KT, respectively) and increased proteinuria after the third year ($P = 0.012$ and $P = 0.012$ at 3 and 5 years post-KT, respectively). However, we found no significant differences concerning recipient and donor characteristics or immunosuppressive regimens.

Risk factors for recurrence and graft loss

In univariable Cox regression analysis, rMN was associated with the recipient's age at transplantation, proteinuria at 3 months after KT, and KT decade (Table 3). After multivariable analysis, only proteinuria at three months after KT [HR 4.28 (95% CI: 1.47–12.48); $P = 0.008$] and recent KT decade [HR 3.03 (95% CI: 1.02–8.97); $P = 0.046$] remained associated with recurrence. Unfortunately, the presence and levels of autoantibodies could not be included in the analysis due to the limited number of immunological tests (both anti-PLA2R and anti-THSD7A) during follow-up (Table S4, see online supplementary material for a color version of this figure). When analyzing predictors of death-censored graft loss, the multivariate Cox regression model showed that eGFR after recurrence treatment [HR 0.85 (95% CI: 0.72–0.99), $P = 0.037$; eGFR <30 ml/min per 1.73 m^2: RR = 6.2] was the only determinant of poorer graft survival (Table 4).

De novo or unclassified MN after transplantation

Table S5 (see online supplementary material for a color version of this figure) shows the clinical characteristics and management of four patients MN considered *de novo* or unclassified. All patients had a lacking native kidney biopsy and developed with a maximum of 15 months after KT. Proteinuria rates were very varied, and only one had concomitant ABMR. Despite all of them reaching partial or CR, only one patient had a functioning graft at the end of follow-up.

DISCUSSION

Herein, we report the characteristics and outcomes of a multicenter observational cohort study, including patients with MN diagnosed after KT. Up to 25.4% of patients with biopsy-proven MN as primary kidney disease recurred after KT, without a clear impact on graft survival. Early-onset proteinuria could be a monitorable risk factor for recurrence. Although patients with graft loss had higher median proteinuria rates during follow-up, eGFR values after recurrence treatment were the only determinant of poorer graft survival. We did not observe an association between the doses and levels of maintenance immunosuppression and recurrence diagnosis. But, interestingly, patients with SR had higher C_0/D ratio of tacrolimus before recurrence. To date, rituximab has been restricted to recurrences with proteinuria >3 g/24 h. The increase in cases observed in the last decade indicates an improvement in its diagnosis. However, the performance of pre- and post-KT immunological tests for monitoring rMN remains limited.

Reported rates of rMN (between 18% and 57% [12, 14–20]) are highly heterogeneous among transplant centers due to different rates of native kidney biopsies, surveillance biopsy policies, data collection period, and follow-up time after KT. The incidence of rMN in our cohort hovers in the lower range. Nonetheless, more than 50% of the cohort received a KT before 2010, when most centers' surveillance biopsies were still not established. Indeed, our data showed a significant increase in recurrences in the last decade, indicating an improvement in its diagnosis, which could be a consequence of introducing protocol biopsy policies and ameliorating the diagnosis of native kidney disease.

Understandably, surveillance biopsies provide the earliest diagnosis of rMN and may be crucial for detecting a subclinical disease [10, 12, 14, 25, 33]. However, our data revealed that proteinuria rates were significantly higher from 3 months post-KT in those patients who were later diagnosed with rMN. Thus, early-onset proteinuria (>0.3 g/24 h) could be a monitorable predictor for recurrence, indicating the need for early protocol biopsy. This is noteworthy considering that isolated nonnephrotic-range proteinuria and insidious manifestations seem to be the predominant clinical presentation in ours and previous studies, in contrast to the primary disease [10, 12, 14, 17, 33]. Yet, the disease can progress quickly regardless of low amounts of proteinuria [12, 17, 34]. Careful monitoring of proteinuria in the posttransplant period is an advised standard procedure to detect recurrence early [12, 23]. But the evolution of proteinuria rates prior to recurrence has scarcely been analyzed [18]. Instead, Grupper *et al.* studied the higher recurrence risk in patients with higher proteinuria pretransplant [12].

Anti-PLA2R antibody concentration has also been associated with clinically significant rMN. The positive predictive value of pretransplant anti-PLA2R antibodies for disease recurrence is 83%. In the posttransplant period, high titers have been shown to correlate with a higher risk of recurrence and may associate with disease progression or resistance to treatment [16, 17, 34]. Lamentably, the performance of pre- and post-KT immunological assays monitoring early rMN in our cohort was

Table 3: Cox regression analyses for determinants of MN recurrence after transplantation*.

Variable	Univariate HR (95% CI)	*P* value	Multivariate HR [95% CI]	*P* value
Age at transplantation, per year	1.06 (1.01–1.10)	**0.011**	1.02 (0.98–1.07)	0.310
Sex				
Male	1.00 (ref.)			
Female	1.68 (0.48–5.87)	0.418	NS	
Hypertension				
No	1.00 (ref.)			
Yes	5.31 (0.70–40.43)	0.107	NS	
Time to kidney failure on native kidneys, per year	0.98 (0.88–1.08)	0.635	NS	
Time on dialysis, per month	1.00 (0.98–1.01)	0.604	NS	
KT decade				
1991–2000	1.00 (ref.)			
2001–2010	6.20 (0.68–56.16)	0.105		
2011–2020	11.34 (1.29–99.95)	**0.029**	3.03 (1.02–8.97)	**0.046**
Preemptive KT				
No	1.00 (ref.)			
Yes	2.91 (0.81–10.40)	0.100	NS	
Type of donor				
DBD	1.00 (ref.)			
DCD	0.95 (0.20–4.49)	0.944		
Living donor	1.51 (0.43–5.33)	0.518		
Living related donor	1.07 (0.24–4.78)	0.925	NS	
HLA-A/B/DR mismatch				
≤3	1.00 (ref.)			
>3	1.03 (0.38–2.77)	0.949	NS	
HLA-DRB1*03	0.47 (1.61–1.34)	0.157	NS	
CIT, per hour	1.01 (0.94–1.08)	0.758	NS	
Induction therapy				
None	1.00 (ref.)			
Basiliximab/Daclizumab	2.28 (0.74–7.01)	0.151		
ATG/ALG/ATGAM	0.48 (0.10–2.40)	0.370	NS	
Maintenance with CCT + CNI + AMF				
No	1.00 (ref.)			
Yes	1.90 (0.23–16.01)	0.555	NS	
Steroid free/early steroid withdrawal				
No	1.00 (ref.)			
Yes	0.41 (0.05–3.30)	0.403	NS	
DGF				
No	1.00 (ref.)			
Yes	0.89 (0.32–2.41)	0.818	NS	
Rejection episode during follow-up				
No	1.00 (ref.)			
Yes	1.73 (0.61–4.93)	0.307	NS	
eGFR 3 months after KT, per ml/min/1.73 m^2	1.00 (0.97–1.02)	0.743	NS	
Proteinuria 3 months after KT, per g/24 h	7.55 (2.49–22.86)	**<0.001**	4.28 (1.47–12.48)	**0.008**

* Number of events: 18

limited. Therefore, there is still a long way toward improving recurrence monitoring for a prompt diagnosis and adequate treatment.

The impact of recurrence on graft survival is still controversial. Some authors have reported no significant difference in graft survival between recipients with and without rMN [15, 35]. In contrast, others have shown a progression to end-stage kidney disease or allograft loss between 45% and 65% of recipients with recurrence within 4 to 6 years from diagnosis [12, 20, 36, 37]. Pippias *et al.* evaluated death-censored graft survival in 708 patients with primary MN compared with patients with autosomal dominant polycystic kidney disease ($n = 7\,181$) using the ERA-EDTA registry database. They described a detrimental effect of MN recurrence [38]. We found no significant differences in death-censored graft survival between groups in both Kaplan–Meier and competing risk analyses. Nonetheless, graft losses were more numerous in the recurrence group and up to 83.3% were due to recurrence.

As expected, our data showed that those patients who lost their grafts had higher protein rates during follow-up. But, more importantly, despite the frequent insidious clinical presentation in patients with recurrence, up to 83.4% of patients with graft loss developed nephrotic-range proteinuria with or without nephrotic syndrome. Additionally, no recipients with rMN who achieved CR lost their allograft. Recipients with diminished graft survival also had worse kidney function during follow-up. In fact, we observed that eGFR values after recurrence treatment were the only determinant of poorer graft survival. Similarly, others have identified proteinuria rates and kidney function as prognostic factors associated with poor graft outcomes in

Table 4: Cox regression analyses for determinants of death-censored graft failure*.

Variable	Univariate HR (95% CI)	*P* value	Multivariate HR [95% CI]	*P* value
Age at transplantation, per year	1.05 (1–1.09)	**0.034**	1.04 (0.96–1.13)	0.339
Sex				
Male	1.00 (ref.)			
Female	2.05 (0.46–9.24)	0.348	NS	
Hypertension				
No	1.00 (ref.)			
Yes	3.23 (0.42–24.80)	0.259	NS	
Diabetes				
No	1.00 (ref.)			
Yes	0.89 (0.20–3.92)	0.862	NS	
Time on dialysis, per month	1.00 (0.98–1.02)	0.918	NS	
Preemptive KT				
No	1.00 (ref.)			
Yes	2.21 (0.49–10.09)	0.305	NS	
Type of donor				
DBD	1.00 (ref.)			
DCD	1.56 (0.34–7.18)	0.567	NS	
Living donor	1.28 (0.27–5.90)	0.747	NS	
HLA-A/B/DR mismatch				
≤3	1.00 (ref.)			
>3	2.39 (0.66–8.64)	0.184	NS	
CIT, per hour	1.01 (0.94–1.09)	0.741	NS	
Induction therapy				
None	1.00 (ref.)			
Basiliximab/Daclizumab	1.79 (0.43–7.43)	0.421	NS	
ATG/ALG/ATGAM	2.87 (0.67–12.26)	0.155	NS	
Steroid free/early steroid withdrawal				
No	1.00 (ref.)			
Yes	1.56 (0.35–6.99)	0.561	NS	
DGF				
No	1.00 (ref.)			
Yes	1.19 (0.41–3.45)	0.744	NS	
Rejection episode during follow-up				
No	1.00 (ref.)			
Yes	1.07 (0.30–3.83)	0.922	NS	
MN recurrence				
No	1.00 (ref.)			
Yes	2.50 (0.86–7.24)	0.092	NS	
Recurrence clinical presentation				
Isolated nonnephrotic proteinuria	1.00 (ref.)			
Nephrotic proteinuria/Nephrotic syndrome	7.51 (0.85–66.41)	0.070	NS	
eGFR 1 year after KT, per ml/min/1.73 m^2	0.96 (0.92–0.99)	**0.010**	1.04 (0.97–1.13)	0.245
eGFR at recurrence, per ml/min/1.73 m^2	0.93 (0.86–1.00)	0.085	NS	
Proteinuria at recurrence, per g/dl	1.07 (0.94–1.21)	0.327	NS	
eGFR after recurrence treatment, per ml/min/1.73 m^2	0.90 (0.82–0.99)	**0.036**	0.85 (0.72–0.99)	**0.037**
Proteinuria after recurrence treatment, per g/24 h	1.07 (0.94–1.21)	0.327	NS	

* Number of events: 14

KT recipients with posttransplant glomerulonephritis and in primary MN [4, 39, 40].

Induction therapy and standard maintenance immunosuppression have been shown to induce immunologic remission in selected cases [10, 17]. Consequently, the question arises as to whether maintenance immunosuppression drugs used for treating primary MN (i.e. tacrolimus, steroids) might modulate the development and clinical course of rMN [16, 25]. In a Spanish study, one patient with negative PLA2R antibodies before KT had positive anti-PLA2R antibodies at the time of recurrence, presumably due to minimized immunosuppression [16]. Furthermore, in a French cohort, a reduced immunosuppressive regimen that did not include both induction therapy and combined treatment with a calcineurin inhibitor and mycophenolate was associated with a persistently positive anti-PLA2R activity and recurrence [34]. In contrast, Mulay *et al.* did not find any relation between maintenance immunosuppression drugs and the risk of graft loss due to a glomerulonephritis recurrence [27]. We did not observe an association between the doses and levels of maintenance immunosuppression and recurrence diagnosis. But, notably, patients with SR had higher C_0/D ratio of tacrolimus before recurrence. SR has been associated with a lower incidence of death and end-stage kidney disease in patients with idiopathic MN and nephrotic syndrome [41]. Unfortunately, we could not assess this query due to the small number of recurrences. In fact, our data showed an increased percentage of globally sclerotic glomeruli in patients with SR, probably due to a sample size effect.

Regarding recurrence treatment, most studies agree that intensive treatment with immunosuppression therapy should be considered if significant proteinuria is present (>1 g/24 h) [17, 23, 25]. Particularly, rituximab has shown promising results with high rates of clinical remission [10, 14, 15, 33]. Yet, our data showed that, to date, rituximab had been restricted to recurrences with proteinuria >3 g/24 h. Considering that most patients from the recurrent group lost their graft due to recurrence, we should hereinafter contemplate rituximab use in earlier proteinuria stages, as recently suggested by the new clinical practice guidelines [26].

Our study has the inherent limitations of all retrospective observational studies, and the results may be interpreted with caution. Despite its multicenter study design, the number of events is probably not large enough to show significant results regarding risk factors for recurrence or graft loss. Moreover, many patients did not have high-resolution HLA analysis performed to assess genetic predisposition nor serological monitoring for anti-PLA2R (or anti-THSD7A) levels before or after KT. One-third of patients did not have a follow-up biopsy performed, which may have underdiagnosed some cases of recurrent disease. Last, recurrence management was done at the discretion of the treating physician. Thus, we could not evaluate the use of rituximab in patients with mild proteinuria. However, this is a large series that explores allograft outcomes in patients with MN after KT according to proteinuria rates and maintenance immunosuppression management.

CONCLUSIONS

Our data show that one-fourth of patients with biopsy-proven MN as primary kidney disease recurred after transplantation, without a clear impact on graft survival. Early-onset proteinuria could be a monitorable risk factor for recurrence. Still, creatinine value after recurrence treatment was the only determinant of poorer graft survival. As a high tacrolimus exposure before rMN was associated to SR, maintenance immunosuppression seeking higher mean tacrolimus levels may be beneficial.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

ACKNOWLEDGEMENTS

We are grateful to the members of the SENTRA and GLOSEN working groups for their participation in helping this study become a reality.

FUNDING

AB has support from a Rio Hortega contract (CM19/00004, ISCIII), a M-AES grant (MV20/00072, ISCIII), and a Spanish Society of Nephrology scholarship.

AUTHORS' CONTRIBUTIONS

Conception and design: A.B., M.J.P.-S., M.P., and J.P. Data acquisition: A.B., F.C.-F., L.A.V., A.M., J.L.P., E.R., E.C., A.S., A.C., and E.M. Analysis and interpretation of data: A.B., M.J.P.-S., and J.P. Draft of the manuscript: A.B. and M.J.P.-S. Critical revision or mentoring: A.M., E.M., E.R., A.S., M.P., M.J.P.-S., and J.P. A.B. was the major contributor in writing the manuscript. All the authors revised and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

Nothing to disclose.

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