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Original Article

Recurrence of membranous nephropathy after kidney transplantation: A multicenter retrospective cohort study

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Abbreviations: CI, confidence interval; CMV, cytomegalovirus; ELISA, enzyme-linked immunosorbent assay; ESKD, end-stage kidney disease; HR, hazard ratio; IIF, indirect immunofluorescence; IQR, interquartile range; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; RAAS, renin-angiotensin-aldosterone system; RU, relative unit; TANGO, Post-Transplant Glomerular Disease; THSD7A, thrombospondin type-1 domain containing 7A.

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A B S T R A C T

Membranous nephropathy (MN) is a leading cause of kidney failure worldwide and frequently recurs after transplant. Available data originated from small retrospective cohort studies or registry analyses; therefore, uncertainties remain on risk factors for MN recurrence and response to therapy. Within the Post-Transplant Glomerular Disease Consortium, we conducted a retrospective multicenter cohort study examining the MN recurrence rate, risk factors, and response to treatment. This study screened 22,921 patients across 3 continents and included 194 patients who underwent a kidney transplant due to biopsy-proven MN. The cumulative incidence of MN recurrence was 31% at 10 years posttransplant. Patients with a faster progression toward end-stage kidney disease were at higher risk of developing recurrent MN (hazard ratio [HR], 0.55 per decade; 95% confidence interval [CI], 0.35-0.88). Moreover, elevated pretransplant levels of anti-phospholipase A2 receptor (PLA2R) antibodies were strongly associated with recurrence (HR, 18.58; 95% CI, 5.37-64.27). Patients receiving rituximab for MN recurrence had a higher likelihood of achieving remission than patients receiving renin-angiotensin-aldosterone system inhibition alone. In sum, MN recurs in one-third of patients posttransplant, and measurement of serum anti-PLA2R antibody levels shortly before transplant could aid in risk-stratifying patients for MN recurrence. Moreover, patients receiving rituximab had a higher rate of treatment response.

1. Introduction

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease (ESKD). While the short-term outcomes of kidney transplantation have significantly improved, long-term outcomes have only marginally improved over the past 30 years.[1] Excluding death as a cause of graft loss, recurrence of glomerular disease is the second leading cause of kidney graft loss.[2-6] Among the glomerular diseases that recur after transplantation, membranous nephropathy (MN) is one of the most common.[7-11] Therefore, investigating MN recurrence posttransplant is vital to improve the long-term outcomes of kidney transplant recipients.

MN is the leading cause of nephrotic syndrome in nondiabetic adults worldwide, frequently leading to ESKD.[8,9] The reported recurrence rate of MN following renal transplantation ranges from 6% to 55% (Supplementary Table 1). This considerable variation is likely attributed to the limited sample sizes of single-center studies and different criteria for the detection of recurrence, with centers performing protocol biopsies reporting higher rates.[10-14] MN recurrence has been associated with a higher risk of accelerated graft failure.[15-17] However, the recent identification of multiple autoantibodies against podocyte antigens has revolutionized the understanding and management of MN in native kidneys.[18] In particular, antibodies against phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain containing 7A (THSD7A) may be detectable in approximately 70% of all MN cases.[19,20] Treatment with B cell–depleting agents such as rituximab has changed the course of MN in native kidneys, leading to better responses and less toxicity,[21] but the impact of these discoveries in posttransplant recurrent MN remains to be determined.

We conducted a multicenter, international study on MN recurrence posttransplantation within the Post-Transplant Glomerular Disease (TANGO) Consortium. This collaborative effort between 39 transplant centers worldwide, spread across 5 continents, is dedicated to improving our understanding of glomerular disease posttransplant.[22] By utilizing retrospective clinical data and patient serum samples, we examined the incidence, associated risk factors, and treatment approaches of recurrent MN and evaluated subsequent graft outcomes.

2. Methods

2.1. Study design and endpoints

Sixteen transplant centers from the TANGO Consortium in Europe, North America, and South America participated in this retrospective cohort study. Our primary endpoint was the incidence of biopsy-proven MN recurrence after kidney transplantation in patients with a biopsy-proven diagnosis of primary MN in their native kidneys. Secondary endpoints included risk factors for MN recurrence, clinical outcomes, and response to treatment (complete, partial, or no remission).

A more detailed description can be found in the Supplementary Methods.

2.2. Patient selection

Participating centers screened all patients who underwent a kidney transplant between January 2005 and December 2020, amounting to 22,921 transplant recipients.

A total of 208 patients were considered for the study and entered into a dedicated online database.[22] The study inclusion criteria

comprised adult patients who received a kidney transplant within the aforementioned timeframe and had biopsy-confirmed primary MN as the cause of their ESKD. Patients with a secondary cause of MN and those with de novo MN after transplantation were excluded.

In total, 194 adult patients (≥18 years) met our inclusion criteria for primary analysis (Supplementary Fig. 1). Patients with a secondary cause of MN, death, or loss to follow-up immediately after transplant and/or patients with de novo MN were excluded. See Supplementary Figure 1 for further details.

In addition, patients from one Brazilian center without a native kidney biopsy due to advanced kidney disease at time of biopsy consideration were excluded from primary analysis. They were included in secondary analyses as they had biopsy-proven MN recurrence and pretransplant clinical course suggestive of MN.

The overall protocol of the TANGO Consortium was approved by the ethical committee of the Partners Human Research Committee at Massachusetts General Hospital in Boston (protocol number: 2015P000993) and adheres to the principles outlined in the Declaration of Helsinki. Additional information can be found in the Supplementary Methods.

2.3. Data and sample collection

Detailed deidentified health information was extracted from medical records. Patients were censored at the time of graft loss, patient death, loss to follow-up, or in December 2022. Patients were only classified as having recurrent MN if their recurrence was biopsy-proven. Clinical indication-guided biopsy was standard for most centers, whereas 2 centers performed protocol biopsies posttransplantation as part of routine care. Serum samples from included patients were retrospectively requested from participating transplant centers. These serum samples were required to be collected shortly before transplantation.

2.4. Antibody detection in sera

Serum PLA2R and THSD7A antibodies were detected using indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). Serum PLA2R antibodies were assessed using both IIF and ELISA, whereas IIF was exclusively used to detect circulating THSD7A autoantibodies. Quantitation of positive anti-PLA2R sera was determined using the Euroimmun ELISA Kit. Positive and negative controls were extrapolated using the standard curve fit, positive $\geq$ 20 relative units (RU)/mL, borderline $\geq$ 14 to $<$ 20 RU/mL, and negative $<$ 14 RU/mL. See Supplemental Methods for further details.

2.5. Statistical analysis

Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as medians and interquartile ranges or means ± standard deviations. Complete case analysis was used for statistical analysis of Table 1. *t* tests were used for continuous variables, whereas chi-square or Fisher exact tests were used for binary and categorical variables, depending on group size.

Log-rank tests were used to compare 2 groups, whereas log-rank tests for trend were used for 3 or more groups. Missing data are shown in Supplementary Table 2 and were imputed using STATA's multiple imputation by chained equations procedure. See Supplementary Methods for more details. Univariable and multivariable Cox proportional hazards regression was performed with imputed data in Table 2, with categorical variables entered as binary variables. Schoenfeld residuals were evaluated to assess proportional hazard assumptions, and deviance residuals were used to evaluate model accuracy and outliers. Adverse events after kidney transplantation (acute rejection, cytomegalovirus [CMV], cancer, and BK viremia) were treated as time-varying covariates to assess the association between their occurrence and subsequent development of recurrent MN. Prism 9.4.1 (GraphPad) and STATA (version 17.0, StataCorp LLC) were employed to carry out statistical analysis and generate graphics.

3. Results

3.1. Cohort demographics

Our overall cohort included 194 transplant recipients with biopsy-proven primary MN in their native kidneys. Most patients were White (72%). Approximately 16% of patients underwent a pre-emptive transplant, and 37% received a transplant from a living donor. Basiliximab was the most commonly used induction therapy (42%) along with triple maintenance immunosuppression consisting of tacrolimus, mycophenolate, and steroids (70%). Additionally, 16% of the patients were on an early steroid withdrawal regimen. One center used alemtuzumab induction with tacrolimus maintenance monotherapy and short-course steroids for most of their patients. Additional information about the cohort demographics can be found in Table 1.

3.2. Incidence of MN recurrence after kidney transplantation

During a median follow-up period of 5.9 years (interquartile range [IQR], 3.2-8.6 years), 43 patients experienced recurrent MN. The prevalence of MN recurrence increased gradually after transplant (Fig. 1), with a cumulative incidence of 31% at 10 years (95% CI, 23-41) posttransplantation. The median time to recurrence was 1.9 years (IQR, 0.4-4.3), with 7% (n = 4) of recurrences diagnosed on protocol biopsy and 93% (n = 39) detected on a clinically indicated biopsy. The 10-year cumulative incidence rate of MN recurrence per continent is shown in Supplementary Figure 2.

Patients who experienced MN recurrence were younger at the time of primary MN diagnosis in their native kidneys (36 years vs 46 years, $P = .02$, Wilcoxon rank sum test) and had a shorter time from MN diagnosis to ESKD (65 months vs 116 months, $P = .02$, Wilcoxon rank sum test). No differences were observed when comparing tacrolimus trough levels posttransplant according to remission rates in patients with recurrent MN (Supplementary Fig. 3).

Table 1
Baseline characteristics of recipients and donors in all patients and according to MN recurrence.

Characteristic	Overall cohort (n = 194)	No recurrence (n = 151)	Recurrence (n = 43)
Follow-up, y	5.9 [3.2-8.6]	5.1 [3.2-8.2]	7.1 [3.3-10.4]
Age at transplantation, y	54 [43-64]	52 [41-64]	56 [48-64]
Age at diagnosis, y	37 [26-51]	36 [24-48]	46 [33-53]
Male sex	142 (73)	109 (72)	33 (77)
Race			
Asian	5 (3)	5 (3)	0 (0)
Black	13 (7)	11 (7)	2 (5)
White	139 (72)	106 (70)	33 (77)
Mixed	5 (3)	4 (3)	1 (2)
BMI at transplantation	25.4 [22.5-29.2]	25.1 [22.1-29.2]	26.3 [24.3-29.1]
Time from diagnosis to ESKD, mo	95 [44-213]	116 [51-225]	65 [37-122]
Time on dialysis, mo	29 [14-60]	29 [14-59]	26 [14-60]
Type of dialysis			
Hemodialysis	133 (69)	99 (67)	34 (79)
Peritoneal dialysis	17 (9)	16 (11)	1 (2)
Both	11 (6)	11 (7)	0 (0)
None (pre-emptive transplant)	33 (16)	23 (15)	8 (19)
Number of prior transplants			
None	167 (86)	129 (85)	38 (88)
One or more transplant	27 (14)	22 (15)	5 (12)
DSA at time of transplant	14 (7)	13 (9)	1 (2)
Deceased donor	121 (62)	94 (62)	27 (63)
Extended criteria donor (KDPI >85%)	40 (33)	34 (36)	6 (22)
Cold ischemia time, h	17 ± 8	17 ± 8	16 ± 7
Living donor	73 (38)	57 (38)	16 (37)
Living related donor	37 (51)	27 (47)	10 (63)
Donor age, y	52 [42-61]	52 [42-61]	55 [43-61]
HLA-A/B/DR mismatch	3 [2-5]	3 [2-5]	3 [3-4]
Induction therapy			
None	14 (7)	9 (6)	5 (11)
Basiliximab	83 (42)	60 (40)	15 (35)
Anti-thymocyte globulin	75 (39)	64 (42)	19 (44)
Alemtuzumab	17 (9)	13 (9)	4 (9)
Daclizumab	5 (3)	5 (3)	0 (0)
Baseline immunosuppressive regimen			
Tacrolimus + MMF + steroids	135 (70)	110 (73)	25 (58)
Cyclosporine + MMF + steroids	12 (6)	9 (6)	3 (7)
Tacrolimus + MMF	19 (10)	12 (8)	7 (16)
Tacrolimus	16 (8)	13 (9)	3 (7)

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Overall cohort (n = 194)	No recurrence (n = 151)	Recurrence (n = 43)
Other	8 (4)	5 (3)	3 (7)
Steroid free/early steroid withdrawal	29 (16)	22 (15)	7 (17)

Values represent frequency (percentage), mean ± standard deviation (SD), or median [interquartile range].
MN, membranous nephropathy; BMI, body mass index; ESKD, end-stage kidney disease; DSA, donor-specific antibodies; KPDI, kidney donor profile index; HLA, human leukocyte antigen, MMF, mycophenolate mofetil.

Table 2
Associations of clinical characteristics with recurrence of MN. Values represent frequency (percentage) unless otherwise stated. Significant values are shown in bold.

Variable	Missing values (%)	Total number of events	Unadjusted analysis hazard ratio (95% CI)	Multivariable analysis hazard ratio (95% CI)	*P* value Multivariable analysis
Geographic location					
North America	0 (0)	13	Ref	Ref	
Europe	0 (0)	23	0.84 (0.46-1.54)	0.70 (0.36-1.39)	0.31
Brazil	0 (0)	7	0.81 (0.36-1.82)	0.64 (0.25-1.60)	0.34
BMI	12 (6)	41	1.02 (0.96-1.08)	1.01 (0.95-1.08)	0.71
Time from diagnosis to ESKD, per 10 y	24 (12)	40	**0.64 (0.43-0.94)**	**0.55 (0.35-0.88)**	**0.013**
HLA-mismatch	11 (6)	41	1.02 (0.84-1.23)	1.04 (0.85-1.28)	0.68
Living Tx	0 (0)	16	0.84 (0.45-1.57)	0.83 (0.41-1.70)	0.61
Age of donor, per 10 y	25 (13)	37	1.10 (0.87-1.39)	1.17 (0.90-1.52)	0.23
Pre-emptive transplant	0 (0)	8	1.16 (0.54-2.51)	1.92 (0.78-4.68)	0.15
Use of induction	0 (0)	38	0.71 (0.28-1.82)	0.84 (0.31-2.29)	0.73
History of prior kidney Tx	0 (0)	5	0.81 (0.32-2.06)	1.70 (0.58-4.68)	0.33
Immunosuppression with CNI + MMF + steroids	1 (1)	43	0.55 (0.29-1.03)	0.60 (0.30-1.19)	0.14

MN, membranous nephropathy; CI, confidence interval; Ref, reference; BMI, body mass index; ESKD, end-stage kidney disease; HLA, human leukocyte antigen; Tx, transplant; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil.

3.3. Identification of risk factors for MN recurrence

Both univariable and multivariable Cox regression analyses were performed to identify potential risk factors based on patients' characteristics (Table 2). Univariable analysis revealed that patients who had a faster progression toward ESKD were at a higher risk of developing recurrent MN. This remained significant in the multivariable model after adjusting for confounding factors, with a HR of 0.55 per decade (95% CI, 0.35-0.88). The geographical location (Europe, North America, or South America) of the patient was not associated with recurrence (Table 2). Additionally, neither body mass index, human leukocyte antigen mismatch, whether the kidney transplant came from a living donor, donor age, pre-emptive transplantation, use of induction immunosuppression, history of a prior kidney transplant, nor use of a triple immunosuppressive regimen consisting of calcineurin inhibitors, mycophenolate mofetil, and steroids was correlated with MN recurrence.

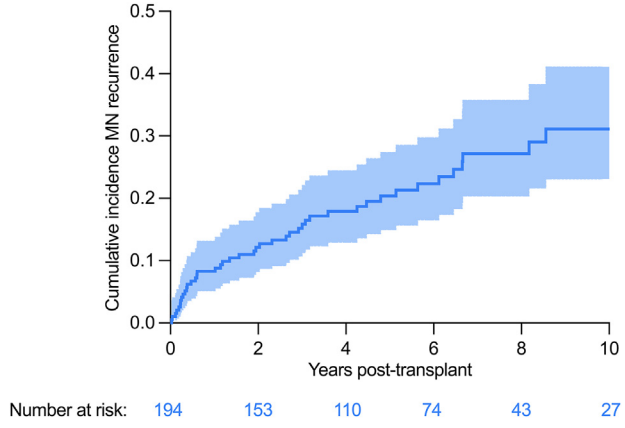

Figure 1. Cumulative incidence of MN recurrence posttransplantation. Error bands represent 95% CI. CI, confidence interval; MN, membranous nephropathy.

3.4. Circulating anti-podocyte antibodies and MN recurrence

Antibodies against PLA2R and THSD7A frequently cause MN, though they are not universally tested prior to transplantation.[23] Among the 194 patients in our cohort, 9 were screened for pretransplant anti-PLA2R antibodies at their transplant center, whereas none were screened for anti-THSD7A

antibodies. Therefore, we systemically assessed for the presence of these antibodies in pretransplant sera of 46 patients with available samples. Using IIF and ELISA, anti-PLA2R antibodies were confirmed in pretransplant sera from 19 patients. The remaining 27 tested negative for anti-PLA2R antibodies. To resolve borderline anti-PLA2R ELISA values for binary analyses, we utilized IIF to categorize patients into with or without antibodies against PLA2R (Supplementary Fig. 4). For quantification of anti-THSD7A antibodies, collected serum samples were assessed through IIF. All 46 patients tested negative for anti-THSD7A antibodies.

We combined the data from 9 patients with available pretransplant anti-PLA2R titers, along with those patients (n = 46) for whom pretransplant sera was accessible, resulting in a total of 55 patients for assessment of anti-PLA2R antibodies. Sera were collected with a median of 3 days prior to transplant (IQR, 0-46 days). In univariable Cox regression analysis, the presence of anti-PLA2R antibodies shortly before transplant was strongly associated with recurrence (HR, 18.58; 95% CI, 5.37-64.27). The overall sensitivity and specificity of pretransplant anti-PLA2R antibodies for predicting recurrence were 0.85 (95% CI, 0.76-0.94) and 0.91 (95% CI, 0.84-0.99), respectively.

Subsequently, we performed quantitative analysis of ELISA results and compared anti-PLA2R antibody levels of patients with (n = 20) and without (n = 35) MN recurrence (Fig. 2). Of the 20 patients with recurrence, 17 tested positive for anti-PLA2R antibodies prior to transplant. Among the 35 patients without recurrence, only 3 tested positive for anti-PLA2R antibodies prior to transplant. Higher pretransplant anti-PLA2R antibody values were associated with recurrence of MN ($P < .0001$, Wilcoxon rank sum test). In addition, when we categorized patients based on their pretransplant antibody status, those with confirmed positive pretransplant anti-PLA2R antibodies were more likely to develop MN recurrence ($P < .0001$, Wilcoxon rank sum test), as depicted in Figure 3A. Patients with confirmed pretransplant antibodies against PLA2R were further stratified into 2 groups based on their quantitative anti-PLA2R ELISA values, using a cutoff of 150 RU/mL (Fig. 3B).[24] Patients with a high titer had earlier MN recurrence (median time to recurrence 0.57 years; IQR, 0.38-0.89), compared with those with a titer <150 RU/mL (median time to recurrence 1.78 years; IQR, 1.01-4.79).

Overall, patients with serum anti-PLA2R antibodies shortly before transplant were more likely to develop recurrence, with high pretransplant titer levels being associated with developing recurrence more frequently and earlier after transplant.

3.5. Graft failure and recurrence

During the follow-up period, allograft failure was comparable between patients with and without recurrent MN, with 9% of patients experiencing allograft failure in each group (4 and 13 patients, respectively). The 10-year graft survival rate was 87% in the recurrent group compared with 90% in the nonrecurrent group. Kaplan-Meier graft survival, conducted on patients with recurrent MN after the confirmation of recurrence, showed a 6-year graft survival rate of 89%.

In patients with recurrent MN, graft failure was mainly attributed to MN recurrence (n = 3) and infection (n = 1). In patients without recurrence, allograft failure was caused by rejection (n = 7), followed by chronic allograft nephropathy (n = 2), unknown causes (n = 2), infection (n = 1), or urological complications (n = 1).

In patients with recurrent MN, patients who achieved complete or partial remission showed a favorable trend toward better graft survival rates compared with those who did not (see Supplemental Fig. 5).

In the recurrent group, 6 patients (14%) died, compared with 16 patients (11%) in the nonrecurrent group. Of the 27 patients who had received a prior kidney transplant, 6 lost their prior kidney allograft due to recurrent MN. Of the 6 patients who experienced allograft loss due to recurrence, 3 had recurrence again in their subsequent allograft.

3.6. MN recurrence and complications after transplantation

We investigated whether patients with recurrent MN were more prone to posttransplant complications, such as acute rejection, CMV infection, BK viremia, posttransplant diabetes mellitus, cancer, and cardiovascular disease, given their increased use of immunosuppressive drugs and the risk of adverse events associated with nephrotic syndrome. Cox regression analyses were performed for acute rejection, CMV infection, BK viremia, and cancer, whereas linear regression analysis was used to assess any association with posttransplant diabetes and cardiovascular disease. We adjusted for several confounders, including pretransplant donor-specific antibody and pre-emptive kidney transplant for patients with acute rejection and recipient/donor CMV IgG status for those with CMV infection. Our findings showed no difference in association between MN recurrence and the incidence of adverse events (Table 3).

3.7. Response to treatment of recurrent MN

We evaluated the treatment regimen and response in 51 patients with MN posttransplantation: 43 patients of the general cohort and 8 patients from the Brazilian center without native kidney biopsies due to advanced kidney disease at time of biopsy consideration (refer to Methods). Although treatments varied, the majority of patients received RAAS (renin-angiotensin-aldosterone system) inhibitors and/or rituximab.

Among the 51 patients with posttransplant MN, 25 received rituximab, either with or without additional RAAS inhibition. Eighteen patients were treated with RAAS inhibition alone. The remaining 8 patients received either spironolactone (n = 3), RAAS inhibition in combination with immunosuppressants other than rituximab (n = 2), or did not receive any additional treatment (n = 3) (Fig. 4). Rituximab with or without RAAS inhibition was associated with partial or complete remission in 17 patients (68%), whereas RAAS inhibition alone led to partial or complete remission in 6 patients (33%).

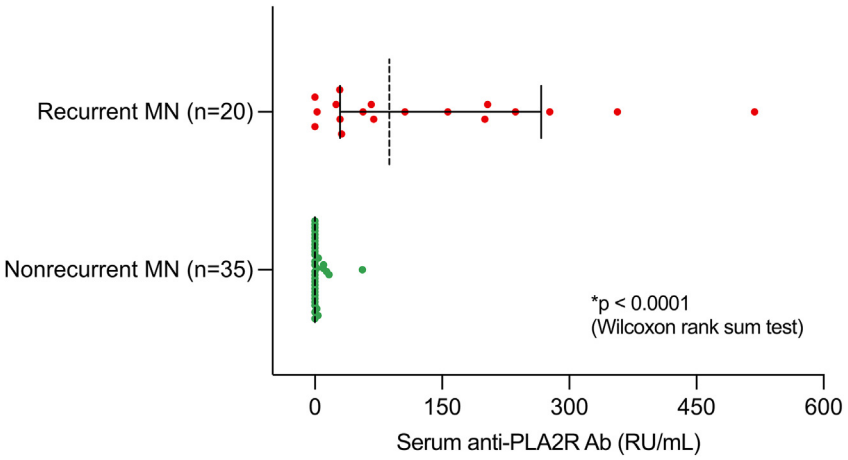

Figure 2. Quantitative ELISA results of anti-PLA2R antibodies between the nonrecurrent and recurrent group. Titer results reported as single values, including median and IQR. Wilcoxon rank sum test was used for comparison analysis. Ab, antibody; ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; RU, relative unit.

4. Discussion

In this large multicenter retrospective cohort study, designed to investigate MN recurrence using clinical data and serum samples, the cumulative incidence of recurrent MN was 31% at 10 years posttransplant. Faster progression toward ESKD in the native kidneys was associated with a higher risk of developing recurrent MN. Moreover, the presence of pretransplant serum antibodies against PLA2R was strongly associated with recurrence. Patients with MN recurrence receiving rituximab exhibited improved remission rates compared with patients with solely RAAS inhibition, resulting in minimal impact on medium-term graft survival.

The recurrence rate of MN following kidney transplantation has been variable across studies, ranging from 6% to 55%, reflective of limited sample sizes of single-center studies and different criteria for the detection of recurrence such as in centers performing protocol biopsies.[10-15,25-32] Studies using registry

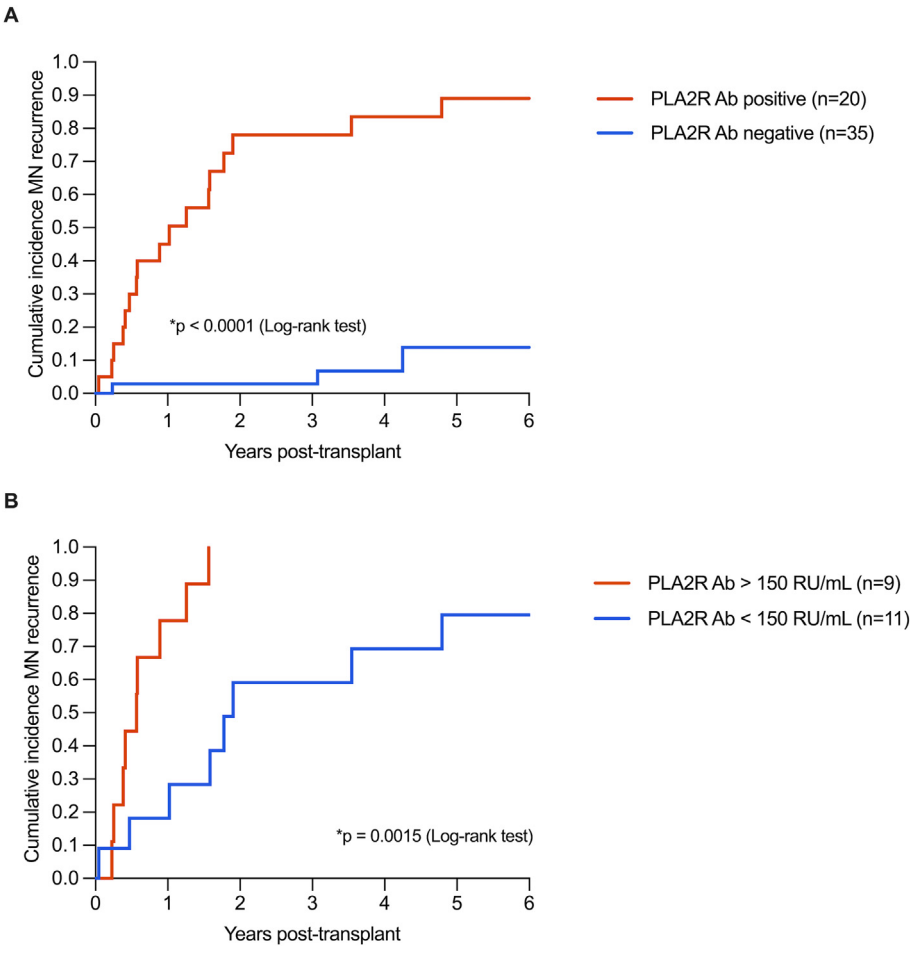

Figure 3. Cumulative incidence curve of recurrent MN stratified by pretransplant anti-PLA2R antibody status and levels. (A) Cumulative incidence of recurrent MN stratified by either negative or positive pretransplant anti-PLA2R results. (B) Cumulative incidence of recurrent MN stratified by level of pretransplant anti-PLA2R antibodies (higher or lower than 150 RU/mL). Log-rank test was used for comparison analysis. Ab, antibody; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; RU, relative unit.

Table 3
Associations of posttransplantation time-dependent adverse events with recurrent MN.

Adverse event	Overall cohort (n = 194)	No recurrence (n = 151)	Recurrence (n = 43)	Hazard ratio (95% CI)
Acute rejection[a]	43 (22)	35 (23)	8 (19)	0.86 (0.39-1.88)
Cellular mediated	34 (18)	27 (18)	7 (16)	
Antibody mediated	6 (3)	6 (4)	0 (0)	
Mixed	3 (2)	2 (1)	1 (2)	
CMV viremia[b]	19 (10)	15(10)	4(9)	0.70 (0.22-2.20)
BK viremia	20 (11)	14(10)	6(15)	1.55 (0.59-4.03)
Cancer	31 (15)	22 (15)	9 (21)	1.26 (0.58-2.75)
New-onset DM	40 (21)	32 (21)	8 (19)	OR: 0.84 (0.36-2.00)
CAD	10 (5)	8 (5)	2 (5)	OR: 0.87 (0.18-4.24)
Heart failure	7 (4)	4 (3)	3 (7)	OR: 2.74 (0.59-12.73)

Values represent frequency (percentage) unless otherwise stated.
Acute rejection, CMV, BK viremia, and cancer were assessed by Cox regression. New-onset DM, CAD, and heart failure were analyzed by logistic regression.
MN, membranous nephropathy; CI, confidence interval; CMV, cytomegalovirus; DM, diabetes mellitus; OR, odds ratio; CAD, coronary artery disease.

[a] Hazard ratio is corrected for pretransplant DSA and pre-emptive kidney transplant.

[b] Hazard ratio is corrected for pretransplant recipient/donor CMV IgG status.

data often fail to capture cases of MN recurrence that did not lead to graft loss, represented by a lower reported recurrence rate.[3,13] Conversely, studies from centers performing protocol biopsies reported higher incidence rates.[11,12] To increase the sample size, we collaborated with multiple transplant centers worldwide, ensuring representation of diverse ethnicities and immunosuppression regimens. Moreover, the contemporary data collection reflects the more recent understanding of MN pathogenesis as primarily mediated by autoantibodies against podocyte proteins while also highlighting the impact of rituximab use on MN outcomes, as it has become the immunosuppressive treatment of choice.

Among risk factors for MN recurrence, few patient demographics have been found to be consistently associated with recurrent MN (Supplementary Table 1). Of these, high levels of proteinuria pretransplant, shorter waitlist times, being of White race, older age at the time of transplant, and steroid-free immunosuppressive regimens were identified as potential predictors for recurrence.[11,31,32] We found that MN recurrence was associated with a shorter duration between diagnosis of native kidney disease and ESKD. This finding is consistent with reports of other glomerular diseases, such as IgA nephropathy and focal segmental glomerulosclerosis, in which a more aggressive native disease course is associated with an increased risk of recurrence after transplantation.[33,34]

The identification of autoantibodies against podocytes was a major revolution in the understanding of the pathogenesis of MN in native kidneys. Indeed, the detection of autoantibodies against the podocyte antigen PLA2R has been used for the diagnosis of MN as well as to monitor response to therapy and predict relapses in patients with native MN.[19,35-38] In these patients, the presence of anti-PLA2R antibodies is associated with the

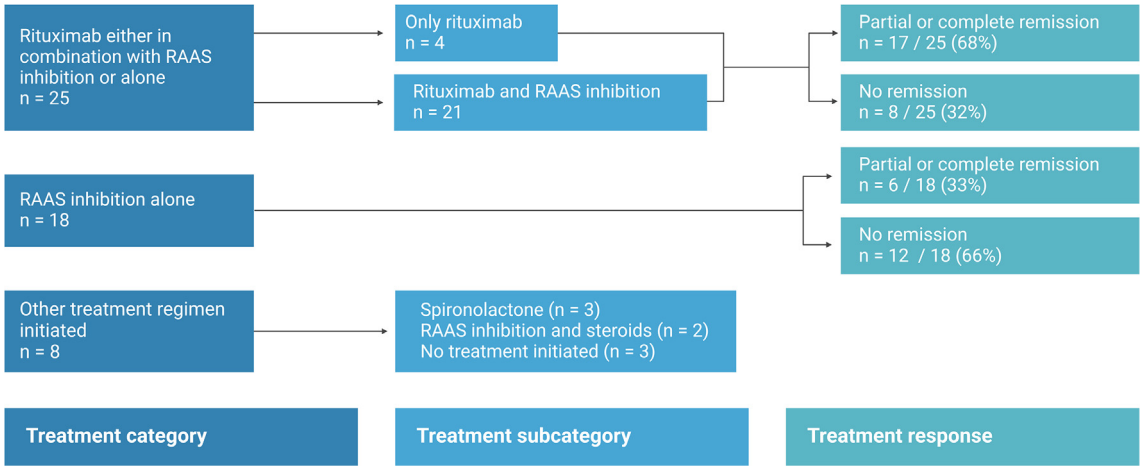

Figure 4. Initiated treatment regimens in patients with MN posttransplantation. MN, membranous nephropathy; RAAS, renin-angiotensin-aldosterone system. This figure was created with BioRender.com.

development of MN months to years before clinical disease, and trends in anti-PLA2R antibody titers correlate with proteinuria. However, reports describing the use of anti-PLA2R antibody measurement pre- and posttransplant are more limited, with only few small studies indicating that it could aid in the prediction and detection of recurrence.[11,30,39] Our results support and expand these initial findings, as they indicate a strong correlation between the presence of serum anti-PLA2R antibodies prior to transplant and MN recurrence posttransplant. Furthermore, our findings highlight the importance of anti-PLA2R antibody levels, as patients with high levels (>150 RU/mL) shortly before transplantation are prone to earlier recurrence, suggesting that titers can be used to stratify the risk of recurrence. Our cutoff of 150 RU/mL is aligned with the 2021 Kidney Disease: Improving Global Outcomes guidelines, which state that an anti-PLA2R antibody level above 150 RU/mL is suggested as a clinical criterion for a high risk of progressive kidney function loss in MN in native kidney disease.[24] In sum, our data support the utility of measuring serum anti-PLA2R antibody levels in MN patients on the transplant waitlist to establish baseline values. In patients with highly elevated pretransplant serum anti-PLA2R antibody titers, further studies are needed to define if a pre-emptive B cell depletion approach is warranted or closer surveillance with early treatment is recommended to minimize the potential impact of MN recurrence.[12]

In recent years, multiple other antibody targets have been identified in MN including THSD7A, neural epidermal growth factor-like 1 protein, and semaphorin 3B, among others.[40-50] The role of different autoantibodies in MN recurrence has not been systemically assessed posttransplantation. Our study provided an initial picture of the dominance of anti-PLA2R antibodies compared to anti-THSD7A antibodies in MN recurrence. Nonetheless, a larger study assessing all potential autoantibodies previously identified as drivers of MN is needed for a more detailed understanding of their role in MN recurrence.

The management of MN recurrence is largely empirical and draws heavily from clinical trials conducted for primary MN patients. Most patients with MN recurrence in our study received RAAS inhibition. Notably, those who were treated with rituximab exhibited a higher rate of proteinuria remission, supporting the use of this treatment approach for patients with MN recurrence, regardless of their clinical phenotype. Studies conducted prior to the identification of serum anti-podocyte antibodies and before the introduction of rituximab therapy demonstrated the notable influence of posttransplant MN on graft survival.[15-17] In our study, which included patients transplanted from 2005 onwards, most participants received RAAS inhibitors and/or rituximab, and we observed high remission rates after administration of rituximab. This is likely the reason why MN recurrence did not impact graft survival in our study.

Certain limitations should be considered when interpreting our data. Despite having one of the largest cohorts to date (Supplementary Table 1), our sample size is still relatively small, which may affect the statistical power of our analysis. Furthermore, the retrospective design of the study presents inherent limitations, including the possibility of selection bias, as patients were not randomly assigned to treatment groups. The imputation of missing data and adjustment of confounders could also introduce bias. Additionally, as only 2 centers performed protocol biopsies, it may be that not all patients with MN recurrence were captured. Lastly, the absence of kidney biopsy PLA2R immunohistochemistry staining could introduce underreporting bias in assessing the correlation between anti-PLA2R antibodies and recurrence. These caveats should be taken into consideration when interpreting our findings, and future studies should aim to address these limitations to improve the reliability of the results. Nonetheless, our study provides a multicenter, real-life picture of MN recurrence, including management and outcomes.

In summary, MN recurs in approximately one-third of transplant patients. The presence of serum anti-PLA2R antibodies before transplant are highly predictive of recurrence, underscoring the need for close monitoring and tailored therapeutic interventions for MN transplant candidates. Patients with MN recurrence receiving rituximab have a high rate of treatment response, with minimal impact on medium-term graft survival.

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Declaration of competing interest

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Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2024.01.036.

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