Original Article

Renal Phospholipase A2 Receptor and the Clinical Features of Idiopathic Membranous Nephropathy

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Abstract

Background: According to the renal phospholipase A2 receptor (PLA2R) immunohistochemistry, idiopathic membranous nephropathy (iMN) could be categorized into PLA2R-associated and non-PLA2R-associated iMN. This study aimed to examine whether the non-PLA2R-associated iMN had any difference in clinical features compared with PLA2R-associated iMN.

Methods: A total of 231 adult patients diagnosed as iMN were recruited to this retrospective study. Renal PLA2R expression was examined by immunofluorescence. Among these patients, 186 (80.5%) with complete baseline clinical data were used for further study. Urinary protein excretion, serum albumin, and creatinine were analyzed. For those patients with follow-up longer than 1 year, the relationship between PLA2R and response to immunosuppressants were analyzed. The *t*-test was used for parametric analysis and the Mann-Whitney *U*-test was used for nonparametric analysis. Categorical variables were described as frequencies or percentages, and the data were analyzed with Pearson's Chi-square test or Fisher's exact test.

Results: Of the 231 iMN patients, 189 showed renal detectable PLA2R expression (81.8%). The baseline serum creatinine, serum albumin, and urine protein excretion were not significantly different between PLA2R-associated (n = 145) and non-PLA2R-associated iMN patients (n = 41). However, about 1/3 of the non-PLA2R-associated iMN had abnormal serological tests, significantly more common than PLA2R-associated iMN (31.7% vs. 8.3%, P = 0.000). The non-PLA2R-associated iMN had lower C4 levels compared with PLA2R-associated iMN (P = 0.004). The non-PLA2R-associated iMN patients also showed a better response to immunosuppressants (complete remission [CR] 42.9%; partial remission [PR] 14.3%) compared with PLA2R-associated iMN (CR 3.2%; PR 48.4%, P = 0.004) at the 3rd month.

Conclusions: There were no significant differences in serum creatinine, albumin, and urine protein excretion between PLA2R-associated and non-PLA2R-associated iMN, while the non-PLA2R-associated iMN patients showed more abnormal serological tests. The non-PLA2R-associated iMN seemed to respond more quickly to the immunosuppressive therapy compared with PLA2R-associated iMN.

Key words: Immunosuppressive Therapy; Membranous Nephropathy; Phospholipase A2 Receptor; Serology

Introduction

Membranous nephropathy (MN) is one of the major causes of nephrotic syndrome in adults. It is characterized morphologically by widespread subepithelial deposits in glomeruli.[1] About 20% of MN is associated with an underlying disease, such as autoimmune diseases, malignancies, infections, and drug exposures. If no secondary causes can be identified; the disease is classified as idiopathic. The clinical course of idiopathic membranous nephropathy (iMN) is heterogeneous, from the spontaneous remission of proteinuria to end-stage renal disease,[2,3] and the response to immunosuppressants is also variable.[4,5] The heterogeneity of iMN may lead to difficulties in clinical management, including whether immunosuppressants need to be used and when the treatment should be initiated.

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The discovery of an autoantibody against M-type phospholipase A2 receptor (PLA2R) on podocytes in approximately 70% patients with iMN makes a critical step forward to understanding the disease.[6] The antibody (PLA2R-Ab) in these patients is reported to be correlated with disease activity and long-term outcome,[7-10] and is suggested to be responsible for the

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disease development. Recently, an autoantibody against thrombospondin type 1 domain containing 7A has been identified in PLA2R-Ab negative patients, though it only accounts for 8–14% of the PLA2R negative patients.[11] However, still in <30% of iMN, no known antibody has been identified yet. Considering different offending autoantibodies may reflect different disease initiation and/or may have different disease pathophysiology because of different antigens affected, it will be interesting to know whether they may cause any differences in clinical pictures, which may be associated with the heterogeneity of iMN. Since serum PLA2R-Ab may turn negative in situations such as automatic remission or following treatment, kidney PLA2R expression is a more reliable marker for PLA2R-associated iMN. In the present study, we classified iMN as PLA2R-associated and non-PLA2R-associated iMN according to renal PLA2R positivity and examined their clinical pictures.

Methods

Patients and study design

A total of 231 paraffin-embedded renal tissue sections from patients with biopsy-proven iMN collected between June 2008 and August 2013 were examined for renal PLA2R expression. Patients with secondary forms of MN, including autoimmune diseases (lupus nephritis, Sjogren's syndrome, *etc*.), infection related MN (HBV-MN, HCV-MN, HIV-MN, and syphilis), and MN with malignancies or exposure to toxic agents, were excluded from the study. Of the included individuals, baseline clinical features at kidney biopsy were compared between patients with and without positive renal PLA2R expression, including urinary protein excretion, blood routine, urine routine, liver function, renal function, electrolytes, coagulation function, fasting blood glucose, blood lipid, urinary protein series, serology, serum complements, immunoglobulins, hepatitis A–E markers, tumor markers, and erythrocyte sedimentation rate. Of these patients, the proportions of receiving immunosuppressive therapy or supportive therapy were compared between PLA2R-associated and non-PLA2R-associated iMN patients whose clinical data were available after 1 year since the biopsy. Response to immunosuppressants at 3rd and 6th month after the start of immunosuppressive therapy was also compared in patients with data available at these time points. Data were analyzed on an intention-to-treat basis. Decisions on therapy were made by physicians independently without knowing the renal PLA2R positivity. Immunosuppressive therapy was commonly started in high-risk patients with severe nephrotic syndrome, proteinuria not responding to supportive therapy or deteriorated renal function. In this study, partial remission (PR) was defined as urinary protein excretion <3.5 g/day (urine protein-to-creatinine ratio [Upcr] <3500 mg/g) and a 50% or greater reduction from peak values. Complete remission (CR) was defined as urinary protein excretion <0.3 g/day (Upcr <300 mg/g). This study was approved by Huashan Hospital and Wuxi People's Hospital.

Staining of renal biopsies for phospholipase A2 receptor

PLA2R was examined in paraffin-embedded sections using rabbit polyclonal anti-PLA2R1 antibodies (Sigma, USA) at a dilution of 1:500 after microwaving at 100% power for a total of 18 min, followed by donkey anti-rabbit FITC IgG (Millipore, USA) at a dilution of 1:100. The stain was evaluated by immunofluorescence microscopy (Nikon ECLIPSE 80i, Japan). No PLA2R expression has been detected in the normal kidney. Positive PLA2R was characteristically exhibited as granular staining along the capillary loops in the glomeruli. Each case was run with a positive and a negative control.

Statistical analysis

The statistical analyses were conducted using SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA). As for the data description, continuous variables with symmetric distribution were presented as mean ± standard deviation (SD), while nonnormally distributed variables as medians (25–75% interquartile range). The *t*-test was used for parametric analysis and the Mann-Whitney *U*-test was used for nonparametric analysis. Categorical variables were described as frequencies or percentages, and the data were analyzed with Pearson's Chi-square test or Fisher's exact test. The differences were considered statistically significant with a $P < 0.05$.

Results

Renal phospholipase A2 receptor staining in patients with idiopathic membranous nephropathy

Two hundred and thirty-one paraffin-embedded renal tissue sections from patients with histology diagnosis of iMN were tested for PLA2R [Figure 1]. One hundred and eighty-nine (81.8%) of these individuals showed granular staining of PLA2R along the capillary loops in their glomeruli [Figure 2].

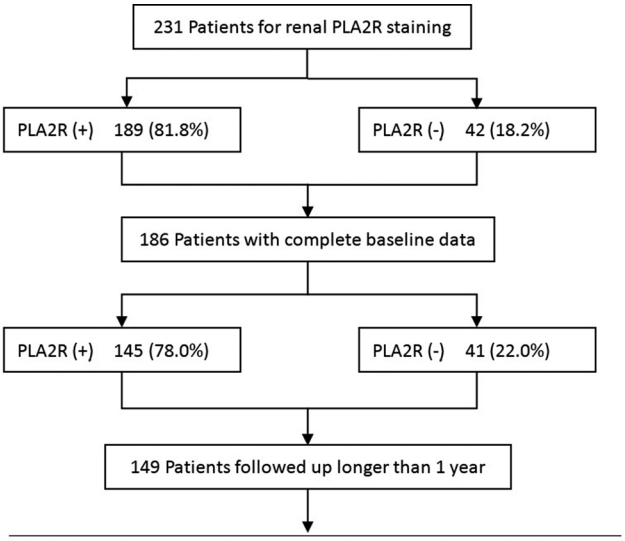
Clinical baseline characteristics

Baseline clinical data at kidney biopsy were available for 186 of these 231 patients, including 145 renal PLA2R positive patients and 41 negative patients as summarized in Table 1. There were no differences in age or gender between the two groups of patients. PLA2R-associated iMN patients did not differ from non-PLA2R-associated iMN patients in the baseline level of serum creatinine, serum albumin, and proteinuria [Figure 3]. However, PLA2R-associated iMN patients had higher levels of uric acid (0.379 ± 0.085 mmol/L vs. 0.332 ± 0.074 mmol/L, $P = 0.001$) and more severe hyperlipidemia ($P < 0.05$ for total cholesterol and triglycerides) than non-PLA2R-associated iMN patients. However, more serological abnormalities (13 of 41, 31.7%) had been detected non-PLA2R-associated iMN patients than in PLA2R-associated iMN patients (12 of 145, 8.3%, $P = 0.000$). Of the 13 non-PLA2R-associated iMN patients with abnormal serology, 10 had detectable titer of antinuclear antibodies, among them 4 with SSA+ and SSB+, 3 with SSA+, 1 with SSB+, 1 with dsDNA+ and SSA+, 1 with high ANA titer (1:3200); 3 patients have

Table 1: Clinical features of patients with PLA2R-associated and non-PLA2R-associated iMN at the time of kidney biopsy

Characteristics	Total	PLA2R (+)	PLA2R (−)	*P*
Number of patients	186 (100.0)	145 (78.0)	41 (22.0)	
Age (years)	54 (44–62)	54 (44–62)	54 (40–62)	0.342
Male	110 (59.1)	88 (60.7)	22 (53.7)	0.473
Serum creatinine (μmol/L)	73 (57–91)	74 (58–92)	68 (55–85)	0.356
Serum albumin (g/L)	23.3 ± 6.9	22.8 ± 6.1	25.0 ± 9.1	0.084
Proteinuria (g/24 h)	4.24 (2.56–5.89)	4.46 (2.75–5.85)	3.39 (1.78–6.02)	0.272
Hemoglobin (g/L)	131.0 ± 19.0	132.3 ± 17.7	126.5 ± 18.6	0.067
Blood urea nitrogen (mmol/L)	5.3 ± 2.8	5.4 ± 2.8	5.0 ± 2.6	0.432
Uric acid (mmol/L)	0.369 ± 0.085	0.379 ± 0.085	0.332 ± 0.074	0.001
Total cholesterol (mmol/L)	7.5 ± 2.4	7.6 ± 2.4	6.8 ± 2.3	0.041
Triglyceride (mmol/L)	2.0 (1.5–3.1)	2.2 (1.6–3.1)	1.7 (1.2–2.9)	0.04
Fasting blood glucose (mmol/L)	5.06 ± 0.78	5.1 ± 0.73	4.93 ± 0.92	0.221
Serum HBsAg (+)	4 (2.2)	3 (2.1)	1 (2.4)	1.000
Serology (+)*	25 (13.4)	12 (8.3)	13 (31.7)	<0.001
C3 (g/L)	1.08 ± 0.30	1.10 ± 0.30	1.02 ± 0.29	0.105
C4 (g/L)	0.25 (0.20–0.29)	0.26 (0.21–0.29)	0.21 (0.17–0.27)	0.004

Data are presented as mean ± SD or *n* (%) or median (range). *Serology (+) includes elevated titer (>1:100) of antinuclear antibodies, positivity of serum autoantibodies against dsDNA, ribose nuclear protein, anti-Sm, SS-A/Ro, SS-B/La, Scl-70, Jo-1, ribosomal P protein, Ro-52, centromere protein P, histone, proliferating cell nuclear antigen, nucleosome, mitochondrial, PM-Scl, MPO or PR3, and elevated rheumatoid factors. SD: Standard deviation; PLA2R: Phospholipase A2 receptor; iMN: Idiopathic membranous nephropathy.



Data available before and after	PLA2R (+)	PLA2R(-)	Total
3 months of immunosuppressive treatment	62	7	69
6 months of immunosuppressive treatment	60	6	66

Figure 1: Flow chart of patients included in the study. Paraffin-embedded renal tissue sections from 231 patients with diagnosis of iMN were stained for PLA2R using immunofluorescence. The baseline clinical features were compared. Among the 186 patients, 149 possessed medical record after 1 year following kidney biopsy and the information about treatment during the 1st year was collected and analyzed. For those whose clinical records of proteinuria before and after 3 or 6 months of immunosuppressive therapy were available, the remission rates were calculated and compared between patients with PLA2R-associated and non-PLA2R-associated iMN. iMN: Idiopathic membranous nephropathy; PLA2R: Phospholipase A2 receptor.

abnormalities other than positive ANA, including 1 with ACA+, 1 with M2+ and nRNP+, and 1 with elevated serum

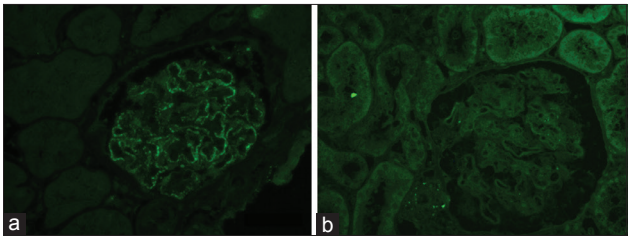


Figure 2: Staining for PLA2R in glomeruli of idiopathic membranous nephropathy. Immunofluorescence microscopy analysis of paraffin kidney biopsy specimens show: (a) granular staining for PLA2R along capillary loop in a PLA2R positive patient with iMN (one representative image from 189 patients; original magnification ×400). (b) PLA2R negative patient with iMN (one representative image from 42 patients; original magnification ×400). iMN: Idiopathic membranous nephropathy; PLA2R: Phospholipase A2 receptor.

RF. In contrast, in PLA2R-associated iMN, only 12 patients out of 145 were positive for of SSA, SSB, Ro52, PM-Scl, centromere protein P and M2 [Figure 4]. None of these patients had reached the diagnostic criteria of secondary causes for MN. In addition, C4 level in the serum of PLA2R-associated iMN patients was slightly lower than in non-PLA2R-associated iMN patients [0.21 (0.17–0.27) g/L vs. 0.26 (0.21–0.29) g/L, $P = 0.004$, Table 1].

Patient follow-up after biopsy

A total of 149 patients were followed up for more than 12 months after biopsy, including 128 positive and 21 negative in renal PLA2R staining. As shown in Figure 5, immunosuppressants were used in 80 (62.5%) PLA2R-associated patients and 11 (52.4%) non-PLA2R-associated patients during the 1st year after biopsy. Cyclophosphamide (CTX) plus glucocorticoids were used in 41 PLA2R positive and six negative patients.

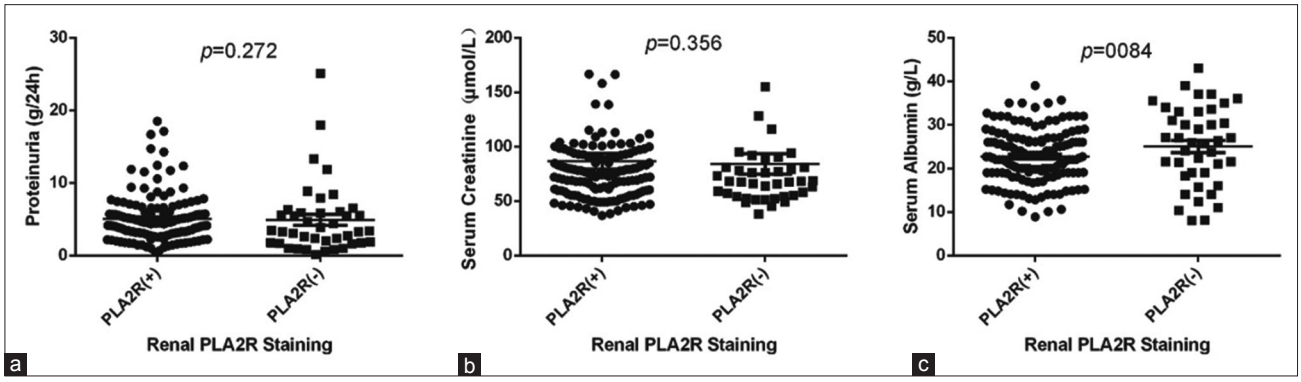


Figure 3: Levels of 24 h urine protein excretion (a), serum creatinine (b) and serum albumin (c) in 145 patients with PLA2R-associated and 41 non-PLA2R-associated iMN at the time of biopsy. iMN: Idiopathic membranous nephropathy; PLA2R: Phospholipase A2 receptor.

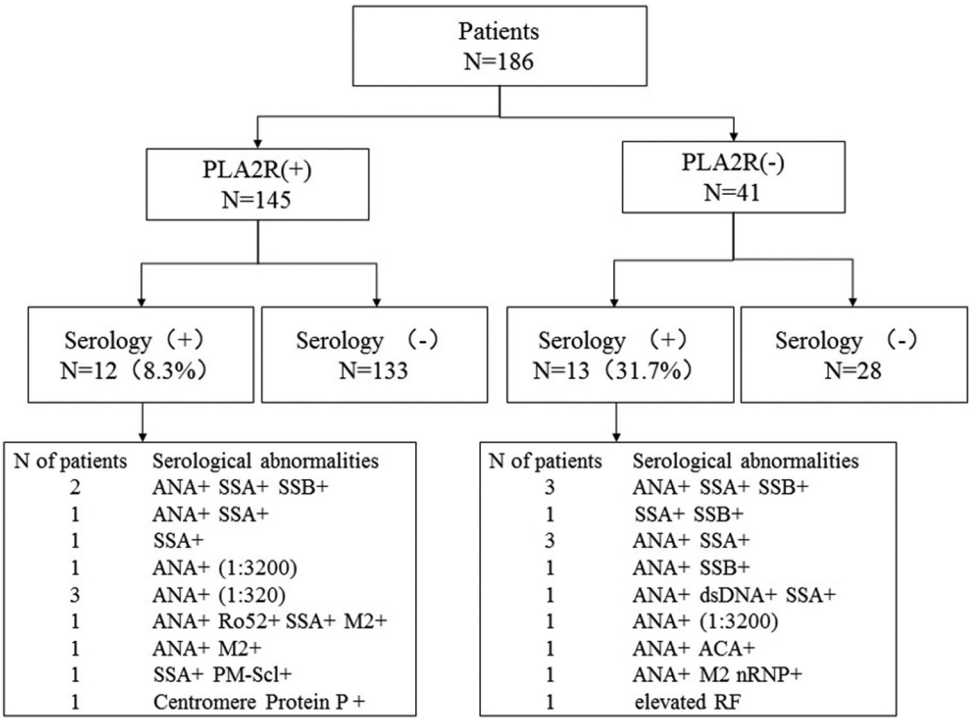


Figure 4: Serological test in patients with PLA2R-associated and non-PLA2R-associated iMN. ANA: Antinuclear antibodies; ACA: Anti-cardiolipin antibodies; nRNP: Nuclear ribonucleoprotein; RF: Rheumatoid factor; + : detectable autoantibodies in serum towards corresponding self-antigens. ANA were considered positive when titer is higher than 1:100. iMN: Idiopathic membranous nephropathy; PLA2R: Phospholipase A2 receptor.

Tacrolimus was used in 27 PLA2R positive and two negative patients, cyclosporin plus glucocorticoids in 14 positive and two negative patients. Four positive and two negative patients received mycophenolate mofetil (MMF), and one positive patient received glucocorticoids only. Tripterygium wilfordii was used in two positive patients. In nine positive patients and one negative patient, immunosuppression was switched from one agent to another [Table 2].

Responses to immunosuppressive therapy

The complete and PR rate of proteinuria after 3 and 6 months of immunosuppressive therapy were analyzed and compared between PLA2R-associated and non-PLA2R-associated iMN patients. The immunosuppressants were classified into 3 types: CTX, calcineurin inhibitors (CNIs, including cyclosporin A and tacrolimus) and others (including MMF, Tripterygium Wilfordii, and glucocorticoids only). Levels of proteinuria after 3 months of immunosuppressive therapy were available for 62 PLA2R positive and 7 negative patients. The average levels of proteinuria at biopsy were not significantly different between the two groups of patients (6.4 ± 4.0 vs. 6.5 ± 4.1, P = 0.948). There were no significant changes in proteinuria between the time of biopsy and the start of therapy. There was also no statistically significant difference in proteinuria among the different immunosuppressive treatment groups. Non-PLA2R-associated patients showed a better achievement of remissions (CR 42.9%, PR 14.3%) compared with PLA2R-associated patients (CR 3.2%, PR 48.4%, P = 0.004). No difference was observed when comparing the

responses of the two groups of patients to a single category of immunosuppressants at this time point [Table 3].

The data after 6 months of immunosuppressive therapy were available in 60 PLA2R-associated and 6 non-PLA2R-associated patients. The average levels of proteinuria at biopsy were not significantly different between the two groups of patients (6.5 ± 4.0 vs. 8.6 ± 6.4, $P = 0.248$). No significant difference in proteinuria among the different immunosuppressive treatment groups as well as between the time of biopsy and the start of therapy was noticed. The CR rate was still higher in renal PLA2R negative patients (CR 50.0%, PR 16.7%) than in positive patients (CR 13.3%, PR 43.3%) at this time point, however, the difference was no longer statistically significant ($P = 0.105$). Notably, a better response to CTX was observed in renal PLA2R negative patients (CR 2/3, 66.7%) than positive patients (CR 1/26, 3.8%; PR 15/26, 57.7%, $P = 0.009$) after 6 months of treatment. No difference in response to CNIs or other agents was detected between the two groups of patients [Table 4].

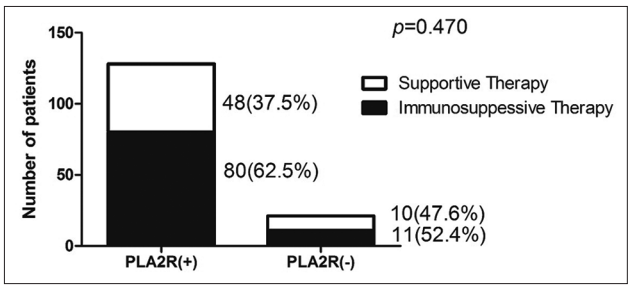


Figure 5: Treatments of patients with PLA2R-associated and non-PLA2R-associated iMN during the 1st year after kidney biopsy. Of 62.5% PLA2R-associated and 52.4% non-PLA2R-associated iMN patients received immunosuppressive therapy in their 1st year of follow-up. iMN: Idiopathic membranous nephropathy; PLA2R: Phospholipase A2 receptor.

Discussion

In this retrospective study in a Chinese cohort, we detected renal PLA2R in 81.8% patients with iMN, classified as PLA2R-associated iMN, using immunofluorescence. Our data confirmed that renal PLA2R negative iMN patients, classified as non-PLA2R-associated iMN, are similar in baseline levels of proteinuria, serum creatinine, and serum albumin with positive patients. However, non-PLA2R-associated iMN patients exhibit more serological abnormalities and better response to immunosuppressants during the initial stage of immunosuppressive therapy. These observations expand our understanding of clinical features of the two subgroups of iMN, and further indicate potential diversities in pathogenesis.

Recent studies show that patients with negative serum PLA2R-Ab are associated with the less severe clinical presentation and better response to treatment.[12] However, serum negative PLA2R-Ab patients may include non-PLA2R-associated patients and PLA2R-associated iMN patients with undetectable serum PLA2R-Ab (positive renal PLA2R). Our previous study, as well as others, shows that most of the patients who have positive serum PLA2R-Ab also have a detectable PLA2R expression in the kidney along capillary loops; while those who have a positive PLA2R in the kidney tissue do not necessarily have positive serum PLA2R-Ab. These data suggest that renal tissue PLA2R is a better marker than serum PLA2R-Ab to determine the involvement of PLA2R-Ab in the pathogenesis

Table 2: Treatment of patients with PLA2R-associated and non-PLA2R-associated iMN in the 1st year after kidney biopsy, *n* (%)

Items	Total	PLA2R (+)	PLA2R (−)	*P*
Number of patients	149 (100.0)	128 (85.9)	21 (14.1)	
Immunosuppressive treatment	91 (61.1)	80 (62.5)	11 (52.4)	0.47
Cyclophosphamide + glucocorticoids	47 (51.6)	41 (51.3)	6 (54.5)	
Tacrolimus (+glucocorticoids)	29 (31.9)	27 (33.8)	2 (18.2)	
Cyclosporin + glucocorticoids	16 (17.6)	14 (17.5)	2 (18.2)	
Other immunosuppressants*	9 (9.9)	7 (8.8)	2 (18.2)	

*Other immunosuppressants include mycophenolate mofetil, *Tripterygium Wilfordii* and glucocorticoids only. PLA2R: Phospholipase A2 receptor; iMN: Idiopathic membranous nephropathy.

Table 3: Remission rates of patients with PLA2R-associated and non-PLA2R-associated iMN after 3 months of immunosuppressive therapy, % (*n*/*N*)

Items	PLA2R (+)			PLA2R (−)			*P*
	CR	PR	Total	CR	PR	Total	
CTX	0 (0/27)	44.4 (12/27)	44.4	33.3 (1/3)	33.3 (1/3)	66.6	0.100
CNIs*	6.3 (2/32)	56.3 (18/32)	62.6	33.3 (1/3)	0 (0/3)	33.3	0.057
Others†	0 (0/3)	0 (0/3)	0	100.0 (1/1)	0 (0/1)	100.0	0.250
Total	3.2 (2/62)	48.4 (30/62)	51.6	42.9 (3/7)	14.3 (1/7)	57.2	0.004

*CNIs include cyclosporin A and tacrolimus; †Others include mycophenolate mofetil, *Tripterygium Wilfordii* and glucocorticoids only. CR: Complete remission; PR: Partial remission; PLA2R: Phospholipase A2 receptor; iMN: Idiopathic membranous nephropathy; CNIs: Calcineurin inhibitors; CTX: Cyclophosphamide.

Table 4: Remission rates of patients with PLA2R-associated and non-PLA2R-associated iMN after 6 months of immunosuppressive therapy, % (*n*/*N*)

Items	PLA2R (+)			PLA2R (−)			*P*
	CR	PR	Total	CR	PR	Total	
CTX	3.8 (1/26)	57.7 (15/26)	61.5	66.7 (2/3)	0	66.7	0.009
CNIs*	21.9 (7/32)	34.4 (11/32)	56.3	50.0 (1/2)	0	50.0	0.706
Others†	0 (0/2)	0 (0/2)	0	0	100 (1/1)	100.0	0.333
Total	13.3 (8/60)	43.3 (26/60)	56.6	50.0 (3/6)	16.7 (1/6)	66.7	0.105

*CNIs include cyclosporin A and tacrolimus; †Others include mycophenolate mofetil, *Tripterygium wilfordii* and glucocorticoids only. CR: Complete remission; PR: Partial remission; CNIs: Calcineurin inhibitors; PLA2R: Phospholipase A2 receptor; iMN: Idiopathic membranous nephropathy; CTX: Cyclophosphamide.

of MN.[7,13,14] We assessed the PLA2R antigen in biopsy specimens of patients with iMN in this Chinese cohort and found PLA2R expression in 81.8% patients. Compared with results obtained in Caucasian patients which showed a PLA2R positivity of approximately 69–75%,[1,7,13,14] ours is slightly higher and consistent with an earlier report of Chinese patients with untreated iMN.[15]

To compare the clinical features of PLA2R-associated and non-PLA2R-associated iMN, the patients with available baseline data were further investigated. Our data showed that PLA2R-associated and non-PLA2R-associated iMN patients had similar levels of disease severity at the time of biopsy. This is in line with early studies with smaller samples by Hoxha[7] and Svobodova.[13] However, our results also showed that non-PLA2R-associated iMN are more likely to have abnormal serology tests. The level of C4 is also lower in non-PLA2R-associated iMN patients. These observations point to the possibility that the non-PLA2R-associated iMN may be more closely related to the disorders of immune system. The autoantibodies that have detected in the sera of our patients are reported to be linked to several autoimmune diseases, including Sjogren's Syndrome, primary biliary cirrhosis, autoimmune hepatitis, systemic lupus erythematosus, antiphospholipid syndrome, mixed connective tissue disease, and rheumatoid arthritis. It is possible that the presentation as MN in these patients could be the early phase of systemic immunological disorders. MN is regarded as an organ-restricted autoimmune disease, and its interaction with the general immune system has recently been suggested. Previous findings have described that the genetic variations within the human leukocyte antigen (HLA) system are associated with the susceptibility to iMN.[16-18] These reports provide possible support for our speculation. The sequence or conformational changes in Class II molecules might alter peptide binding specificities, resulting in triggering self-antigen directed autoantibodies production. The genome-wide association study by Stanescu *et al*.[16] showed that a stronger association of iMN with HLA-DQA1, which encodes a part of the important antigen-presenting molecule, than with PLA2R. Lv *et al*.[17] implicated that MN might be much less common in Chinese population partially due to the lower frequency of risk alleles in HLA-DQA1 in this ancestry. It is conceivable that HLA-DQA1 alleles might facilitate autoantibody development targeting not only PLA2R but also other antigens. Our observations suggest a close and prolonged follow-up of clinical presentations and serological tests for non-PLA2R-associated iMN patients to recognize possible systemic autoimmune diseases. In addition, lower levels of uric acid and blood lipid were observed in non-PLA2R-associated patients. However, these results require confirmation, and the underlying mechanism needs to be investigated.

The use of immunosuppressants for iMN has been shown effective in inducing remission of proteinuria and maintaining renal function.[19-22] However, notable complications including infections, cardiovascular events, and malignancies may occur in treated patients.[23] The optimal strategy of immunosuppressive therapy for iMN remains controversial. Given the potential diverse pathogenesis of PLA2R-associated and non-PLA2R-associated iMN patients, we set out to determine whether the two groups of patients respond differently to immunosuppressants. In our cohort, the percentages of patients in whom immunosuppressive therapy initiated during the 1st year after biopsy were not different between PLA2R-associated and non-PLA2R-associated iMN. The decisions of treatment were made by physicians based on their individual clinical judgment, and it reflected the clinical status for these patients. Our study suggests that non-PLA2R-associated patients exhibit a better response to immunosuppressive therapy than PLA2R-associated after 3 months. The total rate of remission in non-PLA2R-associated patients is still higher after 6 months, although the difference is no longer statistically significant. Of note, the non-PLA2R-associated iMN is significantly correlated with higher CR rate after 6 months' use of CTX. These findings indicate a quicker achievement of clinical remission in non-PLA2R-associated patients in the initial stage of immunosuppressive therapy. However, as reported by Hoxha, PLA2R-Ab negative patients seem to have a higher percentage of spontaneous remission than positive patients, and the use of immunosuppressants did not alter the chance to reach remission in negative patients.[24] More studies are needed to determine the necessity and long-term efficiency of immunosuppressive therapy in treating PLA2R negative patients with iMN.

The main limitation of this retrospective study was that some clinical data were missing. Because of the missing

samples and relatively short follow-up duration, the analyses on long-term outcome, spontaneous remission, and relapse were limited. Therefore, additional study with randomized prospective design and more enrolled patients should be conducted to validate the established correlations and further investigate the outcome after 6 months of immunosuppression.

In conclusion, although the clinical presentation of non-PLA2R-associated iMN patients is similar to that of PLA2R-associated iMN patients, non-PLA2R-associated iMN has more serological abnormalities. The non-PLA2R-associated iMN seems to respond more quickly to the immunosuppressive therapy compared with PLA2R-associated iMN. Future studies are needed to determine the long-term clinical outcome in non-PLA2R-associated iMN patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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