

Original Article

Effects of the expression of serum PLA2R antibody on the diagnosis and immunological therapy of idiopathic membranous nephropathy

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Abstract: Objective: To explore the correlation between the expression of serum phospholipase A2 receptor (PLA2R) antibody and the diagnosis and immunological therapy of idiopathic membranous nephropathy (IMN). Methods: A total of 329 patients undergoing renal biopsy were enrolled and analyzed prospectively, including 142 patients with IMN and 187 patients with non-IMN, and 40 healthy individuals during the same period were also enrolled for control. The expression of serum PLA2R in all enrolled patients was determined, and the efficacy of immunological therapy on IMN patients with different expression of serum PLA2R antibody was evaluated. Results: Among the three groups, the highest serum PLA2R antibody titer was found in the IMN group, which was significantly different from that in the non-IMN group and the healthy group (both $P < 0.001$). The area under the receiver operating characteristic curve of serum PLA2R antibody in diagnosing IMN was 0.961, and when the cut-off value of serum PLA2R antibody was 29.09 RU/mL, its Youden index, specificity, and sensitivity were 0.908, 1 and 0.908, respectively. In addition, comparison of the efficacy between the two patient groups revealed that there were significant differences between the two groups in complete remission, partial remission, and non-remission (all $P < 0.05$). The effective rate of the negative group was significantly higher than that of the positive group (87.50% vs. 66.36%, $P < 0.05$), and the negative group showed higher serum albumin level and less 24 h-proteinuria than the positive group after treatment (both $P < 0.001$). Conclusion: Serum PLA2R antibody is highly expressed in IMN patients and enjoys a high diagnostic value. In addition, the effective treatment rate of the positive serum PLA2R antibody expression group was lower than that of the negative group, implying that the positive expression of serum PLA2R antibody suggested poor prognosis.

Keywords: Serum PLA2R antibody, idiopathic membranous nephropathy, diagnostic value, efficacy

Introduction

Membranous nephropathy (MN) is common pathological type in adult primary nephrotic syndrome, with an incidence of appropriate 25-40%, which can develop into an end-stage renal disease [1]. MN is classified into primary and secondary types according to its pathogenesis. Primary MN, clinically called idiopathic membranous nephropathy (IMN), has an incidence accounting for about 80% of the total number of MN and the incidence is increasing [2]. According to relevant Chinese statistical data, the incidence of IMN in China is on the rise, and accounts for 29.35% of the incidence of all primary glomerular diseases [3, 4]. In recent years, with the deepening of research, a

breakthrough progress has been achieved in the diagnosis of IMN patients, and the diagnostic value of phospholipase A2 receptor (PLA2R) antibody in IMN has been unanimously recognized [5]. Further studies have shown that the positive rate of serum PLA2R expression in IMN patients is high, so the determined serum PLA2R has become a specific clinical indicator for diagnosing IMN [6]. Moreover, some studies have also revealed that the positive rate of serum PLA2R expression in IMN patients is between 46% and 82%, and it is different in people from different areas [4, 7], and there is still a controversy over the optimal cut-off value of serum PLA2R for diagnosing IMN [8]. In addition, one foreign study for the clinical signifi-

cance of serum PLA2R detection has pointed out that a higher positive titer of serum PLA2R indicates poorer clinical efficacy, faster disease progression, and more unfavorable prognosis [9, 10]. However, one other foreign study has revealed that there was no significant difference between patients with positive expression of serum PLA2R and those with negative expression of it in disease severity and prognosis [11]. Based on the above studies, this study explored the diagnostic value of serum PLA2R for IMN patients, and further studied the correlation between different serum PLA2R expression and prognosis of IMN treatment.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of The First Affiliated Hospital of USTC. A total of 329 patients undergoing renal biopsy in the nephrology department of The First Affiliated Hospital of USTC from January 2017 to March 2019 were enrolled and analyzed prospectively, including 142 patients with IMN and 187 patients with non-IMN, and 40 healthy individuals during the same period were enrolled for control. All enrolled patients were between 18 and 75 years old, with an average age of 42.9 ± 12.0 years, and their family members signed informed consent forms.

Inclusion and exclusion criteria

The inclusion criteria of the patients: Patients meeting the pathologic diagnostic criteria of IMN; patients diagnosed with non-IMN based on the pathological diagnosis of nephropathy; patients between 18 and 75 years old; patients diagnosed with IMN for the first time; and patients who had not received treatment with hormone or immunosuppressant [12].

The exclusion criteria of them: Patients with severe heart or lung diseases; patients with hepatic or renal insufficiency; patients who had undergone repeated biopsy; patients with disease changes or unable to tolerate treatment during the treatment; pregnant women, and lactating women.

Methods

Determination of the expression of serum PLA2R antibody in enrolled patients

Fasting venous blood (5 mL) was sampled from each enrolled patient at 8 o'clock in the morn-

ing before renal biopsy, and fasting venous blood (5 mL) was also sampled from each healthy individual at 8 o'clock in the morning. The expression of serum PLA2R antibody in the sampled blood was determined using an enzyme linked immunosorbent assay (EIASA) with an EIASA kit (Euroimmun Company, Germany) in accordance with the kit instructions. The PLA2R expression >14 RU/mL was considered positive, otherwise, PLA2R expression was considered negative.

Determination of therapeutic regimen and efficacy for IMN patients

Therapeutic regimen for IMN patients:

According to the expression of PLA2R, patients were assigned to a positive group ($n=110$) and a negative group ($n=32$). Patients diagnosed with IMN ($n=142$) were treated with glucocorticoid prednisolone (Pharmaceuticals Sine, Shanghai, China) combined with cyclophosphamide (CTX) (Hengrui Pharmaceutical Co., Ltd., Jiangsu, China) as follows. Each patient of them was treated with prednisolone at 1 mg/kg/d for 8-12 weeks, and then treated with prednisolone at a dosage reduced by 5 mg/d every two weeks after the patient's proteinuria turned negative. After 4-8 weeks, the patient was treated with prednisolone at a dosage reduced by 2.5 mg/d every two weeks until the dosage was reduced to 10 mg/d, and then the patient was treated with prednisolone at 10 mg/d for 6 months. Additionally, each patient of them was treated with CTX at 0.3 g each time, once a week, for 3 consecutive weeks. After the 3 weeks, the treatment of CTX for the patient was stopped for one week. So the cumulative monthly dosage of CTX for each patient was 0.9 g. The patients were treated with CTX for 12 months in total.

Determination of efficacy: The efficacy on the patients was determined according to the efficacy criteria developed in the 2012 Kidney Disease: Improving Global Outcomes [13]. Complete remission: the urine protein was less than 0.3 g, and serum albumin reached the normal level. Partial remission: the urine protein was less than 3.5 g, and urine protein excretion decreased by more than 50%. Non-remission: the urine protein was continuously equal to 3.5 g or more, and there was hypoproteinemia. The effective rate = (the number of

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Table 1. CKD-EPI equation

Gender	Age	Ser ($\mu\text{mol/L}$) GFR (CKD-EPI) ($\text{mL}\cdot\text{min}^{-1}$ (1.73 m^2) ⁻¹)
Female	<62 (include 62)	$144^*(\text{Ser}/62)^{-0.329}*(0.993)^{\text{age}}$
	>62	$144^*(\text{Ser}/62)^{-1.209}*(0.993)^{\text{age}}$
Male	<80 (include 80)	$141^*(\text{Ser}/80)^{-0.411}*(0.993)^{\text{age}}$
	>80	$141^*(\text{Ser}/80)^{-1.209}*(0.993)^{\text{age}}$

Note: CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; GFR: glomerular filtration rate.

Table 2. Comparison of serum PLA2R antibody titer among the three groups ($\bar{x} \pm \text{sd}$)

Group	Serum PLA2R antibody expression (RU/mL)
IMN group (n=142)	225.92 ± 147.25
Non-IMN group (n=187)	$10.01 \pm 7.86^{***}$
Healthy group (n=40)	$8.23 \pm 5.21^{***}$
F	241.234
P	<0.001

Note: Compared with IMN group, ***P<0.001. IMN: idiopathic membranous nephropathy; PLA2R: phospholipase A2 receptor.

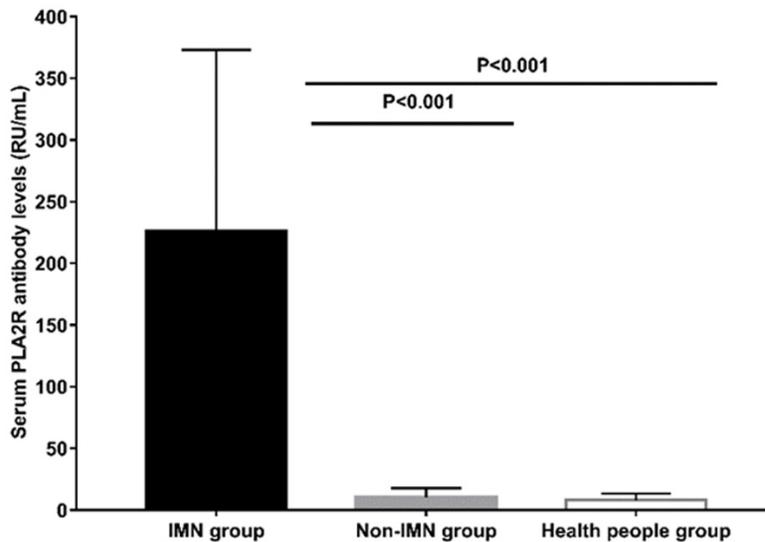


Figure 1. Comparison of serum PLA2R antibody expression among the three groups. IMN: idiopathic membranous nephropathy; PLA2R: phospholipase A2 receptor.

patients with complete remission + the number of patients with partial remission)/the total number of patients \times 100%.

Estimation of glomerular filtration rate: Fasting venous blood (5 mL) was sampled from each patient before treatment and at 12 months after treatment, and the serum creatinine and serum albumin levels, and 24 h-proteinuria

quantity of the sampled blood was determined, and then the glomerular filtration rate was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14]. See **Table 1.**

Statistical analysis

In this study, the data were analyzed using SPSS 17.0. Continuous variables were expressed as the mean \pm standard deviation ($\bar{x} \pm \text{sd}$) and those in normal distribution and homoscedasticity were analyzed using the independent-samples T test. One-way ANOVA was adopted for comparison among multiple groups to analyze if there was difference among them, and data with difference were subjected to post hoc pairwise comparison through bonferroni. Enumeration data were expressed as %, and analyzed using the Pearson chi-square test. In addition, receiver operating characteristic (ROC) curves were drawn using SPSS 17.0, and the area under the ROC (AUROC) curve was calculated, including 95% confidence interval. P<0.05 indicates a significant difference.

Results

Comparison of the expression of serum PLA2R antibody among the three groups

Among the three groups, the highest serum PLA2R antibody titer was found in the IMN group, which was significantly different from that in the non-IMN group and the healthy group (both P<0.001). See **Table 2** and **Figure 1.**

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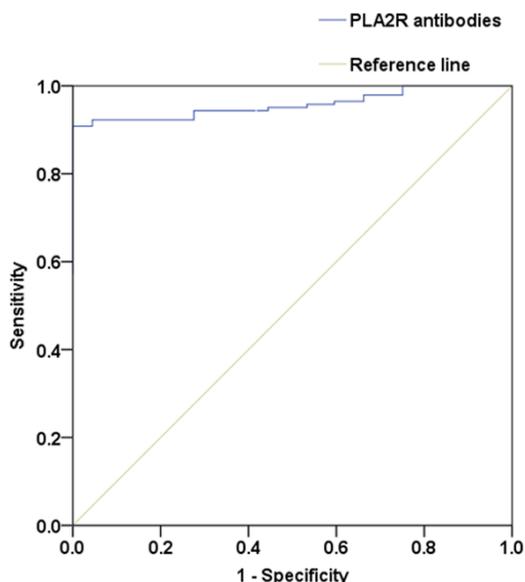


Figure 2. ROC curve of serum PLA2R antibody for IMN diagnosis. ROC: receiver operating characteristic; IMN: idiopathic membranous nephropathy; PLA2R: phospholipase A2 receptor.

ROC curve of serum PLA2R antibody for IMN diagnosis

The AUROC of serum PLA2R antibody for IMN diagnosis was 0.961, and when the cut-off value of serum PLA2R antibody was 29.09 RU/mL, its Youden index, specificity, and sensitivity were 0.908, 1 and 0.908, respectively. See **Figure 2**.

Comparison of general data between IMN patients with negative expression of serum PLA2R antibody and those with positive expression

Of the 142 IMN patients, 110 patients showed positive expression of serum PLA2R antibody, and the positive rate was 77.46%. In addition, there was no significant difference between IMN patients with negative expression of serum PLA2R antibody and those with positive expression in general data and baseline data, so the two kinds of patients were comparable ($P>0.05$). See **Table 3**.

Comparison of efficacy between IMN patients with negative expression of serum PLA2R and those with positive expression

Comparison of efficacy between the two patient groups revealed that there were differences

between the two groups in complete remission, partial remission, and non-remission ($P<0.05$). The effective rate of the negative group was significantly higher than that of the positive group (87.50% vs. 66.36%, $P<0.05$). See **Table 4**.

Comparison of relevant indexes between the two patient groups before and after treatment

Before treatment, there was no difference between the two groups in serum albumin, 24 h-proteinuria, and estimated glomerular filtration rate (eGFR) level (all $P>0.05$), while after treatment, the negative group showed higher serum albumin level and lower 24 h-proteinuria protein quantity than the positive group after treatment (both $P<0.001$), but there was no difference between them in eGFR ($P>0.05$). In addition, the difference of serum albumin level and 24 h-proteinuria quantity in the negative group before and after treatment was significantly higher than that in the positive group before and after treatment ($P<0.001$). See **Table 5**.

Discussion

IMN is a glomerular podocyte disease and belongs to an autoimmune disease. As the main target antigen on the surface of podocytes is PLA2R, if PLA2R antibody increases in human serum, it can bind to the PLA2R target antigen on the surface of podocytes to form an immune complex, which can activate complement to further form a membrane attack complex and damage podocytes [15]. Therefore, PLA2R antibody becomes a specific indicator for diagnosing IMN. Some studies have revealed that the expression of serum PLA2R antibody in IMN patients is strongly positive [16]. In this study, it was also found that the expression of serum PLA2R antibody in IMN patients was significantly higher than that in patients with other types of kidney diseases and healthy individuals, which was consistent with the above research results. However, there are regional differences in the positive rate of PLA2R antibody expression in the serum of IMN patients, so the optimal cutoff value of serum PLA2R antibody is controversial [4, 7, 8]. Previous studies have revealed that serum PLA2R antibody shows the best sensitivity and specificity

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Table 3. Comparison of general and baseline data ($\bar{x} \pm sd$, n)

Program	Positive group (n=110)	Negative group (n=32)	χ^2/t	P
Gender (male/female)	65/45	21/11	0.443	0.506
Ages (years)	40.7±14.0	40.8±13.5	0.041	0.968
Systolic pressure (mmHg)	142.18±7.19	142.05±8.20	0.072	0.943
Diastolic pressure (mmHg)	88.18±7.19	88.20±7.82	0.015	0.988
Triglyceride (mmol/L)	1.77±0.64	1.78±0.64	0.052	0.958
Total cholesterol (mmol/L)	5.56±0.76	5.60±0.78	0.217	0.829
High-density lipoprotein (mmol/L)	1.07±0.35	1.11±0.33	0.624	0.534
Low density lipoprotein (mmol/L)	3.82±0.84	3.95±0.68	0.759	0.450
Hemoglobin (g/L)	132.52±10.46	133.45±9.73	0.409	0.683
Serum albumin (g/L)	21.78±9.76	21.81±9.86	0.033	0.974
Body mass index (kg/m ²)	24.07±1.80	24.14±2.50	0.138	0.890
Blood glucose (mmol/L)	5.86±0.42	5.87±0.42	0.027	0.979
Urea nitrogen (mmol/L)	4.89±1.56	4.92±1.76	0.052	0.958
Serum creatinine (μmol/L)	60.22±10.89	61.29±11.29	0.101	0.920
24 h proteinuria (g/24 h)	6.95±9.29	7.12±8.45	0.562	0.613
eGFR (mL/(min·1.73 m ²))	91.23±16.34	92.34±18.02	0.723	0.456

Note: eGFR: estimated glomerular filtration rate.

Table 4. Comparison of efficacy between IMN patients with negative expression of serum PLA2R and those with positive expression (n (%))

Group	Positive group (n=110)	Negative group (n=32)	χ^2	P
Efficacy			6.179	0.046
Complete remission	35 (31.82)	16 (50.00)		
Partial remission	38 (34.54)	12 (37.50)		
Non-remission	37 (33.64)	4 (12.50)		
Total efficiency (%)	73 (66.36)	28 (87.50)	5.392	0.020

Note: IMN: idiopathic membranous nephropathy; PLA2R: phospholipase A2 receptor.

when its level is 20 RU/mL, and further studies have found that when the cutoff value of serum PLA2R antibody is lowered to 2.0 RU/mL, the serum PLA2R antibody shows a significantly increased sensitivity and a specificity close to 20 RU/mL [17, 18]. In addition, one other study has pointed out that the cutoff value of serum PLA2R antibody should be 2.6 RU/mL, because at this time, the sensitivity and specificity of serum PLA2R antibody can reach 91.7% and 86.5%, respectively [19]. In this study, when the cutoff value of serum PLA2R antibody was 29.09 RU/mL, its Youden index, specificity, and sensitivity were 0.908, 1, and 0.908, respectively, which was different from the above results and may be related to the difference in

the expression of serum PLA2R antibody in people from different regions.

One previous study has concluded that high expression of serum PLA2R antibody has an impact on the prognosis of IMN patients, and indicates poor prognosis [20]. In addition, some studies have determined the expression of serum PLA2R antibody, and have regarded it as an indicator for

reexamination of IMN patients after renal transplantation [21, 22]. Furthermore, some studies have reported that the complete remission rate of patients with high serum PLA2R antibody titer after immunological therapy was lower than that of patients with low serum PLA2R antibody titer after it [23]. Our study also revealed that the effective treatment rate of patients with positive expression of serum PLA2R antibody was lower than that of patients with negative expression, implying that high PLA2R antibody expression was positively correlated with poor efficacy, which was consistent with the above results. One study has found that the expression of PLA2R antibody in urine is related to proteinuria, disease severity, and

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Table 5. Comparison of relevant indexes between the two patient groups before and after treatment ($\bar{x} \pm sd$)

Program	Serum albumin (g/L)	24 h-proteinuria (g/24 h)	eGFR (mL/(min·1.73 m ²))
Before treatment			
Negative group	21.78±9.76	6.95±9.29	91.23±16.34
Positive group	21.81±9.86	7.12±8.45	92.34±18.02
t	0.033	0.562	0.723
P	0.974	0.613	0.456
After treatment			
Negative group	35.92±10.29*	2.01±3.84*	92.39±17.92
Positive group	29.92±9.02*	3.02±3.34*	93.23±16.29
t	9.361	5.203	0.575
P	<0.001	<0.001	0.672
Difference before and after treatment			
Negative group	14.23±3.22	4.28±3.23	0.88±0.64
Positive group	8.92±2.43	3.23±2.78	0.92±0.69
t	32.960	8.978	0.768
P	<0.001	<0.001	0.492

Note: eGFR: estimated glomerular filtration rate. Compared with the same group before treatment, *P<0.05.

the expression of serum PLA2R antibody [24], and one other study has revealed that patients with serum PLA2R antibody expression lower than 40 RU/mL and proteinuria quantity less than 4 g can benefit more from the treatment [25]. One study on disease progression has uncovered that patients with positive expression of PLA2R antibody are prone to renal dysfunction and poor prognosis [26]. In our study, after treatment, the negative group showed higher serum albumin level and less 24 h-proteinuria than the positive group, but there was no difference between them in eGFR, suggesting that patients with positive expression of serum PLA2R antibody had a lower remission after treatment, which resulted in a lower increase of serum albumin and a lower decrease of 24 h-proteinuria after treatment. However, there was no difference in eGFR between the two groups after treatment, which was inconsistent with the above results and may be related to the short follow-up time.

There are shortcomings in this study, including small sample size and short follow-up time. We can further expand the sample size to carry out a multi-center study and extend the follow-up time to observe the correlation between the expression of serum PLA2R antibody and prognosis.

To sum up, serum PLA2R antibody is highly expressed in IMN patients, and enjoys a high diagnostic value. In addition, the effective treatment rate of the positive serum PLA2R antibody expression group was lower than that of the negative group, implying that the positive expression of serum PLA2R antibody suggested poor prognosis.

Disclosure of conflict of interest

None.

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