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RESEARCH ARTICLE

Comparative analysis of membranous and other nephropathy subtypes and establishment of a diagnostic model

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Abstract **This study aimed to compare clinical features between membranous nephropathy (MN) and nonmembranous nephropathy (non-MN), to explore the clinically differential diagnosis of these two types, and to establish a diagnostic model of MN. After renal biopsy was obtained, 798 patients were divided into two groups based on their examination results: primary MN group (n = 248) and non-MN group (n = 550). Their data were statistically analyzed. Logistic regression analysis indicated that anti-PLA2R antibodies, IgG, and Cr were independently correlated with MN, and these three parameters were then used to establish the MN diagnostic model. A receiver operating characteristic (ROC) curve confirmed that our diagnostic model could distinguish between patients with and without MN, and their corresponding sensitivity, specificity, and AUC were 79.9%, 89.4%, and 0.917, respectively. The cutoff value for this combination in MN diagnosis was 0.34. The established diagnostic model that combined multiple factors shows a potential for broad clinical applications in differentiating primary MN from other kidney diseases and provides reliable evidence supporting the feasibility of noninvasive diagnosis of kidney diseases.**

Keywords multiparameter analysis; diagnosis; model; membranous nephropathy

Introduction

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults, and this condition accounts for 20% of nephrotic syndromes [1,2]. MN is also one of the main causes of chronic glomerular disease in China [3]. In the recent years, the incidence rate of MN has increased gradually and has become a leading cause of primary glomerular disease in Beijing, Shanghai, Nanjing, and other metropolises in this country; its rate ranks second to IgA nephropathy [4]. MN can be divided into idiopathic membranous nephropathy (IMN) and secondary membranous nephropathy (SMN); the former type accounts for about 2/3 to 4/5 of the total MN cases, but its etiology and pathogenesis are poorly understood [5,6]. IMN diagnosis depends on renal biopsy, and the pathological features of this disease, including the deposition of immune complexes in glomerular basement membrane (GMB) and its diffuse thickening [7]. The diagnostic measures for IMN should be able to rule out SMN [8]. The common causes of MN are a variety of immune and infectious diseases (e.g., systemic lupus erythematosus and hepatitis B virus [HBV]), drugs, toxins (e.g., nonsteroidal anti-inflammatory drugs and heavy metal poisoning), and tumors. However, in clinical practice, the diagnosis of MN is entirely dependent on the pathological examination of renal tissues; as such, the primary disease of SMN may not be diagnosed for a few months or even years, thereby affecting treatment plans and patients' prognosis [9]. Therefore, a sensitive and specific index should be determined for the clinical diagnosis and treatment of primary MN.

In this study, we retrospectively analyzed the data of patients with and without MN and investigated the clinical pathological features of the two groups to improve the diagnosis of MN.

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Materials and methods

Design

The following methods were carried out in accordance with the approved guidelines. All authors reviewed the results and approved the final version of the manuscript. This study was approved by the Ethics Committee of the Chinese PLA General Hospital.

All of the experimental protocols were approved by Chinese PLA General Hospital, written informed consent was obtained from each patient. The present research was a retrospective cohort study. The diagnosis of the patients was based on the pathological diagnosis of percutaneous renal biopsy under B ultrasound guidance. The patients pathologically diagnosed with primary MN were included in the MN group, whereas the individuals who did not have MN were assigned in the non-MN group. Primary MN was clinically confirmed without secondary causes, such as lupus, chronic infection, malignancy, or relevant drug exposures. Furthermore, they yielded negative serological testing results for antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and human immunodeficiency virus (HIV). The patients without complete clinical evaluations for secondary etiologies were excluded from the current study.

Patients

A total of 798 patients were confirmed with primary MN or non-MN (other nephropathy) via renal biopsies in Chinese PLA General Hospital from January 1, 2013, to March 15, 2016. These patients did not undergo any treatments before they were diagnosed. The complete history, clinical information, and pathological data of the enrolled patients were collected. In the MN group, all of the cases were pathologically diagnosed with primary MN. In the control group, 550 non-MN cases were included. A total of 273 IgAN cases, 97 minor glomerular abnormalities, 116 nephritis cases, and other cases, such as diabetic nephropathy, hypertensive nephropathy, obesity nephropathy, and minimal change nephrotic syndrome, were recorded.

Research data

Fasting blood samples were collected from the individuals in the initial diagnosis. All of the blood specimens were set for the following examinations: blood coagulation test, blood routine examination, clinical biochemistry test, immunoglobulin-complement test (BNII particular globin analyzer, Siemens), and tumor marker test (Roche Modular E170, Roche). General clinical data, including age, gender, hypertension, diabetes, systolic blood pressure, diastolic pressure, nephrotic syndrome (NS), and immunoglobulin A nephropathy (IgAN), were recorded. Laboratory examinations, including anti-PLA2R antibodies, ALT, AST, TP, ALB, and other specific parameters, are listed in Table 1. All of the parameters were recorded in the initial diagnosis.

Statistical analysis

In this experiment, all of the data were analyzed using SPSS 21 (SPSS Inc., Chicago, IL, USA). All of the measured data were tested for normality, and normal distribution was expressed as the mean ± standard deviation (SD). Student's t test was used to examine the difference between the two groups. Chi-square test was performed for categorical variable analysis. Logistic regression was applied to assess the related factors. $P < 0.05$ represented the statistical significance.

Results

Patient characteristics

Table 1 lists the tested biological parameters, including anti-PLA2R antibodies, ALT, AST, TP, ALB, TB, DB, ALP, GGT, GLU, UN, Cr, Ua, CH, TG, CK, LDH, HDL, LDL, TT, PT, FIB, D2, IgA, IgG, IgM, IgE, C3, C4, BMI, APTT, and PTA. Table 1 summarizes the reference ranges of the biological parameters. The differences in the general clinicopathological characteristics of the patients between the MN and non-MN groups were analyzed in our study. We found significant differences in age, hypertension, NS, and IgAN features between the two groups ($P < 0.05$), but no obvious differences were observed in gender or diabetes ($P > 0.05$; Table 2).

Differences in biological parameters between MN and non-MN groups

The differences in all of the 32 biological parameters were determined between the MN and non-MN groups. Table 3 shows the mean ± SD and significance analysis results for all of the parameters. Of the 32 parameters, TP, ALB, TB, DB, ALP, LDL, D2, and IgA significantly differed between the two groups ($P < 0.05$). In addition, 5 more parameters, namely, anti-PLA2R antibodies, UN, Cr, IgG, and IgE (Table 3), exhibited highly significant differences ($P < 0.01$) between the two groups. We selected these 5 parameters for further analysis.

Diagnostic performance of anti-PLA2R antibodies, UN, Cr, IgG, and IgE for MN

For anti-PLA2R antibodies, UN, Cr, IgG, and IgE, we determined their diagnostic value in MN through ROC analysis. The AUCs of anti-PLA2R antibodies, UN, Cr, IgG, and IgE were 0.854, 0.640, 0.730, 0.755, and 0.481, respectively. The results indicated that the diagnostic levels

Table 1 Biological parameters assessed in the present study

Index full name	Abbreviation	Reference range
Anti-phospholipase A2 receptor antibodies	Anti-PLA2R antibodies	0 – 20 RU/mL
Alanine aminotransferase	ALT	0 – 40 U/L
Aspartate aminotransferase	AST	0 – 40 U/L
Total protein	TP	55 – 80 g/L
Albumin	ALB	35 – 50 g/L
Total bilirubin	TB	0 – 21 μmol/L
Direct bilirubin	DB	0 – 8.6 μmol/L
Alkaline phosphatase	ALP	0 – 130 U/L
γ-Glutamyltransferase	GGT	0 – 50 U/L
Glucose	GLU	3.4 – 6.2 mmol/L
Urea nitrogen	UN	1.8 – 7.5 mmol/L
Creatinine	Cr	30 – 110 μmol/L
Uric acid	Ua	104 – 444 μmol/L
Total cholesterol	CH	3.1 – 5.7 mmol/L
Triglyceride	TG	0.4 – 1.7 mmol/L
Creatine kinase	CK	2 – 200 U/L
Lactate dehydrogenase	LDH	40 – 250 U/L
High-density lipoprotein cholesterol	HDL	1 – 1.6 mmol/L
Low-density lipoprotein cholesterol	LDL	0 – 3.4 mmol/L
Thrombin time	TT	16.0 – 18.0 s
Prothrombin time	PT	11.0 – 15.0 s
Plasma fibrinogen	FIB	200 – 400 mg/dL
D-dimer	D2	0.0 – 0.5 μg/L
Immunoglobulin A	IgA	70 – 180 mg/dL
Immunoglobulin G	IgG	700 – 1600 mg/dL
Immunoglobulin M	IgM	40 – 230 mg/dL
Immunoglobulin E	IgE	0 – 100 IU/mL
Complement 3	C3	90 – 180 mg/dL
Complement 4	C4	10 – 40 mg/dL
Body mass index	BMI	18.5 – 24.99
Activated partial thromboplastin time	APTT	30 – 45 s
Prothrombin activity	PTA	70% – 150%

Table 2 Differences in clinicopathological features between MN and non-MN groups

Clinicopathologic features	Number of cases (*n*, %)	MN group (*n*, %)	Non-MN group (*n*, %)	χ^2	*P* value
Total	798 (100)	248 (31.08)	550 (68.92)		
Age (year)					
<45	464 (58.15)	99 (39.91)	365 (66.36)	49.115	0.000
⩾45	334 (41.85)	149 (60.09)	185 (33.64)		
Hypertension					
Yes	370 (46.37)	91 (36.69)	279 (50.73)	13.537	0.000
No	428 (53.63)	157 (63.31)	271 (49.27)		
Gender					
Male	487 (61.03)	143 (57.66)	344 (65.55)	1.714	0.190
Female	311 (38.97)	105 (42.34)	206 (37.45)		
Diabetes					
Yes	115 (14.41)	30 (12.10)	85 (15.45)	1.562	0.211
No	683 (85.59)	218 (87.90)	465 (84.55)		

(*Continued*)

Clinicopathologic features	Number of cases (*n*, %)	MN group (*n*, %)	Non-MN group (*n*, %)	χ^2	*P* value
NS					
Yes	311 (38.97)	176 (70.97)	135 (24.55)	154.875	0.000
No	487 (61.03)	72 (29.03)	415 (75.45)		
IgAN					
Yes	280 (35.09)	7 (2.82)	273 (49.64)	164.466	0.000
No	518 (64.91)	241 (97.18)	277 (50.36)		

NS, nephrotic syndrome; IgAN, immunoglobulin A nephropathy.

Table 3 Differences in biological parameters between MN and non-MN groups

Parameter	Mean±SD	
	MN group	Non-MN group
BMI	25.89±4.69	25.22±4.23
Anti-PLA2R antibodies	97.56±183.78**	2.73±8.75
ALT (U/L)	21.05±16.64	23.69±25.27
AST (U/L)	18.53±9.06	19.13±12.13
TP (g/L)	49.36±9.94*	61.07±11.70
ALB (g/L)	26.98±6.99*	36.10±8.90
TB (μmol/L)	7.77±3.57*	8.96±4.63
DB (μmol/L)	1.49±1.15*	2.16±1.33
ALP (U/L)	58.95±16.55*	69.50±36.20
GGT (U/L)	35.42±48.55	33.97±55.55
GLU (mmol/L)	4.91±1.21	4.98±1.90
UN (mmol/L)	5.21±2.41**	6.83±3.97
Cr (μmol/L)	75.86±25.93**	115.20±75.14
Ua (μmol/L)	345.78±95.38	374.43±104.02
CH (mmol/L)	7.08±2.33	5.38±2.23
TG (mmol/L)	2.54±1.86	2.09±1.38
CK (U/L)	101.31±135.22	93.31±76.94
LDH (U/L)	194.79±58.53	179.47±59.33
HDL (mmol/L)	1.45±0.52	1.22±0.95
LDL (mmol/L)	4.86±2.02*	3.55±1.86
TT (s)	17.24±1.62	16.43±1.52
APTT	36.27±5.99	37.45±4.61
PT (s)	12.96±2.10	13.21±1.16
PTA	107.92±15.88	100.74±13.56
Serum fibrinogen	4.88±1.49	4.03±1.49
D2 (μg/L)	1.28±2.32*	0.86±1.48
IgA (mg/dL)	215.11±84.46*	276.09±123.41
IgG (mg/dL)	622.33±280.82**	935.78±380.02
IgM (mg/dL)	115.39±77.72	112.30±139.87
IgE (IU/mL)	124.77±187.59**	262.64±1071.52
C3 (mg/dL)	113.95±24.64	105.47±26.91
C4 (mg/dL)	27.99±9.68	25.91±9.40

Compared with the non-MN group, * $P<0.05$, ** $P<0.01$.

of anti-PLA2R antibodies, IgG, and Cr were higher in MN than in non-MN (Fig. 1). Therefore, we finally chose anti-PLA2R antibodies, IgG, and Cr for the next analysis.

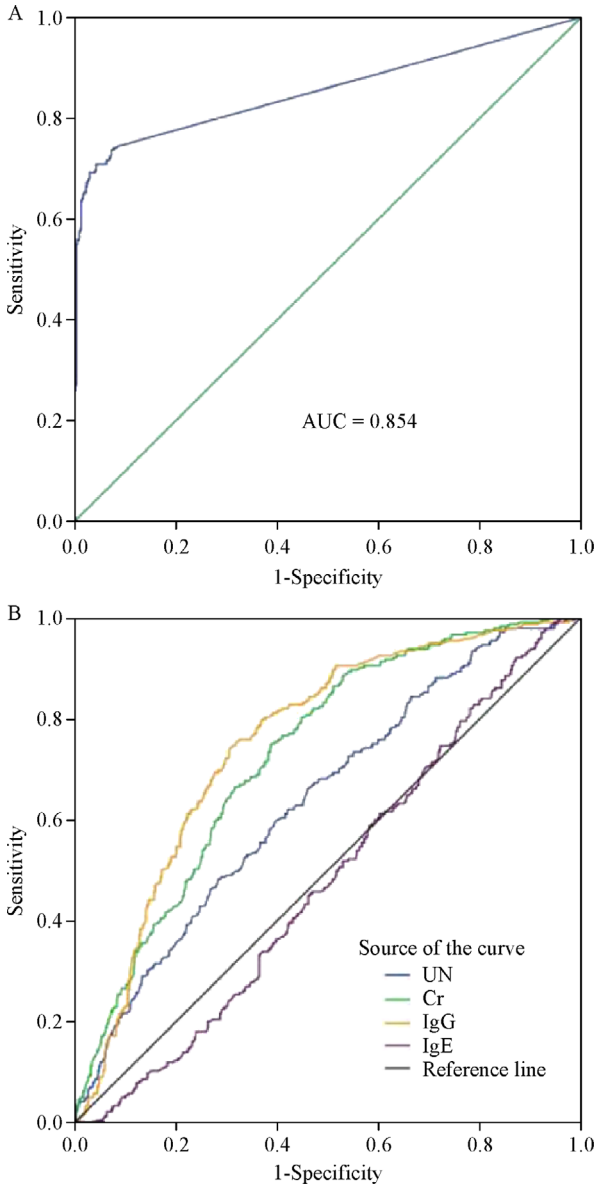

Fig. 1 Diagnostic values of anti-PLA2R antibodies, UN, Cr, IgG, and IgE were analyzed in 798 patients through ROC analysis. (A) The diagnostic value of anti-PLA2R antibodies; (B) the diagnostic values of UN, Cr, IgG, and IgE. The AUCs of anti-PLA2R antibodies, UN, Cr, IgG, and IgE were 0.854, 0.640, 0.730, 0.755, and 0.481, respectively.

Logistic regression analysis and diagnostic model establishment

Logistic regression analysis was performed to establish a diagnostic model that could be used to distinguish between MN and non-MN according to the three selected parameters, namely, anti-PLA2R antibodies, IgG, and Cr. The results demonstrated that anti-PLA2R antibodies, IgG, and Cr were independently correlated with MN (Table 4). The equation of MN diagnostic probability regression was established on the basis of the parameters of logistic regression analysis.

$$P_{MN} = \frac{e^{2.290+0.080\text{antiPLA2R}-0.030\text{Cr}-0.002\text{IgG}}}{1+e^{2.290+0.080\text{antiPLA2R}-0.030\text{Cr}-0.002\text{IgG}}}$$

The diagnostic model with these three parameters was evaluated using the MN diagnostic probability regression equation. The ROC curve confirmed that the "anti-PLA2R antibodies + IgG + Cr" combination could markedly distinguish patients with MN from patients without MN, and the sensitivity, specificity, and AUC value were 79.9%, 89.4%, and 0.917, respectively. The cutoff value for this combination in MN diagnosis was 0.34 (Fig. 2).

Discussion

MN is one of the most common nephrotic syndromes in adults, and it is characterized by the deposition of an epithelioid cell immune complex, leading to the thickening of the glomerular capillary basement membrane. MN can be divided into two types, namely, idiopathic and secondary [10–12]. As a common glomerular disease in China, MN accounts for 1/10 of primary glomerular disease [13]. The prognosis of this disease varies among different people. Some cases can spontaneously recover, whereas other cases may develop renal failure. Therefore, the prevention, diagnosis, and treatment of MN have abstracted more and more attention.

In the present study, a total of 798 patients received renal biopsy, and 248 of them accounting for 31.1% were diagnosed with MN. We analyzed the clinical features of the 798 patients and found that MN was significantly associated with age, hypertension, NS and IgAN ($P < 0.05$). Of 32 biological parameters chosen for the analysis of the differences between MN and non-MN groups, 8 showed significant differences between the two

Table 4 Parameters used in multivariate logistic regression analysis for diagnostic model establishment

	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP(B)	
							Lower	Upper
Anti-PLA2R antibodies	0.080	0.014	32.146	1	0.000	1.083	1.054	1.113
Cr	−0.030	0.005	38.813	1	0.000	0.971	0.962	0.980
IgG	−0.002	0.000	30.439	1	0.000	0.998	0.998	0.999
Constant	2.290	0.477	23.043	1	0.000	9.872		

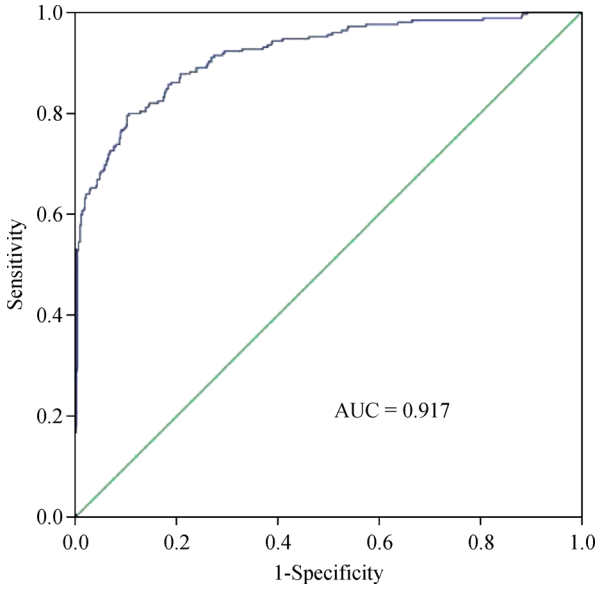

Fig. 2 Diagnostic value of the "anti-PLA2R antibodies + IgG + Cr" combination in MN was examined through ROC analysis. The ROC curve revealed that the "anti-PLA2R antibodies + IgG + Cr" combination could be used to distinguish between patients with MN and patients without MN, with an AUC value of 0.917, a cutoff value of 0.34, a sensitivity of 79.9%, and a specificity of 89.4%.

groups (all $P < 0.05$), and 5 additional manifested highly significant differences ($P < 0.01$). For these 5 parameters, we determined their diagnostic values in MN by adopting ROC analysis. The diagnostic model based on the three parameters, namely, anti-PLA2R antibodies, IgG, and Cr, yielded high diagnostic values. The diagnostic yield of the multiple parameters model was superior to the diagnostic yield based on one factor. The present study might provide a novel approach for the diagnosis of MN.

PLA2R is overexpressed in renal tissues among patients with IMN, whereas the PLA2R expression is negligible in normal kidney tissues and in patients with SMN [14]. Immune complexes formed by anti-PLA2R antibody and PLA2R antigen binding to GMB can cause injuries in podocytes, thickening of GMB, and changes in permeability, which may further lead to the IMN occurrence [15]. According to existing statistics, serum anti-PLA2R antibody has a positive rate of 50%–80% in patients with IMN but yields a negative rate in SMN cases; furthermore, few reports have discovered a 20% positive rate in patients with SMN. However, the positive rate is almost 0 in patients without MN and in the general population [16–18].

The antibody specificity of PLA2R is high, and its sensitivity is good. High PLA2R levels in serum indicate a high risk of the deterioration of kidney functions, and clinical remission is unlikely or may be achieved after a longer period, possibly accompanied by high recurrence rate [19]. In our study, anti-PLA2R antibody was significantly higher in the patients with MN than in the patients without MN and had a high diagnostic value. These results were similar to those in previous studies.

IgG is the main component of antibody in blood and extracellular fluid and implicated in immunological effects, such as the regulation of antibody-dependent cell-mediated cytotoxicity (ADCC) and anti-infection [20–22]. The expression of IgG is increased in patients with IMN. In our study, the IgG level was distinctly decreased in patients with MN compared with those in the non-MN group. Abnormal results might be attributed to IgAN cases in the non-MN group. IgAN is also characterized by high IgG levels [23]. Therefore, we did not observe the high IgG level in the MN group in the current research.

Creatinine (Cr) is an important metabolic product in human muscle [24,25]. In normal muscle tissues of the human body, the physiological functions of Cr include continuous Cr release into the body during irreversible nonenzymatic dehydration and excretion through the urinary system. Cr, a small molecule in the human body, can pass through the glomerulus, and only a small amount of Cr can be absorbed by tubules. Therefore, the detection of serum Cr can effectively reveal the clinical renal functions of patients [26], and the levels of serum Cr can be used as a marker of the severity of MN; changes in Cr levels predict the alterations in disease severity [27–29]. However, we found that Cr levels were not significantly upregulated in the MN group, and this abnormality might be attributed to the study subjects. In our study, a large proportion of IgAN cases were included in the non-MN group.

Several limitations were observed in the current study. First, the sample size was not large enough. Second, the model obtained in our study was not verified in another cohort. The diagnostic model was constructed on the basis of the subjects in our study, and whether the model could be applied to other MN cases remained unclear. Third, all of the cases in the MN group were diagnosed with primary MN. However, some of the individuals in the non-MN group were diagnosed with secondary nephropathy that might cause bias to the final results. Finally, whether the diagnostic model could be used for the diagnosis of secondary MN was still unknown. Some parameters that were reported to be associated with MN were not investigated in the current study. For instance, Dong *et al*. [30] revealed that IgG4 deposition is frequently observed in primary MN cases and can be employed as a biomarker to distinguish between primary MN and secondary MN. Proteinuria is also an important factor of MN surveillance. Monitoring the changes in proteinuria may be an efficient tool to diagnose MN [31]. These factors might help improve the diagnostic accuracy of the diagnostic model obtained in our study. Further well-designed investigations are required to verify and optimize

our diagnostic model and its application value.

In conclusion, the established diagnostic model that combined multiple factors can distinguish patients with MN from those without MN with high sensitivity and specificity.

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Compliance with ethics guidelines

Hanyu Zhu, Bo Fu, Yong Wang, Jing Gao, Qiuxia Han, Wenjia Geng, Xiaoli Yang, Guangyan Cai, Xiangmei Chen, and Dong Zhang declare that they have no conflict of interest. This study was approved by the Ethics Committee of the Chinese PLA General Hospital. Written informed consent was obtained from each patient.

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