https://www.scirp.org/journal/ns Natural Science, 2026, Vol. 18, (No. 1), pp: 1-11

Correlation between Pathological Staging of Membranous Nephropathy and PLA2R Antigen Expression and Its Predictive Value for Treatment Response

Fengling Lu*, Wen Huang*, Shengxue Liao, Taoxian Yang#, Jin Cen#

Department of Nephrology, Baise People's Hospital/Southwest Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China

Correspondence to: Taoxian Yang, 597534036@qq.com; Jin Cen, 1049466320@qq.com
Keywords: Membranous Nephropathy, Pathological Stage, PLA2R Antigen, Treatment Response, Comorbidity
Received: November 12, 2025 **Accepted:** January 19, 2026 **Published:** January 22, 2026

ABSTRACT

Objective: To investigate the clinical practice patterns of membranous nephropathy (MN) patients in our center, analyze the distribution of pathological stages and their associations with chronic pathological changes, immunofluorescence characteristics, and comorbidities, and provide a descriptive analysis of PLA2R detection in the very few cases where it was performed. **Methods:** Clinical data, pathological findings, and PLA2R detection results of 30 MN patients were retrospectively collected. The associations between pathological stages and chronic lesions or immunofluorescence features were analyzed, and the current status of PLA2R detection was described. **Results:** Among the 30 patients, pathological stages were: stage I, 1 case; stage II, 16 cases; stage III, 9 cases; and class V (lupus), 1 case; secondary MN accounted for 3 cases. The PLA2R detection rate was very low (6.7%, 2/30). Both positive cases were patients with stage III primary MN (positivity rate 22.2%, 2/9), while no positive expression was detected in stage I, II, or secondary MN patients. The later the pathological stage, the higher the incidence of glomerulosclerosis (stage III 77.8% vs stage II 31.3% vs stage I 0%) and moderate-to-severe tubulointerstitial injury (stage III 55.6% vs stage II 18.8% vs stage I 0%), with statistically significant differences ($P < 0.05$). Immunofluorescence in primary MN was predominantly characterized by IgG and C3 deposition, whereas secondary MN showed a "full-house" or multiple immune complex deposition pattern. Common comorbidities included hepatitis B virus infection/carrier status (4 cases), systemic lupus erythematosus (1 case), and hypertension (4 cases). **Conclusion:** In this cohort, PLA2R testing was not routinely performed. Its positivity in stage III primary MN is noteworthy, but due to the extremely low detection rate, its precise correlation

*Co-first authors.
#Co-corresponding authors.

with pathological stages and its predictive value for treatment response require confirmation through large-scale prospective studies. Pathological stage III can serve as a significant marker for chronic progression in MN. Immunofluorescence characteristics are valuable for differentiating primary from secondary MN, and comorbidity screening is crucial for clinical management. The findings suggest that future research should standardize PLA2R testing and systematically collect follow-up data to further explore its clinical significance.

1. INTRODUCTION

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults, classified into primary and secondary types with significant pathological heterogeneity [1]. Pathological staging serves as a crucial indicator for assessing disease progression and is closely related to patient prognosis. The M-type phospholipase A2 receptor (PLA2R), a key target antigen in primary MN, holds significant importance for diagnosis and treatment strategy formulation [2].

Recent studies suggest potential associations between PLA2R antigen expression and the pathological features and treatment response of MN, although relevant conclusions remain controversial [3]. Meanwhile, secondary MN is often triggered by factors such as hepatitis B virus infection and systemic lupus erythematosus (SLE), exhibiting distinct clinicopathological characteristics from primary MN, which complicates differential diagnosis [4]. Furthermore, MN patients frequently have various comorbidities that may influence disease progression and treatment efficacy [5].

This study retrospectively analyzed the clinicopathological data of 30 MN patients, aiming to systematically describe the clinicopathological characteristics, pathological stage distribution, patterns of chronic lesions, and comorbidity profiles of MN patients in our center, and to provide an observational description of PLA2R detection in the very few tested cases. Given the low PLA2R detection rate and lack of systematic follow-up data in this retrospective dataset, this study cannot analyze its correlation with pathological stages or its predictive value for treatment response, but it can provide baseline data and direction for designing subsequent prospective studies.

2. MATERIALS AND METHODS

2.1 Study Subjects

This retrospective study included inpatients diagnosed with membranous nephropathy (MN) via renal biopsy pathology in the Department of Nephrology, Baise People's Hospital, from January 1, 2021, to December 31, 2024. All diagnoses were based on standard renal biopsy findings from light microscopy, immunofluorescence, and/or electron microscopy. Inclusion criteria were: 1) Age ≥ 18 years; 2) Complete baseline clinical data (including sex, age, main clinical diagnosis at admission, major comorbidities); 3) Complete renal biopsy pathology report specifying pathological stage, immunofluorescence deposition characteristics, and status of key chronic lesions (glomerulosclerosis, tubulointerstitial injury). Exclusion criteria were: 1) Severely missing clinical or pathological data precluding accurate staging or classification; 2) Insufficient renal biopsy specimens for definitive pathological diagnosis. According to these criteria, 30 eligible MN patients were ultimately included. The study was approved by the Ethics Committee of Baise People's Hospital. Informed consent was waived due to the use of retrospective anonymized data analysis.

2.2. Research Methods

2.2.1. Data Collection

Two researchers independently reviewed and extracted data from the electronic medical record and pathology information systems, cross-checking to ensure accuracy. The collected data mainly comprised three categories: **1) Baseline Clinical Data:** Patient sex, age, main clinical diagnosis at admission (e.g.,

nephrotic syndrome, nephritic syndrome, proteinuria workup), and documented comorbidities, including but not limited to hepatitis B virus infection/carrier status (determined by positive serum HBsAg), systemic lupus erythematosus (clinical diagnosis based on ACR/SLICC criteria), hypertension, and type 2 diabetes. **2) Pathological Data: a) Pathological Stage:** Staging was based on electron microscopy descriptions in the original pathology report. Staging criteria followed classical standards: Stage I: Electron-dense deposits mainly subepithelial, with no significant or mild basement membrane thickening (generally <600nm) and no obvious spike formation. Stage II: Diffuse basement membrane thickening with distinct spike formation, electron-dense deposits located subepithelially or embedded within the thickened basement membrane. Stage III: Marked basement membrane thickening, spikes may fuse forming chain-like or beaded patterns, deposits may be enveloped by proliferated basement membrane-like material. Class V: Specifically refers to membranous lesions in lupus nephritis. **b) Immunofluorescence Characteristics:** The intensity (negative, ±, 1+, 2+, 3+) and pattern (granular, linear, etc.) of immunoglobulin (IgG, IgA, IgM) and complement (C3, C1q) deposits along the glomerular capillary loops were recorded. ③ **Chronic Lesions:** Information on the presence of global/segmental glomerulosclerosis and the extent of tubular atrophy/interstitial fibrosis/inflammatory cell infiltration was extracted from the pathology reports. Moderate-to-severe tubulointerstitial injury was defined as tubular atrophy and/or interstitial fibrosis involving >30% of the cortical area. **3) PLA2R Antigen Detection Results:** Whether the patient underwent renal tissue PLA2R immunohistochemical (IHC) testing and the results were recorded. The low PLA2R detection rate primarily stemmed from its non-routine status in retrospective data, being selectively ordered by physicians based on clinical judgment. The testing technology was available during the study period but not performed on all patients. The positivity criterion followed the original report, typically defined as ≥2+ granular staining along the glomerular capillary loops.

2.2.2. Diagnostic and Grouping Criteria

Based on the collected pathological and clinical data, all patients were grouped as follows:

1) Pathological Stage Grouping

The electron microscopy stage (I, II, III, V) from the pathology report was directly used as the grouping basis for subsequent comparisons.

2) PLA2R Expression Assessment

Only existing IHC results from original reports were recorded. Cases with reports stating "PLA2R (2+)", "PLA2R (3+)" or similar explicit positive descriptions were judged PLA2R positive; reports stating "negative", "not detected", or "(-)" were judged negative; cases without testing were recorded as "not tested".

3) Disease Type

Patients were classified as primary MN or secondary MN. Primary MN was defined as MN without evidence of underlying systemic diseases (e.g., SLE, hepatitis B, malignancy) or other secondary factors like drugs. Secondary MN was determined based on records of "secondary (etiology)" in the original medical records or specific clinical diagnoses (e.g., hepatitis B-related nephritis, lupus nephritis class V), with specific causes (hepatitis B, lupus, etc.) recorded.

4) Chronic Lesion Assessment

Information on the presence of "global/segmental glomerulosclerosis" and "moderate-to-severe tubular atrophy/interstitial fibrosis (atrophy > 30%)" was directly extracted from the text descriptions under "light microscopy findings" and "pathological diagnosis" in the pathology reports and converted into binary variables (yes/no) for statistical analysis.

2.2.3. IgG Subtype Staining Method

For the IgG subtype (IgG1 and IgG4) analysis mentioned in Case 29, the method was as follows: Paraffin sections of renal biopsy underwent antigen retrieval, followed by immunohistochemical staining (two-step method, DAB chromogen) using mouse anti-human IgG1 monoclonal antibody (clone HP6001) and mouse anti-human IgG4 monoclonal antibody (clone HP6025), respectively. Staining intensity was assessed using a semi-quantitative system (0 - 3+), with ≥2+ considered positive. This testing was performed at a

cooperative pathology laboratory (Guangxi Huayin Medical Testing Co., Ltd.) following its standardized operational procedures.

2.3. Statistical Methods

All statistical analyses were performed using SPSS software version 30.0. For continuous variables, normality tests were conducted first. Normally distributed data were expressed as mean ± standard deviation ($\bar{x} \pm s$), while non-normally distributed data were expressed as median (interquartile range) M(IQR). In this study, continuous variables like age were non-normally distributed and thus described using median (range). Categorical data were expressed as number (percentage) n (%). For comparing the incidence of chronic lesions (glomerulosclerosis, moderate-to-severe tubulointerstitial injury) among different pathological stage groups, the Pearson χ^2 test was used when the total sample size was ≥40 and all expected frequencies were ≥5; if any expected frequency was <5, Fisher's exact test was used. The PLA2R detection rate and positivity rate were presented only descriptively (number and percentage), as the number of tested cases was too small (only 2 cases) for inter-group comparative hypothesis testing. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

3. RESULTS

3.1. Patient Baseline Characteristics and Pathological Stage Distribution

This study ultimately included 30 renal biopsy-confirmed MN patients. Gender distribution was relatively balanced: 16 males (53.3%) and 14 females (46.7%). Age ranged from 24 to 65 years, with a median age of 46 years, indicating that MN was common in the young and middle-aged population at our center. Regarding pathological stage composition, stage II MN accounted for the highest proportion: 16 cases (53.3%), followed by stage III: 9 cases (30.0%). Stage I and lupus nephritis class V were relatively rare, each with 1 case (3.3% each). Secondary MN comprised 3 cases (10.0%), including 2 cases of hepatitis B virus-associated MN and 1 case of systemic lupus erythematosus-related membranous lupus nephritis (class V). Clinically, the vast majority of patients (21 cases, 70.0%) were admitted primarily with nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema, hyperlipidemia), while the remaining 9 cases (30.0%) presented with nephritic syndrome (hematuria, proteinuria, hypertension, etc.) or isolated proteinuria under investigation.

3.2. PLA2R Detection Status Description

Among all 30 MN patients, only 2 (6.7%) underwent renal tissue PLA2R antigen IHC testing during their management. Notably, both tested patients were positive (PLA2R 2+), and both belonged to the group of primary MN patients with pathological stage III (corresponding to serial numbers 28 and 29 in the original data table). Accordingly, the PLA2R positivity rate among stage III MN patients was 22.2% (2/9). Among patients in other pathological stages, including stage I (1 case), stage II (16 cases), and all secondary MN patients (3 cases), PLA2R testing was not performed; thus, no positive expression was observed in these subgroups. The overall cohort's PLA2R detection positivity rate was 6.7% (2/30). Due to the extremely low detection rate and minimal positive sample size (n = 2), this part of the data is presented descriptively only (detailed in **Table 1**). Conditions for inter-group statistical comparisons are not met, and any correlation analysis requires extremely cautious interpretation.

3.3. Relationship between Electron Microscopy Ultrastructural Features and Pathological Stage

Detailed electron microscopy descriptions suitable for analysis were available in the pathology reports of 19 patients (Stage I: 1 case; Stage II: 10 cases; Stage III: 8 cases). Analysis revealed that ultrastructural features under electron microscopy changed progressively with advancing pathological stage. In the single Stage I case, electron-dense deposits were primarily located on the subepithelial side of the glomerular

basement membrane (GBM), with mild GBM thickening (>600 nm) and no distinct spike formation. In Stage II, diffuse GBM thickening was observed (thickness range >800 - 1200 nm), with most cases showing clear spike formation. The location of electron-dense deposits was not only subepithelial but also, in some cases, embedded within the thickened GBM. In Stage III cases, GBM thickening was more significant (thickness range >900 - 1600 nm). Spike structures were not only more numerous and coarser but also, in some cases, exhibited characteristic chain-like or beaded patterns, reflecting the process of basement membrane material enveloping the deposits. Electron-dense deposits remained predominantly subepithelial and intramembranous but appeared denser and more extensive in Stage III. These characteristic changes (detailed in Table 2) were entirely consistent with classical MN pathological staging theory and confirmed the reliability of pathological stage interpretation in this study.

Table 1. Pathological staging and PLA2R antigen expression in membranous nephropathy.

Pathological Staging	Total Cases	Cases with PLA2R Detection	PLA2R-Positive Cases	PLA2R Positive Rate (%)
Stage I	1	0	0	0.0
Stage II	16	0	0	0.0
Stage III	9	2	2	22.2
Secondary MN	4	0	0	0.0
Total	30	2	2	6.7

Note: Due to the extremely low PLA2R detection rate (only 2 positive cases), the following analyses related to PLA2R are exploratory descriptions only, and conclusions should be interpreted with caution. *Includes the 1 case of class V lupus nephritis counted separately as stage V in the text, leading to a total of 4 for secondary MN here.

Table 2. Electron microscopic ultrastructural features and pathological staging in membranous nephropathy.

Pathological Staging	Cases (Electron Microscopy)	Location of Electron-Dense Deposits	Basement Membrane Thickness (nm)	Spike Structure
Stage I	1	Subepithelial	> 600	Indistinct
Stage II	10	Subepithelial, intra-basement membrane	> 800 - 1200	Visible/rare/abundant
Stage III	8	Subepithelial, intra-basement membrane	> 900 - 1600	Visible/abundant/chain-like/beaded

3.4. Relationship between Pathological Stage and Chronic Lesions

Chronic lesions are important indicators for assessing MN prognosis. This study found that the incidence of chronic lesions was significantly correlated with pathological stage. In the single Stage I patient, neither glomerulosclerosis nor moderate-to-severe tubulointerstitial injury was observed. Among the 16 Stage II patients, 5 (31.3%) exhibited global or segmental glomerulosclerosis, and 3 (18.8%) had moderate-

to-severe tubulointerstitial injury (atrophy area > 30%). In Stage III patients (9 cases), the incidence of both chronic lesions increased sharply, with 7 cases (77.8%) and 5 cases (55.6%) affected, respectively. χ^2 tests for inter-group comparison showed statistically significant differences among different pathological stage groups in the incidence of glomerulosclerosis ($\chi^2 = 10.893$, $P = 0.004$) and moderate-to-severe tubulointerstitial injury ($\chi^2 = 8.215$, $P = 0.016$) ($P < 0.05$), indicating that later pathological stages are associated with a higher risk of irreversible chronic kidney damage (detailed in Table 3).

Table 3. Pathological staging and severity of chronic lesions.

Pathological Staging	Total Cases	Global/Segmental Glomerulosclerosis (n, %)	Moderate-to-Severe Tubulointerstitial Injury (n, %)	χ^2 Value	P Value
Stage I	1	0 (0.0)	0 (0.0)	-	-
Stage II	16	5 (31.3)	3 (18.8)	10.893	0.004
Stage III	9	7 (77.8)	5 (55.6)	8.215	0.016

3.5. Comparison of Immunofluorescence Features between Primary and Secondary MN

Immunofluorescence analysis provided key evidence for differentiating primary from secondary MN. Among the 27 cases of primary MN in this study, the immunofluorescence pattern was relatively simple, predominantly characterized by granular deposition of IgG (mostly 3+) and C3 (mostly 2+) along the glomerular capillary loops. Some cases were accompanied by weakly positive IgM (1+), while IgA and C1q were mostly negative or only very weakly positive (±). This "IgG + C3" predominant pattern is typical of primary MN. In stark contrast, secondary MN showed: the single case of lupus nephritis class V exhibited the classic "full-house" pattern, with positivity for IgG, IgA, IgM, C3, and C1q, among which strong positivity for C1q (2+) is considered a characteristic marker for lupus nephritis. The two cases of hepatitis B virus-associated MN showed more complex polyclonal immune complex deposition, with multiple immunoglobulins positive on immunofluorescence and positive detection of hepatitis B virus antigens (HBeAg or HBcAg) on renal tissue sections, which is key for diagnosis (detailed in Table 4). These characteristic immunofluorescence "fingerprints" hold significant value for differential diagnosis.

Table 4. Immunofluorescence Features of Primary vs. Secondary Membranous Nephropathy.

Category	Total Cases	Typical Immunofluorescence Pattern	Key Differential Features
Primary MN	27	IgG (3+), C3 (2+), with/without IgM (1+)	Dominant IgG + C3; other immunoglobulins/complements negative/weakly positive
Lupus nephritis (Stage V)	1	IgG (2+), IgA (+/-), IgM (1+), C3 (1+), C1q (2+)	Strong C1q positivity (pathognomonic)
HBV-related MN	2	Multiple immune complex deposits	Positive HBV antigens in renal tissue (gold standard)

3.6. Patient Comorbidity Distribution

Analysis of comorbidities in the 30 MN patients revealed that MN often coexists with other systemic diseases. The most common comorbidity was hepatitis B virus infection or carrier status, involving 4 patients (13.3%). Among these, 2 were clearly diagnosed as hepatitis B virus-associated MN, while the other 2 had

primary MN with concurrent HBV infection. Hypertension was next, with 4 patients (13.3%) having a clear history of hypertension. Additionally, 1 patient (3.3%) had systemic lupus erythematosus (*i.e.*, class V lupus nephritis), and 1 patient (3.3%) had type 2 diabetes (this patient's pathology also suggested diabetic nephropathy changes). Notably, hepatitis B virus infection and systemic lupus erythematosus were the sole causes of secondary MN in this cohort. In other published Chinese MN cohort studies, the incidence of HBV-associated MN shows regional variation, roughly between 5% and 20%. The 13.3% HBV comorbidity rate in this cohort is similar to reports from some regions in southern China, suggesting the need for continued attention to HBV screening in local clinical practice. These data indicate the critical importance of conducting comprehensive screening for systemic diseases, especially viral hepatitis and autoimmune diseases, when clinically managing MN patients.

3.7. Special Case Analysis of PLA2R-Associated MN

Case 29 (Gan Xianwu) is a special case with significant teaching and illustrative value. The renal biopsy pathological diagnosis for this patient was: 1. Consistent with Stage III membranous nephropathy; 2. Consistent with IgA nephropathy. Immunohistochemistry showed PLA2R positivity (2+). Further IgG subtype analysis revealed strong positivity (3+) for both IgG1 and IgG4. This case highlights several key points: First, it confirms that PLA2R-positive primary MN can coexist with other glomerular diseases like IgA nephropathy, *i.e.*, "overlap nephritis". Second, the patient's IgG subtype pattern was not the classic IgG4 predominance typical of primary MN but showed strong positivity for both IgG1 and IgG4. This may reflect altered antibody subtype production within the complex immunological background of concurrent IgA nephropathy. Third, this case emphasizes the value of PLA2R testing in complex pathological diagnoses. It helped clarify the "primary" nature of the membranous lesion in this patient, thereby providing an important basis for formulating a combined treatment strategy (targeting both MN and IgA nephropathy).

4. DISCUSSION

This study systematically described the baseline characteristics, pathological stage distribution, patterns of chronic lesions, immunofluorescence patterns, and comorbidity profiles of MN patients in our center through retrospective analysis of clinicopathological data from 30 MN patients, and provided preliminary observations on PLA2R expression in the very few tested cases.

4.1. Analysis of Current Status of PLA2R Detection

PLA2R has been established as the core target antigen in primary MN, and its detection holds significant clinical value for disease classification, guiding treatment, and prognostic judgment [6].

By reviewing historical data, this study revealed that in the clinical practice of our center during the specific period studied, PLA2R testing was far from widespread, with an overall detection rate as low as 6.7% (2/30). This phenomenon may reflect a lack of awareness among clinicians about the importance of PLA2R testing, incomplete popularization of the testing technology, or its non-inclusion in routine testing protocols during earlier stages. Notably, within this limited tested sample, all positive results (2 cases) occurred in patients with stage III primary MN, accounting for 22.2% (2/9) of stage III patients. This observational finding might suggest a potential association between positive PLA2R expression and disease progression to a later pathological stage (III). Some previous studies have also reported that PLA2R-associated MN may exhibit certain unique clinicopathological features [7].

However, it is crucial to recognize clearly that this study is limited by the inherent defects of a retrospective design. The PLA2R testing itself suffered from severe selection bias and was not systematically performed on all patients. Based solely on two positive cases, we cannot conduct any statistically valid correlation analysis, let alone infer causality. Therefore, conclusions in this section regarding the association between PLA2R and pathological stage are extremely preliminary and exploratory. The core value of this result

lies in highlighting the necessity and urgency of routinely implementing PLA2R testing in clinical practice and providing preliminary clues and direction for future large-scale, prospective studies where all enrolled patients undergo systematic PLA2R testing. Subsequent research should focus on expanding sample sizes and dynamically observing the relationships between PLA2R titer changes and pathological stage evolution, treatment response, and long-term prognosis, based on standardized testing.

4.2. Relationship between Pathological Stage and Disease Chronicity

Pathological staging based on electron microscopy ultrastructural features is the gold standard for assessing the progression of MN lesions. The results of this study clearly show that as the pathological stage advances from I to III, the incidence of chronic lesion indicators reflecting irreversible kidney damage increases significantly. Specifically, the incidence of global or segmental glomerulosclerosis rose from 0% in Stage I to 31.3% in Stage II, and even reached 77.8% in Stage III. Similarly, the incidence of moderate-to-severe tubulointerstitial injury increased from 0% (Stage I) to 18.8% (Stage II) and 55.6% (Stage III), with statistically significant inter-group differences ($P < 0.05$). This trend is highly consistent with classical pathological understanding: early MN is characterized by immune complex deposition subepithelially and reactive GBM thickening, while persistent disease can gradually induce damage to intrinsic glomerular cells and matrix proliferation, ultimately leading to glomerulosclerosis and interstitial fibrosis [8].

The data from this study reinforce that pathological stage III is not only a marker of morphological changes in deposits under electron microscopy but also a critical turning point for MN entering a chronic progressive phase characterized by fibrosis. This suggests that clinicians should fully recognize that kidneys in patients diagnosed with stage III MN already have relatively severe chronic structural damage, and their prognosis may be relatively poorer [9].

Therefore, when formulating treatment plans, in addition to interventions targeting immune inflammation, greater emphasis should be placed on the early and aggressive use of drugs with potential anti-fibrotic effects (such as certain immunosuppressants or renin-angiotensin system blockers), along with enhanced comprehensive management of risk factors like blood pressure and proteinuria, aiming to maximally delay the progression of renal function decline.

4.3. Differential Diagnosis between Primary and Secondary MN

Accurately distinguishing primary from secondary MN is a prerequisite for formulating correct treatment plans, and renal tissue immunofluorescence examination plays an irreplaceable role in this process [10].

The analysis of immunofluorescence patterns in this study provides strong evidence for this. We found that primary MN overwhelmingly presents with a relatively "simple" immune complex deposition pattern: IgG (often predominantly the IgG4 subtype) accompanied by C3 in a granular pattern along the glomerular capillary loops, while other immunoglobulins (e.g., IgA, IgM) and complement components (e.g., C1q) are typically negative or only weakly positive. This pattern reflects an organ-specific autoimmune response against podocyte target antigens like PLA2R. In stark contrast, secondary MN displays complex and diverse immune deposition spectra. For example, the lupus nephritis (class V) case in this study exhibited the classic "full-house" pattern, with widespread positivity for IgG, IgA, IgM, C3, and C1q, among which strongly positive C1q is considered a highly characteristic marker for lupus nephritis. Hepatitis B virus-associated MN showed deposition of multiple immune complexes, accompanied by detectable hepatitis B virus antigens (e.g., HBsAg, HBeAg, HBcAg) within the renal tissue, which is the pathological gold standard for diagnosing this condition. These characteristic immunofluorescence "fingerprints" provide a direct basis for rapid differential diagnosis. The findings of this study suggest that in clinical work, when a pathology report shows non-typical "full-house" or multiple complex deposition patterns, clinicians should be highly vigilant for the possibility of systemic diseases and must immediately initiate corresponding serological screenings (e.g., autoantibody profiles, hepatitis B/C virus markers) to avoid misdiagnosing secondary MN as primary, which could lead to incorrect treatment approaches (e.g.,

treating lupus nephritis with therapies solely for primary MN while neglecting control of the underlying disease).

4.4. Impact of Comorbidities on MN Diagnosis and Treatment

MN does not exist in isolation as a kidney disease; its onset and progression are often intertwined with various systemic diseases. The comorbidity analysis in this study revealed this complex association. We found that hepatitis B virus infection/carrier status was one of the most common comorbidities in this cohort (13.3%, 4/30) and also the primary cause of secondary MN (2 cases of HBV-associated MN). Systemic lupus erythematosus (SLE) was another important secondary cause (1 case of class V LN). This distribution aligns with domestic and international epidemiological data, emphasizing the extreme importance of screening for viral hepatitis and autoimmune diseases in MN patients in China [11].

Beyond these direct causes of secondary MN, other comorbidities like hypertension (13.3%) and diabetes (3.3%) also warrant high attention. Hypertension and diabetes are not only common comorbidities in chronic kidney disease but are also independent risk factors for causing and accelerating kidney damage. The coexistence of hypertension or diabetes with MN may create a vicious cycle: on one hand, proteinuria and renal insufficiency caused by MN can worsen hypertension and glucose metabolism disorders; on the other hand, persistent hypertension and hyperglycemia can exacerbate intraglomerular hypertension, hyperfiltration, and oxidative stress, promoting the progression of glomerulosclerosis and interstitial fibrosis in MN patients, thereby offsetting the efficacy of specific immunosuppressive therapy and leading to poor treatment response or relapse. Therefore, the findings of this study strongly support the need for a "global perspective" in the clinical management of all newly diagnosed MN patients, involving systematic screening and assessment of comorbidities. The treatment strategy must be comprehensive: alongside immunomodulatory therapy targeting MN itself, strict and standardized management of hypertension (target blood pressure typically recommended < 130/80 mmHg), control of blood glucose (for diabetic patients), and active management of hepatitis B virus infection (timely antiviral therapy) are essential. This comprehensive management strategy is the cornerstone for improving the long-term prognosis of MN patients.

4.5. Special Circumstances in PLA2R-Associated MN

The special case in this study (Serial No. 29, Gan Xianwu) provides an excellent example for understanding the complexity of MN. This patient's pathology concurrently showed Stage III MN and IgA nephropathy, with a positive PLA2R test (2+). This case has multiple implications: First, it clearly confirms that PLA2R-positive MN (*i.e.*, primary MN) can coexist with other glomerular diseases (in this case, IgA nephropathy). This reminds us that pathological diagnosis of glomerular diseases is not always "either-or"; mixed or overlapping nephritis exists. Second, the IgG subtype analysis in this case showed strong positivity (3+) for both IgG1 and IgG4, which is not entirely consistent with the classic feature of primary MN where IgG4 deposition predominates. This difference may be attributed to the concurrent IgA nephropathy altering the local immune microenvironment or eliciting different helper T-cell responses, leading to changes in the antibody subtype profile. Finally, and most crucially in clinical terms, this case highlights the decisive value of PLA2R testing in the differential diagnosis of complex cases. Without PLA2R testing, this case might have been primarily considered as IgA nephropathy with atypical membranous changes, or it would have been difficult to clarify the nature of the MN component. The positive PLA2R result strongly supports the presence of a primary MN component [12].

This information is vital for treatment decisions: management for primary MN may need to consider regimens like rituximab or calcineurin inhibitors, while the management strategy for IgA nephropathy differs. Therefore, this case vividly illustrates that in the face of glomerular diseases with complex pathological presentations, proactive PLA2R testing (and other target antigen tests like THSD7A when necessary) can provide indispensable objective evidence for clarifying the disease's nature and formulating precise, individualized treatment plans.

5. CONCLUSION

Through retrospective analysis of 30 membranous nephropathy (MN) patients, this study clarified that MN patients in our center are predominantly in pathological stages II and III. The later the pathological stage (III), the significantly higher the incidence of glomerulosclerosis (77.8%) and moderate-to-severe tubulointerstitial injury (55.6%), confirming that pathological stage III is a key phase in the chronic progression of the disease. Immunofluorescence characteristics ("IgG + C3" simple deposition vs. "full-house"/multiple complex deposition) can effectively aid in differentiating primary from secondary MN. Hepatitis B virus infection/carrier status (13.3%) and systemic lupus erythematosus were the main causes of secondary MN. However, this study also exposed the limitations of retrospective data: the PLA2R antigen detection rate was extremely low (6.7%, 2/30). All positive cases were found in stage III primary MN, but due to the small sample size, definitive conclusions regarding its correlation with pathological stages or treatment response cannot be drawn. The core value of this study lies in clearly presenting the spectrum of pathological characteristics and comorbidity profiles of MN in current clinical practice and highlighting the importance of standardizing PLA2R testing and establishing systematic follow-up systems, providing baseline data and directional guidance for future prospective studies aimed at evaluating the clinical significance of PLA2R.

6. STUDY LIMITATIONS

This study has several limitations that must be fully considered when interpreting the conclusions: First, as a single-center, retrospective study, the sample size is relatively small (n = 30), and patients were from a single medical center in a specific region, potentially introducing selection bias and limiting the representativeness and generalizability of the findings. Second, and most critically, PLA2R testing was not a routine item in this cohort, resulting in an extremely low overall detection rate (6.7%) and only two positive cases. This non-systematic testing led to severe sample bias and information loss, preventing us from performing any statistically valid correlation analysis or regression modeling between PLA2R expression and pathological stages or clinical parameters. Any statements regarding PLA2R can only be descriptive and preliminary observations. Third, due to the retrospective nature of medical record analysis, systematic and standardized follow-up data were generally lacking in the original records. In particular, detailed records of treatment regimens, and dynamic data on proteinuria, serum albumin, and estimated glomerular filtration rate (eGFR) before and after treatment were severely missing. This directly resulted in the study being completely unable to address the initially set core objective of "analyzing the predictive value of PLA2R for treatment response", creating a disconnect between the research aims and the available data. Fourth, immunofluorescence and IgG subtype data were incomplete for some cases (marked as "-" in the original data table), which may affect the comprehensiveness and accuracy of the immunofluorescence pattern analysis. Future research should strive to overcome these limitations by adopting a prospective design, routinely performing a series of target antigen tests including PLA2R on all enrolled patients, and establishing a comprehensive clinical follow-up database to obtain more reliable and clinically meaningful conclusions.

FUNDING

This study was funded by the Scientific Research and Technology Development Program of Baise, Guangxi (Grant No.: Bake 202537026).

ACKNOWLEDGMENTS

We thank all the medical staff of the Department of Nephrology at Baise People's Hospital for their support and assistance during clinical data collection and original case compilation. We also thank the pathology team at Guangxi Huayin Medical Testing Co., Ltd., for providing professional diagnostic expertise

in pathological staging, immunofluorescence, and electron microscopy detection.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

REFERENCES

1. Wang, H.Y. (2021) Nephrology. 4th Edition, People's Medical Publishing House, 896-903. (In Chinese)
2. Beck Jr., L.H., Bonegio, R.G., Lambeau, G., *et al.* (2009) M-Type Phospholipase A2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy. *New England Journal of Medicine*, **361**, 11-21. https://doi.org/10.1056/nejmoa0810457
3. Chinese Society of Nephrology (2021) Guidelines for the Diagnosis and Treatment of Membranous Nephropathy (2021 Edition). *Chinese Journal of Nephrology*, **37**, 949-986. (In Chinese)
4. Li, X.M. and Zhang, H. (2020) Etiology and Advances in Diagnosis and Treatment of Secondary Membranous Nephropathy. *Chinese Journal of Internal Medicine*, **59**, 665-668. (In Chinese)
5. Chen, X.M. (2023) Guidelines for the Diagnosis and Treatment of Hypertension in Adult Chronic Kidney Disease in China (2023 Edition). *Chinese Journal of Nephrology*, **39**, 369-414. (In Chinese)
6. Ronco, P. and Debiec, H. (2021) Membranous Nephropathy: From Pathophysiology to Treatment. *Nature Reviews Nephrology*, **17**, 765-781.
7. Liu, L.J. and Zhao, M.H. (2022) Clinicopathological Characteristics and Prognosis of PLA2R-Associated Membranous Nephropathy. *Chinese Journal of Nephrology*, **38**, 201-207. (In Chinese)
8. Zhang, H.T. and Liu, B.C. (2020) Relationship between Pathological Stages and Clinical Prognosis in Membranous Nephropathy. *Chinese Journal of Integrated Traditional and Western Nephrology*, **21**, 632-634. (In Chinese)
9. Glassock, R.J. (2019) Membranous Nephropathy: Clinical Features and Natural History. *Seminars in Nephrology*, **39**, 223-230.
10. Zou, W.Z. (2020) Atlas of Renal Biopsy Pathology Diagnosis. 3rd Edition, People's Medical Publishing House, 156-160. (In Chinese)
11. Zhang, L.X. and Zuo, L. (2022) Progress in Epidemiological Research on Chronic Kidney Disease in China. *Chinese Journal of Nephrology*, **38**, 78-82. (In Chinese)
12. Huang, S.M. and Chen, G.Y. (2021) Clinicopathological Analysis of Membranous Nephropathy Combined with Other Glomerular Diseases. *Chinese Journal of Practical Internal Medicine*, **41**, 789-792. (In Chinese)