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ORIGINAL RESEARCH

# Influencing Factors of Treatment Response to Rituximab in Refractory Membranous Nephropathy

Lianzi Ma, Li Yang, Jing Zheng

Nephrology Department, Nanfang Hospital, Guangzhou, 510515, People's Republic of China

Correspondence: Lianzi Ma, Nephrology Department, Nanfang Hospital, Southern Medical University, Guangzhou, 510515, People's Republic of China, Email 13428860575@163.com



**Objective:** This study aims to identify influencing factors associated with the efficacy of rituximab in treating refractory membranous nephropathy (MN), characterized by persistent proteinuria and unresponsive to conventional immunosuppressive therapies. We sought to determine clinical and biochemical predictors for positive therapeutic outcomes and optimize patient selection criteria.

**Methods:** A total of 160 patients with biopsy-confirmed refractory MN (meeting criteria of eGFR > 30 mL/min/1.73 m², significant proteinuria, positive PLA2R-Ab, and prior treatment failure) were studied. Patients received rituximab (375 mg/m²) with 24-month monitoring. Baseline demographic, clinical, and biochemical data underwent univariate and multivariate logistic regression analyses, while ROC curve analysis evaluated predictive accuracy.

**Results:** Responders (n=113) exhibited higher serum albumin, lower serum creatinine, reduced 24-hour urine protein, higher eGFR, and lower PLA2R-Ab levels (all $P < 0.001$) versus non-responders (n=47). Multivariate analysis identified these as independent predictors. The combined indices yielded an AUC of 0.99 (with 93.8% sensitivity and 97.9% specificity; $P < 0.001$), demonstrating excellent accuracy for identifying patients most likely to benefit from rituximab therapy.

**Conclusion:** Rituximab demonstrates efficacy in treating refractory MN, with specific clinical and biochemical markers providing significant predictors of treatment success. The biomarker combination (serum albumin, creatinine, 24-hour urine protein, eGFR, PLA2R-Ab) offers exceptional predictive accuracy for treatment outcomes, providing clinicians with a practical tool to guide personalized treatment decisions and optimize resource allocation in refractory MN management.

**Keywords:** refractory membranous nephropathy, rituximab, predictive factors, univariate and multivariate logistic regression analysis, ROC

## Background

Membranous nephropathy (MN) stands as a prominent contributor to adult nephrotic syndrome, representing a significant portion of cases globally.[1,2] This condition is primarily characterized by the deposition of immune complexes within the subepithelial layer of the glomerular basement membrane, which initiates a cascade of pathological events, including complement system activation, podocyte damage, and subsequent proteinuria.[3,4] MN is categorized into two main forms: primary and secondary. The primary form, often idiopathic, is frequently linked to the presence of autoantibodies directed against the phospholipase A2 receptor (PLA2R).[5,6] Disease progression varies widely, with outcomes ranging from spontaneous remission to chronic deterioration, potentially advancing to chronic kidney failure (CKF).[7,8] Refractory MN is defined as cases that fail to achieve partial or complete remission despite prolonged treatment with conventional immunosuppressive therapies, such as glucocorticoids or calcineurin inhibitors, typically for at least 12 months.[7,9] These patients often exhibit persistent heavy proteinuria (>3.5 g/24 h), hypoalbuminemia, and elevated anti-PLA2R antibody levels, placing them at a significantly higher risk of progressing to CKF.[7,8,10]

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The management of refractory MN presents a considerable clinical challenge. Patients demonstrating an inadequate response to conventional treatments are at a notably higher risk of advancing to CKF, which is strongly linked to increased morbidity and mortality rates.[7,10] The persistence of nephrotic syndrome, marked by significant proteinuria, low albumin levels, and fluid accumulation, worsens clinical symptoms and predisposes patients to severe complications, including thromboembolic events, infections, and cardiovascular problems.[11,12] Considering the limitations of existing therapeutic approaches and the serious outcomes associated with disease progression, there is a pressing need to develop more effective interventions that can modify the disease trajectory in patients with refractory MN.

Rituximab, a monoclonal antibody that targets the CD20 antigen found on B cells, has garnered considerable attention as a therapeutic option for MN in recent years. By depleting B cells, rituximab reduces the production of autoantibodies such as anti-PLA2R antibodies, which play a central role in the pathogenesis of primary MN.[13,14] Multiple clinical trials have highlighted rituximab's effectiveness in treating patients with refractory MN, with many experiencing either a partial or complete reduction in proteinuria.[15,16] Consequently, rituximab presents a promising alternative to traditional immunosuppressive therapies, especially for those who do not respond well to or cannot tolerate conventional treatments. However, patient responses to rituximab are inconsistent, with some individuals failing to achieve optimal therapeutic outcomes.[13,17] This variability emphasizes the need for further research to better understand the factors that affect rituximab's efficacy in treating MN.

This retrospective study tries to assess both the safety profile and the factors influencing rituximab's effectiveness in a clearly defined group of refractory MN patients. Using rigorous statistical methods, such as uni- and multi-variate logistic regression, alongside ROC construction, the research seeks to construct a predictive model that integrates various clinical and biochemical parameters. This approach offers a comprehensive evaluation of the potential determinants of treatment response, which could enhance the ability to predict outcomes in this patient population.

# Methods

## Patients

Patients with refractory MN who were eligible for rituximab treatment at Nanfang hospital were selected based on the following inclusion criteria: (1) a biopsy-confirmed diagnosis of MN; (2) an estimated glomerular filtration rate (eGFR) above 30 mL/min/1.73 m²; (3) proteinuria greater than 3.5 g/24 hours and a serum albumin concentration below 30 g/l; (4) a positive serum PLA2R-Ab result prior to enrollment; and (5) failure to respond to at least 12 months of prior immunosuppressive therapy. Importantly, patients diagnosed with secondary MN were excluded from the study. Significant proteinuria was strictly defined as >3.5 g/24h measured on ≥2 occasions pre-treatment. Refractory status required documented treatment failure with either corticosteroids/calcineurin inhibitors for ≥12 months. All participants provided written informed consent for rituximab treatment, ensuring compliance with the Declaration of Helsinki guidelines. The study protocol was approved by the Ethics Committee of Nanfang Hospital (Approval No. NFEC-202212-Y2), and written informed consent was obtained from all participants prior to enrollment.

## Therapeutic Approaches and Monitoring

Rituximab was administered at a dose of 375 mg/m², diluted in saline to reach a final concentration of 1 mg/mL. The infusion started at a rate of 50 mL/h, gradually increasing to 200 mL/h depending on patient tolerance. Circulating B cell counts were evaluated the following day and at each follow-up visit. If the B cell count exceeded 5/μL, an additional rituximab dose was given. Patients in the study were monitored for at least 24 months. Prior to treatment, baseline laboratory values were recorded, and these parameters were re-evaluated at 1, 3, 6, 9, and 12 months after the first rituximab infusion, with further assessments every 3 months thereafter. The rituximab dosing regimen (375 mg/m² weekly ×4 doses or adjusted based on B-cell monitoring) aligns with established protocols for refractory membranous nephropathy.[18] While alternative regimens exist (eg, 1000 mg ×2 doses),[19] this approach was recommended by KDIGO guidelines.

## Demographic Characteristics and Observational Parameters

In this study, patient demographics and general information, including age, sex, body mass index (BMI), and disease duration, were collected prior to rituximab therapy and analyzed alongside several critical clinical and biochemical parameters to assess the effectiveness of rituximab in treating refractory membranous nephropathy. Clinical parameters included serum albumin (ALB, g/L) to evaluate protein levels, serum creatinine (SCr, μmol/L) as an indicator of kidney function, 24-hour urine protein (24h-UP, g/d) to measure proteinuria, estimated glomerular filtration rate (eGFR, mL/min/1.73 m²) to assess kidney filtration capacity, and PLA2R antibody levels (PLA2R-Ab, RU/mL), a key biomarker for membranous nephropathy. All laboratory examinations (including ALB, SCr, 24h-UP, eGFR, and PLA2R-Ab levels) were performed at baseline prior to rituximab initiation, and repeated at scheduled intervals (1, 3, 6, 9, 12 months post-treatment and every 3 months thereafter) to monitor treatment response. These demographic and clinical variables were methodically recorded and analyzed to explore their association with treatment outcomes, offering a detailed evaluation of the safety and factors influencing rituximab therapy in this patient cohort.

## Statistical Analysis

All statistical analyses were conducted using SPSS version 21. Continuous data were reported as means ± standard deviation or as medians with interquartile ranges, based on their distribution. Group comparisons were made using the Student's *t*-test for normal distributions and the Wilcoxon signed-rank test for non-normal data. Categorical variables were analyzed via Pearson's $\chi^2$-test or Fisher's exact test where applicable. Univariate logistic regression was employed to identify factors potentially associated with treatment efficacy, and those showing significance ($p < 0.05$) were subsequently included in a multivariate logistic regression model to establish independent predictors. To prevent model overfitting given the sample size of 160 patients and the number of predictors, only variables with $p < 0.05$ in univariate analysis were included in the multivariate model, reducing the risk of including non-significant predictors. Additionally, the sample size was deemed adequate based on the guideline of at least 10 events per predictor variable, with 113 responders providing sufficient statistical power for the five key predictors (serum albumin, serum creatinine, 24-hour urine protein, eGFR, and PLA2R-Ab levels) evaluated in the multivariate analysis.[20] Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). ROC analysis was utilized to determine the predictive accuracy of clinical indices, with the AUC serving as a performance measure. A p-value less than 0.05 was considered indicative of statistical significance. This study analyzed complete datasets without imputation for missing values.

# Results

## Comparison of Clinical and Biochemical Characteristics Between Effective and Ineffective Groups

In this study, 160 patients diagnosed with refractory membranous nephropathy were enrolled, including 127 males (79.38%) and 33 females (20.62%), with a mean age of 35.56±4.71 years. The cohort was divided into two groups based on their response to rituximab: the effective group (n=113) and the ineffective group (n=47). Baseline demographic and clinical characteristics were comprehensively analyzed to assess their association with treatment efficacy. No statistically significant differences were found between the groups in terms of sex distribution (P=0.527), age (34.83±4.61 vs 35.96 ±4.75 years, P=0.167), body mass index (23.54±1.83 vs 24.00±1.88 kg/m², P=0.152), disease duration (31.96±4.68 vs 30.44±5.34 years, P=0.093), total cholesterol levels (6.70±0.47 vs 6.54±0.53 mmol/L, P=0.084), or triglycerides (2.27 ±0.37 vs 2.39±0.44 mmol/L, P=0.094). However, significant differences were observed in other key clinical markers. Patients in the effective group had notably higher serum albumin levels (26.74±3.43 vs 22.26±3.40 g/L, P<0.001), lower serum creatinine (81.11±9.33 vs 94.96±12.40 μmol/L, P<0.001), reduced 24-hour urine protein excretion (6.08±1.96 vs 8.24±1.97 g/d, P<0.001), higher estimated glomerular filtration rates (89.10±10.18 vs 76.83±10.23 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$, P<0.001), and lower PLA2R antibody levels (41.41±8.65 vs 49.86±8.98 RU/mL, P<0.001) than the ineffective group. (Table 1) These results indicate that higher baseline serum albumin and eGFR, along with lower serum creatinine, 24-hour proteinuria, and PLA2R-Ab levels, are predictive of a better therapeutic response to rituximab in refractory membranous nephropathy.

**Table 1** Baseline Demographic of the Ineffective and Effective Groups Treated with Rituximab for Refractory Membranous Nephropathy

| Indices | Ineffective Group (n=47) | Effective Group (n=113) | P |
|---|---|---|---|
| Sex [n (%)] | | | 0.527 |
| Male | 39 (82.98) | 88 (77.88) | |
| Female | 8 (17.02) | 25 (22.12) | |
| Age (years) | 34.83±4.61 | 35.96±4.75 | 0.167 |
| BMI (kg/m2) | 23.54±1.83 | 24.00±1.88 | 0.152 |
| Course (years) | 31.96±4.68 | 30.44±5.34 | 0.093 |
| ALB (g/L) | 22.26±3.40 | 26.74±3.43 | <0.001 |
| SCr (umol/L) | 94.96±12.40 | 81.11±9.33 | <0.001 |
| 24h urine protein (g/d) | 8.24±1.97 | 6.08±1.96 | <0.001 |
| eGFR [mL·min-1 · (1.73 m2)-1] | 76.83±10.23 | 89.10±10.18 | <0.001 |
| T-CHO (mmol/L) | 6.70±0.47 | 6.54±0.53 | 0.084 |
| TG (mmol/L) | 2.27±0.37 | 2.39±0.44 | 0.094 |
| PLA2R-Ab (RU/mL) | 49.86±8.98 | 41.41±8.65 | <0.001 |

**Abbreviations**: BMI, body mass index; ALB, serum albumin; SCr, serum creatinine; 24h-UP, 24-hour urine protein; eGFR, estimated glomerular filtration rate; T-CHO, total cholesterol; TG, triglycerides; PLA2R-Ab, phospholipase A2 receptor antibody;

## Univariate and Multivariate Logistic Regression Analysis of Factors Influencing Rituximab Efficacy in Refractory Membranous Nephropathy

After evaluating the clinical and biochemical characteristics of the effective and ineffective treatment groups, univariate and multivariate analyses were performed to identify the factors that are independently linked to the efficacy of rituximab in managing refractory membranous nephropathy. In the univariate logistic regression, several variables were found to be significantly associated with treatment outcomes. Elevated serum albumin levels (OR: 1.430, 95% CI: 1.263–1.620, P<0.001), reduced serum creatinine levels (OR: 0.884, 95% CI: 0.846–0.923, P<0.001), decreased 24-hour urinary protein excretion (OR: 0.558, 95% CI: 0.444–0.701, P<0.001), increased eGFR (OR: 1.122, 95% CI: 1.076–1.171, P<0.001), and lower PLA2R antibody levels (OR: 0.899, 95% CI: 0.859–0.940, P<0.001) were all strongly correlated with a more favorable rituximab response. However, variables such as age, BMI, disease duration, total cholesterol, and triglyceride levels did not show significant associations with treatment outcomes. Multivariate logistic regression further supported that higher baseline serum albumin (OR: 1.854, 95% CI: 1.351–2.544, P<0.001), lower serum creatinine (OR: 0.837, 95% CI: 0.763–0.919, P<0.001), reduced 24-hour urinary protein excretion (OR: 0.461, 95% CI: 0.276–0.769, P=0.003), increased eGFR (OR: 1.218, 95% CI: 1.092–1.357, P<0.001), and lower PLA2R antibody levels (OR: 0.890, 95% CI: 0.804–0.985, P=0.024) were significant independent predictors of a positive response to rituximab treatment (Table 2).

## Predictive Accuracy of Independent Influencing Factors Based on ROC Analysis

After conducting the multivariate analysis, a ROC analysis was applied to assess the predictive value of independent influencing factors for determining rituximab efficacy in treating refractory membranous nephropathy. For albumin (ALB), the AUC was 0.826 (95% CI: 0.757–0.894), and the optimal cut-off point was 24.93 g/L, yielding a sensitivity of 74.3% and a specificity of 80.9% (P<0.001). Serum creatinine (SCr) had an AUC of 0.819 (95% CI: 0.740–0.897) and an optimal cut-off value of 85.17 μmol/L, with a sensitivity of 69.9% and a specificity of 83.0% (P<0.001). For 24-hour urine protein (24h-UP), the AUC was 0.794 (95% CI: 0.717–0.872) with a cut-off value of 7.72 g/d, resulting in a sensitivity of 82.3% and a specificity of 66.0% (P<0.001). The eGFR demonstrated an AUC of 0.801 (95% CI: 0.725–0.877) and an optimal cut-off value of 81.375 mL/min/1.73 m², showing a sensitivity of 77.0% and a specificity of 72.3% (P<0.001). PLA2R antibody (PLA2R-Ab) levels had an AUC of 0.768 (95% CI: 0.685–0.852) with a cut-off value of 43.03 RU/mL, achieving a sensitivity of 67.3% and specificity of 83.0% (P<0.001). Interestingly, when these factors were combined, the AUC reached a remarkable 0.99 (95% CI: 0.980–1.000), with a sensitivity of 93.8%, and a specificity of 97.9% (P<0.001). (Table 3, Figure 1) This indicates that the combined model offers a highly reliable

**Table 2** Univariate and Multivariate Logistic Regression Analysis of Factors Associated with the Efficacy of Rituximab in Patients with Refractory Membranous Nephropathy

| Indices | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P | OR (95% CI) | P |
| Age | 1.053 (0.978~1.134) | 0.167 | | |
| BMI | 1.145 (0.951~1.380) | 0.153 | | |
| Course | 0.944 (0.882~1.010) | 0.094 | | |
| ALB | 1.430 (1.263~1.620) | <0.001 | 1.854 (1.351~2.544) | <0.001 |
| SCr | 0.884 (0.846~0.923) | <0.001 | 0.837 (0.763~0.919) | <0.001 |
| 24h-UP | 0.558 (0.444~0.701) | <0.001 | 0.461 (0.276~0.769) | 0.003 |
| eGFR | 1.122 (1.076~1.171) | <0.001 | 1.218 (1.092~1.357) | <0.001 |
| T-CHO | 0.552 (0.280~1.087) | 0.086 | | |
| TG | 2.018 (0.083~4.611) | 0.096 | | |
| PLA2R-Ab | 0.899 (0.859~0.940) | <0.001 | 0.890 (0.804~0.985) | 0.024 |

**Abbreviations**: BMI, body mass index; ALB, serum albumin; SCr, serum creatinine; 24h-UP, 24-hour urine protein; eGFR, estimated glomerular filtration rate; T-CHO, total cholesterol; TG, triglycerides; PLA2R-Ab, anti-phospholipase A2 receptor antibody.

**Table 3** ROC Analysis of Clinical Indices for Predicting Rituximab Efficacy in Patients with Refractory Membranous Nephropathy

| Indices | AUC | 95% CI | Optimal Cut-Off Value | Youden Index | Sensitivity | Specificity | P value |
|---|---|---|---|---|---|---|---|
| ALB | 0.826 | 0.757~0.894 | 24.93 | 0.552 | 0.743 | 0.809 | <0.001 |
| SCr | 0.819 | 0.740~0.897 | 85.17 | 0.529 | 0.699 | 0.83 | <0.001 |
| 24h-UP | 0.794 | 0.717~0.872 | 7.72 | 0.483 | 0.823 | 0.66 | <0.001 |
| eGFR | 0.801 | 0.725~0.877 | 81.375 | 0.493 | 0.77 | 0.723 | <0.001 |
| PLA2R-Ab | 0.768 | 0.685~0.852 | 43.03 | 0.503 | 0.673 | 0.83 | <0.001 |
| Combined | 0.99 | 0.980~1.000 | | 0.917 | 0.938 | 0.979 | <0.001 |

**Abbreviations**: ALB, serum albumin; SCr, serum creatinine; 24h-UP, 24-hour urine protein; eGFR, estimated glomerular filtration rate; PLA2R-Ab, anti-phospholipase A2 receptor antibody.

method for predicting rituximab efficacy in this patient population. These results highlight the critical role of integrating multiple biomarkers to improve predictive precision, ultimately enhancing patient selection and optimizing treatment outcomes in refractory membranous nephropathy.

## Discussion

The findings of this study provide important insights into the safety and efficacy of rituximab in the treatment of refractory membranous nephropathy (MN), particularly through the identification of key clinical and biochemical predictors of treatment response. Our results confirm that higher baseline serum albumin levels, lower serum creatinine levels, reduced 24-hour urine protein excretion, higher eGFR, and lower PLA2R antibody levels are significant predictors of a positive response to rituximab. These findings not only support the use of rituximab as a therapeutic option for refractory MN but also highlight the potential for optimizing patient selection and tailoring treatment strategies based on these predictive markers.

Serum albumin emerged as a strong predictor of rituximab efficacy, with higher baseline levels being associated with favorable treatment outcomes. This finding is consistent with the role of hypoalbuminemia in MN, where severe proteinuria leads to significant loss of albumin in the urine, contributing to the nephrotic syndrome.[21,22] The observed correlation suggests that patients with relatively preserved serum albumin levels may have less severe glomerular injury or a more intact glomerular filtration barrier, which might facilitate a better therapeutic response.[23,24] Furthermore, albumin's role as a carrier protein for various substances, including drugs, could influence the pharmacokinetics and

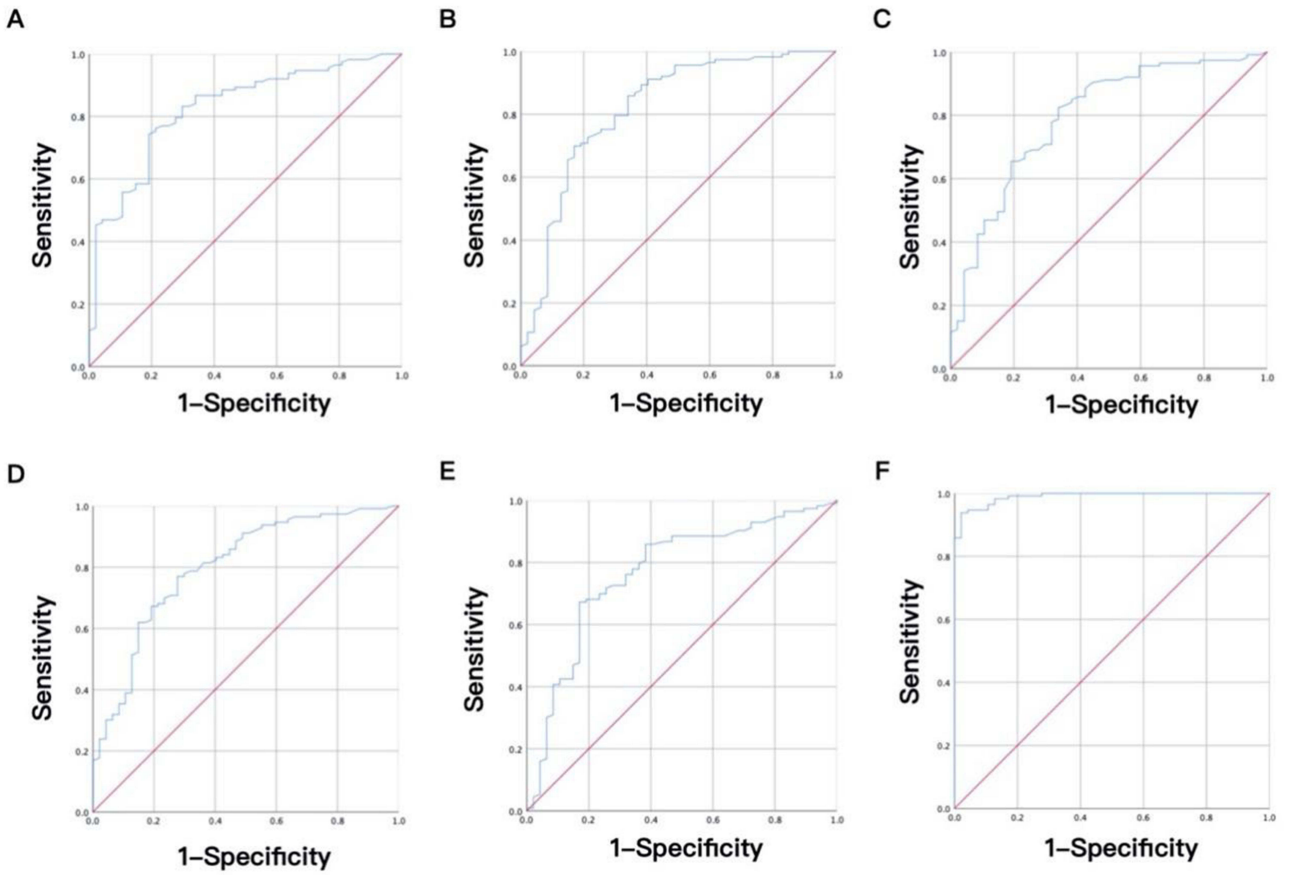


**Figure 1** ROC analysis for predicting rituximab efficacy in refractory membranous nephropathy using (**A**) ALB; (**B**) SCr; (**C**) 24h-UP; (**D**) eGFR; (**E**) PLA2R-Ab; and (**F**) combined indices.

distribution of rituximab, potentially enhancing its efficacy in patients with higher albumin levels.[25,26] The identification of serum albumin as an independent predictor underscores the importance of early intervention to preserve albumin levels, which could improve the therapeutic outcomes of rituximab in MN.

Lower baseline serum creatinine levels were also found to be significantly associated with a better response to rituximab, reflecting the importance of kidney function preservation in the treatment of MN. Serum creatinine is a well-established marker of kidney function, and elevated levels indicate reduced glomerular filtration rate (GFR) and more advanced kidney damage.[27] Patients with lower serum creatinine levels at baseline likely have a higher eGFR, indicating less severe kidney impairment and a greater likelihood of achieving remission with rituximab therapy. This finding aligns with previous studies that have shown that patients with better-preserved kidney function respond more favorably to immunosuppressive therapy, including rituximab.[21,28,29] The clinical implication of this finding is that early initiation of rituximab in patients with refractory MN, before significant kidney function decline, could enhance the likelihood of achieving a positive therapeutic outcome.

Proteinuria levels, determined through 24-hour urine protein excretion measurements, were also identified as a crucial factor affecting the effectiveness of rituximab treatment. Our study demonstrated that lower baseline proteinuria was associated with a higher likelihood of treatment success. Proteinuria is a direct consequence of glomerular damage in MN, and its reduction is a key therapeutic goal.[30,31] The association between lower baseline proteinuria and better outcomes suggests that patients with less extensive glomerular injury may have a more reversible disease process, which could be more amenable to B-cell depletion therapy. This finding also emphasizes the potential role of rituximab in inducing remission in patients with less severe proteinuria, supporting its use as an early intervention to prevent further progression of MN.

Higher eGFR at baseline was independently associated with a favorable response to rituximab, further underscoring the importance of kidney function in predicting treatment outcomes. eGFR is a comprehensive indicator of kidney function, and higher values reflect better kidney reserve.[32] The positive correlation between eGFR and treatment response suggests that patients with preserved kidney function may benefit more from rituximab, possibly due to the lesser extent of chronic kidney damage and a greater potential for recovery.[13,16,33] This finding is particularly relevant for clinical practice, as it highlights the need to assess eGFR as part of the decision-making process for rituximab therapy in MN patients. Early intervention with rituximab in patients with high eGFR could be a strategy to maximize therapeutic benefits and delay the progression to end-stage kidney disease.

The role of PLA2R antibodies in the pathogenesis of MN is well established, with higher levels correlating with disease activity and severity.[34–36] In our study, lower baseline PLA2R antibody levels were associated with a better response to rituximab, suggesting that patients with lower immunologic activity may have a more favorable response to B-cell depletion. This finding is consistent with the mechanism of action of rituximab, which targets CD20-positive B cells responsible for antibody production. The lower the baseline antibody levels, the less the antigenic burden, potentially leading to a more effective and rapid resolution of immune-mediated glomerular damage.[37,38] This result supports the use of PLA2R antibody levels as a biomarker for guiding rituximab therapy, particularly in selecting patients who are more likely to benefit from treatment.

The predictive model that combined measurements of serum creatinine, eGFR, serum albumin, 24-hour urine protein and PLA2R antibody levels showed exceptionally high precision in forecasting treatment results, achieving an AUC of 0.99. This finding highlights the value of a multifactorial approach to patient selection and treatment planning in refractory MN. By integrating multiple clinical and biochemical indices, this model provides a comprehensive assessment of the patient's likelihood of responding to rituximab, allowing for more personalized and effective therapeutic decisions. The implementation of such a predictive model in clinical practice could improve the overall management of MN by ensuring that rituximab is administered to patients most likely to benefit from it, thereby optimizing resource use and improving patient outcomes.

While this study primarily focused on the efficacy of rituximab, it is also essential to consider the safety profile of the drug in this patient population. Rituximab is generally well tolerated, but its use is associated with potential risks, including infusion-related reactions, infections due to immunosuppression, and long-term depletion of B cells.[39–41] Monitoring for these adverse events is crucial, particularly in patients with compromised kidney function, who may be more susceptible to complications. The results of this study suggest that careful patient selection, based on the identified predictive factors, could not only enhance efficacy but also minimize the risk of adverse events by targeting therapy to those most likely to respond.

Although the findings from this study are robust, certain limitations must be considered. The retrospective design, coupled with the single-center approach, may reduce the generalizability of the outcomes. The single-center nature of this study limits the diversity of the patient population and may introduce selection bias, which could affect the external validity of the results. Furthermore, while several key predictive factors were identified, the complex pathophysiology of membranous nephropathy (MN) implies that additional, unmeasured variables might influence treatment response. To address these gaps, future research should prioritize prospective, multicenter studies to validate the current predictive model and investigate further biomarkers that could refine patient selection for rituximab therapy. Additionally, long-term follow-up studies are necessary to evaluate the persistence of rituximab-induced remission and the potential for disease relapse.

In summary, this study presents strong evidence that specific clinical and biochemical markers can reliably predict the efficacy of rituximab in treating refractory MN. The combination of serum albumin, serum creatinine, 24-hour urine protein, eGFR, and PLA2R antibody levels offers a valuable predictive tool to enhance patient selection and optimize treatment results. These findings add to the growing evidence supporting rituximab's role in MN management and highlight the critical need for a personalized treatment approach. Future investigations should focus on confirming these results and identifying additional factors that could further enhance the precision of rituximab therapy in this challenging condition.

## Data Sharing Statement

The experimental data used to support the findings of this study are available from the corresponding author upon request.

## Ethical Approval and Consent to Participate

All experimental protocols were approved by the Ethics Committee of Nanfang Hospital. Informed consent was obtained from all the participants. All methods were carried out in accordance with Declaration of Helsinki (Approval number: NFEC-202212-Y2).

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## Disclosure

The authors declared that they have no conflicts of interest regarding this work.

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