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*Original Article*

# A comparative study on the efficacy of rituximab combined with tacrolimus and methylprednisolone in the treatment of patients with moderate-high risk idiopathic membranous nephropathy

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**Abstract:** Objective: To compare the efficacy of combining methylprednisolone with either rituximab or tacrolimus for treating idiopathic membranous nephropathy (IMN). Method: This research is designed as a prospective study (TCTR20260515001, URL: https://www.thaiclinicaltrials.org/show/TCTR20260515001). A total of 210 IMN patients treated at Binzhou People's Hospital from October 2021 to October 2024 were enrolled and randomly assigned to one of three groups: a control group, intervention group 1, and intervention group 2. The control group received methylprednisolone alone. Intervention group 1 underwent the same methylprednisolone therapy plus intravenous rituximab, while intervention group 2 received methylprednisolone combined with oral tacrolimus. General data, clinical efficacy after treatment, phospholipase A2 receptor (PLA2R), renal function indicators, inflammatory indicators, urinary immune indicators, quality of life, and adverse reactions were compared. Multivariate logistic regression analysis was used to examine whether the treatment regimen was an independent influencing factor for the patient's therapeutic effect. Subgroup analysis was used to compare the efficacy differences among patients with different characteristics after receiving different treatment plans. Results: The total effective rate of treatment in intervention group 1 was higher than that in intervention group 2 and the control group ($P<0.05$). With increasing treatment time, PLA2R, 24-hour urine protein quantification, serum creatinine (SCr), blood urea nitrogen (BUN), inflammatory indicators, and urinary immune indicators of all patients declined, and intervention group 1 exhibited lower values than both intervention group 2 and the control group ($P<0.05$); while plasma albumin (ALB) and Short Form-36 Health Survey score (SF-36) gradually increased with treatment time, and intervention group 1 exhibited higher values than intervention group 2 and the control group ($P<0.05$). However, no discernible statistical difference was observed in the total incidence of adverse reactions among the three groups ($P>0.05$). Multivariate logistic regression analysis showed that after adjusting for confounding factors, the rituximab combination regimen was an independent influencing factor for better therapeutic effects in patients with moderate to high-risk idiopathic membranous nephropathy ($P<0.05$). The results of the subgroup analysis showed that the therapeutic advantages of rituximab combined with methylprednisolone remained consistent across patients with different clinical characteristics. Conclusion: After adjusting for confounding factors such as age, diabetes, and baseline renal function, concurrent rituximab and methylprednisolone showed a more favorable therapeutic outcome compared to the tacrolimus regimen, and it was applicable to a wider range of patients.

**Keywords:** Rituximab, tacrolimus, methylprednisolone, idiopathic membranous nephropathy, efficacy

## Introduction

Roughly 20% to 30% of cases of primary nephrotic syndrome are caused by idiopathic membranous nephropathy (IMN), one of the primary causes of adult nephrotic syndrome [1]. In recent years, with the continuous deepening of understanding of the pathogenesis of IMN, especially the discovery of anti-phospholipase A2 receptor antibodies, the diagnosis and treatment of IMN have seen significant progress [2, 3]. The optimal treatment for moderate to high-risk IMN patients remains controversial and has thus become an important clinical issue that urgently needs to be addressed in nephrology.

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Currently, glucocorticoids (such as prednisone and methylprednisolone) are the primary medications for patients with moderate to high-risk IMN [4, 5]. However, long-term or high-dose use of these drugs may cause adverse reactions such as metabolic disorders, digestive system reactions, and mental and neurological symptoms, limiting the application of this treatment plan [6, 7]. Rituximab is a monoclonal antibody directed against the $CD20^+$ antigen on B lymphocytes. It can specifically eliminate B cells in the body by binding to $CD20^+$, reduce the production of autoantibodies, and control immune damage to the kidneys [8, 9]; when combined with methylprednisolone, it can exert a synergistic effect: methylprednisolone can rapidly inhibit widespread immune inflammation [10], while rituximab precisely eliminates pathogenic B cells from the source, induces immune remission, and helps reduce the cumulative dosage of hormones, showing good application prospects in IMN treatment [11]. Furthermore, tacrolimus is a potent calcineurin inhibitor that can prevent T cell activation and proliferation, thereby regulating aberrant immune responses that damage the kidneys [12]; it can also directly stabilize the cytoskeleton of glomerular podocytes through non-immune mechanisms, reduce protein leakage [13], and when combined with methylprednisolone, can simultaneously enhance the dual inhibition of humoral and cellular immunity [14], and may rapidly reduce proteinuria through its unique non-immune pathways, achieving multi-pathway renal protective effects [15]. Current studies on the efficacy of rituximab combined with tacrolimus and methylprednisolone for moderate to high-risk IMN, along with direct comparisons between these regimens, remain limited.

Therefore, research was performed to compare the clinical outcomes and tolerability of rituximab versus tacrolimus (both used in combination with methylprednisolone) in patients with moderate to high-risk IMN. It is expected to provide a reference for the formulation of personalized treatment strategies.

## Materials and methods

### *Participants*

Based on the design of a randomized controlled clinical trial, the sample size was estimated using PASS 15.0 software. The control group's treatment efficacy rate was roughly 70%, intervention group 1's was roughly 95%, and intervention group 2's was roughly 76%. With $\alpha$=0.05, $\beta$=0.90, P1=0.7, P2=0.95, and P3=0.76, the total sample size calculated by the software was at least 177 patients (59 patients in each group). The overall recruitment goal was set at 198 patients (66 patients in each group), taking into account a 10% dropout rate.

To enhance statistical validity and reduce the risks associated with a possible and unexpected higher dropout rate or data loss that may occur in the research, this study included a total of 210 patients with IMN treated at Binzhou People's Hospital from October 2021 to October 2024. They were prospectively enrolled and randomly assigned to one of three groups: a control group, intervention group 1, and intervention group 2, with 70 participants in each group. There was no statistically significant difference in baseline data among the three groups, and they were comparable. The excess enrollment of 12 patients beyond the planned 198 cases was intended to further improve the statistical power of the study, reduce the potential impact of unforeseen high dropout rates or data loss, and enhance the reliability and generalizability of the study results. The control group received methylprednisolone alone. Intervention group 1 underwent the same methylprednisolone therapy plus intravenous rituximab, while intervention group 2 received methylprednisolone combined with oral tacrolimus, as shown in **Figure 1**. Ethical approval for this research was authorized by Binzhou People's Hospital (Approval number: 2022350), and all patients signed the written informed consent form.

### *Diagnostic criteria*

IMN diagnostic criteria: Diagnosis was made in accordance with the 2021 KDIGO Clinical Practice Guidelines for the Management of Glomerular Diseases [16]: ① Diagnosed as idiopathic membranous nephropathy through renal biopsy and clinical examination; ② In cases of confirmed IMN, patients who, after 3 to 6 months of conservative treatment, still had 24-hour urine protein quantification higher than 4 g/d and showed no downward trend,

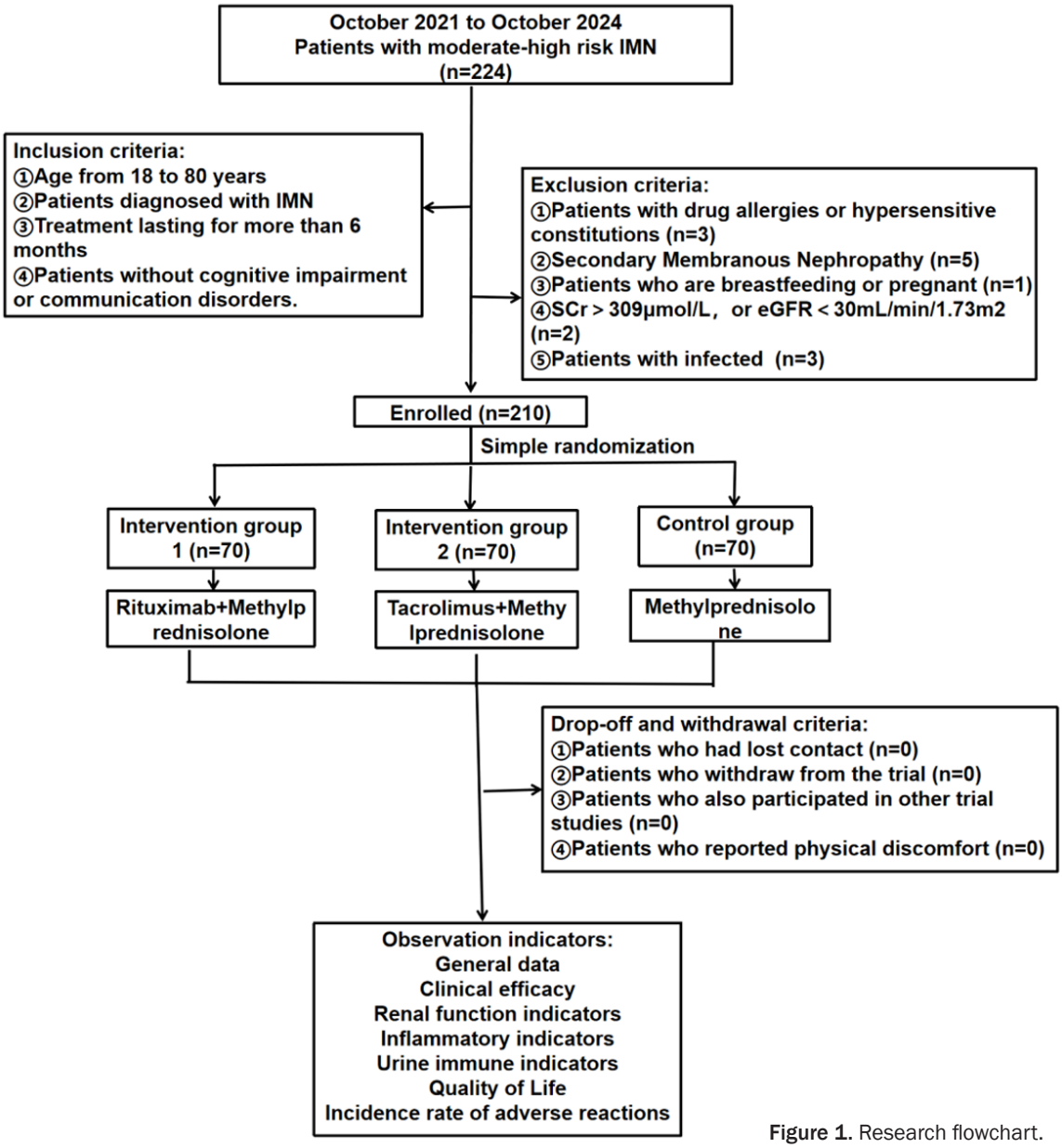


**Figure 1.** Research flowchart.

were classified as moderate to high-risk patients; ③ Secondary membranous nephropathy was excluded.

*Inclusion, exclusion, dropout and withdrawal criteria*

Inclusion criteria: ① Patients aged between 18 and 80 years; ② Patients with IMN; ③ Had received treatment according to the study protocol for more than 6 months; ④ Patients without cognitive impairment or communication disorders.

Exclusion criteria: ① Patients with known allergy or hypersensitivity to the study drugs; ② Patients with secondary membranous nephropathy caused by infections, autoimmune diseases, tumors, or drugs; ③ Patients who were breastfeeding or pregnant; ④ Patients with serum creatinine (SCr) persistently above 309 μmol/L or an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 $m^2$ and a kidney length diameter lower than 8 cm; ⑤ Patients with serious or potentially fatal infections.

Dropout and withdrawal criteria: ① Loss to follow-up; ② Voluntary withdrawal by the patients or their guardian; ③ Concurrent participation in another interventional trial; ④ Experiencing adverse events that led to discontinuation.

*Research methods*

All patients were given the corresponding treatment according to their group assignment, and all three groups were treated for 6 months.

Control group: Monotherapy with methylprednisolone. Methylprednisolone tablets (Shandong Xinhua Lu'an Anti-Pathogen Pharmaceutical Co., Ltd., 4 mg/tablet) were administered orally. The initial dose was 16-24 mg once daily. The dosage was reduced following the recovery of the patient's condition, and the medication was taken for 8 weeks. The dosage was reduced by 10% every 2 weeks, and finally a maintenance dose of 8-12 mg was used for clinical treatment.

Intervention group 1: Patients were treated with methylprednisolone tablets combined with rituximab. Patients were required to receive intravenous injection of dexamethasone sodium phosphate (5 mg) and intramuscular injection of promethazine hydrochloride (25 mg) orally 30 to 60 minutes before each infusion of rituximab to prevent infusion-related reactions. Rituximab (Xinda Biopharmaceutical Co., Ltd., National Drug Approval No. S20200022, 100 mg/vial) was administered intravenously in combination with the control group's regimen. A dose of 500 mg was administered intravenously for a total of 4 doses (cumulative dose 2 g). The initial infusion rate was 50 mg/h, and the rate was gradually increased, with a maximum rate of 400 mg/h. To reduce the cumulative risk of combined immunosuppression, in intervention group 1, the dose reduction rate of methylprednisolone after the first infusion of rituximab was accelerated compared to the control group. Specifically, starting from the 4th week of treatment, the dose was reduced by 20% every 2 weeks, with the goal of reducing the dose to the maintenance level (4-8 mg/day) by the 12th week of treatment.

Intervention group 2: Patients were treated with methylprednisolone tablets combined with tacrolimus. Tacrolimus capsules (Hangzhou China-US Huadong Pharmaceutical Co., Ltd., National Drug Approval No. H20094027, 0.5 mg/capsule) were administered orally in combination with the control group's regimen, taken twice daily, at a dose between 0.05 and 0.1 mg/kg per day. During the medication period, it was necessary to regularly monitor the blood drug concentration. The monitoring frequency was as follows: one measurement on day 3 and one measurement on day 7 after starting the medication, then one measurement every week thereafter. Once the blood drug concentration stabilized, it was adjusted to one measurement every 2 weeks. The target range of the blood drug concentration was controlled within 5 to 10 ng/mL. Based on the monitoring results, the dosage of tacrolimus was adjusted in a timely manner to ensure the safety and effectiveness of the drug treatment. Given the immunosuppressive synergy of tacrolimus, the glucocorticoid tapering schedule for intervention group 2 was the same as that for the control group. That is, tapering began after the patient's condition stabilized (usually starting from the 8th week of treatment), with a 10% reduction every two weeks, and finally maintained at a dose of 8-12 mg.

*Observation indicators*

(1) General information: General information of the patients at the time of admission was collected, including gender, age, disease course, BMI, diabetes, hypertension, laboratory indicators (white blood cell count, hemoglobin, platelet count, eGFR, PLA2R antibody, fasting blood glucose, glycosylated hemoglobin, B-cell reconstitution within 6 months, B-cell reconstitution within 12 months), previous treatment (initial treatment, relapse treatment), and concomitant medications [angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor antagonists (ARB) drugs, statins].

(2) Clinical efficacy: After 6 months of treatment, efficacy data were collected. Clinical efficacy was classified as complete remission, partial remission, or ineffective. Complete remission was defined as the patient's 24-hour urine protein quantification being less than 0.3 g, with serum albumin higher than 35 g/L, and renal function-related indicators remaining stable. Partial remission was defined as a reduction in 24-hour urine protein quantification of ≥50% after treatment, with serum albumin lower than 35 g/L, and renal function-related

indicators remaining stable. Patients who did not meet the above treatment standards were considered ineffective. Total effective rate = (complete remission + partial remission/total number) × 100%.

(3) Renal function indicators: Before treatment, 3 months after treatment, and 6 months after treatment, renal function indicators were collected, including 24-hour urine protein quantification, blood urea nitrogen (BUN), serum creatinine (SCr), and plasma albumin (ALB) levels. After collection of venous blood and 24-hour urine samples, blood samples were centrifuged for 10 minutes at room temperature to obtain serum at 3000 rpm. Levels of BUN, SCr, and ALB were then evaluated using an automatic biochemical analyzer (cobas 8000, Roche Diagnostics). The urine samples were first measured for total volume and mixed well. A portion of the sample was centrifuged to obtain the supernatant, which was then measured by the biochemical analyzer to determine the urine protein concentration, and finally the total 24-hour urine protein volume was calculated.

(4) Serum M-type phospholipase A2 receptor (PLA2R): This study collected morning fasting venous blood samples from all patients at three time points: before treatment, at the end of 3 months of treatment, and at the end of 6 months of treatment. After centrifugation to separate the serum, enzyme-linked immunosorbent assay was used to quantitatively detect the antibody levels of PLA2R in the serum to evaluate its dynamic changes.

(5) Inflammatory indicators: Before treatment, 3 months after treatment, and 6 months after treatment, inflammatory indicators were collected, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and C-X-C motif chemokine ligand 13 (CXCL13). Serum samples were collected and analyzed via enzyme-linked immunosorbent assay (ELISA kit, Shanghai Enzyme-Linked Biotechnology) to detect hs-CRP. CXCL13 levels were measured using chemiluminescence immunoassay (kit, Roche Diagnostics). IL-6 levels were examined by double-antibody sandwich enzyme-linked immunosorbent assay (kit, Wuhan Huamei Biotechnology).

(6) Urinary immune indicators: Before treatment, 3 months after treatment, and 6 months after treatment, urinary immune indicators were collected, including urinary immunoglobulin G4 (IgG4) and membrane attack complex (C5b-9). Midstream urine was collected using a disposable plastic cup and kept for testing at -20°C. Urinary C5b-9 concentration was determined by enzyme-linked immunosorbent assay (ELISA) using the human C5b-9 kit from Shanghai Elion Biotechnology Co., Ltd. (item number: ml003742, lower detection limit: 0.1 ng/mL, intra-assay coefficient of variation <8%, inter-assay coefficient of variation <10%). Urinary IgG4 concentration was determined by double-antibody sandwich method using the human IgG4 detection kit from Wuhan Huamei Biotechnology Co., Ltd. (item number: CSB-E08424h, lower detection limit: 0.1 ng/mL, intra-assay coefficient of variation <6%, inter-assay coefficient of variation <9%). All operations were carried out strictly in accordance with the instructions, and duplicate wells and high, medium, and low concentration quality control samples were set up.

(7) Quality of life: Before treatment, 3 months after treatment, and 6 months after treatment, quality of life data were collected. Quality of life was measured using the 36-item Short Form Health Survey (SF-36) [17], a 100-point scale comprising 36 items where higher scores indicate better quality of life.

(8) Incidence of adverse reactions: During the entire treatment period, the occurrence of adverse reactions was collected, including hair loss, nausea, vomiting, fever, infection, liver function impairment, and gastrointestinal reactions. The severity of adverse reactions was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, classified as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4). The incidence of adverse reactions was calculated as the proportion of patients experiencing any adverse event (all grades) during the treatment period. Total incidence of adverse reactions = (number of patients who had at least one adverse reaction/total number of patients) × 100%.

*Statistical methods*

Data were analyzed using SPSS 27.0. The Shapiro-Wilk (SW) test was used to assess normality. Measurement data with normal distribution were expressed as mean ± standard

**Table 1.** Comparison of general information

| Indicator | Intervention group 1 | Intervention group 2 | Control group | $F/\chi^2$ | *P* |
|---|---|---|---|---|---|
| Gender (n, %) | | | | 0.155 | 0.926 |
| Male | 38 (54.29) | 40 (57.14) | 40 (57.14) | | |
| Female | 32 (45.71) | 30 (42.86) | 30 (42.86) | | |
| Age (year, $\bar{x}\pm sd$) | 53.27±3.62 | 53.55±3.84 | 53.61±3.58 | 0.607 | 0.546 |
| Disease course (month, $\bar{x}\pm sd$) | 7.52±2.27 | 7.46±2.21 | 7.39±2.13 | 0.485 | 0.617 |
| BMI (kg/m$^2$, $\bar{x}\pm sd$) | 24.65±2.76 | 24.73±2.84 | 24.81±2.89 | 0.317 | 0.728 |
| Diabetes (n, %) | 20 (28.57) | 18 (25.71) | 19 (27.14) | 0.144 | 0.930 |
| Hypertension (n, %) | 47 (67.14) | 45 (64.29) | 44 (62.86) | 0.292 | 0.864 |
| White blood cell (×10$^9$/L, $\bar{x}\pm sd$) | 6.45±1.43 | 6.34±1.41 | 6.53±1.46 | 0.500 | 0.607 |
| Hemoglobin (g/L, $\bar{x}\pm sd$) | 122.67±21.62 | 121.56±20.68 | 118.48±19.73 | 2.474 | 0.087 |
| Platelet (×10$^{12}$/L, $\bar{x}\pm sd$) | 231.83±63.86 | 230.69±61.94 | 238.93±64.94 | 0.033 | 0.967 |
| eGFR (n, %) | | | | 3.005 | 0.223 |
| <60 (ml/min/1.73 m$^2$) | 23 (41.82) | 18 (32.73) | 14 (25.46) | | |
| ≥60 (ml/min/1.73 m$^2$) | 47 (67.14) | 52 (74.29) | 56 (80.00) | | |
| PLA2R antibody (n, %) | 60 (85.71) | 58 (82.86) | 61 (87.14) | 0.530 | 0.767 |
| Fasting blood glucose (mmol/L, $\bar{x}\pm sd$) | 5.26±1.05 | 5.29±1.08 | 5.23±1.01 | 1.224 | 0.296 |
| Glycated hemoglobin (%, $\bar{x}\pm sd$) | 5.94±0.68 | 5.96±0.68 | 6.00±0.71 | 0.257 | 0.773 |
| B-cell reconstitution within 6 months (n, %) | 41 (58.57) | 43 (61.43) | 39 (55.71) | 0.471 | 0.790 |
| B-cell reconstitution within 12 months (n, %) | 57 (81.43) | 60 (85.71) | 61 (87.14) | 0.959 | 0.619 |
| Previous treatments (n, %) | | | | 0.496 | 0.780 |
| Initial treatment | 31 (44.29) | 34 (48.57) | 35 (50.00) | | |
| Relapse treatment | 39 (55.71) | 36 (51.43) | 35 (50.00) | | |
| Concomitant medications (n, %) | | | | 1.060 | 0.589 |
| ACEI/ARB drugs | 44 (62.86) | 41 (58.57) | 38 (54.28) | | |
| Statins drugs | 26 (37.14) | 29 (41.43) | 32 (45.71) | | |

Note: BMI, body mass index; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

deviation ($\bar{x}$ ± sd). Comparisons between two groups were performed using the independent samples t-test, while comparisons within the same group before and after treatment were conducted using the paired samples t-test. Comparisons of indicators in different groups at various time points were conducted by repeated measures analysis of variance. Non-normally distributed data were expressed as *M* ($Q_{25}$, $Q_{75}$), and the rank sum test was used for group comparisons. Count data were reported as n (%), and the $\chi^2$ test was used for group comparisons. Multivariate logistic regression analysis was used to explore independent influencing factors for therapeutic efficacy in patients with moderate to high-risk idiopathic membranous nephropathy after treatment. Subgroup analysis was performed to compare efficacy differences of various treatment regimens among patients with different characteristics. Statistical significance was defined as a *P* value less than 0.05.

## Result

### *Comparison of general data*

Baseline general data of the three groups are summarized in **Table 1**. There were no statistically significant differences among the three groups in gender, age, disease duration, BMI, diabetes, hypertension, laboratory indicators, previous treatment history, or concomitant medication use (all P>0.05).

### *Comparison of clinical efficacy among the three groups*

Clinical efficacy among the three groups is shown in **Table 2**. The total effective rates were 92.86%, 80.00%, and 77.14% for intervention

**Table 2.** Comparison of clinical validity among the three groups

| Indicator | Intervention group 1 | Intervention group 2 | Control group | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Complete remission (n, %) | 37 (52.86) | 30 (42.86) | 24 (34.29) | | |
| Partial remission (n, %) | 28 (40.00) | 26 (37.14) | 30 (42.86) | | |
| Ineffective (n, %) | 5 (7.14) | 14 (20.00) | 16 (22.86) | | |
| Total effective (n, %) | 65 (92.86) | 56 (80.00) | 54 (77.14) | 7.063 | 0.029 |

**Table 3.** Comparison of PLA2R among the three groups ($\overline{x} \pm sd$)

| Indicator | Intervention group 1 | Intervention group 2 | Control group | *F* | *P* |
|---|---|---|---|---|---|
| PLA2R (ug/mL) | | | | | |
| Before therapy | 14.37±2.04 | 14.52±2.09 | 14.71±2.13 | 0.08 | 0.08 |
| Following 3 months of therapy | 8.35±1.21 | 9.01±1.04 | 10.37±1.28 | 7.42 | 0.001 |
| Following 6 months of therapy | 2.32±0.93 | 4.17±1.05 | 5.24±1.07 | 18.56 | <0.001 |
| $F_{Time}/P_{Time}$ | | 125.67/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 32.45/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 4.87/0.009 | | | |

Note: PLA2R, phospholipase A2 receptor; $F_{Time}$, F-value of the time factor; $F_{Group}$, F-value of the group factor; $F_{Interaction}$, F-value of the interaction between groups factor and time factor; $P_{Time}$, *P*-value of the time factor; $P_{Group}$, *P*-value of the group factor; $P_{Interaction}$, *P*-value of the interaction between groups factor and time factor.

group 1, intervention group 2, and the control group, respectively. The efficacy of intervention group 1 was significantly higher than that of the other two groups (P<0.05).

*Comparison of PLA2R among the three groups*

PLA2R levels among the three groups are shown in **Table 3**. There were no statistically significant differences in baseline PLA2R levels among the three groups (P>0.05). After treatment, PLA2R levels in intervention group 1 were significantly lower than those in intervention group 2 and the control group (P< 0.05), indicating a significant inter-group effect. Additionally, all three groups showed a decrease in PLA2R levels after treatment, indicating a significant time effect (P<0.05). Moreover, a significant interaction between time and group was also found (P<0.05).

*Comparison of renal function indicators among the three groups*

Renal function indicators (24-hour urine protein, BUN, SCr, and ALB) are shown in **Table 4** and **Figure 2**. There were no statistically significant differences in baseline levels among the three groups (all P>0.05). After treatment, intervention group 1 exhibited significantly lower levels of 24-hour urine protein, BUN, and SCr, but higher ALB levels, compared to both intervention group 2 and the control group (all P<0.05), indicating a significant group effect. Furthermore, all three groups showed decreased levels of 24-hour urine protein, BUN, and SCr, alongside increased ALB levels after treatment, demonstrating a significant time effect (all P<0.05). A significant interaction between time and group was also identified (P<0.05).

*Comparison of inflammatory indicators among the three groups*

hs-CRP, IL-6, and CXCL13 levels are shown in **Table 5**. There were no statistically significant differences in baseline levels among the three groups (all P>0.05). After treatment, intervention group 1 exhibited significantly lower levels of hs-CRP, IL-6, and CXCL13 compared to both intervention group 2 and the control group, indicating a group effect (all P<0.05). Moreover, all three groups showed a reduction in these inflammatory markers after treatment, indicating a time effect (P<0.05). A significant interaction between time and group was identified (P<0.05).

**Table 4.** Comparison of kidney function indicators among the three groups ($\bar{x}\pm sd$)

| Indicator | Intervention group 1 | Intervention group 2 | Control group | *F* | *P* |
|---|---|---|---|---|---|
| 24 h urine protein (g/d) | | | | | |
| Before therapy | 6.04±0.51 | 6.07±0.53 | 6.11±0.59 | 0.100 | 0.905 |
| Following 3 months of therapy | 3.51±0.44 | 4.21±0.46 | 4.98±0.51 | 123.041 | <0.001 |
| Following 6 months of therapy | 1.37±0.36 | 1.71±0.41 | 1.97±0.48 | 18.004 | <0.001 |
| $F_{Time}/P_{Time}$ | | 3928.27/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 82.43/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 28.90/<0.001 | | | |
| BUN (mmol/L) | | | | | |
| Before therapy | 12.37±2.31 | 12.29±2.28 | 12.26±2.19 | 1.118 | 0.329 |
| Following 3 months of therapy | 9.05±1.57 | 10.21±1.63 | 10.74±1.85 | 25.680 | <0.001 |
| Following 6 months of therapy | 5.92±1.01 | 6.74±1.42 | 7.59±2.03 | 12.012 | <0.001 |
| $F_{Time}/P_{Time}$ | | 492.786/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 19.078/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 6.357/<0.001 | | | |
| SCr (umol/L) | | | | | |
| Before therapy | 298.35±36.42 | 297.92±36.03 | 297.57±35.75 | 0.857 | 0.426 |
| Following 3 months of therapy | 192.63±23.15 | 215.46±25.65 | 225.64±26.93 | 26.993 | <0.001 |
| Following 6 months of therapy | 93.56±10.51 | 110.67±12.67 | 129.58±14.72 | 147.524 | <0.001 |
| $F_{Time}/P_{Time}$ | | 2291.159/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 36.809/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 10.073/<0.001 | | | |
| ALB (g/L) | | | | | |
| Before therapy | 22.64±3.67 | 22.71±3.69 | 22.58±3.61 | 0.431 | 0.650 |
| Following 3 months of therapy | 31.28±4.03 | 29.31±3.92 | 27.63±3.86 | 257.932 | <0.001 |
| Following 6 months of therapy | 39.94±4.71 | 36.31±4.60 | 34.03±4.26 | 39.421 | <0.001 |
| $F_{Time}/P_{Time}$ | | 606.215/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 37.168/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 10.109/<0.001 | | | |

Note: BUN, blood urea nitrogen; SCr, serum creatinine; ALB, albumin; $F_{Time}$ F-value of the time factor; $F_{Group}$ F-value of the group factor; $F_{Interaction}$ F-value of the interaction between groups factor and time factor; $P_{Time}$ *P*-value of the time factor; $P_{Group}$ *P*-value of the group factor; $P_{Interaction}$ *P*-value of the interaction between groups factor and time factor.

*Comparison of urinary immune indicators among the three groups*

IgG4 and C5b-9 levels are shown in **Table 6**. There were no statistically significant differences in baseline levels among the three groups (both P>0.05). After treatment, intervention group 1 demonstrated a more significant reduction in both markers compared to intervention group 2 and the control group, indicating a group effect (both P<0.05). Furthermore, all groups exhibited a decline in IgG4 and C5b-9 levels over time, indicating a time effect (both P<0.05). A significant interaction between time and group was observed (P<0.05).

*Comparison of quality of life among the three groups*

SF-36 scores are shown in **Table 7**. There were no statistically significant differences in baseline SF-36 scores among the three groups (P>0.05). After treatment, intervention group 1 demonstrated greater improvement in SF-36 scores compared to both intervention group 2 and the control group, indicating a group effect (P<0.05). While scores increased in all groups over time, indicating a time effect (P<

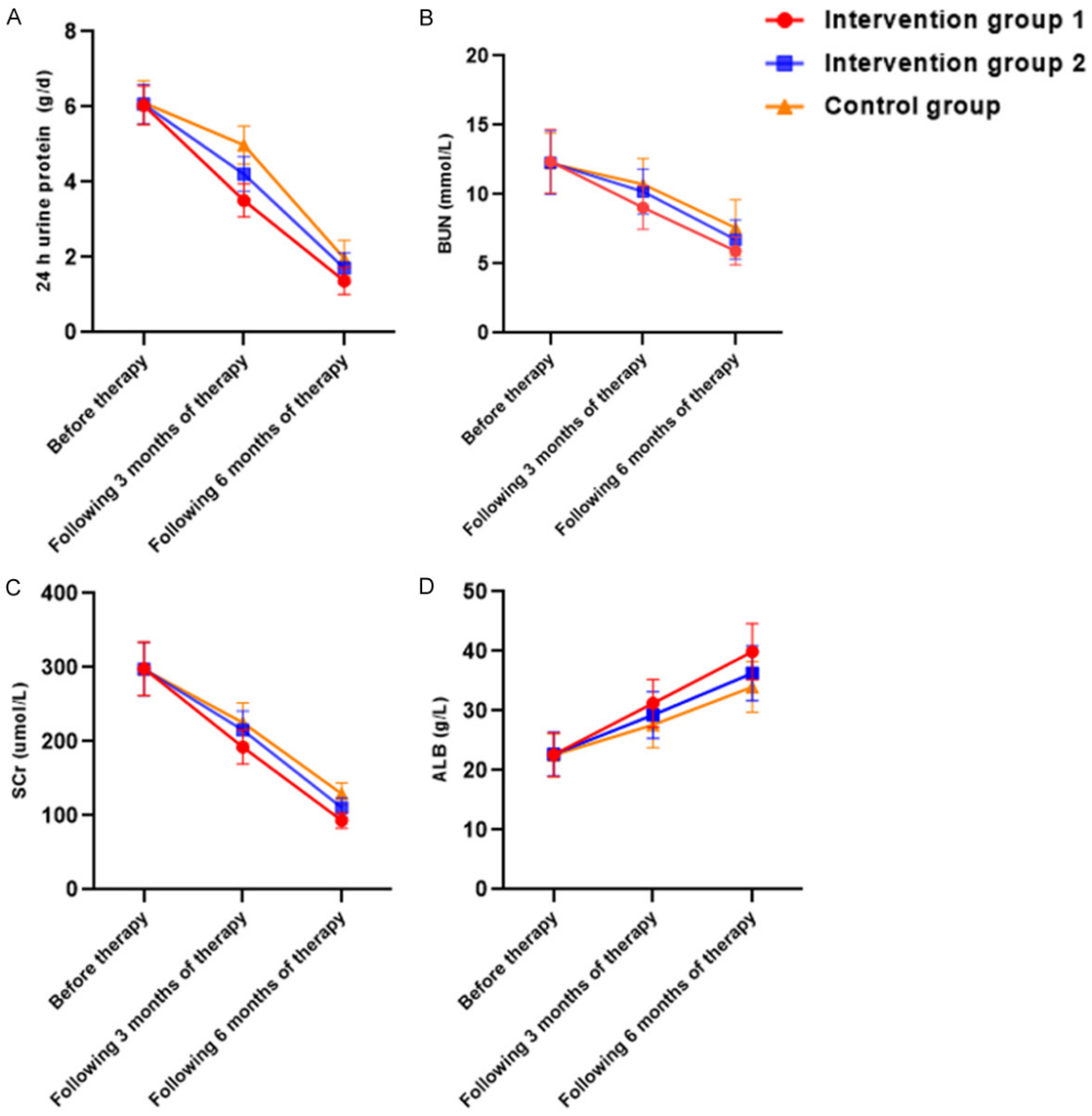


**Figure 2.** The trend of changes in renal function indicators for the three groups of patients (A) 24-hour urine protein; (B) BUN; (C) SCr; (D) ALB. Note: BUN, blood urea nitrogen; SCr, serum creatinine; ALB, albumin.

0.05), a significant interaction between time and group was observed ($P<0.05$).

*Comparison of adverse reaction occurrence among the three groups*

Adverse reactions are summarized in **Table 8**. Among the three groups, the majority of adverse reactions were mild to moderate in severity (grade 1 or 2). No grade 3 or 4 adverse events were observed in any group. The total incidence rate was 8.57% in intervention group 1, compared to 7.14% in both intervention group 2 and the control group. No statistically significant difference in the overall incidence of adverse reactions was observed among the groups ($P>0.05$).

*Multivariate logistic regression analysis of therapeutic effects in patients with moderate to high-risk idiopathic membranous nephropathy*

Taking clinical efficacy as the dependent variable (with "effective" coded as 1 and "ineffective" coded as 0), and using treatment regimen

**Table 5.** Comparison of inflammatory indicators among the three groups ($\bar{x}\pm sd$)

| Indicator | Intervention group 1 | Intervention group 2 | Control group | *F* | *P* |
|---|---|---|---|---|---|
| hs-CRP (mg/L) | | | | | |
| Before therapy | 15.71±3.51 | 15.75±3.54 | 15.78±3.61 | 0.062 | 0.940 |
| Following 3 months of therapy | 10.62±2.48 | 11.95±2.61 | 12.62±2.91 | 53.920 | <0.001 |
| Following 6 months of therapy | 5.32±1.73 | 6.27±1.81 | 7.54±2.16 | 28.693 | <0.001 |
| $F_{Time}/P_{Time}$ | | 663.671/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 22.405/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 19.832/<0.001 | | | |
| IL-6 (pg/mL) | | | | | |
| Before therapy | 33.54±8.51 | 33.32±8.42 | 33.15±8.41 | 2.259 | 0.107 |
| Following 3 months of therapy | 21.45±5.61 | 25.16±5.83 | 27.18±6.02 | 25.350 | <0.001 |
| Following 6 months of therapy | 9.26±2.63 | 11.46±3.21 | 13.18±3.63 | 36.204 | <0.001 |
| $F_{Time}/P_{Time}$ | | 478.875/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 9.713/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 9.599/<0.001 | | | |
| CXCL13 (pg/mL) | | | | | |
| Before therapy | 89.24±17.35 | 89.15±17.27 | 89.17±17.21 | 0.015 | 0.985 |
| Following 3 months of therapy | 54.17±12.63 | 61.58±13.84 | 66.94±13.97 | 26.129 | <0.001 |
| Following 6 months of therapy | 25.76±7.57 | 33.47±8.59 | 39.35±9.56 | 37.834 | <0.001 |
| $F_{Time}/P_{Time}$ | | 880.850/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 27.781/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 6.005/<0.001 | | | |

Note: hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; CXCL13, C-X-C motif chemokine ligand 13; $F_{Time}$ F-value of the time factor; $F_{Group}$ F-value of the group factor; $F_{Interaction}$ F-value of the interaction between groups factor and time factor; $P_{Time}$ *P*-value of the time factor; $P_{Group}$ *P*-value of the group factor; $P_{Interaction}$ *P*-value of the interaction between groups factor and time factor.

**Table 6.** Comparison of urine immune indicators among the three groups ($\bar{x}\pm sd$)

| Indicator | Intervention group 1 | Intervention group 2 | Control group | *F* | *P* |
|---|---|---|---|---|---|
| IgG4 (ug/mmoL) | | | | | |
| Before therapy | 15.63±2.46 | 15.57±2.38 | 15.26±2.34 | 0.960 | 0.385 |
| Following 3 months of therapy | 6.47±1.41 | 8.45±1.79 | 9.67±1.95 | 39.189 | <0.001 |
| Following 6 months of therapy | 1.26±0.26 | 2.65±0.63 | 3.25±0.83 | 138.001 | <0.001 |
| $F_{Time}/P_{Time}$ | | 2884.481/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 41.468/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 7.816/<0.001 | | | |
| C5b-9 (ng/mg) | | | | | |
| Before therapy | 85.48±11.74 | 85.27±11.65 | 84.96±11.23 | 0.634 | 0.531 |
| Following 3 months of therapy | 61.83±10.64 | 70.84±11.35 | 74.85±11.08 | 14.294 | <0.001 |
| Following 6 months of therapy | 42.65±9.23 | 51.61±10.35 | 58.95±10.86 | 66.635 | <0.001 |
| $F_{Time}/P_{Time}$ | | 518.472/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 49.362/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 11.112/<0.001 | | | |

Note: IgG4, immunoglobulin G4; C5b-9 membrane attack complex; $F_{Time}$ F-value of the time factor; $F_{Group}$ F-value of the group factor; $F_{Interaction}$ F-value of the interaction between groups factor and time factor; $P_{Time}$ *P*-value of the time factor; $P_{Group}$ *P*-value of the group factor; $P_{Interaction}$ *P*-value of the interaction between groups factor and time factor.

**Table 7.** Comparison of quality of life among the three groups ($\bar{x}\pm sd$)

| Indicator | Intervention group 1 | Intervention group 2 | Control group | *F* | *P* |
|---|---|---|---|---|---|
| SF-36 (score) | | | | | |
| Before therapy | 57.26±5.14 | 56.87±5.18 | 56.63±5.07 | 1.537 | 0.218 |
| Following 3 months of therapy | 78.57±6.05 | 68.85±5.96 | 63.58±5.76 | 121.448 | <0.001 |
| Following 6 months of therapy | 89.93±6.93 | 81.84±6.42 | 74.85±6.27 | 68.391 | <0.001 |
| $F_{Time}/P_{Time}$ | | 814.337/<0.001 | | | |
| $F_{Group}/P_{Group}$ | | 145.508/<0.001 | | | |
| $F_{Interaction}/P_{Interaction}$ | | 30.159/<0.001 | | | |

Note: SF-36, short form 36 health survey; $F_{Time}$ F-value of the time factor; $F_{Group}$ F-value of the group factor; $F_{Interaction}$ F-value of the interaction between groups factor and time factor; $P_{Time}$ *P*-value of the time factor; $P_{Group}$ *P*-value of the group factor; $P_{Interaction}$ *P*-value of the interaction between groups factor and time factor.

**Table 8.** Comparison of adverse reactions occurrence in the three groups of patients (n, %)

| Degree | Type of adverse reaction | Intervention group 1 | Intervention group 2 | Control group | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|
| Grade 1 | Hair loss | 0 (0.00) | 1 (1.43) | 0 (0.00) | | |
| | Nausea | 2 (2.86) | 1 (1.43) | 2 (2.86) | | |
| | Vomiting | 1 (1.43) | 1 (1.43) | 0 (0.00) | | |
| | Fever | 1 (1.43) | 0 (0.00) | 1 (1.43) | | |
| | Infection | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| | Liver function impairment | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| | Gastrointestinal reactions | 1 (1.43) | 1 (1.43) | 1 (1.43) | | |
| Grade 2 | Hair loss | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| | Nausea | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| | Vomiting | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| | Fever | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| | Infection | 1 (1.43) | 0 (0.00) | 1 (1.43) | | |
| | Liver function impairment | 0 (0.00) | 1 (1.43) | 0 (0.00) | | |
| | Gastrointestinal reactions | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| Grade 3 | - | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| Grade 4 | - | 0 (0.00) | 0 (0.00) | 0 (0.00) | | |
| Total incidence (n, %) | | 6 (8.57) | 5 (7.14) | 5 (7.14) | 0.135 | 0.935 |

and general information as independent variables, a multivariate logistic regression analysis was conducted. The results are shown in **Table 9**. The findings revealed that after adjusting for various baseline confounding factors such as age, disease duration, and comorbidities, the rituximab treatment regimen (compared with the control group) was an independent factor associated with better therapeutic effects (OR=3.851, 95% CI: 1.325-11.196, *P*=0.013), while the included baseline data were not independent influencing factors, and the tacrolimus regimen also did not show an independent association (OR=1.185, *P*=0.680).

*Subgroup analysis forest plot of the efficacy of three treatment methods for moderate to high-risk idiopathic membranous nephropathy patients in different populations*

Subgroup analysis of efficacy differences among various treatment regimens for patients with different characteristics is shown in **Figure 3**. The results of the subgroup analysis forest plot indicate that the efficacy of the RTX+MP treatment regimen was consistently superior to that of the MP regimen in all subgroups (diabetes, hypertension, eGFR, and PLA2R antibody); while the TAC+MP regimen showed no statisti-

**Table 9.** Multivariate logistic regression analysis of therapeutic effects in patients with moderate and high-risk idiopathic membranous nephropathy

| Indicators | B | SE | Wald $\chi^2$ | OR | 95% CI | p |
|---|---|---|---|---|---|---|
| Gender (n, %) | 0.115 | 0.063 | 3.332 | 1.122 | 0.992-1.270 | 0.067 |
| Age | -0.051 | 0.047 | 1.177 | 0.950 | 0.865-1.043 | 0.278 |
| Disease course | 0.033 | 0.080 | 0.170 | 1.034 | 0.883-1.210 | 0.679 |
| BMI | 0.098 | 0.060 | 2.668 | 1.103 | 0.980-1.241 | 0.102 |
| Diabetes | 0.988 | 0.689 | 2.056 | 2.688 | 0.696-10.366 | 0.152 |
| Hypertension | -0.095 | 0.519 | 0.034 | 0.909 | 0.330-2.514 | 0.855 |
| White blood cell | 0.250 | 0.134 | 3.481 | 1.284 | 0.987-1.670 | 0.063 |
| Hemoglobin | 0.010 | 0.008 | 1.563 | 1.010 | 0.994-1.026 | 0.211 |
| Platelet | -0.001 | 0.002 | 0.250 | 0.999 | 0.995-1.003 | 0.617 |
| eGFR | 0.971 | 0.619 | 2.461 | 2.640 | 0.785-8.870 | 0.116 |
| PLA2R antibody | -0.587 | 0.596 | 0.970 | 0.556 | 0.172-1.788 | 0.325 |
| Fasting blood glucose | 0.135 | 0.166 | 0.661 | 1.144 | 0.827-1.584 | 0.416 |
| Glycated hemoglobin | -0.064 | 0.274 | 0.055 | 0.938 | 0.548-1.605 | 0.815 |
| B-cell reconstitution within 6 months | -0.007 | 0.078 | 0.225 | 0.993 | 0.852-1.157 | 0.929 |
| B-cell reconstitution within 12 months | -0.226 | 0.476 | 0.225 | 0.798 | 0.314-2.028 | 0.635 |
| Previous treatments | 0.441 | 0.297 | 2.205 | 1.555 | 0.868-2.781 | 0.138 |
| Concomitant medications | 0.031 | 0.037 | 0.702 | 1.032 | 0.959-1.109 | 0.402 |
| Treatment method | | | 6.402 | | | 0.041 |
| rituximab | 1.348 | 0.544 | 6.141 | 3.850 | 1.325-11.180 | 0.013 |
| tacrolimus | 0.169 | 0.412 | 0.168 | 1.184 | 0.527-2.654 | 0.682 |

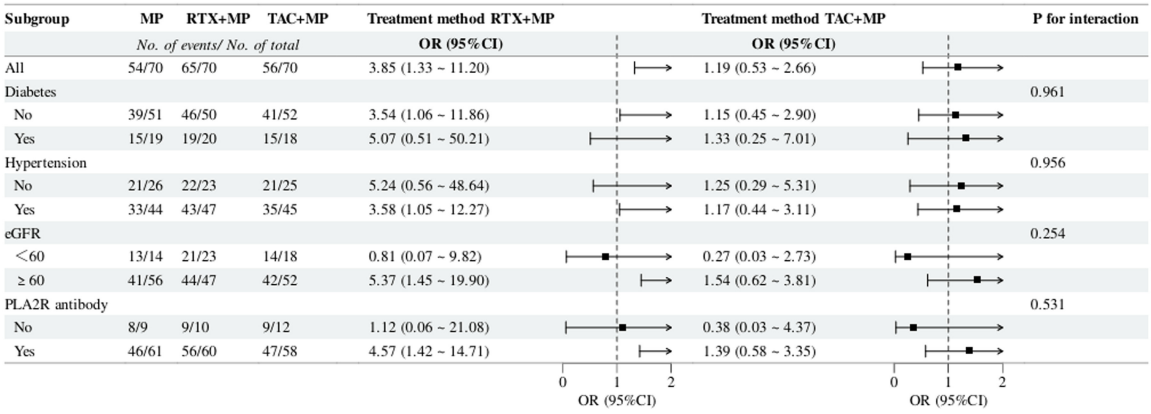


**Figure 3.** Subgroup analysis forest plot of the efficacy of three treatment methods for moderate-high risk idiopathic membranous nephropathy patients in different populations. Note: MP, Methylprednisolone; RTX, Rituximab; TAC, Tacrolimus.

cally significant difference in efficacy compared to the MP regimen in all populations and subgroups. Moreover, the *P* values for interaction effects in all subgroup analyses were not statistically significant, indicating that the pattern of the above efficacy advantages was basically consistent across different patient subgroups, and no factors were found to significantly alter the efficacy differences between the two combination regimens and the MP regimen.

## Discussion

The treatment of IMN focuses on suppressing pathogenic antibody production through immunosuppression, thereby delaying disease progression and preserving renal function [18]. For patients with moderate to high-risk IMN, simple supportive treatment or monotherapy with glucocorticoids often fails to achieve the desired remission rate [19, 20]. Therefore, combination

treatment regimens have become the focus of clinical exploration. This study, through a prospective randomized controlled design, compared the efficacy of rituximab plus methylprednisolone versus tacrolimus plus methylprednisolone in patients with moderate to high-risk IMN. The results showed that the rituximab combination regimen demonstrated significant advantages in inducing clinical remission, improving renal function, inhibiting inflammation and immune responses, and enhancing quality of life, without increasing the risk of adverse reactions.

In terms of overall therapeutic efficacy, this study found that the rituximab-based regimen was superior to both the tacrolimus-based regimen and methylprednisolone monotherapy. This result is similar to those of previous studies [21]. This is likely because rituximab is a monoclonal antibody targeting B cells, which can eliminate $CD20^+$ B cells that produce autoantibodies (such as anti-PLA2R antibodies) at the source, potentially inducing deeper and more sustained immune remission [22]. Although tacrolimus can rapidly inhibit T cell activation and podocyte damage, reducing proteinuria, its efficacy may depend to some extent on continuous drug exposure, and there is a risk of recurrence after discontinuation [23].

In terms of renal function indicators, this study found that after receiving rituximab combined with methylprednisolone, patients had lower 24-hour urine protein quantification, SCr, and BUN compared to those treated with tacrolimus plus methylprednisolone or methylprednisolone alone, while ALB levels were higher. These results are consistent with those of previous studies [19, 24]. This indicates that rituximab has more obvious advantages in controlling protein leakage, promoting recovery of serum albumin, and stabilizing renal function. This is because rituximab eliminates B cells that produce pathogenic antibodies, inhibiting the core immune process at its source, more thoroughly reducing antibody levels, alleviating glomerular damage, and continuously reducing urine protein, increasing plasma albumin, and improving renal function indicators (such as serum creatinine and urea nitrogen) [25, 26]. In contrast, tacrolimus mainly acts by inhibiting T cells and stabilizing podocytes, acting at a downstream level, and is not thorough in eliminating the pathogenic root, so its long-term improvement effect on renal function is relatively limited [27].

In terms of inflammatory indicators and urinary immune indicators, this study found that after receiving rituximab combined with methylprednisolone, patients had lower levels of hs-CRP, IL-6, CXCL13, IgG4, and C5b-9 compared to those treated with tacrolimus plus methylprednisolone or methylprednisolone alone. These results are similar to those of a previous study [11]. This indicates that rituximab treatment has a more powerful and extensive inhibitory effect on the core immunopathological processes of idiopathic membranous nephropathy. This is because rituximab can specifically target and eliminate $CD20^+$ B cells, not only reducing the production of pathogenic antibodies (affecting IgG4) at the source, but also significantly weakening the activation of the complement terminal pathway (reducing C5b-9), and directly inhibiting B cell-related inflammatory signals (such as the B cell chemokine CXCL13 and the pro-inflammatory cytokine IL-6), thereby achieving in-depth regulation of the humoral immune system and the inflammatory network [28, 29]. In contrast, tacrolimus can effectively inhibit T cell activation and podocyte damage but has limited effects on plasma cell formation and autoantibody production [30].

In terms of quality of life, this study revealed that patients treated with rituximab combined with methylprednisolone had higher SF-36 scores than those treated with tacrolimus combined with methylprednisolone or methylprednisolone alone. This result is similar to those of previous studies. This is because the rapid and sustained clinical remission brought by rituximab treatment directly improved the physiological functions and physical sensations of the patients [31]; in addition, its efficient therapeutic effect enhanced patients' confidence in treatment, reduced the psychological burden caused by the disease, and thus comprehensively elevated patients' quality of life in multiple dimensions such as physiological function and mental health [32].

Regarding the occurrence of adverse reactions, this study found that adverse reactions in all three groups were mild to moderate, and the combination therapy of rituximab and methyl-

prednisolone was not associated with a greater risk of adverse reactions. This is because rituximab has a high degree of B-cell targeting, and its mechanism of action is more precise compared to traditional immunosuppressants, avoiding extensive cytotoxic side effects [33]. At the same time, standardized premedication and infusion management effectively prevented acute infusion reactions, and during the study period, close monitoring of indicators such as blood counts and liver function was conducted to ensure the safety of short-term medication [34]. However, the long-term safety of rituximab still requires longer follow-up for assessment.

Furthermore, considering potential confounding bias among patients, this study further employed a multivariate logistic regression model to adjust for factors such as age, diabetes, baseline eGFR, hypertension, disease duration, and PLA2R antibody titer. After these adjustments, it was confirmed that the rituximab combination regimen is an effective treatment, a factor contributing to the reduction in urinary protein and the increase in serum albumin. This eliminated the interference of baseline differences on the conclusion, making the results more reliable. In subgroup analysis, the efficacy of rituximab combination therapy remained consistent across patients with different clinical characteristics (such as whether they had diabetes or hypertension), which provides a basis for its application in a wide range of populations and enhances the generalizability and clinical applicability of the research conclusions.

In conclusion, after adjusting for age, diabetes, baseline estimated glomerular filtration rate, and related confounding factors, rituximab combined with methylprednisolone in the treatment of patients with moderate to high-risk IMN can effectively improve treatment outcomes, enhance renal function, inhibit inflammation and immune responses, improve patients' quality of life without increasing short-term adverse event risk, and is applicable to a wide range of patients. Nevertheless, as a single-center study, this research has several limitations. First, the follow-up period was relatively short, precluding assessment of long-term remission rates, relapse rates, and renal prognosis with the two regimens. Second, as a single-center study, the generalizability and robustness of the conclusions require further validation. Third, the study lacked pre-specified subgroup analyses (e.g., based on baseline eGFR or PLA2R antibody titers), limiting the ability to identify which patient subgroups might benefit most from a particular regimen. Fourth, the study design did not include a triple-therapy arm (rituximab plus tacrolimus plus methylprednisolone); therefore, the potential synergy or safety profile of such a combination remains unexplored. Future research should involve multicenter collaboration, extend the follow-up period, and further evaluate the long-term efficacy and safety of these treatments.

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## Disclosure of conflict of interest

None.

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