Heliyon 10 (2024) e28836

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

# Traditional Chinese medicine for idiopathic membranous nephropathy: A systematic review and meta-analysis

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ARTICLE INFO

*Keywords:*
Idiopathic membranous nephropathy
Traditional Chinese medicine
Systematic review
Meta-analysis

ABSTRACT

*Background:* Idiopathic membranous nephropathy (IMN) is a rare autoimmune disorder that causes nephrotic syndromes in adults. Conventional immunosuppressive therapies often exhibit limited efficacy in achieving remission and may result in notable adverse reactions, warranting the exploration of novel therapeutic approaches for IMN treatment. Traditional Chinese medicine (TCM), which is extensively used for kidney disease management, is a promising alternative.

*Objective:* This study aimed to examine the safety and efficacy of TCM alone or in combination with Western medicine for the management of patients diagnosed with IMN.

*Methods:* This study employed a systematic search of English and Chinese electronic databases to identify randomized controlled trials (RCTs) that examined the application of TCM in the treatment of IMN. RCTs that met the predetermined inclusion and exclusion criteria and assessed the safety and efficacy of TCM alone or in combination with Western medicine in patients with IMN were included in the analysis. The methodological quality of the included studies was evaluated by using a risk-of-bias tool. All statistical analyses were performed using the RevMan software (version 5.4.2). The evidence was evaluated on the https://www.gradepro.org/website.

*Results:* This study included 29 randomized controlled trials (RCTs) involving 1982 patients with moderate methodological quality that met the inclusion criteria. The results showed that, compared to Western medicine alone therapy, the use of TCM alone or in combination with Western medicine significantly improved total remission (TR) rate (risk ratios [RR] 1.38, 95% confidence interval [CI] 1.29–1.46, $I^2 = 0\%$, $P < 0.00001$), complete remission (CR) rate (RR 1.78, 95% CI 1.48–2.15, $I^2 = 0$, $P < 0.00001$), partial remission (PR) rate (RR 1.27, 95% CI 1.161.40, $I^2 = 0\%$, $P < 0.00001$), and serum albumin (ALB) levels (MD: 4.05, 95% CI: 3.02–5.09, $I^2 = 91\%$, $P < 0.00001$). TCM alone or in combination with Western medicine also reduced proteinuria levels (mean difference [MD]: 1.05, 95% CI: 1.30 to −0.79, $I^2 = 95\%$, $P < 0.00001$),

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https://doi.org/10.1016/j.heliyon.2024.e28836
Received 15 October 2023; Received in revised form 23 March 2024; Accepted 26 March 2024
Available online 31 March 2024

serum creatinine (SCr) levels (MD: 7.47, 95% CI: 13.70 to −1.24, $I^2 = 97\%$, P = 0.02), and serum antibodies against M-type phospholipase A2 receptor levels (aPLA2Rab) (MD: 19.24, 95% CI: 33.56 to −4.93, $I^2 = 87\%$, P = 0.008). Moreover, the efficacy of combined TCM and Western medicine is superior to that of Western medicine alone in reducing the incidence of infection, hepatotoxicity, and thrombosis. Although the primary and secondary outcomes were consistent, the evidence was generally moderate.

*Conclusion:* The results of this study suggest that TCM alone or in combination with Western medicine may be a feasible alternative therapeutic approach for the treatment of IMN. Nevertheless, additional, rigorously designed, high-quality, and extensive clinical trials are imperative to provide substantial evidence regarding the effectiveness of TCM in managing IMN.

## 1. Introduction

Membranous nephropathy (MN) is a form of glomerulonephritis characterized by increased proteinuria resulting from the accumulation of immune complexes beneath the glomerular epithelium [1]. Approximately 80% of MN cases manifest without a discernible cause, termed as idiopathic MN (IMN), whereas the remaining 20% are associated with comorbidities or exposure to toxins and specific medications (secondary MN, [SMN]), including hepatitis, systemic lupus erythematosus (SLE), and malignancy [2]. MN is frequently observed in adults aged between 50 and 60 years of age, exhibiting a higher predilection in men with a male-to-female ratio of 2:1 [3]. The prevalence of MN in non-diabetic Caucasian adults is estimated to be as high as 8–10 cases per 1 million individuals [1]. Approximately one-third of patients with MN progress to end-stage renal disease (ESRD) within a decade, and the likelihood of developing ESRD increases with elevated proteinuria [4]. Conventional treatment for patients with severe proteinuria caused by IMN typically involves a combination of corticosteroids and immunosuppressive agents administered for a duration of 6 to 12 months [5]. However, immunosuppressive therapy has potential adverse effects, including infections and myelosuppression [6]. Moreover, the prolonged treatment period, substantial treatment burden, and severe side effects associated with immunosuppressive therapy greatly limit its clinical applicability for IMN [2,3]. Therefore, exploring alternative treatment strategies for IMN is imperative, and traditional Chinese medicine (TCM) is a viable option.

Kidney diseases have been managed using TCM for extensive periods. Based on the expertise of professionals from diverse regions in China, patients diagnosed with IMN are administered distinct herbal formulations as part of their treatment regimens. Animal studies have substantiated the efficacy of these formulations in ameliorating proteinuria and increasing serum albumin (ALB) [7,8]. TCM interventions potentially exert their influence on IMN through multifaceted mechanisms, including anti-inflammatory and immunosuppressive effects and improving podocyte injury [9,10]. Advancements in theoretical and clinical studies on the use of TCM for the treatment of IMN have demonstrated the efficacy of TCM. Notably, *Astragalus membranaceus* has successfully induced clinical remission in an older woman with IMN, eliminating the need for immunosuppressive agents [11]. The findings of a multicenter randomized controlled clinical trial demonstrated that Shenqi particles have a similar remission rate in patients with IMN and a better safety profile than the standard therapy with corticosteroids and cyclophosphamide [12]. Although the specific names of TCM compound formulas may vary, their underlying principles and constituent ingredients are mostly similar. These formulas predominantly consist of huangqi (*Astragalus membranaeus* (Fisch.) Bunge.), Fulins (*Poria cocos* (Schw.) Wolf.), Baizhu (*Atractylodes macrocephala* Koidz.), Danggui (*Angelica sinensis* (Oliv.)), Dangshen (*Codonopsis pilosula* (Franch.) Nannf.), Dilong (*Lumbricus*), Shuizhi (*Whitmania pigra* Whitman), Shanyao (*Rhizoma Dioscoreae*), Chuanxiong (*Ligusticum chuanxiong* Hort.), Zexie (*Alisma plantago-aquatica Linn.*), Dihuang (*Rehmannia glutinosa* (Gaertn.) Libosch. [*R.glutinosa* Libosch.], and *F. Hueichingensis* (Chao et Schih) Hsiao). Furthermore, the available multicenter, large-sample, randomized controlled clinical trials pertaining to this subject are scarce. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) to provide evidence-based information on the effectiveness and adverse events of TCM for IMN treatment, including the total effective rate, complete and partial remission rates, 24-hour urinary total protein (24-h UTP), serum ALB, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), antibodies against the M-type phospholipase A2 receptor (aPLA2Rab), and adverse events.

## 2. Materials and methods

This systematic review and meta-analysis were conducted in accordance with the guidelines specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement for reporting systematic reviews [13]. The study was registered in PROSPERO under the registration number CRD42022354113.

### 2.1. Search strategy

Two reviewers (WS and HYG) systematically searched five English electronic databases (Web of Science, Embase, PubMed, Cochrane Library, and Clinical Trials.gov) and four Chinese electronic databases (Wanfang Med Database, Chinese VIP Information Database, China National Knowledge Infrastructure, and SinoMed) to identify randomized RCTs from the beginning date to August 11, 2022. The search was conducted using standard medical subject heading terms, as outlined in Supplementary Table 1.

### 2.2. Inclusion criteria

The inclusion criteria were as follows.

(1) Participants included in the studies were diagnosed with IMN based on biopsy findings or positive serum anti-phospholipase A2 receptor antibody (aPLA2Rab) titers.
(2) RCTs that focused on the treatment of IMN using Chinese herbal medicine formulas.
(3) The intervention group received either TCM alone or in combination with Western medicine as recommended by the relevant guidelines. Only studies that utilized Chinese herbal medicine formulas in the form of decoctions or granules were included, with no restrictions on the dosage or duration of treatment. The control group was administered Western medicine exclusively.
(4) The primary outcome metric was the total effective (TR) rate, which comprised both complete remission (CR) and partial remission (PR) rates. TR was determined by evaluating proteinuria and serum ALB levels. CR was defined as the maintenance of stable renal function with stable 24-h UTP $<$0.3 g/24 h and normal or near-normal ALB levels ($\geq$35 g/L). PR was defined as maintenance of stable renal function with 24-h UTP of 0.3–3.5 g/24 h, a decrease of $\geq$50% in 24-h UTP compared to pre-treatment values, and a significant improvement in ALB levels. The secondary outcome metrics were 24-h UTP, serum ALB, SCr, eGFR, serum aPLA2Rab, and adverse events.

### 2.3. Exclusion criteria

(1) Studies that included participants with SMN secondary to hepatitis B, SLE, medications, malignancies, or other etiologies.
(2) Clinical trials that failed to yield sufficient data regarding diagnostic criteria, interventions, and, specifically, TR.
(3) RCTs that lacked a control group or intervention drugs in the control group that used TCMs.
(4) Articles for which full texts were not available.

### 2.4. Data extraction

Two reviewers (WS and HWG) independently extracted relevant data based on predetermined inclusion and exclusion criteria. Any discrepancies were reviewed and evaluated by a third reviewer (XQ). The information extracted from the included studies consisted of publication year, first author, diagnosis, participants' sex and age, sample size, withdrawal rates, course of treatment, remission rates in complete and partial cases, adverse events, and outcomes.

### 2.5. Risk of bias assessment

The Cochrane Collaboration Risk of Bias Assessment Tool [14] was utilized to evaluate the eligible studies. Each study was subjected to an independent risk of bias assessment conducted by two reviewers (XH and PL), and the results were subsequently compared. In cases of disagreement, an independent third reviewer (KB) was consulted.

### 2.6. Quality of evidence

The certainty of the evidence pertaining to key comparisons and outcomes was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [15]. The level of evidence for each outcome was independently assessed according to the Cochrane Handbook for Systematic Evaluation by two reviewers (PL and HWG); however, controversial outcomes were further discussed and evaluated by a third reviewer (YX).

### 2.7. Statistical analysis

All statistical analyses were performed using RevMan 5.4 software. Owing to the diverse sample sizes of the studies, a randomized effects model was employed for all meta-analyses. Continuous data were assessed using mean difference (MD) and 95% confidence intervals (CI), and dichotomous data were expressed as risk ratios (RR) with a 95% CI. A P-value less than 0.05 indicated statistical significance. Subgroup analyses were performed based on the treatment duration, types of comparison treatments, and baseline 24-h UTP, if feasible. Statistical heterogeneity was assessed using the chi-square test and the $I^2$ statistic. An I-squared value $>$ 50% was indicative of significant heterogeneity. If feasible, sensitivity analyses were performed to assess the robustness of the synthesized results. Funnel plots were used to evaluate publication bias.

## 3. Results

### 3.1. Study selection

Nine databases were searched, resulting in the identification of 2346 studies, of which 1557 remained after excluding duplicate articles. A review of the article titles identified 199 potential trials relevant to the subject. Among them, 170 trials, including those that did not meet the inclusion criteria, had incomplete data, and were non-randomized, were excluded. After a thorough evaluation of the

full text, 29 trials were finally included for data synthesis. The screening process is illustrated in Fig. 1.

### 3.2. Characteristics of eligible studies

A total of 1982 participants were included in the 29 eligible studies, of whom 1000 and 982 were experimental and control participants, respectively. The participant characteristics were similar across the treatment groups in terms of sex, age, and baseline metrics. Regarding the disease duration, 6 [16–21], 11 [22–32], and 4 trials [24,33–35] were mainly within 6 months, 12 months, and more than a year, respectively. Other trials did not provide detailed information on disease duration. Only one eligible trial [32] adopted TCM alone as the experimental treatment, whereas the other trials used a combination of TCM and Western medicine as the experimental treatment. The treatment duration varied between 1.5 and 12 months. Participants in 13 studies received short-term treatment, including one study [30] with a 1.5-month treatment, four studies [18,19,35,36] with a 2-month treatment, seven studies [21,23,26,34,37–39] with a 3-month treatment, and one study [40] with a 4-month treatment. The participants in 14 studies [16,17,22,24,25,27–29,31,33,41–44] received a 6-month midterm treatment. Participants in two studies [20,32] received 12-month long-term treatment. All included studies reported the outcomes of TR, CR, PR, 24-h UTP and serum ALB. The outcomes of TR, CR, PR, 24-h UTP and serum ALB were reported in all the studies that were included, and the outcomes of SCr were reported in 21 studies [18, 20–26,28–34,36,37,39,41,43,44] reported. Six studies [24,30,31,34,35,37] reported eGFR outcomes, and five studies [16,20,22,38, 43] reported serum aPLA2Rab outcomes. Supplementary Table 19 illustrates the characteristics of the included studies. The components of the Chinese herbal formulas are listed in Supplementary Table 20.

### 3.3. Quality assessment of studies

Fig. 2 and Supplementary Fig. 1 show the moderate methodological quality of the included studies. Twenty-seven included studies [16–29,31–35,37–44] adopted the method of randomization, whereas two studies [30,36] did not provide details. Only one of the included studies reported the blinding of the outcome assessment [33]; however, the methodology was not specified. Thirteen studies reported withdrawals or dropouts [17,22,24–29,31,32,38,39,43], and the statistical analyses did not include data on patients who dropped out or were lost to follow-up. No selective reporting bias was found in any of the studies. No other biases were observed among the included studies.

### 3.4. Primary outcomes

#### 3.4.1. Total remission rate

The data integration presented in Fig. 3 demonstrates a higher TR rate in the experimental group than in the control group (RR 1.38, 95% CI: 1.29–1.46, $I^2 = 0\%$, $P < 0.00001$). The strength and quality of the evidence were assessed using the GRADE methodology, which determined that the findings possessed a moderate level of certainty (Supplementary Table 18). The TR rates after short-term, mid-term, and long-term treatments were reported in 13 (839 patients) [18,19,21,23,26,30,34–40], 14 (1008 patients) [16,17,

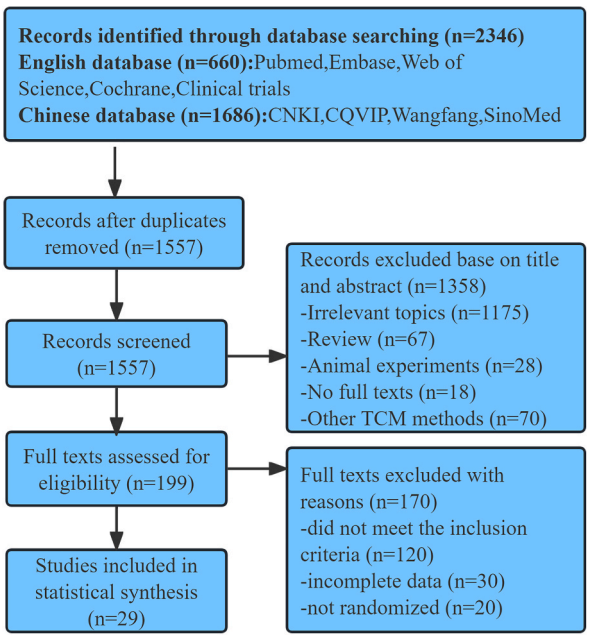


**Fig. 1.** Flow chart of study selection.

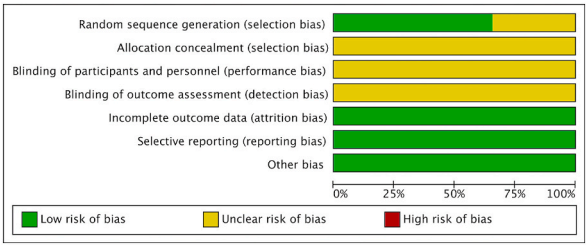


**Fig. 2.** Risk of bias graph.

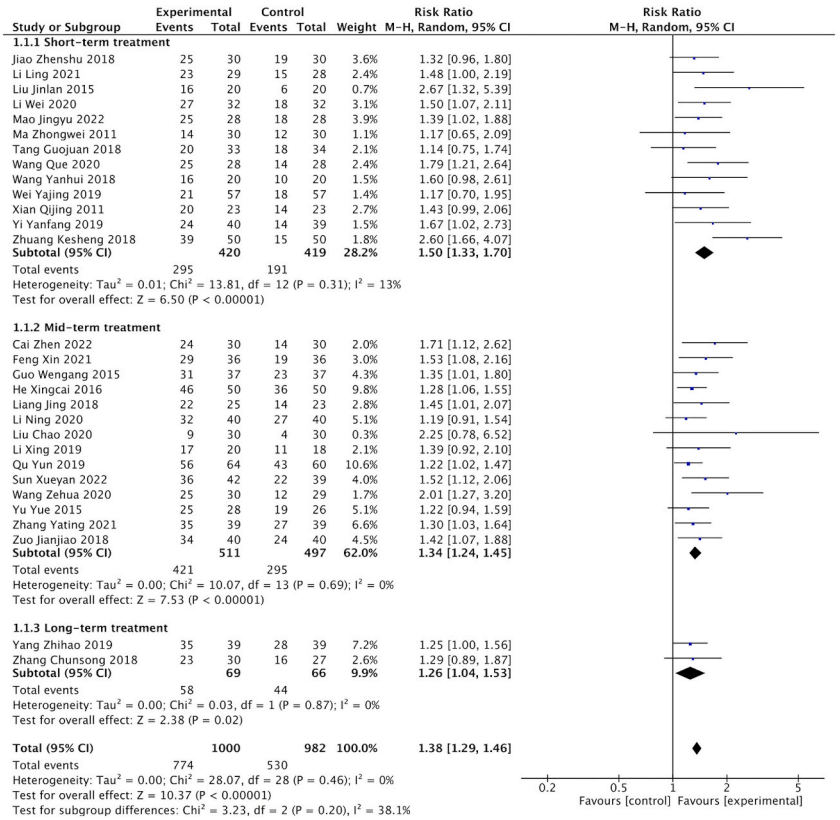


**Fig. 3.** Comparison of TR rates between TCM alone, TCM coupled with Western medicine, and Western medicine alone.

22,24,25,27–29,31,33,41–44], and 2 studies (135 patients) [20,32], respectively. After a short-term treatment, the experimental group demonstrated a higher TR rate than did the control group (RR 1.50, 95% CI 1.33–1.70, $I^2 = 13\%$, $P < 0.00001$). This benefit was observed in both mid-term treatment (RR 1.34, 95% CI 1.24–1.45, $I^2 = 0$, $P < 0.00001$) and long-term treatment (RR 1.26, 95% CI 1.04–1.53, $I^2 = 0\%$, $P = 0.02$). Subgroup analysis was conducted based on different treatment comparisons, and the TR rates remained consistent across basic treatments, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), corticosteroids, and immunosuppressive agents (Supplementary Table 2). Regardless of the baseline 24-h UTP levels (either < or > 4 g), the experimental group exhibited increased TR rates (Supplementary Table 10).

### *3.4.2. Complete remission rate*

Fig. 4 illustrates the superior effect of the experimental group on the CR rate in the eligible studies than in the control group (RR 1.78, 95% CI 1.48–2.15, $I^2 = 0$, $P < 0.00001$). The study findings indicated a low level of certainty following assessment using the GRADE evaluation of the strength and quality of evidence (Supplementary Table 18). The CR rates following short-, mid-, and long-term treatments were examined in 13 studies (839 patients) [18,19,21,23,26,30,34–40], 14 studies (1008 patients) [16,17,22,24,25,27–29,31,33,41–44], and 2 studies (135 patients) [20,32], respectively. The findings revealed that the experimental group exhibited superior CR rates than did the control group in both short-term (RR 2.63, 95% CI 1.83–3.78, $I^2 = 0\%$, $P < 0.00001$) and mid-term treatments (RR 1.55, 95% CI 1.22–1.96, $I^2 = 0\%$, $P = 0.0003$); however, this was not observed in long-term treatment (RR 1.50,

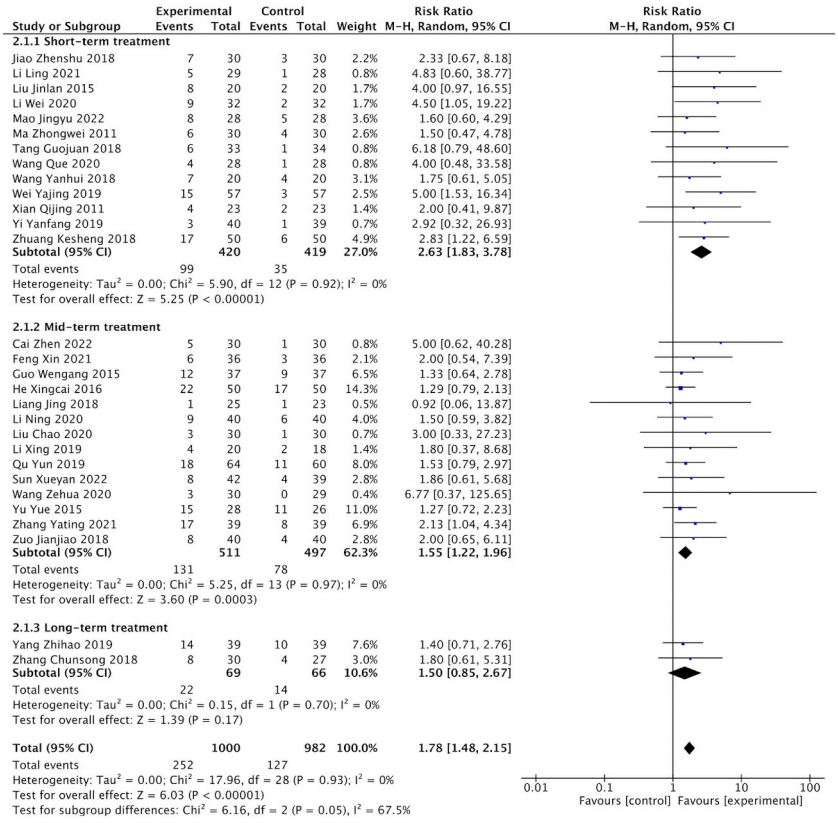


**Fig. 4.** Comparison of CR rates between TCM alone, TCM coupled with Western medicine, and Western medicine alone.

95% CI 0.85–2.67, $I^2 = 0\%$, P = 0.17). Subgroup analysis was performed to compare the treatments, which revealed that the CR rates of the TCM plus glucocorticoids and cyclophosphamide (CTX), TCM plus glucocorticoids and tacrolimus, and TCM plus tacrolimus groups were better than those of the control group. However, TCM plus basic treatment, TCM plus ACEI/ARB, and TCM plus glucocorticoids and cyclosporine A did not show statistically significant CR rates than in the control treatment (Supplementary Table 3). Regardless of whether the baseline 24-h UTP levels (less than or greater than 4 g), the experimental group exhibited increased CR rates (Supplementary Table 11).

### *3.4.3. Partial remission rate*

As shown in Fig. 5, the eligible studies demonstrated a superior effect of the experimental group in terms of PR rate (RR 1.27, 95% CI 1.16–1.40, $I^2 = 0\%$, P < 0.00001) than did the control group. The strength and quality of the evidence were assessed using GRADE, which indicated a moderate level of certainty (Supplementary Table 18). The PR rates following short-, mid-, and long-term treatments were reported in 13 (839 patients) [18,19,21,23,26,30,34–40], 14 (1008 patients) [16,17,22,24,25,27–29,31,33,41–44], and 2 studies (135 patients) [20,32], respectively. The experimental group exhibited higher rates of PR than did the control group following short-term treatment (RR 1.26, 95% CI 1.05–1.52, $I^2 = 26\%$, P = 0.01) and mid-term treatment (RR 1.30, 95% CI 1.15–1.46, $I^2 = 0\%$, P < 0.0001). However, no statistically significant differences in PR rates (RR 1.15, 95% CI 0.81–1.63, $I^2 = 0\%$, P = 0.43) were observed between the two groups after long-term treatment. Subgroup analysis revealed that the PR rates of TCM plus basic treatment, ACEIs/ARBs, and glucocorticoids and CTX were superior to those in the control group. Conversely, no statistically significant differences in PR rates were found when comparing the TCM plus glucocorticoids and tacrolimus, TCM plus tacrolimus, and TCM plus glucocorticoids and cyclosporine A groups with the control group (Supplementary Table 4). Regardless of whether the baseline 24-h UTP levels (below or above 4 g), the experimental group exhibited an increased PR (Supplementary Table 12).

## *3.5. Secondary outcomes*

### *3.5.1. Changes in 24-h UTP*

Supplemental Fig. 2 demonstrates that compared to the control treatment, the eligible studies consistently showed a superior effect of the experimental group in terms of 24-h UTP (MD -1.05, 95% CI -1.30 to −0.79, $I^2 = 95\%$, P < 0.00001). The lack of consistency in the instrumentation and standards employed in various studies has resulted in a high degree of heterogeneity in the findings. Therefore, a sensitivity analysis was performed to determine the robustness and reliability of the results. The change in 24-h UTP was

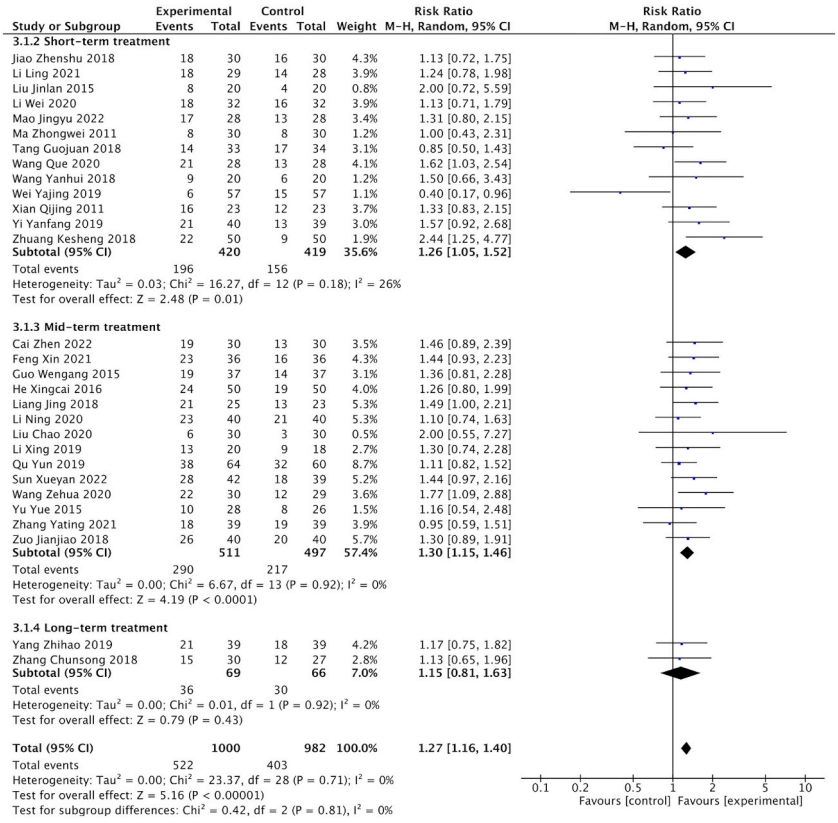


**Fig. 5.** Comparison of PR rates between TCM alone, TCM coupled with Western medicine, and Western medicine alone.

assessed based on 13 studies [18,19,21,23,26,30,34–40] involving 839 patients after short-term treatment, 14 studies [16,17,22,24,25,27–29,31,33,41–44] involving 1008 patients after mid-term treatment, and 2 studies [20,32] involving 135 patients after long-term treatment. Compared to the control group, the experimental group demonstrated a significant reduction in proteinuria following short-term treatment (MD -0.91, 95% CI -1.34 to −0.48, $I^2 = 96\%$, $P < 0.0001$) and mid-term treatment (MD -1.21, 95% CI -1.56 to −0.86, $I^2 = 92\%$, $P < 0.00001$). Furthermore, this benefit persisted even with long-term treatment (MD -0.64, 95% CI -1.26 to −0.01, $I^2 = 21\%$, $P = 0.05$). The results of the subgroup analysis showed that 24-h UTP was consistent for basic treatment, ACEIs/ARBs, corticosteroids, and immunosuppressive agents (Supplementary Table 5). Regardless of the baseline 24-h UTP levels (below or above 4 g), 24-h UTP decreased in the experimental group (Supplementary Table 13).

### *3.5.2. Changes in serum ALB*

As shown in Supplemental Fig. 3, the eligible studies demonstrated a significant improvement in serum ALB levels in the experimental group than did the control treatment (MD 4.05, 95% CI 3.02–5.09, $I^2 = 91\%$, $P < 0.00001$). The lack of consistency in the instrumentation and standards employed in various studies has resulted in a high degree of heterogeneity in findings. However, following sensitivity analysis, the results were determined to be robust and reliable. Specifically, changes in serum ALB were assessed in 13 studies (839 patients) [18,19,21,23,26,30,34–40] after short-term treatment, 14 studies (1008 patients) [16,17,22,24,25,27–29,31,33,41–44] after mid-term treatment, and 2 studies (135 patients) [20,32] after long-term treatment. In this study, a comparison between the experimental and control groups revealed a significant increase in serum ALB levels following short-term treatment. This beneficial effect was observed to persist throughout mid-term and long-term treatments (MD 4.16, 95% CI 2.53–5.79, $I^2 = 91\%$, $P < 0.00001$). And the benefit persisted through mid-term treatment (MD 3.93, 95% CI 2.17–5.69, $I^2 = 88\%$, $P < 0.0001$), long-term treatment (MD 4.05, 95% CI 3.57–4.54, $I^2 = 0\%$, $P < 0.00001$). Subgroup analysis was conducted to compare different treatment approaches. Patients who received TCM in combination with basic treatment, TCM in combination with glucocorticoids and CTX, or TCM in combination with glucocorticoids and cyclosporine An exhibited higher serum ALB levels than did the control group. However, the studies revealed no statistically significant difference in serum ALB levels between TCM plus basic treatment, TCM plus ACEIs/ARBs, or TCM plus glucocorticoids and tacrolimus vs. control treatment (Supplementary Table 6). Regardless of whether the baseline 24-h UTP levels were less than or greater than 4 g, the experimental group exhibited increased serum ALB levels (Supplementary Table 14).

### 3.5.3. Changes in SCr

As shown in Supplemental Fig. 4, the eligible studies demonstrated a more pronounced impact of the experimental group on SCr levels than in the control (MD -7.47, 95% CI -13.70 to −1.24, $I^2 = 97\%$, P = 0.02). The lack of consistency in the instrumentation and standards employed in various studies has resulted in a high degree of heterogeneity in the findings. However, following sensitivity analysis, the results were determined to be robust and reliable. Specifically, alterations in SCr were monitored in 9 studies (646 patients) [18,21,23,26,30,34,36,37,39] following short-term treatment, 10 studies (738 patients) [22,24,25,28,29,31,33,41,43,44] following mid-term treatment and 2 studies (135 patients) [20,32] following long-term treatment. The results indicated no statistically significant differences in SCr levels between the two groups after short-term (MD -6.67, 95% CI -16.57 to 3.24, $I^2 = 98\%$, P = 0.19) and mid-term treatment (MD -8.68, 95% CI -20.71 to 3.36, $I^2 = 98\%$, P = 0.16). However, a significant decrease in SCr levels was observed in the experimental group than in the control group after long-term treatment (MD -6.01, 95% CI -8.28 to −3.75, $I^2 = 0\%$, P < 0.00001). Subgroup analysis revealed that the combination of TCM plus glucocorticoids and tacrolimus resulted in higher serum creatinine levels than in the control group. However, the study revealed that there were no statistically significant differences in Scr levels when comparing TCM plus basic treatment, TCM plus ACEI/ARB, TCM plus glucocorticoids, TCM plus tacrolimus, and TCM plus glucocorticoids and cyclosporine A vs. the control group (Supplementary Table 7). Furthermore, the studies demonstrated no statistically significant variations in SCr levels between the two groups, regardless of whether the baseline 24-h UTP levels were less than or greater than 4 g (Supplementary Table 15).

### 3.5.4. Changes in eGFR

As shown in Supplemental Fig. 5, six studies (373 patients) [24,30,31,34,35,37] reported an alteration in eGFR. The findings of these studies revealed no statistically significant differences in eGFR between the two groups (MD 1.95, 95% CI -0.46 to 4.35, $I^2 = 0\%$, P = 0.11). Subsequently, we performed a subgroup analysis based on the different treatments and baseline levels of 24-h UTP, which indicated no statistically significant differences in eGFR between the two groups (Supplementary Tables 8 and 16).

### 3.5.5. Changes in serum aPLA2Rab

As shown in Supplemental Fig. 6, a total of four studies (268 patients) [16,22,38,43] examined alterations in serum aPLA2Rab levels. The experimental group exhibited a noteworthy decrease in serum aPLA2Rab levels in comparison to the control group (MD -19.24, 95% CI -33.56 to −4.93, $I^2 = 87\%$, P = 0.008). The lack of consistency in the instrumentation and standards employed in various studies has resulted in a high degree of heterogeneity in the findings. However, following sensitivity analysis, the results were determined to be robust and reliable. Subgroup analysis conducted based on the comparison treatments revealed that the serum aPLA2Rab levels in the TCM plus tacrolimus, and TCM plus glucocorticoids and cyclosporine A groups were superior to those in the control group. However, no statistically significant differences in serum aPLA2Rab levels were observed between the control group and the TCM plus basic treatment and TCM plus glucocorticoids and CTX groups. (Supplement Table 9). Furthermore, a subgroup analysis was conducted to compare the baseline 24-h UTP levels, which revealed no statistically significant differences in serum aPLA2Rab levels between the experimental and control groups for patients with baseline 24-h UTP levels of <4 g. However, in patients with baseline 24-h UTP levels exceeding 4 g, the experimental group exhibited decreased serum aPLA2Rab levels (Supplementary Table 17).

### 3.5.6. Adverse events

Eleven articles [16,17,20,22,24,29,32,38,41,43,44] provided data on adverse events, which included incidences of infection (7.04%, 20/284), gastrointestinal symptoms (4.23%, 9/213), glucose intolerance (8.05%, 14/174), thrombosis (2.02%, 2/99), hepatotoxicity (1.45%, 3/207), leukocytopenia (0, 0/109), and other adverse effects (11.04%, 18/163) in TCM combined with Western medicine group. Incidences of infection (16.07%, 45/280), gastrointestinal symptoms (10.1%, 21/208), glucose intolerance (10.98%, 19/173), thrombosis (13%, 13/100), hepatotoxicity (5.91%, 12/203), leukocytopenia (8.49%, 9/106), and others (20.99%, 34/162) were observed in the control group. No statistically significant differences in gastrointestinal symptoms (RR 0.49, 95% CI 0.23–1.05, $I^2 = 0\%$, P = 0.07) and glucose intolerance (RR 0.76, 95% CI 0.41–1.44, $I^2 = 0\%$, P = 0.40) were observed between the two groups. However, the control treatment exhibited greater susceptibility to infection (RR 0.47, 95% CI 0.29–0.76, $I^2 = 0\%$, P = 0.002), thrombosis (RR 0.22, 95% CI 0.06–0.87, $I^2 = 0\%$, P = 0.03), hepatotoxicity (RR 0.33, 95% CI 0.12–0.94, $I^2 = 0\%$, P = 0.04), and leukocytopenia (RR 0.14, 95% CI 0.03–0.77, $I^2 = 0\%$, P = 0.02) than that of the TCM coupled with Western medicine treatment. Table 1 lists the details of the adverse events.

**Table 1**
Adverse events among IMN patients receiving TCM/Western medicine and control treatments.

| Adverse events | Trials | E (A/N) | C (A/N) | RR (95%CI) | P value | Heterogeneity |
|---|---|---|---|---|---|---|
| Infection | 8 | 20/284 | 45/280 | 0.47 [0.29, 0.76] | 0.002 | $P = 0.91$ $I^2 = 0\%$ |
| Gastrointestinal syndrome | 6 | 9/213 | 21/208 | 0.49 [0.23, 1.05] | 0.07 | $P = 0.78$ $I^2 = 0\%$ |
| Glucose intolerance | 5 | 14/174 | 19/173 | 0.76 [0.41, 1.44] | 0.40 | $P = 0.96$ $I^2 = 0\%$ |
| Thrombosis | 3 | 2/99 | 13/100 | 0.22 [0.06, 0.87] | 0.03 | $P = 0.58$ $I^2 = 0\%$ |
| Hepatotoxicity | 6 | 3/207 | 12/203 | 0.33 [0.12, 0.94] | 0.04 | $P = 1$ $I^2 = 0\%$ |
| Leukocytopenia | 3 | 0/109 | 9/106 | 0.14 [0.03, 0.77] | 0.02 | $P = 0.96$ $I^2 = 0\%$ |
| Others | 5 | 18/163 | 34/162 | 0.56 [0.34, 0.94] | 0.03 | $P = 0.40$ $I^2 = 1\%$ |

E: experimental group; C: control group; A: number of adverse events; N: Total number of participants.

### 3.5.7. Funnel plot

This was performed to examine the presence of publication bias in 29 studies that reported TR rates and compared the efficacy of TCM alone or TCM plus Western medicine with a control treatment. The funnel plot displayed an asymmetrical distribution of studies, suggesting the potential existence of a publication bias within the included studies (Fig. 6).

## 4. Discussion

This study conducted a comprehensive assessment of the effectiveness and safety of TCM alone or in combination with Western medicine in patients with IMN. The evaluation was based on 29 RCTs involving 1982 IMN patients.

### 4.1. Summary of main results

The study findings suggest that TCM, used alone or in conjunction with Western medicine, has positive therapeutic effects and offers advantages in mitigating specific adverse effects. Compared with the control treatment, the experimental treatment significantly enhanced the TR rate and ALB levels following short-term treatment, and this benefit persisted throughout the mid- and long-term treatments. Moreover, the experimental treatment was superior to the control treatment in improving the CR and PR rates while also reducing 24-h UTP levels after both short- and mid-term treatments. Although no statistically significant differences were observed between the two groups following long-term treatment, there was a tendency toward an increase in both CR and PR rates. This tendency could mainly be attributed to the inadequate sample size. Furthermore, despite the lack of improvement in eGFR with experimental treatment involving TCM alone or in combination with Western medicine, it was more effective in reducing serum aPLA2Rab and SCr levels than did the control treatment. Notably, TCM alone or in combination with Western medicine demonstrated an improvement in SCr levels after long-term treatment, suggesting their potential benefits on renal function.

A subgroup analysis was conducted to compare the effects of TCM alone and TCM combined with Western medicine on various disease indicators. Although the results indicated that both treatment approaches showed improvements in one or more disease indicators, the statistical insignificance observed in certain treatment subgroups contradicted the findings in other subgroups. This inconsistency may be attributed to the limited sample size of this study. Regardless of whether the baseline 24-h UTP levels were below or above 4 g, the administration of TCM alone or in combination with Western medicine resulted in improvements in TR, CR, PR, 24-h UTP, and ALB. However, statistical analysis revealed no significant differences in the eGFR or SCr levels between the two groups. Notably, the short treatment duration in most patients may have limited the accuracy of eGFR and SCr data in reflecting long-term renal prognosis. Moreover, the findings for subgroups with baseline 24-h UTP levels $<4$ g were inconsistent with those of other subgroups. An insufficient sample size was identified as the main factor contributing to this phenomenon. The combination of TCM and Western medicine demonstrates the ability to decrease serum aPLA2Rab levels when the baseline 24-h UTP levels exceed 4 g.

Furthermore, data pertaining to adverse reactions such as infections, gastrointestinal symptoms, glucose intolerance, thrombosis, hepatotoxicity, and leukocytopenia were extracted from 13 trials. The experimental group exhibited a reduction in infection, hepatotoxicity, and thrombosis than did the control group.

A comprehensive review by Lu et al. [45] conducted in China examined the use of TCM as an adjuvant therapy for IMN. The findings of their systematic review indicated that TCM had a significant effect on patients with IMN, which was consistent with our findings. To provide an updated assessment, we incorporated recently published trials into our systematic review. To ensure the robustness of our analysis, we established stringent inclusion criteria by precisely defining CR and PR rates. In addition to evaluating the effects of TCM on 24-h UTP and ALB levels, we focused on its effect on SCr, eGFR, and aPLA2Rab levels because these biomarkers are strongly associated with disease prognosis. Although previous studies have failed to consider the impact of TCM treatment courses on the development of IMN, our study successfully addresses this gap in the literature.

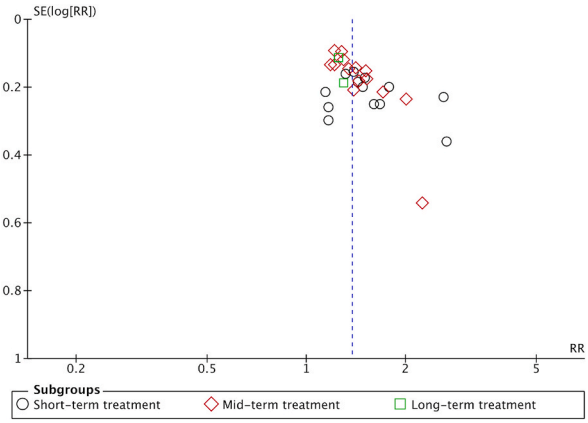


**Fig. 6.** Funnel plot.

### 4.2. Rationality of TCM for IMN

MN, a renal-limiting immune disease, contributes substantially to the onset of nephrotic syndrome in adults. According to the 2021 clinical guidelines, the initial treatment approach for IMN involves the administration of glucocorticoids in conjunction with alkylating agents [5]. Nevertheless, these treatment modalities may not always be effective and may result in notable adverse effects. For instance, the use of cyclophosphamide as part of the treatment regimen may increase the risk of myelosuppression, gonadal toxicity, hemorrhagic cystitis, infections, and malignancies [46,47].

Calcineurin inhibitors (CNIs) such as cyclosporin A and tacrolimus resulted in high relapse rates upon discontinuation, with relapse rates ranging from 40% to 50% [48–50]. Additionally, the administration of rituximab has been associated with incidents of pruritus and infusion-related reactions [49,51]. Consequently, managing high recurrence rates and serious adverse reactions remains challenging for physicians when standard immunosuppressive therapies are ineffective, necessitating the search for an optimal treatment.

TCM has gained considerable attention as an effective approach for the treatment of IMN. A preliminary study showed that Zhenwu-tang was effective in MN model rats by significantly reducing 24-h UTP levels and ameliorating renal damage. These favorable outcomes were attributed to the inhibition of the nuclear factor-kappa B pathway and the NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome [10]. Moreover, Wenyang Lishui decoction effectively treated MN model rats by reducing proteinuria and improving podocyte damage, which was associated with the modulation of p53 and Bcl-2 expression [52]. Additional experimental studies [53] conducted on rats with passive Heymann nephritis have provided further evidence that Mahuang Fuzi and Shenzhuo Decoction have notable advantages in reducing urinary protein levels and exerting renoprotective effects. These benefits have been attributed to the facilitation of autophagy and the suppression of the Wnt/β-catenin pathway.

The efficacy of TCM in treating patients with MN has been increasingly supported by a growing body of research. Chen et al. [12] conducted the first multicenter randomized controlled clinical trial to specifically investigate the use of Shenqi particles in the treatment of IMN. The trial yielded findings indicating that the administration of Shenqi particles can effectively decelerate the decline in eGFRs and reduce the occurrence of adverse events. A multicenter, non-randomized, single-arm clinical trial demonstrated that the utilization of Mahuang Fuzi and Shenzhuo Decoction in the treatment of patients with MN led to remission in 61.4% of individuals, with no significant adverse effects observed during a 3-year follow-up period. This remission rate was notably higher than the 35% observed in the target group [54]. Additionally, another study discovered that the modified Jianpi Qushi Heluo decoction exhibited beneficial effects in patients with MN following a two-month treatment regimen [55]. The modified Jianpi Qushi Heluo decoction demonstrated notable efficacy in reducing 24-h urinary albumin levels and enhancing plasma albumin levels. Additionally, it exhibits immunomodulatory effects in patients with MN by decreasing Th1 and Th17 levels and increasing Th2 levels in the peripheral blood.

## 5. Limitations

Although our study findings corroborated those of previous studies and demonstrated the efficacy of TCM as an adjuvant treatment for IMN, there were certain potential limitations. The primary limitation of this review was that the methodological quality of the eligible studies was moderate, while none of the included studies reported whether allocation concealment was performed, and no detail about blinding was described. As the primary outcome measure of this study is objective test results, the impact of whether participants are aware of their allocation to a specific treatment group during the implementation of the clinical trial is relatively minor on the outcomes. However, if researchers are aware of the intervention information between treatment groups, there may be a tendency to allocate participants with milder conditions to the treatment group, which could potentially influence the outcomes. Therefore, the overall quality evaluation was medium quality. The relapse rate serves as an indicator of the long-term efficacy of the medication. However, only one study [42] recorded recurrence rates, whereas others did not conduct long-term follow-up assessments. Considering that TCM was used as the sole experimental group drug in only one study [32], supporting evidence is insufficient. Consequently, future clinical trials incorporating TCM alone should be designed to enhance the strength of this evidence. Therefore, prudence should be exercised when interpreting the statistical findings of this study.

Because the inclusion of numerous studies in the data collection process has been hindered by the inconsistent utilization of response criteria across studies, future research endeavors should primarily employ the response criteria outlined in the KIDGO guidelines to facilitate a comparative analysis of the effectiveness of diverse treatment alternatives. Furthermore, most studies on TCM treatment for MN are limited to a duration of 3–6 months, with a lack of long-term follow-up; therefore, comprehensive data on the long-term remission and prognosis of patients with MN remain scarce. Hence, future studies prioritizing long-term follow-up in their research design with a recommended follow-up period of 1–2 years are warranted.

To overcome these limitations, meticulously planned, high-caliber, and extensive clinical trials are imperative to provide additional evidence of the efficacy of TCM in the treatment of IMN.

## 6. Conclusion

The current review shows that TCM have potential advantages in terms of increasing remission rate and serum ALB levels, decreasing 24 h-UTP, SCr and serum aPLA2Rab levels. Besides, TCM can help reduce the adverse reactions of corticosteroids and immunosuppressive agents to a certain extent. TCM may be an adjuvant treatment for IMN. Well-designed randomized controlled trials (RCTs) are necessary in the future to provide clinical decision-makers with valuable information regarding the effectiveness of TCM prescriptions for the treatment of IMN.

## Data availability statement

Although the data associated with our study have not yet been deposited in a publicly available repository. Any inquiries regarding the original data presented in this article may be addressed to the corresponding author. The original data will be made available on request.

## Funding

The work is supported by Special Project of State Key Laboratory of Dampness Syndrome of Chinese Medicine (Nos. SZ2021ZZ36 and SZ2021ZZ09), the 2020 Guangdong Provincial Science and Technology Innovation Strategy Special Fund (Guangdong-Hong Kong-Macau Joint Lab) (No. 2020B1212030006), the Natural Science Foundation of Guangdong Province (No.2022A1515011628), the Traditional Chinese Medicine Bureau of Guangdong Province (No. 20211194) and the Guangzhou Science and Technology Plan Project (No.202102010212), Guangdong Provincial Key Laboratory of Chinese Medicine for Prevention and Treatment of Refractory Chronic Diseases (No. MB2020KF06), Special Funding for Scientific and Technological Research on Traditional Chinese Medicine, Guangdong Provincial Hospital of Traditional Chinese Medicine (YN2023HL03)

## CRediT authorship contribution statement

**Wenjun Shan:** Writing – original draft, Methodology, Conceptualization. **Haiyu Guan:** Writing – original draft, Data curation. **Haowen Gu:** Investigation, Data curation. **Rongrong Wang:** Visualization, Investigation. **Xiaoyan Huang:** Visualization, Investigation. **Ping Li:** Validation. **Ying Xie:** Supervision. **Kun Bao:** Writing – review & editing. **Xindong Qin:** Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

Not applicable.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28836.

## Abbreviation

| | |
|---|---|
| IMN | idiopathic membranous nephropathy |
| TCM | traditional Chinese medicine |
| RCTs | randomized controlled trials |
| TR | total remission |
| RR | risk ratios |
| CI | confidence interval |
| CR | complete remission |
| PR | partial remission |
| SMN | secondary membranous nephropathy |
| SLE | systemic lupus erythematosus |
| ESRD | end stage renal disease |
| 24-h UTP | 24-hour urinary total protein |
| ALB | serum albumin |
| SCr | serum creatinine |
| eGFR | estimated glomerular filtration rate |
| aPLA2Rab | antibodies against M-type phospholipase A2 receptor |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| MD | mean difference |
| ACEI | angiotensin converting enzyme inhibitor |
| ARB | angiotensin receptor blocker |
| CTX | cyclophosphamide |
| CNIs | calcineurin inhibitors |

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