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Original Article

Network meta-analysis of best treatment strategies for adult Chinese patients with idiopathic membranous nephropathy combined with nephrotic syndrome

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Abstract: The current study aimed to evaluate the best treatment strategies for adult Chinese patients with idiopathic membranous nephropathy (IMN) combined with nephrotic syndrome (NS) using network meta-analysis. Pubmed, Embase, Cochrane Library, MEDLINE, CNKI, CBM, and Wanfang databases were searched for clinical randomized controlled trials in adult Chinese patients with IMN combined with NS. R 3.03, Stata 14.0, and ADDIS software were used for statistical analysis of data. Thirty-six clinical randomized controlled trials, including 2,481 patients with IMN combined with NS and 16 types of clinical treatment, were studied. There was good convergence and no statistical differences, according to inconsistency testing ($P > 0.05$). Surface under the cumulative ranking curve (SUCRA) ranking of predicted efficacy for therapeutic measures revealed the following: (1) Induced remission (complete remission+partial remission) was the primary endpoint of efficacy; (2) Relapse after remission was a secondary endpoint of efficacy; and (3) Cluster analysis for comprehensive evaluation of remission and relapse rates revealed that mycophenolic mofetil+prednisone+*T. wilfordii* led to the highest remission rate and lowest recurrence rate, while FK506 monotherapy or cyclosporine combined with prednisone had relatively poor efficacy. In adult Chinese patients with IMN combined with NS, mycophenolic mofetil combined with prednisone and *T. wilfordii* is appropriate as a first-line treatment program. Moreover, glucocorticoids combined with tacrolimus can serve as a substitute treatment program. Multi-target treatment with *T. wilfordii* and other immunosuppressants can increase efficacy.

Keywords: Network meta-analysis, adult Chinese patients, idiopathic membranous nephropathy, treatment program

Introduction

Membranous nephropathy (MN) is a pathology often found in glomerular disease, accounting for 20-25% of cases of nephrotic syndrome (NS) in adults. It is a class of disorders characterized by the accumulation of immune complexes below epithelial cells of the glomerular basement membrane (GBM), accompanied by thickening of the GBM in late stages. Idiopathic membranous nephropathy (IMN) accounts for approximately 70% of MN cases [1]. There have been no large-scale epidemiological studies of IMN in China. However, many research centers have reported that incidence rates of IMN have increased by greater than 10% in the last 10 years [2, 3]. Patients with IMN have a long disease course. In addition, many factors influence the disease. There are large differences in prognoses. Early follow-up studies of Chinese patients with IMN revealed that 5-, 10-, and 15-year renal survival rates were 96.9%, 93.5%, and 86.6%, respectively [4]. Therefore, a proactive search for effective therapeutic measures for treatment of IMN is urgently needed, improving long-term prognosis of patients and reducing the economic burden on citizens.

Studies have shown that heavy proteinuria and its duration are important factors in prognosis

of IMN. More severe proteinuria has been reported to increase the likelihood of progression to end-stage renal disease [5]. Therefore, 2012 Edition of Kidney Disease: Improving Global Outcomes (KDIGO) guidelines stated that, for patients with IMN clinically presenting with nephrotic syndrome, having failed hormone monotherapy, "glucocorticoids combined with alkylating agents or calcineurin inhibitors" are recommended as an initial treatment [6]. KDIGO guidelines are based on Western research. Different individuals have been reported to have different clinical responses to the same treatment. For example, some patients with IMN in Japan, Korea, and China have had good clinical outcomes with hormone monotherapy [7-9]. Gene polymorphisms in different races affect the absorption and utilization of drugs, thereby leading to differences in drug sensitivity among patients [10, 11]. Traditional Chinese Medicines *Tripterygium wilfordii* and Shenqi particle have been widely used in the treatment of Chinese patients with IMN, showing relatively good outcomes [12, 13]. This indicates that 2012 KDIGO clinical practice guidelines for IMN may not be completely appropriate for the Chinese population. Therefore, it is unclear which treatment measures are most appropriate for the Chinese population. The current network meta-analysis was conducted to systematically evaluate efficacies of hormone, immunosuppressant, and Traditional Chinese Medicine treatments for adult Chinese patients with IMN combined with nephrotic syndrome, aiming to provide a scientific basis for the rational clinical use of these drugs.

Materials and methods

Search strategy

Search terms included "membranous nephropathy/idiopathic membranous nephropathy/primary membranous nephropathy" and "randomized controlled". The following databases were searched: 1) China National Knowledge Infrastructure from 1979 to January 2018; 2) China Biology Medicine Disc from 1978 to January 2018; 3) Wanfang Data from 1990 to January 2018; 4) PubMed from 1948 to January 2018; 5) MEDLINE Ovid SP from 1946 to January 2018; 6) Embase from 1947 to January 2018; and 7) Cochrane Library from 1999 to January 2018. In addition, primary literature, relevant guidelines, and references in reviews were screened. Publications meeting inclusion criteria were accepted.

Literature inclusion criteria

(1) Study type: Domestic and international publications related to randomized controlled trials (RCTs) for hormone, immunosuppressant, and Traditional Chinese Medicine treatments for primary or idiopathic MN. Language was restricted to only Chinese or English; (2) Study subjects: Chinese individuals aged 18 years or older with renal biopsy pathology consistent with primary MN combined with nephrotic syndrome. There were no restrictions on sex or educational levels; (3) Interventional measures: RCTs of hormone, immunosuppressant, biological agent, or Traditional Chinese Medicine treatments for IMN, with treatment times of 6 months or longer; (4) Clear discrete or continuous data available after follow-up, containing a follow-up period of 6 months or longer; (5) No specific requirements for adjuvant treatments, including blood pressure management, lipid management, anticoagulation, and renin-angiotensin-aldosterone system antagonists; (6) Studies with obvious definitions for nephrotic syndrome, complete remission, partial remission, recurrence, and treatment failure.

Literature exclusion criteria

(1) MN secondary to autoimmune disease, cancer, infections, and medication; (2) Multiple publications of the same study; (3) Reviews or commentaries; (4) Non-RCT studies; (5) RCTs of immunosuppressant treatment for IMN in which the patients did not meet the criteria of nephrotic syndrome; (6) Atypical membranous nephropathy; (7) Traditional Chinese Medicine treatment for IMN with no obvious pharmacological mechanisms; (8) Animal studies or controlled trials with the same treatment methods administered at different doses.

Follow-up outcomes

Follow-up outcomes were classified as complete remission, partial remission, total remission (complete remission+partial remission), and relapse. Different outcomes were defined as follows: (1) Complete remission: Proteinuria ≤ 0.4 g/24 h, serum protein > 35 g/L, and stable renal function (normal serum creatinine lev-

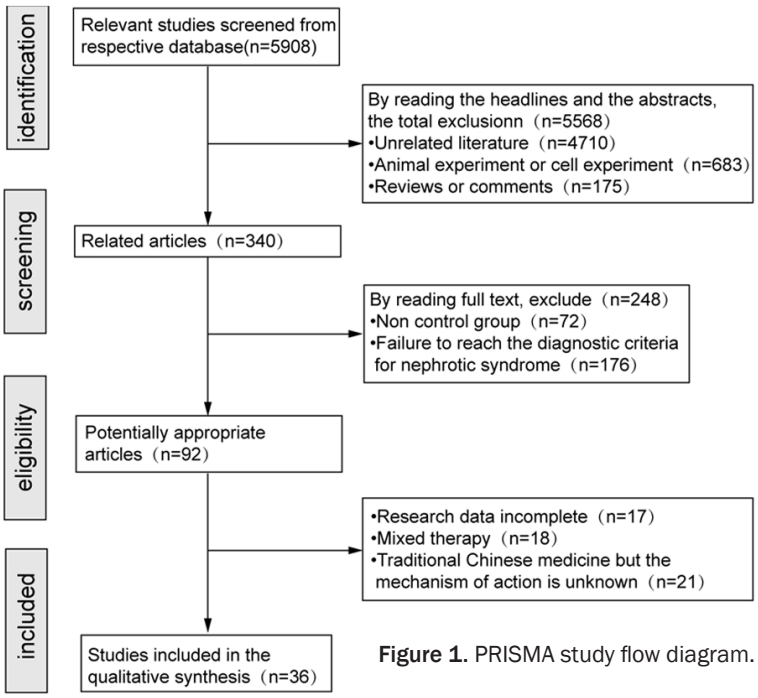

Figure 1. PRISMA study flow diagram.

els with baseline increases of no more than 25%); (2) Partial remission: Proteinuria decreased to over 50% of the baseline value and ≤ 3.5 g/24 h, with stable renal function; (3) Relapse: Patients in complete or partial remission re-developing heavy proteinuria (3.5 g/24 h) that did not undergo remission within 2 weeks.

Literature screening and data collection

Studies selected were independently approved by two researchers. RCTs meeting the inclusion criteria were screened. A pre-designed data extraction table was used to independently extract data after reading full texts. Articles were cross-checked and a third researcher was consulted, resolving any differences in cases of disagreement. Extracted data included author, publication data, number of samples, general characteristics of participants, methodology, interventional me-asure and duration, and endpoint information. The most comprehensive article involving the same study cohort with multiple articles was chosen.

Statistical analysis

If an included study contained trials with three or more arms, they were split into all possible two-arm trials. R 3.03, Stata 14.0, and ADDIS software were used for data processing and analysis. Odds ratios (OR) and 95% confidence intervals (CI) were used to analyze discrete data. R software was used to plot a network diagram of interventional measures. Stata software was used to analyze the consistency of remission data. Loop testing was used for analysis of included studies (significance level $\alpha = 0.05$). Reporting OR (ROR) and 95% CIs were used to evaluate the heterogeneity of each closed loop, with RORs > 1 and 95% CIs not equal to 1 indicating good consistency and RORs < 1 indicating significant inconsistency. Relapse data was analyzed using ADDIS software. The potential scale reduction factor (PSRF) reflects convergence. There is good convergence if the PSRF is close to 1, indicating that conclusions from the consistency model analysis have high reliability. A cumulative ranking probability map based on the Bayesian Markov chain-Monte Carlo (MCMC) random response model was plotted. Surface under the cumulative ranking curve (SUCRA) was used to predict the efficacy ranking of each therapeutic measure. Clustering analysis was used to summarize and evaluate overall remission and relapse rates for each therapeutic measure. A funnel plot was generated. Symmetry was used to evaluate whether observation results were affected by publication bias.

Results

Search results and study characteristics

A total of 5,908 articles were obtained. After further screening according to inclusion and exclusion criteria, a total of 36 articles met the requirements [13-48]. A total of 25 articles were in Chinese, while 11 were in English. A total of 2,481 patients were included. A flowchart for article inclusion is shown in **Figure 1**. All included articles were published between 2003 and 2017. Nine were retrospective studies and 27 were RCTs. The largest sample size was 240 cases, while the smallest sample size was 17 cases. There was a total of 16 treat-

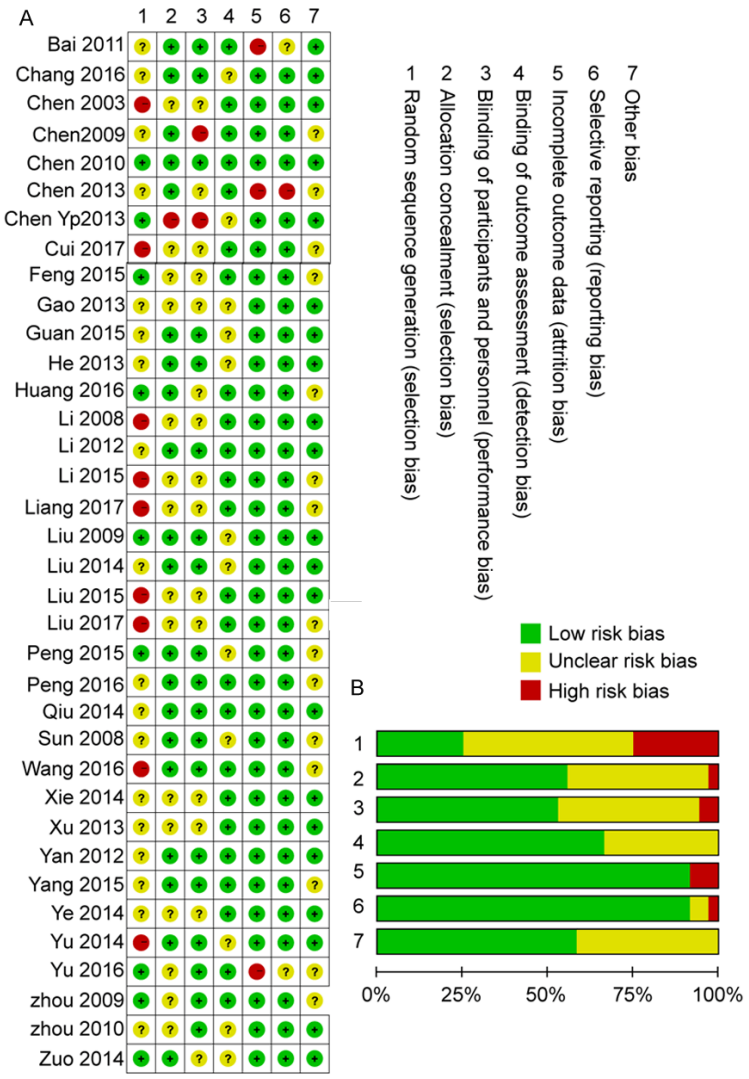

Figure 2. Risk-of-bias analysis: A. Risk of bias summary: a summary of author judgements about each risk of bias item for each included study. B. Risk of bias graph: a summary of author judgements about each risk of bias item presented as percentages across all included studies.

ment methods. The shortest follow-up period was 6 months, while the longest was 18 months. Review Manager 5.3 was used to evaluate the quality of included articles. Risk analysis assessment showed that 9 articles did not mention whether groups were randomized. Moreover, 19 articles did not mention specific randomization methods. Match hiding was mentioned in 20 articles, blinding between patients and physicians was mentioned in 19 articles, and blinding status was unknown in 2 articles. Outcome blinding was mentioned in 24 articles. Results of most studies were complete. There was high-risk selective reporting of results in one article. Results of risk assessment are shown in **Figure 2**. Baseline characteristics of each study are summarized in **Table 1**. Codes for corresponding therapeutic measures are shown in **Table 2**.

Data relationship network

Figure 3A shows the data network diagram for the 16 therapeutic measures for induced remission treatment of IMN combined with nephrotic syndrome. This includes 36 articles, forming 40 two-arm trials and including 2,481 participants. In the diagram, every circle represents a different drug interventional measure. A line connecting two circles indicates that data directly comparing the two interventional measures exists, while the absence of a line between two circles indicates that a direct comparison was not made in the original study. However, indirect comparisons could be made through network analysis. The thickness of the line indicates the number of studies for the two therapeutic measures. The diagram shows that cyclophosphamide+prednisone, cyclosporin A+prednisone, *T. wilfordii*+prednisone, tacrolimus+prednisone, and mycophenolate mofetil+prednisone treatment methods had the most patients. The network density between them was also the highest. **Figure 3B** shows the evidence network diagram of 8 therapeutic measures in which relapse occurred during follow-ups after induced remission. This included 15 studies, forming 17 two-arm trials and including 1,125 participants. The diagram shows that cyclophosphamide combined with prednisone, cyclosporin A combined with prednisone, *T. wilfordii* combined with prednisone, tacrolimus combined with prednisone, and mycophenolate mofetil combined with prednisone treatment

Table 1. Main characteristics of included studies

Author	Year	Follow-up/month	TG intervention	CG intervention	TG male Number	CG male/ Number	TG age	CG age	Outcome
Chen WZ	2009	6	FK506+Pre	CTX+Pre	NO/8	NO/9	NO	NO	①
Liu W	2017	6	FK506+Pre	CTX+Pre	11/21	11/23	28/65	33-68	①
Liu W	2017	6	CsA+Pre	CTX+Pre	11/19	11/23	35/62	33-68	①
Chen XL	2013	6	CsA+Pre	CTX+MP	NO/43	NO/43	NO	NO	①
Huang ZM	2016	12	CsA+MP	CTX+MP	29/50	28/50	24-67	24-69	①
Xie J	2014	12	CsA+Pre	CTX+Pre	24/49	29/56	46.61±16.31	47.41±12.09	①, ②
Yu DC	2016	6	CTX+Pre	Pre	36/48	34/48	53.7±3.5	53.4±3.7	①
Zhou W	2009	12	LEF+Pre	CTX+Pre	7/15	8/15	42.8±11.4	41.6±13.5	①, ②
Liu ZH	2009	12	TW+Pre	TW	31/43	30/41	40.5±12	48.6±10.3	①
Feng SP	2015	6	TW+Pre	Pre	74/120	76/120	45.6±10.4	46.2±9.5	①
Liu CY	2014	12	MMF+Pre	CTX+Pre	19/34	21/34	41.6±15.4	42.2±15.6	①
Zuo K	2014	12	TW+Pre	FK506+Pre	31/50	34/50	45.32±11.33	40.83±12.26	①, ②
Zhou W	2010	12	MMF+Pre	CTX+Pre	9/20	8/20	43.8±14.3	42.6±13.5	①, ②
Yang N	2015	6	MMF+Pre	TW+Pre	25/45	28/45	44.2±13.7	46.3±12.9	①, ②
Chen D	2003	12	MMF+Pre	CTX+Pre	6/10	9/17	38.3±9.4	37.8±10.2	①
Bai GZ	2011	6	FK506+Pre	CTX+Pre	NO/16	NO/16	NO	NO	①
Chang X	2016	6	FK506+Pre	LEF+Pre	26/40	27/40	42.6±5.4	43.2±4.9	①
Yan Y	2012	12	FK506+Pre	MMF+Pre	7/10	7/10	42.4±13.5	43.6±14.7	①, ②
Li Y	2012	6	FK506+Pre	CTX+Pre	NO/15	NO/15	NO	NO	①
Guan Y	2015	6	FK506+Pre	CTX+Pre	12/20	15/20	47.56±10.67	49.9±9.15	①
Yu XG	2014	12	FK506+Pre	CTX+Pre	NO/12	NO/12	NO	NO	①
Sun GD	2008	6	FK506+Pre	LEF+Pre	NO/10	NO/10	NO	NO	①
Ye L	2014	6	FK506+Pre	CTX+Pre	13/21	14/20	44.5±12.8	45.1±13.2	①
Qiu B	2014	12	CsA+Pre	CsA+Pre+TW	20/29	20/29	54.3±17.8	52.5±15.1	①
Gao F	2013	6	FK506+Pre+TW	FK506+Pre	NO/15	NO/15	NO	NO	①
Peng JW	2015	12	FK506+TW	FK506	8/20	9/20	33.7±12.2	25.8±10.9	①
Chen M	2010	6	FK506+Pre	CTX+Pre	23/39	18/34	47.2±11.9	48.6±11.6	①, ②
Peng L	2015	9	FK506+Pre	CTX+Pre	17/30	16/30	43.9±13.2	40.8±13.3	①, ②
Peng L	2015	9	FK506+Pre	MMF+Pre	17/30	14/30	43.9±13.2	39.9±14.3	①, ②
Li XY	2008	6	FK506+Pre	CTX+Pre	12/14	13/16	50.4±14.6	49.4±10.6	①, ②
Wang XC	2016	12	Mizoribine+MP	CTX+MP	20/30	19/25	42.5±13.8	48.6±16.32	①
Cui W	2017	12	FK506+Pre	CTX+Pre	40/60	72/117	48.4±7.8	48.5±6.2	①, ②
Liu SS	2015	9	TW+Pre	FK506+Pre	12/23	22/30	48.82±6.8	43.4±16.1	①, ②
He LY	2013	6	FK506+Pre	CTX+Pre	20/28	19/28	45.4±11.5	47.2±13.4	①, ②
Liang Q	2017	12	FK506	CTX+Pre	16/30	9/28	48.2±13.5	53.9±10.4	①
Chen YP	2013	12	Shenqi Particle	CTX+Pre	60/95	65/95	49.1±14.1	53.1±12.1	①
Li MX	2015	6	CsA	CsA+MP	NO/14	NO/13	75.1±8.2	74.8±7.9	①
Xu J	2013	18	CTX+Pre	FK506+Pre	30/52	31/48	57.8±14.8	56.3±13.2	①, ②

TG: test group; CG: control group; Outcomes: ① complete/partial remission; ② relapse.

methods had the most patients. The network density between them was also the highest.

Consistency analysis

Inconsistency refers to the existence of deviations between direct comparisons and indirect comparisons in network meta-analysis. This affects the validity of network meta-analysis. Therefore, testing for inconsistency is required when conducting network meta-analyses. Factors producing inconsistency should be analyzed. ROR > 1 shows that direct evidence and indirect evidence are extremely consistent. **Figure 4A** shows consistency testing results for induced remission treatments. The 16 therapeutic measures formed a total of 4 closed loops. ROR was between 1.149-7.302 and the 95% CI did not include 1, indicating good consistency in the closed loops formed by therapeutic measures. **Figure 4B** shows consistency testing results for relapse following induced remission. The 8 therapeutic measures formed 2 closed loops. ROR was between 1.541-2.106

Table 2. The 16 encoded therapeutics

Number	Code	Therapy
1	A	Cyclophosphamide+Prednisone
2	B	Cyclosporin A+Prednisone
3	C	Leflunomide+Prednisone
4	D	Tripterygium wilfordii+Prednisone
5	E	Tacrolimus+Prednisone
6	F	Mycophenolate mofetil+Prednisone
7	G	Mycophenolate mofetil+Tripterygium wilfordii+Prednisone
8	H	Tacrolimus monotherapy
9	I	Prednisone monotherapy
10	J	Tripterygium wilfordii monotherapy
11	K	Cyclosporin A+Prednisone+Tripterygium wilfordii
12	L	Tacrolimus+Prednisone+Tripterygium wilfordii
13	M	Mizoribine+Prednisone
14	N	Shenqi particle
15	O	Cyclosporin A monotherapy
16	P	Tacrolimus+Tripterygium wilfordii

and the 95% CI did not include 1, indicating good consistency in the closed loops formed by therapeutic measures.

Comparison of therapeutic efficacy among various therapeutic measures

Regarding induced remission therapy, pairwise comparisons of the 16 therapeutic measures in forest plots in **Figure 5** show that induced remission with tacrolimus combined with prednisone was better than cyclophosphamide combined with prednisone. Mycophenolate mofetil combined with *T. wilfordii* and prednisone was better than mycophenolate mofetil combined with prednisone. *T. wilfordii* combined with prednisone was better than prednisone or *T. wilfordii* monotherapy. These results were statistically significant. This study further ranked each therapeutic measure using a cumulative ranking probability map, based on a MCMC random response model. As shown in **Figure 6A**, measures were ranked in order of decreasing SUCRA as G (highest SUCRA of 94.3) LPEDFKBAHONCMIJ (lowest SUCRA of 15.3). Results of overall comparisons and pairwise comparisons were completely consistent, indicating that combination therapy for IMN combined with nephrotic syndrome using mycophenolate mofetil, *T. wilfordii*, and prednisone had the highest remission rates. These were followed by combination therapy with tacrolimus, prednisone, and *T. wilfordii*. The efficacy of *T. wilfordii* monotherapy was the poorest.

Table 3 uses OR values and 95% confidence intervals to show comparisons between therapeutic measures with relapse after induced remission. The recurrence rate of patients treated with cyclophosphamide combined with prednisone was lower than that of cyclosporin A combined with prednisone. OR and 95% CI rate was 0.012 (0.04-0.40). The recurrence rate for treatment of IMN combined with nephrotic syndrome using cyclosporin A combined with prednisone was markedly elevated, compared to that of leflunomide combined with prednisone, *T. wilfordii* combined with prednisone, and tacrolimus combined with prednisone. ORs and 95% CIs were 2.0*10^8 (1.53,3.2*10^34), 11.51 (1.61, 63.48), and 5.88 (1.29, 24.36), respectively. Cyclophosphamide combined with prednisone, leflunomide combined with prednisone, *T. wilfordii* combined with prednisone, tacrolimus combined with prednisone, mycophenolate mofetil combined with prednisone, and mycophenolate mofetil combined with *T. wilfordii* and prednisone induced significantly lower recurrence rates, compared to that of tacrolimus monotherapy, after induced remission of IMN combined with nephrotic syndrome. ORs and 95% CIs were 0.00 (0.00, 0.20), 0.00 (0.00, 0.01), 0.00 (0.00, 0.14), 0.00 (0.00, 0.27), 0.00 (0.00, 0.29), and 0.00 (0.00, 0.25), respectively. This study further ranked recurrence rates following each therapeutic measure using a cumulative ranking probability map, based on a MCMC random response model. As shown in **Figure 6B**, measures were ranked in order of decreasing SUCRA as B (highest SUCRA of 87.1) HCEFGAD (lowest SUCRA of 19.8). Results of overall comparisons and pairwise comparisons were completely consistent, indicating that recurrence rates of *T. wilfordii* combined with prednisone, cyclophosphamide combined with prednisone, and mycophenolate mofetil combined with *T. wilfordii* and prednisone were the lowest. The recurrence rate of cyclosporin A combined wi-

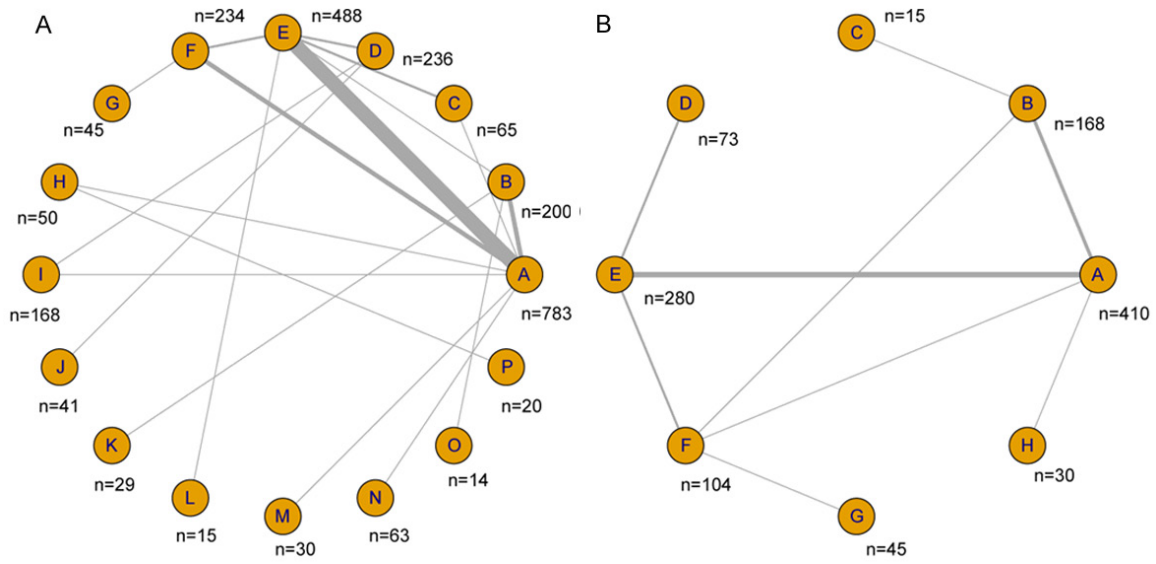

Figure 3. Network diagram of all included studies. Each node represents a treatment type; Widths of lines between two nodes represents the number of studies involved in the head-to-head comparison.

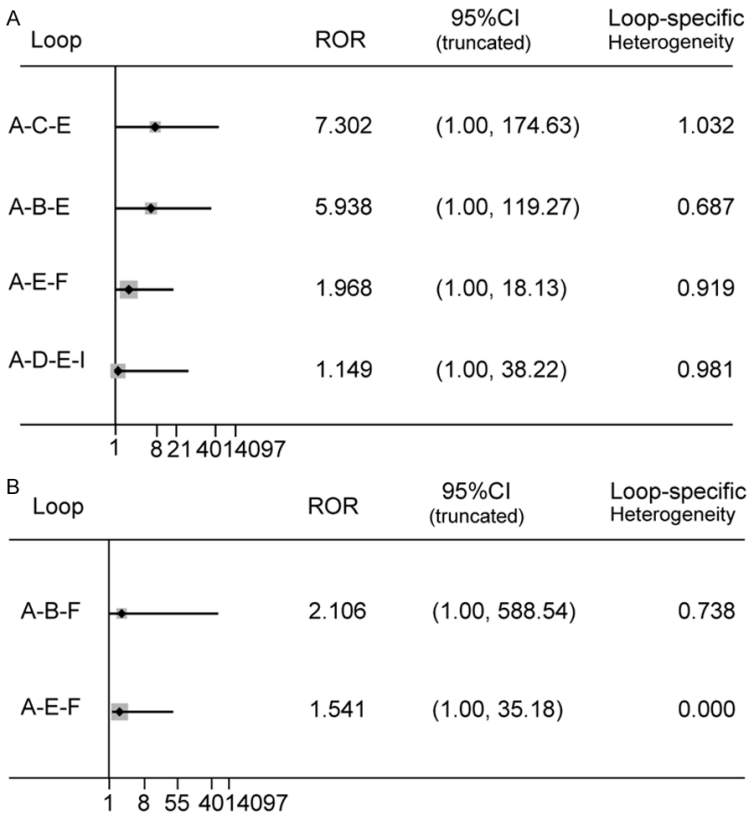

Figure 4. Consistency test in the network meta-analysis. The X-axis is log OR and the vertical line is 1. ROR is the absolute inconsistency factor, meaning the logarithm of the ratio of ORs of direct and indirect evidences for each comparison loop.

th prednisone and tacrolimus monotherapy was the highest.

In addition, cluster analysis was conducted for a comprehensive evaluation of remission and relapse rates. Results in **Figure 7** show that treatment for IMN combined with nephrotic syndrome using mycophenolate mofetil combined with *T. wilfordii* and prednisone can achieve the highest remission rates and lowest recurrence rates. These items are followed by tacrolimus combined with prednisone. Leflunomide combined with prednisone had the poorest efficacy with respect to both remission rates and recurrence rates.

Small-sample effect detection

A funnel plot of the 16 interventional measures involved in the 36 included induced remission studies was made. As shown in **Figure 8A**, the 36 points indicate the 36 included studies. Most of the points fall within the center of the funnel plot and most points are distributed on either side of the red index line in the funnel plot, indicating little publication bias. However, there were still 3

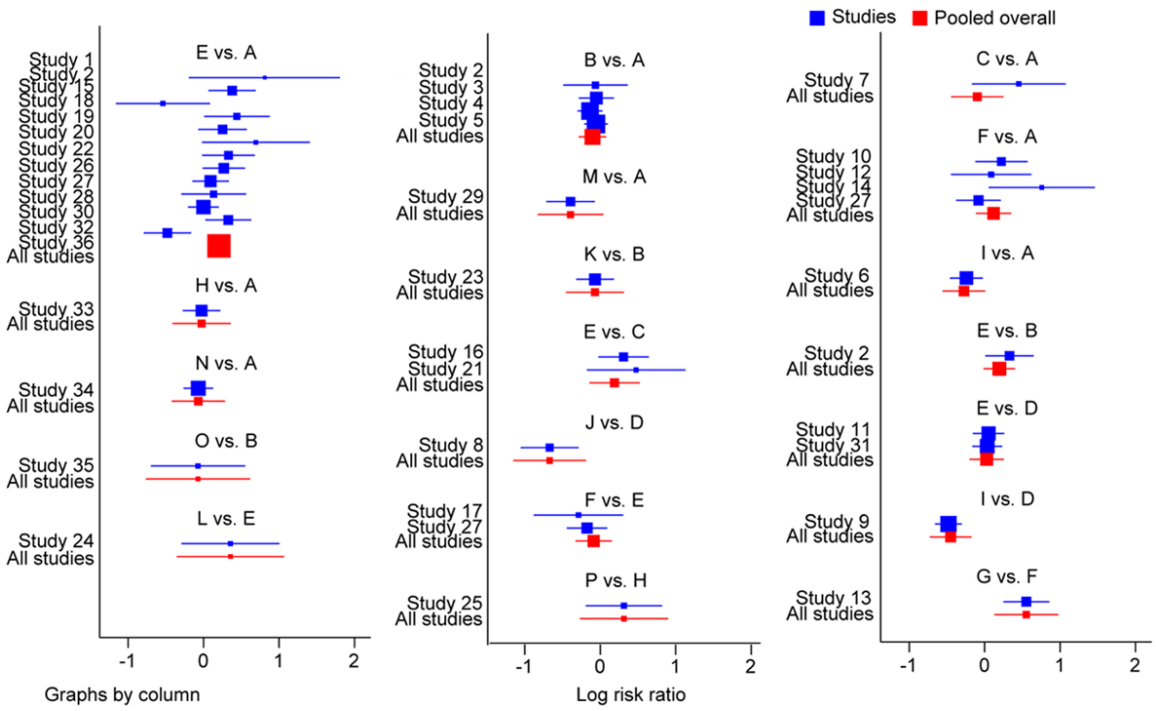

Figure 5. Forest plot of comparison of different therapy effects: a network meta-analysis.

points that were asymmetric, indicating the presence of some bias and small-sample effects. For the 8 interventional measures involved in the 15 included studies on recurrence during follow-ups after induced remission, there was also some bias and small-sample effects (**Figure 8B**).

Discussion

Membranous nephropathy is one of the most common pathological presentations of nephrotic syndrome in adults. It is the most common primary glomerular disease in individuals with transplanted kidneys [49]. MN is a typical nephropathy caused by antigen-antibody reactions. Its etiology is also closely associated with genetic and environmental factors. In addition, recent studies have found that, in regions with high PM2.5 pollution, the proportion of individuals with MN in kidney biopsies is significantly increased, indicating that air pollution also increases risk of MN [2]. Kidney biopsies are still the gold standard for diagnosis of MN. Main pathological characteristics of MN include diffuse deposition of immune complexes in the glomerular capillary basement membrane, leading to diffuse thickening of the basement membrane and spiked formation. In addition, complement-mediated podocyte and membrane rupture damage increases the permeability of glomerular capillaries [50].

Clinical presentation of IMN is varied, resulting in different outcomes. Studies have shown that prolonged heavy proteinuria not only leads to severe complications, but is also an independent risk factor for IMN progression to end-stage renal disease. Therefore, early treatment, especially immunosuppressant treatment, is extremely important for high-risk patients. Since these patients can spontaneously enter remission, along with the toxic side effects of immunosuppressants, studies have recommended extending treatment to follow disease progression. However, this treatment strategy has been shown to significantly increase risks of thrombosis, cardiovascular events, infections, and other complications in patients that did not spontaneously enter remission, as well as progression to end-stage renal disease due to delayed treatment. Therefore, screening of the clinical presentation of patients with IMN that are at a high risk during the early stages may guide treatment. It is essential for reducing risks [51].

Ponticelli et al. used CTX to replace chlorambucil combined with hormones for treatment of IMN in 1998 [52]. Similar evidence from subse-

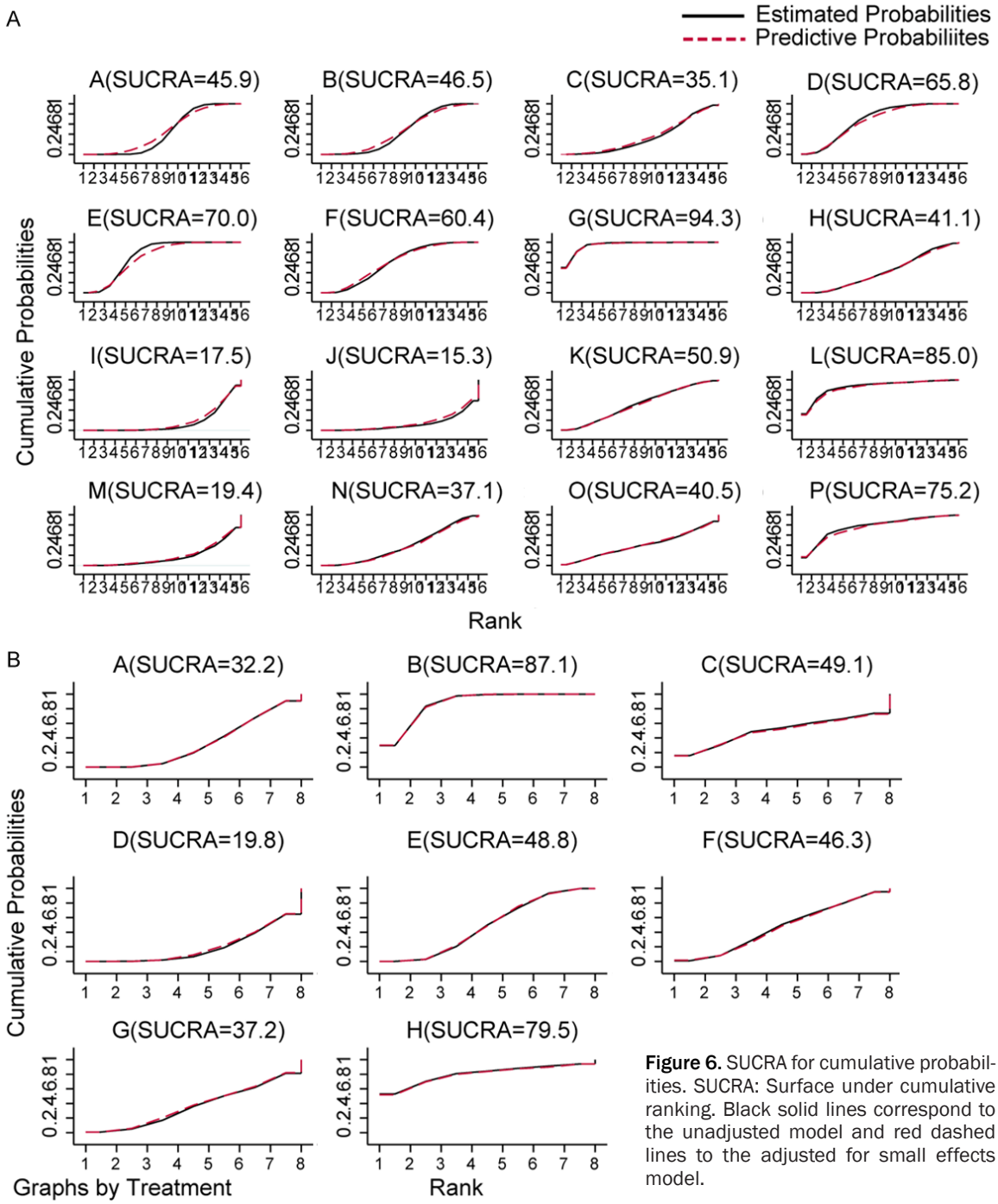

Figure 6. SUCRA for cumulative probabilities. SUCRA: Surface under cumulative ranking. Black solid lines correspond to the unadjusted model and red dashed lines to the adjusted for small effects model.

quent RCTs has been reported over time. Because this regimen has been shown to be effective, the 2012 Edition of KDIGO guidelines recommended glucocorticoids combined with alkylating agents as the first choice for treatment of patients presenting with IMN combined with nephrotic syndrome. For patients in which this regimen is inappropriate, the use of calcineurin inhibitors (CNIs) has been recommended [53]. Because researchers reporting the above findings were European and American, it is possible that these treatment regimens are not the most appropriate for the Asian population. Therefore, examining patients with IMN that have heavy proteinuria, the current study selected the 16 most common treatment regi-

Table 3. Network meta-analysis results

Treatment	A	B	C	D	E	F	G	H
A	A	0.12 (0.04, 0.40)	2.5*10^7 (0.17, 4.1*10^33)	1.45 (0.31, 5.15)	0.73 (0.30, 1.61)	0.91 (0.13, 9.56)	1.18 (0.11, 19.40)	0.00 (0.00, 0.20)
B	8.20 (2.47, 27.45)	B	2.0*10^8 (1.53, 3.2*10^34)	11.51 (1.61, 63.48)	5.88 (1.29, 24.36)	7.08 (0.89, 93.18)	9.36 (0.73, 183.34)	0.00 (0.00, 1.71)
C	0.00 (0.00, 5.76)	0.00 (0.00, 0.65)	C	0.00 (0.00, 8.27)	0.00 (0.00, 4.17)	0.00 (0.00, 7.60)	0.00 (0.00, 11.00)	0.00 (0.00, 0.01)
D	0.69 (0.19, 3.21)	0.09 (0.02, 0.62)	1.8*10^7 (0.12, 3.1*10^33)	D	0.50 (0.18, 1.65)	0.65 (0.08, 9.62)	0.88 (0.07, 18.36)	0.00 (0.00, 0.14)
E	1.38 (0.62, 3.38)	0.17 (0.04, 0.78)	3.4*10^7 (0.24, 6.4*10^33)	2.01 (0.61, 5.65)	E	1.29 (0.19, 14.29)	1.63 (0.15, 27.94)	0.00 (0.00, 0.27)
F	1.10 (0.10, 7.69)	0.14 (0.01, 1.12)	2.7*10^7 (0.13, 3.4*10^33)	1.54 (0.10, 12.93)	0.78 (0.07, 5.32)	F	1.31 (0.30, 5.64)	0.00 (0.00, 0.29)
G	0.84 (0.05, 9.45)	0.11 (0.01, 1.37)	1.8*10^7 (0.09, 2.5*10^33)	1.14 (0.05, 15.10)	0.61 (0.04, 6.46)	0.76 (0.18, 3.34)	G	0.00 (0.00, 0.25)
H	3.9*10^6 (5.02, 1.2*10^21)	4.7*10^5 (0.58, 1.3*10^20)	4.2*10^15 (129.32, 6.9*10^41)	5.6*10^6 (6.96, 1.8*10^21)	2.7*10^6 (3.72, 8.6*10^20)	3.8*10^6 (3.45, 1.3*10^21)	5.6*10^6 (4.06, 1.6*10^21)	H

Odds ratio estimates with 95% confidence intervals of relapse for each pairwise comparison.

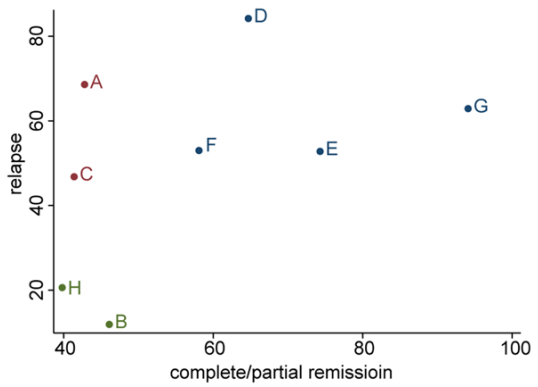

Figure 7. Cluster analysis plot. Cluster results are based on the surface under cumulative ranking area (SUCRA) values for different interventions. The dots located in the top right corner indicate their superiority while the dots located in the left bottom indicate their inferiority.

mens. Main follow-up endpoint indicators included total remission (complete remission+partial remission), remission, and recurrence. The therapeutic measure leading to the highest remission rate was "MMF+prednisone+*T. wilfordii*". This was followed by "tacrolimus+prednisone+*T. wilfordii*". With recurrence following remission as a secondary endpoint indicator, the therapeutic measure with the lowest rate of recurrence following remission was "*T. wilfordii*+prednisone". This was followed by "cyclophosphamide+prednisone" and "MMF+prednisone+*T. wilfordii*". Using clustering analysis to summarize and evaluate overall remission rates and recurrence rates for each therapeutic measure, it was found that "MMF+prednisone+*T. wilfordii*" led to the highest remission rate and a low recurrence rate, indicating that it may be the best therapeutic measure. Glucocorticoid hormones combined with tacrolimus can serve as a substitute treatment regimen. FK506 monotherapy and cyclosporine combined with prednisone have shown relatively poor efficacy. In addition, compared to those of other combination therapies, the efficacy of glucocorticoid hormone monotherapy was not ideal. Although glucocorticoid hormones combined with cyclophosphamide led to a lower remission rate than treatment with CNIs, the rate of recurrence following remission was the lowest with glucocorticoid hormones combined with cyclophosphamide. This is consistent with recommended treatment in 2012 KDIGO guidelines, to some extent.

The current study found that the treatment efficacy of purified *T. wilfordii* combined with glucocorticoids was not ideal. At the same time, the overall remission rate in patients with IMN combined with nephrotic syndrome was significantly higher when MMF or FK506 was combined with *T. wilfordii* treatment. This may be related to multi-target treatments producing synergistic effects, also supporting the use of *T. wilfordii* combination therapy with other immunosuppressants to increase efficacy. Whether used to induce remission or reduce recurrence following remission, Traditional Chinese Medicine Shenqi particle showed no obvious advantages. MMF is a new type of immunosuppressant. Its active metabolite mycophenolic acid can selectively inhibit T and B lymphocyte proliferation. It has immunosuppressive and inflammation modulating functions. This would delay the progression of chronic renal lesions and improve remission of proteinuria in patients [54]. Triptolide can antagonize cell damage mediated by the membrane attack complex C5b-9, promoting repair of podocyte lesions [51]. Further confirming the safety of this treatment regimen, analysis of the 45 patients given oral "glucocorticoids+*T. wilfordii*+MMF" in the original study showed that 3 patients developed mild abnormalities in liver function after 6 months of follow-up, 2 patients developed digestive tract reactions, and 2 patients developed leukopenia. A total of 21 patients with focal segmental glomerulosclerosis or IMN were treated with "glucocorticoids+*T. wilfordii*+MMF" for over 1 year. None of these patients, except one patient that discontinued *T. wilfordii* due to peripheral neuropathy, developed obvious infections, liver function abnormalities, or digestive tract adverse reactions. Nearly 90% of the patients achieved complete remission (unpublished data). Therefore, it is believed that the "glucocorticoids+*T. wilfordii*+MMF" therapeutic regimen is safe and effective.

The present study had several limitations, however: (1) Although many articles were initially screened, relatively few articles were included in the final study. The numbers of samples in each study were relatively small. To avoid small-sample effects, cyclosporin A+prednisone+*T. wilfordii*, tacrolimus+prednisone+*T. wilfordii*, mizoribine+prednisone, cyclosporin A monotherapy, tacrolimus+*T. wilfordii*, and some other

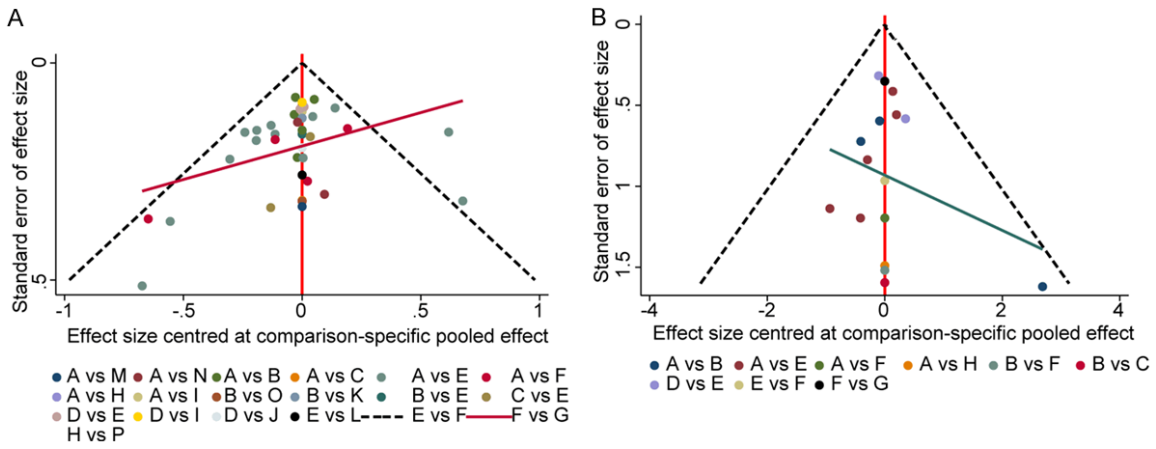

Figure 8. Funnel plot for all included studies.

treatment regiments were not further analyzed; (2) Data in the original studies was limited. Thus, this study was unable to evaluate the safety of all interventional measures; (3) The numbers of samples in included studies were relatively small. This led to reduced testing power. In addition, blinding methods in the original studies were insufficient, a factor that may have led to measurement bias; and (4) Some articles included in this study did not explain randomization methods in detail. This may have led to inclusion of studies with selection bias.

Because pediatric patients have relatively high spontaneous remission rates, the present study only included adult patients. In adult Chinese patients with IMN combined with nephrotic syndrome, glucocorticoid hormones combined with mycophenolate mofetil and *T. wilfordii* may be the most ideal therapeutic regimen, with glucocorticoid hormones combined with tacrolimus as a possible substitute therapeutic measure. In the future, high-quality and large-sample RCTs are necessary for validation.

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Disclosure of conflict of interest

None.

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