Systematic Review and Meta-Analysis

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A PRISMA-compliant systematic review and network meta-analysis on the efficacy between different regimens based on Tripterygium wilfordii Hook F in patients with primary nephrotic syndrome

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Abstract

Background: The present study aims to comprehensively determine the efficacy of different therapy regimens based on Tripterygium wilfordii Hook F (TwHF) for patients with primary nephrotic syndrome (PNS) using network meta-analysis method.

Methods: Seven electronic databases were searched to identify randomized controlled trials (RCTs) that compared the differences between different therapy regimens based on TwHF for patients with PNS. The risk of bias in included RCTs was evaluated according to the Cochrane Handbook version 5.2.0. Network meta-analysis was performed to compare different regimens. Primary outcomes were complete remission rate and total remission rate. The secondary outcomes were hr urinary protein excretion, serum albumin, serum creatinine, and urea nitrogen. Data analysis was performed using R software.

Results: A total of 40 studies involving 2846 patients with PNS were included. Compared with prednisone, the improvement in total remission rate and complete remission rate was associated with TwHF alone (odds ratio [OR] = 4.80, 95% credible intervals [CrI]: 2.20–10.00; OR = 6.30, 95% CrI: 2.90–13.00, respectively), TwHF+prednisone (OR = 2.10, 95% CrI: 1.30–3.50; OR = 2.40, 95% CrI: 1.50–3.80, respectively), TwHF+CPA (OR = 12.00, 95% CrI: 1.10–150.00; OR = 16.00, 95% CrI: 1.60–170.00, respectively), and TwHF+Cyclosporine A (OR = 28.00, 95% CrI: 3.20–250.00; OR = 35.00, 95% CrI: 4.50–270.00, respectively). Compared with TwHF alone, TwHF+prednisone showed less benefit in improving total remission rate and complete remission rate (OR = 0.44, 95% CrI: 0.21–0.91; OR = 0.38, 95% CrI: 0.19–0.77, respectively). TwHF alone, TwHF+prednisone could significantly reduce hr urinary protein excretion (MD = −0.69, 95% CrI: −1.30 to −0.14; MD = −1.00, 95% CrI: −1.90 to −0.14, respectively) and increase serum albumin (MD = 5.90, 95% CrI: 2.50–9.30; MD = 3.40, 95% CrI: 1.30–5.50, respectively) when compared to prednisone alone. TwHF alone showed significant reduction in serum creatinine when compared to CPA (MD = −19.00, 95% CrI: −37.00 to −0.56).

Conclusions: TwHF alone, the addition TwHF to prednisone showed more benefit in improving total and complete remission rate, hr urinary protein excretion, serum albumin, and serum creatinine.

Abbreviations: CBM = Chinese Biological Medical Database, CNKI = Chinese National Knowledge Infrastructure, CPA = cyclophosphamide, CrIs = credible intervals, CSA = Cyclosporine A, GC = glucocorticoid, MD = mean difference, OR = odds ratio, PNS = primary nephrotic syndrome, RCTs = randomized controlled trials, SMD = standard mean difference, TwHF = Tripterygium wilfordii Hook F.

Keywords: network meta-analysis, primary nephrotic syndrome, tripterygium wilfordii Hook F

1. Introduction

Primary nephrotic syndrome (PNS) is an etiology unknown and a relatively rare kidney disease.[1] It is estimated that the incidence is 3/100,000 annually in adults.[2] However, the acute complications caused by PNS are not neglected, which include infection, acute kidney injury, and thromboembolism.[1] Glucocorticoid (GC) and cyclophosphamide (CPA) are the main therapy option for PNS,[3] whereas a considerable part of patients are becoming dependence or resistance to GC, and even cause some toxic effects.[4]. Previous studies have shown that CPA pulse therapy could improve short-term remission; however, some patients still relapsed or could not obtain remission.[5,6]

Tripterygium wilfordii Hook F (TwHF), a traditional Chinese herbal medicine, is a kind of vine-like plant which grows in Southeast China, has been used as an immunosuppressive agent for patients with PNS in China >20 years.[1,3] The ingredient of TwHF contains the bioactive compounds possessing immunosuppressive agents.[3] Combined TwHF with GC has been considered as a beneficial regimen in improving the remission of PNS and preventing the relapse.[7,8] Song et al's study showed that TwHF plus CPA could reduce hr urinary protein excretion and increased serum albumin.[9] Several systematic reviews and meta-analyses have investigated the impact of TwHF, CPA, or

Editor: Jinxian Xu.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:27(e11282)

Received: 2 February 2018 / Accepted: 27 May 2018

http://dx.doi.org/10.1097/MD.0000000000011282

prednisone in patients with PNS[1,10,11]. However, it has been difficult to determine the superiority among treatment agents using pairwise meta-analysis and randomized controlled trial.[12] Network meta-analysis, an increasingly popular statistical method, allows to estimate the relative efficacy between different interventions of interest and to rank the interventions even though head-to-head comparisons are lacking.[12]

The present study aims to comprehensively compare the differences between all alternative regimens based on TwHF in improving patient outcomes for PNS using Bayesian network meta-analysis.

2. Methods

Ethics approval and patient consent are not required because this study is a meta-analysis based on the published original studies.

2.1. Information source

We systematically researched Cochrane Library, EMBASE, PubMed, CNKI (Chinese National Knowledge Infrastructure), CBM (Chinese Biological Medical Database), and WanFang databases from their inception to May 2017. We also tracked the references of relevant systematic reviews, meta-analyses, and included articles to identify additional studies. The search terms were combined as follows: ("lei gong teng" OR "leigong teng" OR Common Threewingnut Root Extract OR Glucosidorum Tripterygll Totorum OR leigongtengduogan OR Tripterygium Wilfordii OR tripterygium OR triptolide OR Tripterygium Glycosides) AND (random*) AND (Nephrotic syndrome [MeSh] OR Nephrotic syndrome OR Nephropathy OR NS).

2.2. Inclusion criteria

Studies met all of the following criteria were included: (1) patients were diagnosed with PNS or refractory PNS; (2) randomized controlled trials (RCTs); (3) treatment regimens based on TwHF; (4) primary outcomes were complete remission and total remission. The secondary outcomes were hr urinary protein excretion, serum albumin, serum creatinine, and urea nitrogen. (5) There were no limitations on year of publication and publication status.

2.3. Study selection

We used ENDNOTE X7 literature management software to manage literature search records. According to a prior eligibility criteria, 2 reviewers independently screened the title and abstract of all the retrieved records. Full-texts of any potentially eligible were downloaded for further screening. Any conflict was resolved by discussion.

2.4. Data items

Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, www.microsoft.com) was used to create a data abstraction form for data collection. One reviewer extracted the following information: first author, year of publication, health status, journal of publication, kidney function, sample, mean age, intervention arms, intervention duration, producer of intervention, and dosage of intervention, and outcomes), and another reviewer checked out them.

2.5. Risk of bias of individual studies

We assessed risk of bias in included RCTs according to the Cochrane Handbook version 5.2.0 that included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other resources of bias.[13] We answered these domains as low, high, or unclear risk of bias by 2 dependent reviewers, and conflict was resolved by a third reviewer.

2.6. Data analysis

We conducted a Bayesian network meta-analysis using *gemtc* package version 0.8.1 of R-3.4.0 software.[14] Four Markov chains ran simultaneously. For each chain we set 5000 simulations as the 'burn-in' period. Then posterior summaries were based on 50, 000 subsequent simulations. The model convergence was estimated using Brooks-Gelman-Rubin plots method.[15]

Heterogeneity across head-to-head trials was assessed using I^2 statistics. The values of 25%, 50%, and 75% for the I^2 were considered as an indication of low, moderate, and high statistical heterogeneity, respectively. Pooled odds ratio (OR) with 95% credible intervals (CrIs) was calculated for dichotomous data. Mean difference (MD) or standard mean difference (SMD) for continuous data. In addition, rank probability was also calculated, which indicated the probability for each treatment to be best, second best, and so on. We assessed statistical inconsistency between direct and indirect evidence at the paired comparison level using node splitting method. A post hoc subgroup analysis was conducted to explore the differences based on the type of PNS (refractory PNS and PNS) for primary outcomes.

3. Results

3.1. Literature selection

A total of 386 records were identified initially. Of them, 158 records were duplicates. Upon further assessment, 17 records were excluded because they were animal studies. 152 citations were excluded during screening of titles and abstracts. After reviewing full-texts, 18 articles were further excluded. Finally, 40 studies with 2846 patients met our inclusion criteria.[16–56] The flow graph of literature selection is presented in Figure 1.

3.2. Characteristics of included studies

The characteristics of included articles are shown in Table 1. Included RCTs were published between 1998 and 2016. A total of 11 intervention regimens were included in this study (Fig. 2): TwHF, CPA, prednisone, CPA+prednisone, TwHF+prednisone, leflunomide+TwHF, leflunomide+prednisone, CSA+TwHF, CSA +prednisone, TwHF+CPA, leflunomide+TwHF+prednisone. A total of 19 studies involving 1260 patients received interventions of TwHF and TwHF+prednisone. However, only one study was identified for the following interventions: leflunomide+TwHF, leflunomide+prednisone, CSA+TwHF, CSA+prednisone, and leflunomide+TwHF+prednisone. The risk of bias of included studies was high. Most of studies did not report the methods of random sequence generation, allocation concealment, blinding, and incomplete outcome (Fig. 3).

3.3. Network meta-analysis

Compared with prednisone, the improvement in total remission rate and complete remission rate were associated with TwHF

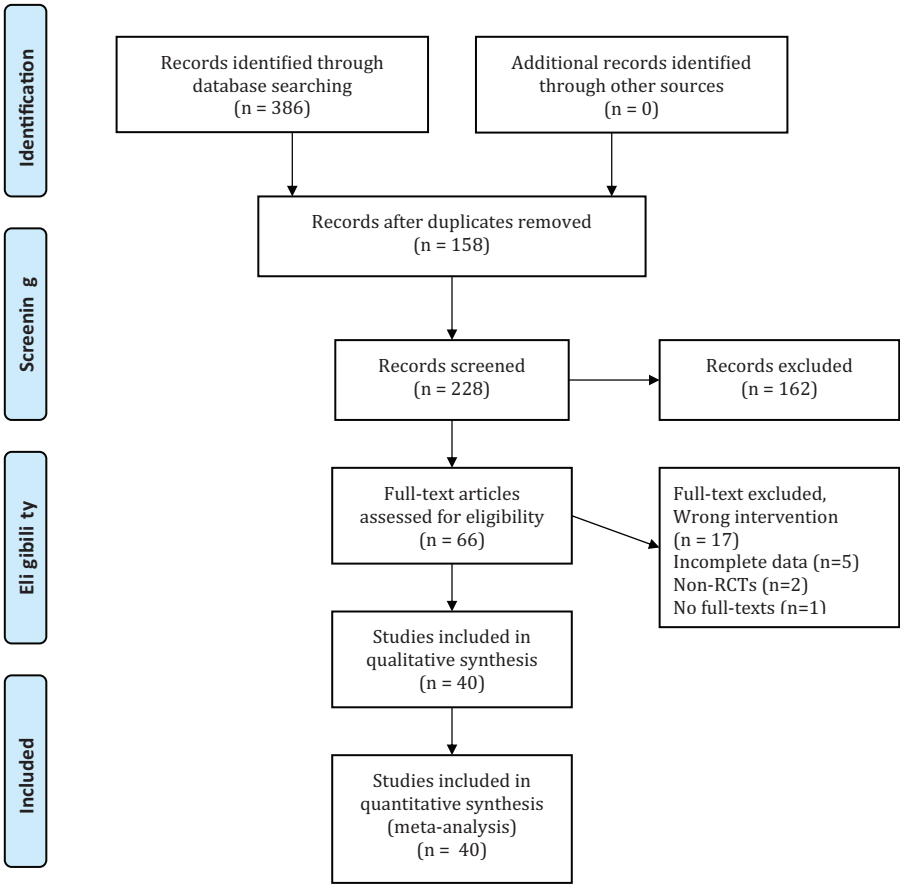

Figure 1. The flow graph of literature selection.

alone (OR = 4.80, 95% CrI: 2.20–10.00; OR = 6.30, 95% CrI: 2.90–13.00, respectively), TwHF+prednisone (OR = 2.10, 95% CrI: 1.30–3.50; OR = 2.40, 95% CrI: 1.50–3.80, respectively), TwHF+CPA (OR = 12.00, 95% CrI: 1.10–150.00; OR = 16.00, 95% CrI: 1.60–170.00, respectively), and TwHF+CSA (OR = 28.00, 95% CrI: 3.20–250.00; OR = 35.00, 95% CrI: 4.50–270.00, respectively). Compared with TwHF alone, TwHF +prednisone showed less benefit in improving total remission rate and complete remission rate (OR = 0.44, 95% CrI: 0.21–0.91; OR = 0.38, 95% CrI: 0.19–0.77, respectively). The differences between other comparisons were minimal (Table 2). For continuous outcomes, TwHF alone, TwHF+prednisone could significantly reduce hr urinary protein excretion (MD = −0.69, 95% CrI: −1.30 to −0.14; MD = −1.00, 95% CrI: −1.90 to −0.14, respectively) and increase serum albumin (MD = 5.90, 95% CrI: 2.50–9.30; MD = 3.40, 95% CrI: 1.30–5.50, respectively) when compared with prednisone (Table 3). TwHF alone showed significant reduction in serum creatinine compared with CPA (MD = −19.00, 95% CrI: −37.00 to −0.56) (Table 4). The detailed results of network meta-analysis and direct meta-analysis are summarized in Appendix 1 and Appendix 2, http://links.lww.com/MD/C313.

3.4. Ranking results

We did not plan to present the results of ranking probability because the number of included studies and the sample size was small, that would be possible to mislead evidence users.

3.5. Inconsistency between direct and indirect comparisons

We used node-splitting model to assess inconsistency between direct and indirect comparisons, the results showed that there were no inconsistency between all comparison groups (all $P >$ 0.05). Results of node-splitting analysis are provided in Appendix 3, http://links.lww.com/MD/C313.

3.6. Subgroup analysis

We conducted a post hoc subgroup analysis to explore the differences between refractory PNS and PNS. The results of subgroup analysis showed that there were no statistically significant differences between patients with refractory PNS and PNS (Appendix S4, http://links.lww.com/MD/C313).

4. Discussion

The main characteristics of nephrotic syndrome include heavy proteinuria, edema, hypoalbuminemia, and hypercholesterolemia. In the past few years, the incidence of PNS was gradually increasing. Pulse therapy with GC is considered as an effective therapeutic method. However, the toxic effects from GC regimens and high recurrence rate have been often neglected. Chinese herbal medicines, such as TwHF, gained growing attention and interest, and may be proved to be one of viable treatment options for PNS patients.[57] Tripdiolide and triptolide were regarded as the major active components of TwHF.[58]

Table 1

Characteristic of included studies.

Study	Patients	Kidney function	Intervention	Control	Sample M/F/N		Outcomes
					I	C	
Shen 2012	Refractory PNS	NA	CPA+Prednisone	TwHF+Prednisone	12/16/28	8/12/20	a; c; d; e
Su 2014	PNS	NA	TwHF+Prednisone	Prednisone	28/12/40	23/17/40	a; b; c; d; e; f; g
Bao 2013	PNS	Regular	TwHF+Prednisone	Prednisone	–/–/36	–/–/36	a; b;c;
Xiao 2007	PNS	Regular	TwHF	CPA+Prednisone	20/12/32	14/10/24	a; c; d; e; f; g
Du 2016	PNS	NA	TwHF+Prednisone	Prednisone	17/14/31	18/16/34	a; b; c; d; e; f; g
Xu 2009	PNS	NA	TwHF+Prednisone	Prednisone	27/15/42	25/11/36	a; b; c; d; e; g
Gong 2014	PNS	NA	TwHF+Prednisone	Prednisone	29/20/49	26/23/49	d; e; g
Jiang 2013	PNS	NA	TwHF+Prednisone	Prednisone	–/–/41	–/–/41	c; d; e; f
Chen 2013	PNS	NA	TwHF+Prednisone	Prednisone	–/–/32	–/–/32	a; b; c; d; e
Guo 2016	PNS	NA	TwHF	CPA	21/19/40	22/18/40	b; c; d; e
Zhou 2015	PNS	NA	TwHF+Prednisone	Prednisone	12/8/20	11/9/20	a; b; c; d; e; g
Wang 2014a	PNS	NA	TwHF+Prednisone	Prednisone	–/–/22	–/–/22	a; c
Guan2012	PNS	NA	TwHF+Prednisone	Prednisone	–/– 40	–/–/40	a; b; c; e
Li 2015	PNS	NA	TwHF+Prednisone	CPA+Prednisone	–/–/40	–/–/40	d; e
Liu 2016	PNS	NA	TwHF+Prednisone	CPA+Prednisone	–/–/38	–/–/38	a; b; c
Tan 2014	PNS	Regular	TwHF+Prednisone	Prednisone	–/–/15	–/–/15	a; b; c
Song 2008	Refractory PNS	Regular	CPA	TwHF	–/–/30	–/–/25	a; b; c
Jiang 2014	Refractory PNS	NA	Leflunomide+TwHF+Prednisone	CPA+Prednisone	18/14/32	16/12/28	a; b; c; d; e; g
Cui 2011	Refractory PNS	NA	Leflunomide+TwHF	CPA+Prednisone	9/6/15	10/5/15	a; b; c
Wang 2000	PNS	NA	TwHF	Prednisone	16/8/24	18/7/25	a; b; c; d; e; g; h
Liu 2011a	Refractory PNS	Regular	Leflunomide+TwHF	Prednisone	18/14/32	16/14/30	a; b; c; d; e; f; g
Ma 1991	PNS	NA	TwHF+Prednisone	CPA+Prednisone	–/–/40	–/–/40	a; b; c
Du 2012	PNS	NA	TwHF+Prednisone	Prednisone	16/14/30	17/13/30	c; d; e
Liu 2011a	refractory PNS	NA	TwHF+Prednisone	Prednisone	18/12/30	20/10/30	a; b; c; d; e; g
Zhou 2016	Refractory PNS	NA	TwHF+Prednisone	Prednisone	25/19/44	16/18/44	c; d; e
Niu 2015	PNS	NA	TwHF+Prednisone	Prednisone	–/– 20	–/–/20	a; b; c; d; e; f; g
Liu 2010	PNS	NA	TwHF+Prednisone	Prednisone	18/8/26	17/8/25	a; b; c; d; e; g
Zhang 2015	Refractory PNS	NA	TwHF+Prednisone	Leflunomide+Prednisone	–/– 40	–/–/40	c
Fan 2014	Refractory PNS	Regular	TwHF+Prednisone	Prednisone	26/22/48	27/21/48	a; b; c; d; e; f; g
Luo 2014	PNS	Regular	TwHF	CPA	26/18/44	26/18/44	d; e
Wu 2015	refractory PNS	Regular	TwHF	Prednisone	15/19/34	18/16/34	a; b; c
Piao 2015	PNS	NA	TwHF	Prednisone	27/22/49	29/20/49	a; b; c; d; e; f; g
Huo 2015	PNS	NA	TwHF	TwHF+Prednisone	28/22/50	27/23/50	a; b; c; d; e; f; g
Wang 2016	Refractory PNS	NA	TwHF	TwHF+Prednisone	24/16/40	23/17/40	a; b; c; d; e
Wang 2014	Refractory PNS	NA	TwHF	TwHF+Prednisone	17/16/33	19/14/33	c; d; e
Chen 2005	PNS	Regular	TwHF	CPA	21/15/36	22/10/32	d
Han 1999	PNS	NA	CSA+TwHF	CSA+Prednisone, TwHF	23/10/33	20/11/31, 22/9/31	a; b; c
Song 1998	Refractory PNS	NA	TwHF+CPA	CPA	19/11/30	18/10/28	a; b; c; g
Zhao 1999	Refractory PNS	NA	Prednisone	TwHF, TwHF+Prednisone	18/14/32	14/16/30, 36/28/64	a; c
Zhao 2009	PNS	Regular	TwHF	CPA	20/6/26	12/8/20	a; c; d; e; g

a = complete remission, b = partial remission, c = total remission, d = hr urinary protein excretion, e = serum albumin, f = Serum creatinine, g = urea nitrogen, h = white blood cell, C = Control, CPA = cyclophosphamide, CSA = Cyclosporine A, F = female, I = Intervention, M = male, N = total sample, NA = not available, PNS = Primary nephrotic syndrome, TwHF = Tripterygium wilfordii Hook F.

Mechanism study indicated that triptolide could inhibit effectively B7, CD40h, and C3 expression in vitro and further to inhibit the immunoregulatory and proinflammatory capacity of TNF-α that activate human renal proximal tubular epithelial cells.[59]

This systematic review aims to provide a comprehensive evidence to compare the efficacy of TwHF in the treatment of PNS. The results combining direct with indirect evidence, in terms of total remission, complete remission, hr urinary protein excretion, serum albumin, serum creatinine, and urea nitrogen, proved that TwHF appeared to provide more benefit for PNS patients, although other regimens also showed slightly differences in improving the outcomes of patients. Chen et al assessed the efficacy of TwHF using traditional meta-analysis methods, resulted that TwHF significantly increased complete remission; however, the effect of TwHF on urinary protein excretion and serum albumin had no significant difference.[1] In the present study, we combined direct with indirect evidence to inform the effect of TwHF. Similar to Chen et al's study, we found that TwHF significantly improved total remission rate and complete remission rate. However, we also found that the addition TwHF to prednisone, CPA, and CSA could significantly improve the total remission rate and complete remission rate compared to prednisone alone. In addition, TwHF alone and TwHF+prednisone could significantly reduce hr urinary protein excretion and increase serum albumin compared to prednisone. Furthermore, we added the evidence of comparing TwHF alone to TwHF +prednisone, which indicated TwHF alone showed more benefit than TwHF+prednisone.

In this meta-analysis, we mainly focused on the efficacy of different therapy regimens based on TwHF. The reporting of included studies on adverse events has been inconsistent; we could not synthesis the data of adverse events. According to the results, TwHF alone and the addition TwHF to prednisone showed more benefit than other regimens in improving total and complete remission rate, hr urinary protein excretion, serum

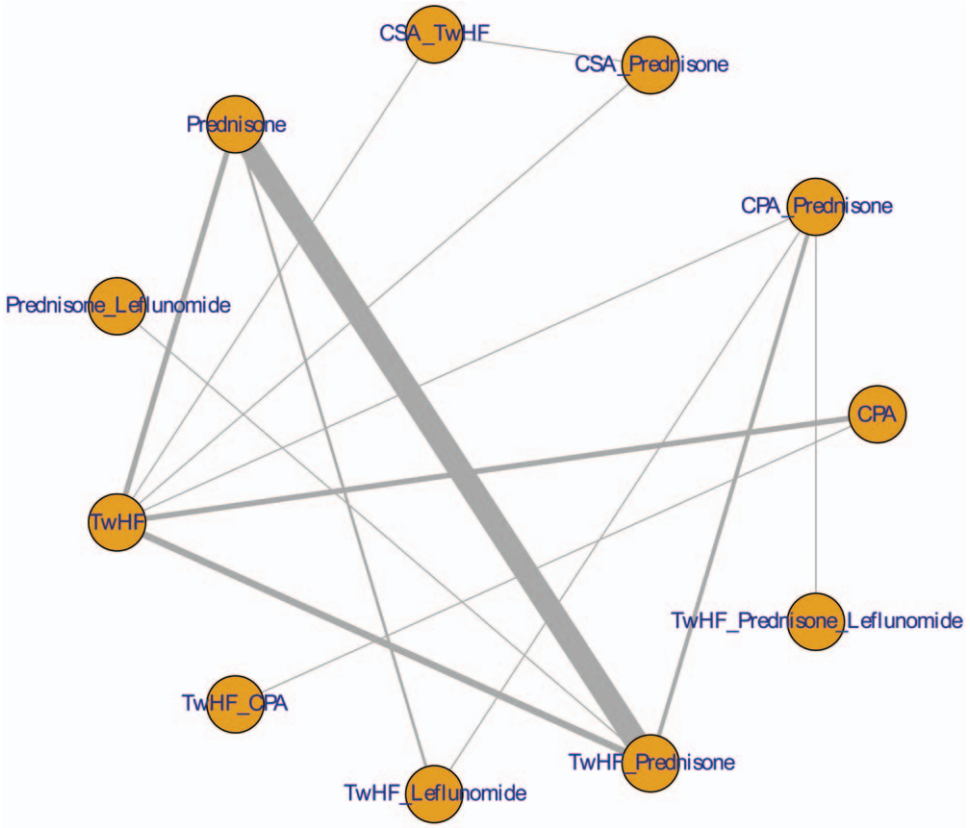

Figure 2. Network plot.

albumin, and serum creatinine for patients with PNS; however, some adverse events related to these regimens were reported in individual studies, including leukopenia (TwHF:1.15%[22,32,51]; TwHF+prednisone: 0.45%[17,26,27]), slightly impaired liver function (TwHF:3.00%[32,52,56]; TwHF+prednisone: 1.49%[16–18,20,27]), gastrointestinal reaction (TwHF:3.93%[27,32,45,51,56]; TwHF+prednisone: 2.24%[17,18,22,23,26,38,44]), cushing syndrome (TwHF:0%; TwHF+prednisone: 0.60%[18,20]), and complicated with bacterial infection (TwHF:0%; TwHF+prednisone: 0.60%[18,20]).

Ranking of interventions is one of the most appealing elements of network meta-analysis, which could indicate the probability for each treatment to be best, second, and so on. Methodological study has showed that treatment rankings derived from network meta-analyses have a substantial degree of imprecision, especially when the sample size was small.[60] In the present study, we

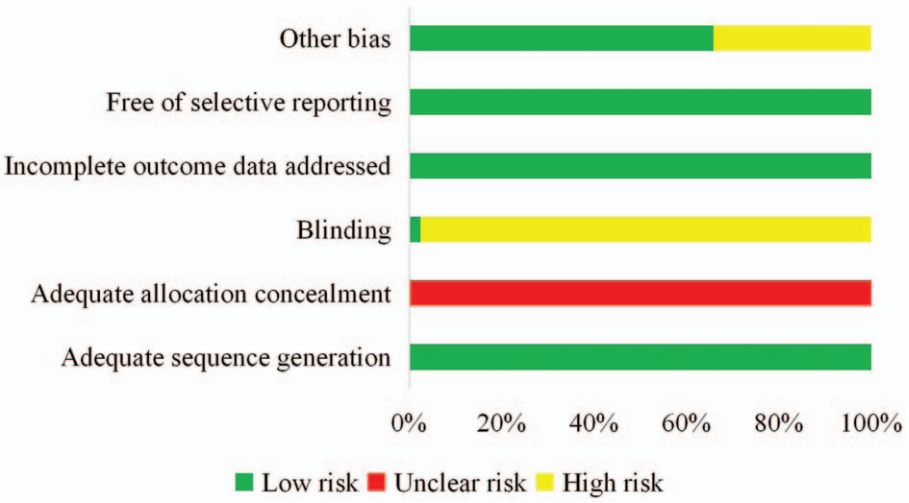

Figure 3. Results of risk of bias.

Table 2

Results of network meta-analysis for total remission and complete remission.

TwHF+ CPA	3.90 (0.54,30.00)	3.90 (0.34, 48.00)	1.70 (0.10, 31.00)	0.44 (0.02, 8.70)	16.00 (1.60, 1.7e+02)	38.00 (1.7, 1.1e+03)	2.50 (0.29, 3.20)	3.60 (0.25, 51.00)	6.70 (0.68, 71.00)	1.80 (0.08, 43.00)
0.26 (0.03,2.00)	**CPA**	0.99 (0.23, 4.40)	0.43 (0.06, 3.50)	0.12 (0.01, 1.00)	4.10 (1.20, 14.00)	9.70 (0.86, 1.5e+02)	0.65 (0.25, 1.80)	0.92 (0.15, 5.10)	1.7 (0.52, 5.80)	0.47 (0.04, 5.20)
0.26 (0.02, 3.50)	0.98 (0.20, 4.70)	**CPA+ Prednisone**	0.44 (0.05, 3.60)	0.12 (0.01, 1.00)	4.10 (1.50, 11.00)	9.70 (0.93, 1.4e+02)	0.65 (0.22, 2.00)	0.93 (0.21, 3.60)	1.70 (0.66, 4.50)	0.47 (0.07, 3.20)
0.59 (0.03,12.00)	2.30 (0.26,20.00)	2.30 (0.24,21.00)	**CSA+ Prednisone**	0.27 (0.04, 1.80)	9.40 (1.30, 63.00)	23.00 (1.20, 5.1e+02)	1.50 (0.25, 9.10)	2.20 (0.20, 20.00)	4.00 (0.58, 27.00)	1.10 (0.06, 19.00)
2.20 (0.10,49.00)	8.70 (0.88, 87.00)	8.50 (0.84, 90.00)	3.80 (0.50, 30.00)	**TwHF+CSA**	35.00 (4.50, 2.7e+02)	84.00 (4.40, 2.0e+03)	5.60 (0.86, 40.00)	8.00 (0.70, 84.00)	15.00 (2.00,1.2e+02)	4.10 (0.22, 76.00)
0.08 (0.006,0.90)	0.31 (0.09,87.00)	0.31 (0.10,0.92)	0.14 (0.02, 1.10)	**0.04 (0.004, 0.31)**	**Prednisone**	2.40 (0.27, 29.00)	**0.16 (0.08, 0.35)**	**0.23 (0.06, 0.78)**	**0.42 (0.26,0.69)**	0.12 (0.01, 1.00)
0.03 (0.001,0.80)	0.13 (0.01,1.60)	0.12 (0.01,1.40)	0.05 (0.002, 1,10)	**0.01 (0.001, 0.32)**	0.40 (0.04, 3.80)	**Prednisone+ Leflunomide**	0.07 (0.0053, 0.64)	0.10 (0.01, 1.1)	0.18 (0.02, 1.50)	0.05 (0.002, 1.00)
0.39 (0.04, 3.90)	1.50 (0.52, 4.30)	1.50 (0.46, 4.70)	0.66 (0.09, 4.50)	0.17 (0.02, 1.30)	**4.80 (2.20, 10.00)**	12.00 (1.2, 1.4e+02)	**TwHF**	1.40 (0.31, 5.7)	2.70 (1.30, 5.30)	0.73 (0.08, 6.50)
0.17 (0.01, 2.60)	0.66 (0.12, 3.90)	0.65 (0.16, 2.80)	0.29 (0.03, 3.20)	**0.08 (0.01, 0.90)**	2.10 (0.64, 7.20)	5.30 (0.42, 76.0)	0.043 (0.11, 1.8)	**TwHF+ Leflunomide**	1.90 (0.52, 7.50)	0.50 (0.05, 5.70)
0.17 (0.014,1.90)	0.66 (0.18, 2.40)	0.65 (0.23, 1.80)	0.29 (0.04, 2.30)	**0.08 (0.01, 0.66)**	**2.10 (1.30, 3.50)**	5.30 (0.59, 55.0)	**0.44 (0.21, 0.91)**	1.00 (0.28, 3.5)	**TwHF+ Prednisone**	0.28 (0.03, 2.30)
0.55 (0.02,14.00)	2.10 (0.16,27.00)	2.10 (0.28,16.00)	0.93 (0.05,20.00)	0.25 (0.01,5.40)	6.80 (0.68,68.00)	17.00 (0.72,4.4e+02)	1.40 (0.14,15.0)	3.20 (0.27,39.0)	3.20 (0.33,31.0)	**TwHF+Prednisone+Leflunomide**

Note: Total remission outcome (left below) and complete remission outcome (right top); left below: each number is a odds ratio and 95% credible interval. The columns are the reference category; right top: each number is a odds ratio and 95% credible interval. The rows are the reference category. CPA=cyclophosphamide, TwHF = Tripterygium wilfordii Hook F,CSA=Cyclosporine A.

Complete remission	Intervention	Total remission

Table 3

Results of network meta-analysis for hr urinary protein excretion and serum albumin.

CPA	-2.20 (-8.90, 4.50)	5.80 (0.06, 11.00)	-0.18 (-4.70, 4.30)	2.00 (-7.80, 12.00)	2.40 (-3.20, 7.80)	-10.00 (-23.00, 2.10)
-0.79 (-2.70, 1.10)	**CPA+ Prednisone**	8.00 (2.90, 13.00)	2.00 (-3.00, 7.10)	4.30 (-5.20, 14.00)	4.60 (-0.15, 9.20)	-8.00 (-19.00, 2.40)
0.55 (-0.94, 2.10)	1.30 (-0.11, 2.80)	**Prednisone**	-5.90 (-9.30, -2.50)	-3.70 (-12.00, 4.30)	-3.40 (-5.50, -1.30)	-16.00 (-28.00, -4.40)
-0.47 (-1.70, 0.76)	0.31 (-1.20, 1.80)	**-1.00 (-1.90, -0.14)**	**TwHF**	2.20 (-6.50, 11.00)	2.50 (-0.57, 5.60)	-10.00 (-22.00, 1.40)
0.91 (-1.70, 3.50)	1.70 (-0.88, 4.30)	0.35 (-1.8, 2.5)	1.40 (-0.94, 3.70)	**TwHF+ Leflunomide**	0.28 (-8.00, 8.60)	-12.00 (-26.00, 1.80)
-0.13 (-1.60, 1.40)	0.65 (-0.71, 2.00)	**-0.69 (-1.30, -0.14)**	0.33 (-0.48, 1.10)	-1.00 (-3.20, 1.20)	**TwHF+ Prednisone**	-13.00 (-24.00, -1.20)
-3.50 (-6.50, -0.45)	**-2.70 (-5.00, -0.38)**	-4.00 (-6.80, -1.30)	-3.00 (-5.80, -0.25)	-4.40 (-7.90, -0.91)	-3.30 (-6.00, -0.65)	**TwHF+Prednisone+ Leflunomide**

Note: Hr urinary protein excretion (left below) and serum albumin (right top); left below: each number is a mean difference and 95% credible interval. The columns are the reference category; right top: each number is a mean difference and 95% credible interval. The rows are the reference category. CPA=cyclophosphamide, TwHF = Tripterygium wilfordii Hook F,CSA=Cyclosporine A.

serum albumin	Intervention	hr urinary protein excretion

included extremely small number of studies and small sample sizes for most of comparisons, for example, only 2 studies involving 47 patients assessed the efficacy of CSA+TwHF, and one study involving 33 patients assessed leflunomide+TwHF. We considered that the present study existed the serious uncertainty of rankings. To avoid mislead evidence users, we did not plan to present the results of ranking.

There was no network meta-analysis to examine relative efficacy between different regimens based on TwHF until now. Our study firstly combined direct with indirect evidence to compare relatively efficacy of TwHF, CPA, prednisone, and their combination regimens. We performed a comprehensive search of the literature including Cochrane Library, EMBASE, and PubMed to identify all potential studies. However, all studies were conducted in China and published in Chinese. The reporting of included studies was poor, which led to the most of answers to risk of bias were unclear. Although the benefit of TwHF was observed, more high quality studies were warned. Second,

Table 4

Results of network meta-analysis for urea nitrogen and serum creatinine.

TwHF+ CPA	-	-	-	-	-	-	-
9.40 (-5.70, 25.00)	**CPA**	-	-	-	-	-	-
11.00 (-28.00, 49.00)	1.50 (-34.00, 36.00)	**CPA+ Prednisone**	-0.40 (-2.80, 2.00)	0.02 (-2.20, 2.20)	-0.46 (-3.30, 2.30)	-0.24 (-2.70, 2.20)	-
-6.00 (-31.00, 19.00)	-15.00 (-36.00, 4.70)	-17.00 (-48.00, 14.00)	**Prednisone**	0.41 (-0.52, 1.40)	-0.073 (-1.50, 1.30)	0.15 (-0.37, 0.66)	-
-9.60 (-33.00, 14.00)	**-19.00 (-37.00, -0.56)**	-21.00 (-50.00, 9.08)	-3.60 (-12.00, 5.20)	**TwHF**	-0.48 (-2.20, 1.20)	-0.26 (-1.20, 0.66)	-
-6.10 (-35.00, 23.00)	-16.00 (-41.00, 9.30)	-17.00 (-51.00,17.00)	-0.18 (-15.00, 14.00)	3.50 (-14.00, 20.00)	**TwHF+ Leflunomide**	0.23 (-1.30, 1.70)	-
-10.00 (-35.00, 15.00)	-20.00 (-40.00, 0.80)	-21.00 (-52.00, 10.00)	-4.30 (-9.30, 1.20)	-0.71 (-9.40, 8.30)	-4.20 (-20.00, 12.00)	**TwHF+ Prednisone**	-
-4.60 (-53.00, 44.00)	-14.00 (-60.00, 31.00)	-16.00 (-45.00, 14.00)	2.10 (-40.00, 46.00)	5.00 (-37.00, 47.00)	1.40 (-44.00, 47.00)	5.70 (-37.00, 48.00)	**TwHF+Prednisone +Leflunomide**

Note: Serum creatinine (left below) and urea nitrogen (right top); left below: each number is a mean difference and 95% credible interval. The columns are the reference category; right top: each number is a mean difference and 95% credible interval. The rows are the reference category. CPA=cyclophosphamide, TwHF = Tripterygium wilfordii Hook F,CSA=Cyclosporine A.

usea nitrogen	Intervention	serum creatinine

because of the inconsistent reporting about adverse effects of TwHF, we could not perform a network meta-analysis to compare the differences of adverse events in different treatment regimens, which indicated that future studies should concern the relevant adverse events of the use of TwHF. In addition, although a detailed subgroup analysis on the type of nephropathy was useful in clinical practice as a kind of precise evidence, because of the limitation of reporting of included studies, we only conducted a subgroup analysis to compare the differences between refractory PNS and primary PNS.

In conclusions, both direct and indirect evidence indicated that TwHF alone, the addition TwHF to prednisone, CPA, and CSA might be better to improve total remission rate, complete remission rate, hr urinary protein excretion, serum albumin, and serum creatinine. However, studies included paid less attention to the adverse effects from the use of TwHF. More RCTs with large sample size and high quality are warned to confirm the important role of TwHF and traditional Chinese medicine.

Author contributions

WXB and DEL planned and designed the research; XGZ and MRL provided methodological support/advice; WXB, DEL, and XGZ tested the feasibility of the study; WXB, DEL, XGZ, and DRL extract data; WXB and WXB performed the statistical analysis; WXB wrote the manuscript; all authors approved the final version of the manuscript.

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