

# Efficacy and safety of immunosuppressive therapies in the treatment of high-risk IgA nephropathy

## A network meta-analysis

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### Abstract

**Background:** IgA nephropathy (IgAN) is one of the significant contributing factors of end-stage renal disease (ESRD). It is reported that over half of patients with IgAN accompany multiple high-risk factors, which increase the risk of ESRD progression. Studies have shown that immunosuppressive agents were beneficial in high-risk IgAN, but the efficacy and safety have not been fully demonstrated yet. The present study aims to elucidate the efficacy of commonly used immunosuppressants in high-risk IgAN and their relative safety profiles via a network meta-analysis strategy.

**Methods:** Randomized controlled trials (RCTs) eligible for this network meta-analysis were included to evaluate the efficacy and safety of different immunosuppressants for high-risk IgAN. Main outcomes and measures include incidence of renal composite end point, the rate of total remission, adverse events, and proteinuria. Besides, subgroup analysis and cluster analysis were carried out.

**Results:** This network meta-analysis of 37 RCTs involving 3012 participants found that Mycophenolate mofetil (MMF) combined with corticosteroids (CS) was superior to other interventions in end point events and proteinuria. Cyclosporine A (CsA) plus CS was the best option for clinical remission rate, and supportive care (SC) was the safest treatment. Cluster analysis showed that MMF+CS and Leflunomide (LEF)+CS were best protocols in efficacy and safety. Subgroup analysis indicated the best benefits of MMF were presented among the Asian population, and the benefits increased with the increase of follow-up duration. The effect of Cyclophosphamide (CTX) +CS on crescent IgAN was better than that of other risk factors. Moreover, the increasing follow-up duration was negatively associated with the effect.

**Conclusions:** MMF+CS and LEF+CS appear to serve as the best choice for treating high-risk IgAN than other immunosuppressive therapies.

**Abbreviations:** Aza = azathioprine, CS = corticosteroids, CsA = cyclosporine A, CTX = cyclophosphamide, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, LEF = leflunomide, MMF = mycophenolate mofetil, SC = supportive care, SUCRA = surface under the cumulative ranking curves, Tap = time-average proteinuria, TW = tripterygium wilfordii.

**Keywords:** efficacy, high-risk IgA nephropathy, immunosuppressive, network meta-analysis, safety

## 1. Introduction

IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide and one of the significant contributing factors of end-stage renal disease (ESRD).<sup>[1]</sup> Around 20% to 40% patients with IgAN will progress to ESRD within 10 to 20 years after

diagnosis.<sup>[2,3]</sup> It is reported that over half of patients with IgAN accompany various high-risk factors like severe renal pathological damage, high proteinuria, hypertension, and lower estimated glomerular filtration rate (eGFR) which confer an increased risk of ESRD by 10 to 15 times.<sup>[4-6]</sup> Therefore, early intervention of high-

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The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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risk IgAN impose great significance. The reno-protective effect of corticosteroids (CS) among high-risk IgAN has been demonstrated via multiple clinical trials and meta-analysis.<sup>[7,8]</sup> However, safety concerns using CS have been raised lately in studies involving patients with IgAN.<sup>[9]</sup> Thus, more safe and effective strategies are urgently required in the treatment of high-risk IgAN. In recent years, increasing evidence suggested that immunosuppressive therapy plus CS was superior to CS alone in patients with high-risk IgAN.<sup>[10,11]</sup> Notably, the effects of different immunosuppressive therapies plus CS have not been systematically assessed. Here, we carried out a network meta-analysis to evaluate the efficacy and safety of commonly used immunosuppressant in high-risk IgAN.

## 2. Methods

We performed this network meta-analysis based on the Cochrane handbook<sup>[12]</sup> and reported it in accordance with the network meta-analysis priority report entries in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement.<sup>[13]</sup>

### 2.1. Data sources

All randomized clinical trials (RCTs), comparing clinical efficacy and safety of different immunosuppressive agents in high-risk IgAN were retrieved from PubMed, EMBASE, the Cochrane Library, CNKI, Wanfang Data, CBM, and VIP databases from database inception through to March 31, 2020. Besides, references from associated literatures were also traced to supplement the relevant research. MeSH terms was applied in combination of subject terms as the retrieval strategy. Search terms included: IgA nephropathy; IgA glomerulonephritides; Berger's disease; Immunoglobulin A nephropathy; IgA type nephritis; IgAN; Nephropathy, IgA; Progressive; Advanced; High-risk; Severe; Pathological damage; Renal failure; Proteinuria; Immunosuppressive treatment; Steroid; Mycophenolate mofetil; Cyclophosphamide; Leflunomide; Cyclosporine A; Azathioprine; Tripterygium wilfordii; Randomized controlled trial; RCT.

### 2.2. Study selection

Clinical trials eligible for this network meta-analysis were those:

1. enrolling participants older than 18 years with biopsy-proven IgAN and accompanied with at least one of the following risk factors<sup>[14,15]</sup>:
  - (a) Active renal pathological lesions (Diffuse mesangial proliferation, crescent formation, and glomerulosclerosis);
  - (b) Estimated glomerular filtration rate (eGFR): 30–90 mL/(min·1.73 m<sup>2</sup>);
  - (c) 24 h-urine total protein (24 h-UTP) ≥ 1 g;
  - (d) The blood pressure was still higher above 140/80 mmHg after conventional antihypertensive treatment.
2. comparing the efficacy of different immunosuppressive agents combined with CS or not, or with supportive care (SC), for more than 6 months;
3. providing data on any of the prespecified primary, secondary, and safety end points.

Trials that did not study the effect of single immunosuppressive agent (two immunosuppressants were used in the same arm, or the study compared different doses or treatment time of the same immunosuppressant) were considered not eligible.

### 2.3. Data extraction and quality assessment

Data were extracted using piloted forms, independently by 2 authors (TTL and YYW), and disagreements were resolved by YLZ through discussion. For similar studies, those with more participants and longer follow-up duration were selected. The extracted information included: Basic information (First author, publication date, country, sample size, and age of participants), characteristics of the intervention (type of immunosuppressive agents, treatment duration, and follow-up duration), outcomes. The risk of bias of included studies was assessed by two authors (HMM and LPY) using the RCT bias risk assessment tool recommended by Cochrane manual 5.1.0, and cross-checked finally.

### 2.4. Outcomes

The primary outcome was the incidence of renal composite end point, including the development of ESRD, the occurrence of 50% increase in serum creatinine (SCr), or death due to kidney disease. The secondary outcomes included:

1. the rate of total remission (defined as 24 h-UTP < 0.5 g, and stable renal function);
2. occurrence of adverse events (including infection, leucopenia, transaminase elevation, etc);
3. 24 h-UTP after treatment.

### 2.5. Statistical analysis

The Bayesian network meta-analysis was performed using STATA (version 14.0) and GeMTC (version 0.14.3) software. STATA was applied to draw the network evidence map of network meta-analysis as well as test the inconsistency (based on closed loops and node-splitting model). If the difference presented statistically significance ( $P > .05$ ), the consistency model was used for analysis and the results were sorted. Otherwise, the inconsistency model was used. Outcomes analysis was performed via GeMTC in the network meta-analysis. STATA was employed to draw a funnel plot for detecting the publication bias, and cluster analysis of different immunosuppressive interventions was conducted according to the incidence of renal composite end point, the rate of overall response and the incidence of adverse events. The odds ratio (OR) and 95% confidence interval (CI) of the dichotomous variables were used as the effect-quantity indexes, and the mean difference (MD) and 95% CI were used as the effect-quantity indexes for the continuous variables. The surface under the cumulative ranking curves (SUCRA) was used to assess the efficacy of each drug intervention program.

### 2.6. Ethics

This is a network meta-analysis and did not contain original data from clinical trials, so ethics approval is not applicable.

## 3. Results

### 3.1. Study selection and characteristics

A total of 6357 relevant literatures were identified through systematic searching, and 37 studies<sup>[9,16–51]</sup> (3012 participants) were finally included in this network meta-analysis to compare the efficacy and safety of 10 immunosuppressive therapies with each other or with supportive care (SC), including CS,

**Table 1**  
Characteristics of included study.

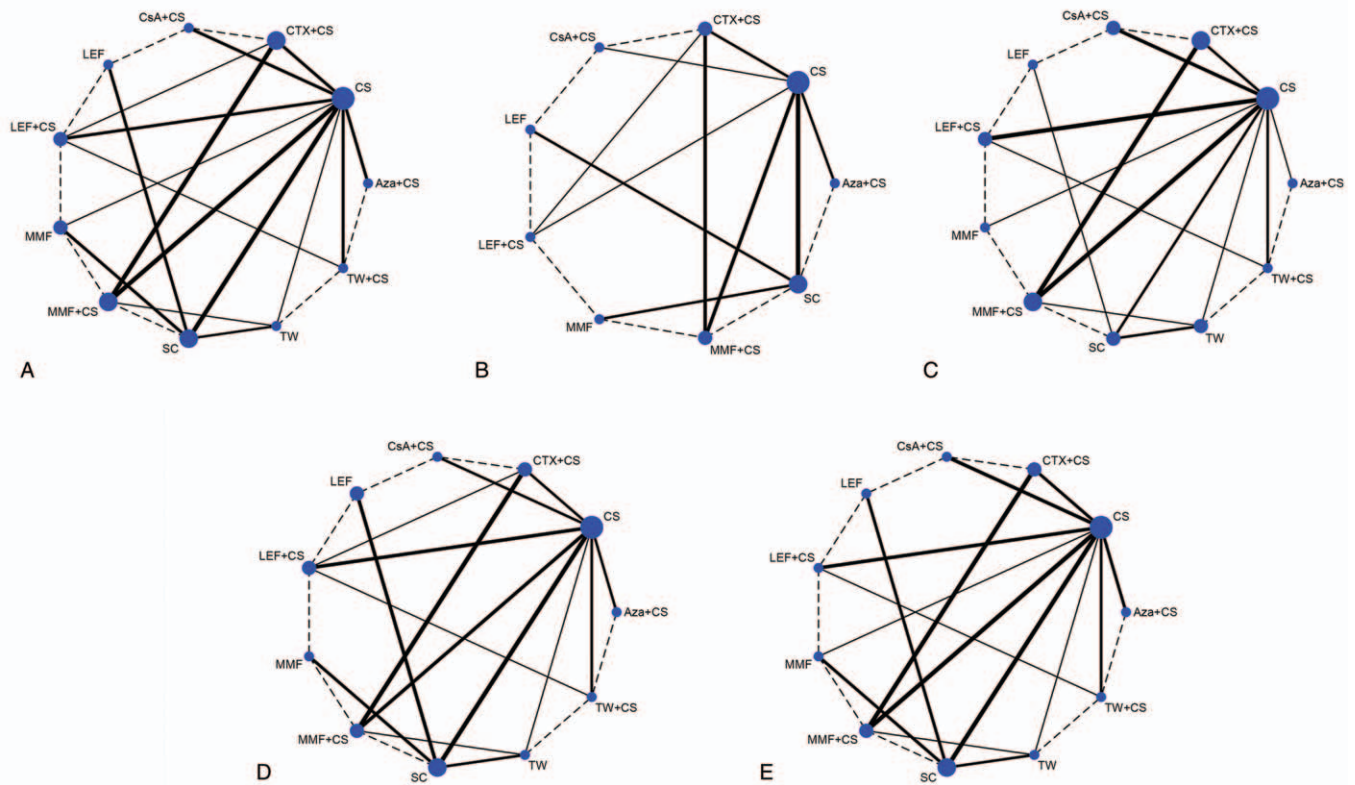
Study	Country	Sample size	Age	Inclusion criteria	Intervention		Intervention course (month)	Follow-up (month)	Outcomes
					Treatment 1	Treatment 2			
Lv 2017 <sup>[9]</sup>	China	136/126	38.6 ± 11.5/38.6 ± 11.7	24 h-UTP ≥ 1 g; eGFR:20–120 mL/min/1.73m <sup>2</sup>	CS	SC	8	25(6.7~45.3)	①③④
Cheng 2015 <sup>[16]</sup>	China	84/84	33.33 ± 8.78/33.98 ± 9.70	Lee's histological grade II–IV	LEF	SC	24	24	①③④
Liu 2014 <sup>[17]</sup>	China	42/42	39.8 ± 3.81/37.4 ± 4.78	Lee's histological grade >III; 24h-UTP ≥ 1.0g; Scr < 267 μmol/L(3mg/dl).	MMF+CS	CTX+CS	12	18	①②③④
Hou 2017 <sup>[18]</sup>	China	87/88	30.83 ± 9.05/33.50 ± 13.57	Active proliferative histologic lesions; 24h-UTP:1.0–2.0g.	MMF+CS	CS	12	12	①②③
Xu 2014 <sup>[19]</sup>	China	48/48	35.4 ± 7.3/34.5 ± 8.0	Lee's histological grade III–V; 24 h-UTP:1.0–3.5g; Scr < 150 mmol/L or eGFR > 60mL/min/1.73m <sup>2</sup>	CsA+CS	CS	12	/	②④
Katafuchi 2003 <sup>[20]</sup>	Japan	43/47	33.6 ± 13.4/32.5 ± 10.8	Glomerular score ranging from 4–7; Scr ≤ 1.5mg/dL (132.6 μmol/L)	CS	SC	60	67 ± 34/63 ± 10	①②③④
Maes 2004 <sup>[21]</sup>	Belgium	21/13	39 ± 11/43 ± 15	eGFR:20–70mL/min/1.73m <sup>2</sup> ; or 24h-UTP > 1.0g; or arterial hypertension; or Lee's histological grade II–IV	MMF	SC	36	12~36	①③④
Liang 2014 <sup>[22]</sup>	China	31/40/48	35.1 ± 9.4/32.9 ± 5.2/34.5 ± 12.2	24h-UTP ≥ 1.0g; eGFR ≥ 30mL/min/1.73m <sup>2</sup>	MMF+CS/CTX+CS	CS	24	30(12~96)	①③④
Pozzi 2013 <sup>[23]</sup>	Italy	20/26	42.67 ± 15.80/40.77 ± 15.37	24h-UTP ≥ 1.0g; Scr > 2.0mg/dL	Aza+CS	CS	12	54(34.8,73.2)	①③④
Liu 2014 <sup>[24]</sup>	China	23/25	42.39 ± 13.10/36.84 ± 8.06	24h-UTP ≥ 1.0g; eGFR > 30mL/min/1.73m <sup>2</sup>	CsA+CS	CS	12	12~60	①②③④
Stangou 2011 <sup>[25]</sup>	Greece	12/10	46.6 ± 12.1/51.3 ± 9.1	24h-UTP ≥ 1.0g; eGFR > 30mL/min/1.73m <sup>2</sup>	Aza+CS	CS	12	/	②③④
LV 2009 <sup>[26]</sup>	China	33/30	27.8 ± 8.9/30.43 ± 8.8	24h-UTP:1.0–5.0g; eGFR > 30 mL/min/1.73m <sup>2</sup>	CS	SC	6~8	27.3 ± 7.7(15~48)	①③④
Frisch 2005 <sup>[27]</sup>	USA	17/15	42.25 ± 14.75/38.75 ± 10.64	24h-UTP > 1.0g and at least two of risk factors	MMF	SC	12	14.75/18.75	①③④
Kobayashi 1996 <sup>[28]</sup>	Japan	20/26	30 ± 7/33 ± 10	24h-UTP ≥ 1.0g; eGFR > 70mL/min; total histological score ≥ 7	CS	SC	18	120	①④
Lou 2006 <sup>[29]</sup>	China	24/22	29 ± 11/34 ± 11	24h-UTP:1.0–3.0g; Scr < 354 μmol/L	LEF	SC	6	/	②③④
Mac 2009 <sup>[30]</sup>	China	19/15/15	36.7 ± 5.6/40.7 ± 11.2/35.4 ± 9.1	Lee's histological grade III–V; 24 h-UPT:1–3g	LEF+CS/TW+CS	CS	6	/	②③④
Tu 2019 <sup>[31]</sup>	China	34/34	42.9 ± 4.4/42.8 ± 5.6	24h-UTP ≥ 1.0g; eGFR > 50mL/min/1.73m <sup>2</sup>	TW+CS	CS	12	/	②③④
Bao 2007 <sup>[32]</sup>	China	19/18	27.4 ± 10.3/27.6 ± 11.0	Proportion of crescents ≥ 15%	MMF+CS	CTX+CS	12	12	①②③④
Li 2016 <sup>[33]</sup>	China	42/42	32.10 ± 8.56	Lee's histological grade II–IV	LEF	SC	12	32.10 ± 8.56	①③④

(continued)

**Table 1**  
(Continued).

Study	Country	Sample size	Age	Inclusion criteria	Intervention		Intervention course (month)	Follow-up (month)	Outcomes
					Treatment 1	Treatment 2			
Manno 2009 <sup>[34]</sup>	Italy	48/49	31.8 ± 11.3/34.9 ± 11.2	Histological grade moderate lesions; 24h-UTP ≥ 1.0g; eGFR ≥ 50 mL/min/1.73 m <sup>2</sup>	CS	SC	6	60(36~108)	①③④
Min 2017 <sup>[35]</sup>	China	40/45	36.90 ± 10.49/36.60 ± 11.53	24h-UTP ≥ 1.0g; eGFR ≥ 30 mL/min/1.73 m <sup>2</sup>	LEF+CS	CS	12	87.22 ± 21.24/ 89.12 ± 22.61	①②③④
Zhang 2014 <sup>[36]</sup>	China	30/26	29.33 ± 12.88/31.22 ± 12.75	Hass histological grade II-IV; 24h-UTP ≥ 1.0g	TW+CS	CS	12	/	③④
Tang 2010 <sup>[37]</sup>	China	20/20	42.1 ± 2.6/43.3 ± 2.8	24h-UTP ≥ 1.0g	MMF	SC	6	36	①③④
Pozzi 1999 <sup>[38]</sup>	Italy	43/43	38(26-45)/40(29-51)	24h-UTP:1-3.5g/d, Scr < 133 μmol/L(1.5 mg/dL)	CS	SC	6	48(12-120)	①②③④
Li 2011 <sup>[39]</sup>	China	30/30	36.43 ± 14.78/37.66 ± 16.12	Lee's histological grade ≥ III; 24h-UTP ≥ 1.0g	LEF+CS	CS	6	/	②③④
Yang 2016 <sup>[40]</sup>	China	52/52	34.4 ± 3.2/34.1 ± 2.3	Lee's histological grade ≥ III; 24h-UTP ≥ 1.0g	LEF+CS	CS	6	/	②③④
Lu 2016 <sup>[41]</sup>	China	55/54	41.36 ± 11.76/37.89 ± 11.14	eGFR:30-90 mL/min/1.73 m <sup>2</sup>	TW	CS	12	/	②③④
Zou 2013 <sup>[42]</sup>	China	25/32	30.3 ± 10.0/31.5 ± 11.0	Lee's histological grade > II	CTX+CS	LEF+CS	12	12	①③
Zhu 2017 <sup>[43]</sup>	China	30/30	39.5 ± 12.5/34.9 ± 11.5	24h-UTP:1.0-3.5g	TW	SC	6	/	②③④
Wang 2017 <sup>[44]</sup>	China	60/60	37.8 ± 5.7/37.6 ± 5.5	Lee's histological grade III-V; Scr < 150 μmol/L; 24h-UTP:1.0-3.5g	CsA+CS	CS	6	/	②③④
Pozzi 2010 <sup>[45]</sup>	Italy	101/106	35.3 ± 3.2/40.65 ± 4.17	Scr ≤ 2.0 mg/dL; 24h-UTP ≥ 1.0g	Aza+CS	CS	6	58.8(36,76.8)	①③④
Wang 2013 <sup>[46]</sup>	China	20/20/20	40.00 ± 11.64/39.45 ± 12.72/ 39.40 ± 11.98	Renal histological moderate lesions; 24h-UTP > 1.0g/d; eGFR:15-60 mL/min/1.73 m <sup>2</sup>	MMF+CS/CTX+CS	CS	12	24.09 ± 13.86	①②③④
Zhu 2019 <sup>[47]</sup>	China	24/24/24	36.2 ± 5.2/36.4 ± 5.3/36.3 ± 5.2	Hass histological grade > III	MMF+CS/CTX+CS	CS	6	/	②③④
Yu 2012 <sup>[48]</sup>	China	40/22	37.4 ± 10.4/37.3 ± 10.5	24h-UTP:1-3.5g	TW	SC	6	/	②③④
Xiong 2007 <sup>[49]</sup>	China	26/21	24.2 ± 8.4/33.3 ± 9.3	24h-UTP:1-3.5g; Scr < 133 μmol/L	CS	SC	12	/	②③④
Zhang 2019 <sup>[50]</sup>	China	36/23	35.69 ± 1.63/36.43 ± 2.41	eGFR:15-60 mL/min/1.73 m <sup>2</sup> ; 24h-UTP > 1.0g	MMF+CS	TW	9	/	②③④
Chen 2002 <sup>[51]</sup>	China	31/31	28 ± 10/29 ± 10	Lee's histological grade IV-V; 24h-UTP ≥ 2.0g; Scr < 355 μmol/L(4 mg/dL)	MMF	CS	>6	18	②④

Outcomes: ① Renal composite end point incidence; ② Total remission; ③ Incidence of adverse effect; ④ Proteinuria.



**Figure 1.** The evidence network graph among different intervention programs. (A) All outcome indicators; (B) renal composite end point incidence; (C) total remission; (D) incidence of adverse effect; (E) proteinuria. The size of nodes reflects the total sample size of participants for each treatment; and the thickness of the line represents the number of related studies.

Mycophenolate mofetil (MMF), Leflunomide (LEF), Tripterygium wilfordii (TW), Cyclosporine A (CsA) combined with CS, Cyclophosphamide (CTX) combined with CS, azathioprine (Aza) combined with CS, MMF combined with CS, LEF combined with CS, TW combined with CS. Twenty-eight studies<sup>[9,16–19,22,24,26,29–33,35–37,39–44,46–51]</sup> were conducted in China, 4 in Italy,<sup>[23,34,38,45]</sup> 2 in Japan,<sup>[20,28]</sup> and one in the United States,<sup>[27]</sup> Greece<sup>[25]</sup> and Belgium,<sup>[21]</sup> respectively. Twenty-one studies<sup>[9,16–18,20–24,26–28,32–35,37–38,42,45–46]</sup> reported the incidence of renal composite end point. The characteristics of the included studies were shown in Table 1 and the evidence network among different intervention programs were shown in Figure 1. These studies theoretically yield 55 different pairwise comparisons. A total of 12 studies<sup>[9,18,20–21,23,26–27,34,37–38,45,51]</sup> were at low risk of bias in all areas, and 8 studies<sup>[30,36,39,41–43,48,50]</sup> were at high risk in the blind method. The bias risks of included studies were detailed in Figure 2.

### 3.2. Network meta-analysis

**3.2.1. Renal composite end point incidence.** Results showed that the risk of endpoint events in high-risk IgAN treated with MMF+CS was lower than that of CTX+CS (RR=0.22, 95%CI [0.07,0.65]), LEF+CS (RR=0.18, 95%CI[0.04,0.90]), Aza+CS (RR=0.09, 95%CI[0.02,0.44]), CS (RR=0.11, 95%CI [0.04,0.36]), MMF (RR=0.04, 95%CI[0.01,0.26]), and SC (RR=0.03, 95%CI[0.01,0.13]); SC had a higher risk of endpoint events than MMF+CS (RR=29.76, 95%CI[7.64,115.96]), CTX

+CS (RR=6.47, 95%CI[1.85,22.59]), LEF+CS (RR=5.42, 95%CI[1.23,23.83]), CS (RR=3.33, 95%CI[1.60,6.93]), and LEF (RR=7.81, 95%CI[1.72,35.39]). Based on the SUCRA analysis of different schemes intervene high-risk IgAN, MMF+CS may be a less risky option for endpoint events. The ranking results of the risk of end-point events of the 11 treatment options were as follows: MMF+CS(1.9%) < LEF(27.7%) < CTX+CS(29.7%) < LEF+CS(36%) < CS(52.5%) < Aza+CS(58.9%) < CsA+CS (75.2%) < MMF(80.2%) < SC(87.9%) (Table 2, Fig. 3).

**3.2.2. The rate of total remission.** For rate of total remission, patients received CsA+CS were higher than that treated with CTX+CS (RR=5.19, 95%CI[1.27,21.21]), LEF (RR=24.79, 95%CI[3.51,175.23]), CS (RR=3.84, 95%CI[1.44,10.28]), TW (RR=4.54, 95%CI[1.33,15.55]) or SC (RR=14.58, 95%CI [4.43,47.95]). Furthermore, patients accepted TW+CS presented a higher rate of total remission than that accepted CTX+CS (RR=5.32, 95%CI[1.02,27.81]), CS (RR=3.94, 95%CI [1.07,14.54]), TW (RR=4.65, 95%CI[1.04,20.89]), LEF (RR=25.40, 95%CI[3.00,214.74]), or SC (RR=14.94, 95%CI [3.45,64.72]). Conversely, LEF therapy was less effective in improving rate of total remission than therapies like MMF+CS (RR=0.09, 95%CI[0.01,0.55]), LEF+CS (RR=0.09, 95%CI [0.01,0.55]), CS (RR=0.16, 95%CI[0.03,0.84]) or MMF (RR=0.10, 95%CI[0.01,0.89]), and similarly, SC intervention was less effective than interventions including MMF+CS (RR=0.15, 95%CI[0.06,0.39]), LEF+CS (RR=0.15, 95%CI[0.06,0.40]), CS (RR=0.26, 95%CI[0.14,0.51]), MMF (RR=0.18, 95%CI

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bao2007	+	+	?	?	+	+	+
Chen2002	+	+	+	+	+	+	+
Cheng2015	+	+	?	?	+	?	+
Frisch2005	+	+	+	+	+	+	+
Hou2017	+	+	+	+	+	+	+
Katafuchi2003	+	+	+	+	+	+	+
Kobayashi1996	+	+	?	?	+	+	+
Li2011	?	?	+	+	?	?	?
Li2016	+	+	?	?	+	+	+
Liang2014	+	?	?	?	+	+	+
Liu H2014	+	+	?	?	+	+	?
Liu X2014	+	+	?	?	+	+	+
Lou2006	+	+	?	?	+	+	+
Lu2016	+	?	+	+	?	?	?
LV2009	+	+	+	+	+	+	+
Lv2017	+	+	+	+	+	+	+
Maes2004	+	+	+	+	+	+	+
Manno2009	+	+	+	+	+	+	+
Mao2009	?	?	+	+	?	?	?
Min2017	+	+	?	?	+	+	+
Pozzi1999	+	+	+	+	+	+	+
Pozzi2010	+	+	+	+	+	+	+
Pozzi2013	+	+	+	+	+	+	+
Stangou2011	+	+	?	?	+	+	+
Tang2010	+	?	+	+	+	+	+
Tu2019	?	?	+	?	+	+	?
Wang2013	+	+	?	?	+	+	+
Wang2017	+	?	+	?	+	?	+
Xiong2007	+	?	?	?	+	?	?
Xu2014	+	?	?	?	?	+	+
Yang2016	+	?	+	?	?	?	?
Yu2012	?	?	+	+	?	?	?
Zhang2014	?	?	+	+	?	?	?
Zhang2019	?	?	+	+	?	?	?
Zhu2017	?	?	+	+	?	?	?
Zhu2019	+	?	?	?	+	?	?
Zou2013	?	?	+	+	?	?	?

Figure 2. Assessment of the risk of bias summary in the study.

Table 2

Matrix of the risk of renal composite end point incidence.

CS	0.11 (0.04,0.36)	0.52 (0.19,1.43)	0.61 (0.17,2.24)	3.40 (0.11,107.78)	1.24 (0.42,3.69)	2.71 (0.65,11.37)	0.43 (0.08,2.29)
MMF+CS	<b>8.92 (2.81,28.32)</b>	<b>4.60 (1.53,13.83)</b>	<b>5.49 (1.11,27.02)</b>	30.34 (0.79,1160.59)	<b>11.08 (2.27,54.14)</b>	<b>24.21 (3.87,151.38)</b>	3.81 (0.50,29.13)
CTX+CS	1.94 (0.70,5.39)	0.84 (0.21,3.33)	1.19 (0.30,4.74)	6.60 (0.18,242.42)	2.41 (0.54,10.71)	5.26 (0.91,30.40)	0.83 (0.12,5.89)
0.18 (0.04,0.90)	0.03 (0.00,1.26)	0.15 (0.00,5.57)	5.53 (0.14,221.46)	2.02 (0.37,10.94)	4.41 (0.64,30.22)	0.69 (0.08,5.76)	0.13 (0.00,5.86)
0.30 (0.14,0.62)	0.03 (0.01,0.13)	<b>0.15 (0.04,0.54)</b>	<b>CsA+CS</b>	0.37 (0.01,13.69)	0.80 (0.02,33.65)	0.81 (0.24,2.78)	<b>0.13 (0.03,0.58)</b>
0.81 (0.27,2.39)	0.09 (0.02,0.44)	0.41 (0.09,1.84)	1.02 (0.03,34.90)	0.37 (0.10,1.38)	<b>AZA+CS</b>	2.18 (0.36,13.21)	0.34 (0.05,2.54)
0.37 (0.09,1.55)	<b>0.04 (0.01,0.26)</b>	0.19 (0.03,1.10)	2.74 (0.07,102.61)	<b>SC</b>	0.46 (0.08,2.77)	<b>MMF</b>	0.16 (0.02,1.11)
2.34 (0.44,12.54)	0.26 (0.03,2.01)	1.21 (0.17,8.58)	1.25 (0.03,52.85)	2.69 (0.72,9.97)	2.91 (0.39,21.49)	6.35 (0.90,44.61)	<b>LEF</b>
			7.96 (0.17,371.22)	1.23 (0.36,4.21)			

The values in bold are statistically significant.

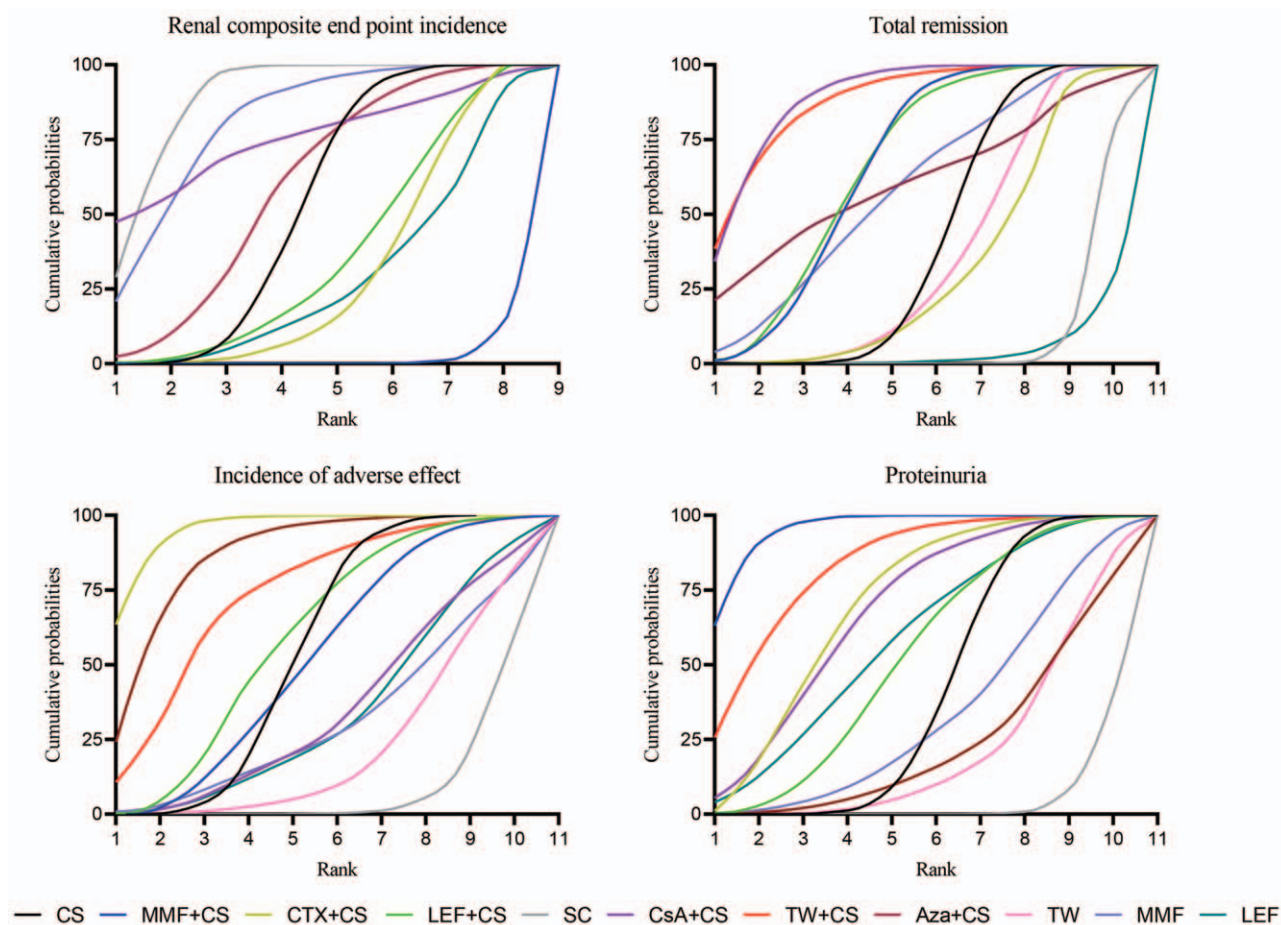


Figure 3. The SUCRA of each outcomes.

[0.04,0.77]), and TW (RR=0.31, 95%CI[0.15,0.67]). SUCRA analysis for rate of total remission of 11 interventions were described as follows in a descending order: CsA+CS(88.6%) > TW+CS(87.4%) > LEF+CS(66.2%) > MMF+CS(66%) > Aza+CS(60.6%) > MMF(58.2%) > CS(41.5%) > TW(36.1%) > CTX+CS(32%) > SC(8.9%) > LEF(4.5%) (Table 3, Fig. 3).

**3.2.3. Incidence of adverse events.** In patients with high-risk IgAN, CTX+CS showed higher risk in incidence of adverse events compared with MMF+CS (RR=4.38, 95%CI[1.66,11.58]), LEF+CS (RR=3.68, 95%CI[1.12,12.13]), CsA+CS (RR=6.89, 95%CI[1.45,32.75]), MMF (RR=8.11, 95%CI[1.20,55.08]), LEF (RR=7.27, 95%CI[1.38,38.20]), TW (RR=9.44, 95%CI[2.39,37.33]), CS (RR=4.15, 95%CI[1.56,11.01]), and SC (RR=13.37, 95%CI[3.79,47.13]). SC notably showed a lower risk in incidence of adverse events compared with LEF+CS (RR=0.28, 95%CI[0.08,0.90]), TW+CS (RR=0.18, 95%CI[0.04,0.83]), Aza+CS (RR=0.12, 95%CI[0.03,0.45]), and CS (RR=0.31, 95%CI[0.14,0.71]), and TW was associated with lower risk in incidence of adverse events than Aza+CS (RR=0.17, 95%CI[0.04,0.76]). The SUCRA analysis of the 11 treatment regimens was sequenced as follows: SC(8.8%) < TW(22.2%) < MMF(30.9%) < LEF(33.5%) < CsA+CS(34.5%) < MMF+CS(51.7%) < CS(54.8%) < LEF+CS(59%) < TW+CS(73.4%) < Aza+CS(86.1%) < CTX+CS(95.1%) (Table 4, Fig. 3).

**3.2.4. Proteinuria.** The improvement of proteinuria was remarkable in the MMF+CS group in comparison with CTX+CS (RR=0.34, 95%CI[0.02,0.67]), LEF+CS (RR=0.53, 95%CI[0.04,1.02]), Aza+CS (RR=0.85, 95%CI[0.25,1.45]), MMF (RR=0.74, 95%CI[0.15,1.32]), TW (RR=0.85, 95%CI[0.39,1.32]), CS (RR=0.64, 95%CI[0.30,0.97]), and SC (RR=1.07, 95%CI[0.65,1.48]). Instead, compared with SC, CTX+CS (RR=0.72, 95%CI[0.26,1.18]), LEF+CS (RR=0.53, 95%CI[0.09,0.98]), CsA+CS (RR=0.70, 95%CI[0.20,1.19]), TW+CS (RR=0.89, 95%CI[0.34,1.44]), CS (RR=0.43, 95%CI[0.16,0.70]), and LEF (RR=0.59, 95%CI[0.14,1.04]) led to notably reduction in proteinuria. In addition, combination therapies TW+CS were superior to TW (RR=0.68, 95%CI[0.05,1.31]). Results of SUCRA analysis in reducing proteinuria was detailed as follows: MMF+CS(95.1%) > TW+CS(82.8%) > CTX+CS(69.7%) > CsA+CS(68%) > LEF(58.2%) > LEF+CS(52.4%) > CS(40.7%) > MMF(33%) > Aza+CS(23.5%) > TW(21.8%) > SC(4.9%) (Table 5, Fig. 3).

### 3.3. Cluster analysis

A cluster analysis based on SUCRA of the incidence of renal composite end point, rate of total remission and incidence of adverse events was carried out for demonstrating the efficacy and safety of the different interventions in high-risk IgAN. The

**Table 3**

**Matrix of comparison of total remission rate.**

CS	1.71 (0.86,3.39)	0.74 (0.27,2.04)	1.77 (0.86,3.67)	<b>3.84 (1.44,10.28)</b>	<b>0.26 (0.14,0.51)</b>	<b>3.94 (1.07,14.54)</b>	1.80 (0.12,26.67)	0.85 (0.40,1.77)	1.48 (0.40,5.44)	<b>0.16 (0.03,0.84)</b>
0.59 (0.29,1.16)	MMF+CS	0.43 (0.18,1.06)	1.04 (0.39,2.78)	2.25 (0.68,7.44)	<b>0.15 (0.06,0.39)</b>	2.31 (0.53,10.10)	1.05 (0.07,17.03)	0.50 (0.21,1.19)	0.87 (0.20,3.78)	<b>0.09 (0.01,0.55)</b>
1.35 (0.49,3.72)	CTX+CS	2.39 (0.70,8.23)	2.39 (0.70,8.23)	<b>5.19 (1.27,21.21)</b>	0.36 (0.11,1.18)	<b>5.32 (1.02,27.81)</b>	2.43 (0.14,43.29)	1.14 (0.35,3.72)	2.00 (0.38,10.39)	0.21 (0.03,1.48)
0.56 (0.27,1.17)	LEF+CS	0.42 (0.12,1.44)	0.46 (0.14,1.56)	2.17 (0.64,7.36)	<b>0.15 (0.06,0.40)</b>	2.22 (0.54,9.14)	1.02 (0.06,16.58)	0.48 (0.17,1.35)	0.83 (0.19,3.71)	<b>0.09 (0.01,0.55)</b>
<b>0.26 (0.10,0.70)</b>	0.44 (0.13,1.47)	<b>0.19 (0.05,0.79)</b>	0.46 (0.14,1.56)	CsA+CS	<b>0.07 (0.02,0.23)</b>	1.02 (0.20,5.26)	0.47 (0.03,8.26)	<b>0.22 (0.06,0.75)</b>	0.38 (0.08,1.97)	<b>0.04 (0.01,0.29)</b>
<b>3.79 (1.95,7.39)</b>	<b>6.48 (2.58,16.24)</b>	2.81 (0.85,9.27)	<b>6.72 (2.49,18.16)</b>	<b>14.58 (4.43,47.95)</b>	SC	<b>14.94 (3.45,64.72)</b>	6.83 (0.43,109.76)	<b>3.21 (1.50,6.86)</b>	<b>5.60 (1.30,24.23)</b>	0.59 (0.12,2.78)
<b>0.25 (0.07,0.94)</b>	0.43 (0.10,1.90)	<b>0.19 (0.04,0.98)</b>	0.45 (0.11,1.85)	0.98 (0.19,5.01)	<b>0.07 (0.02,0.29)</b>	TW+CS	0.46 (0.02,9.14)	<b>0.21 (0.05,0.96)</b>	0.38 (0.06,2.37)	<b>0.04 (0.00,0.33)</b>
0.56 (0.04,8.23)	0.95 (0.06,15.31)	0.41 (0.02,7.32)	0.98 (0.06,16.06)	2.13 (0.12,37.63)	0.15 (0.01,2.35)	2.19 (0.11,43.74)	Aza+CS	0.47 (0.03,7.70)	0.82 (0.04,16.39)	0.09 (0.00,2.07)
1.18 (0.56,2.48)	2.02 (0.84,4.84)	0.87 (0.27,2.84)	2.09 (0.74,5.91)	<b>4.54 (1.33,15.55)</b>	<b>0.31 (0.15,0.67)</b>	<b>4.65 (1.04,20.89)</b>	2.13 (0.13,34.82)	TW	1.75 (0.39,7.81)	0.18 (0.00,1.03)
0.68 (0.18,2.49)	1.16 (0.26,5.04)	0.50 (0.10,2.61)	1.20 (0.27,5.34)	2.60 (0.51,13.32)	<b>0.18 (0.04,0.77)</b>	2.67 (0.42,16.87)	1.22 (0.06,24.34)	0.57 (0.13,2.57)	MMF	<b>0.10 (0.01,0.89)</b>
<b>6.45 (1.19,34.92)</b>	<b>11.01 (1.81,66.85)</b>	4.78 (0.67,33.84)	<b>11.43 (1.81,72.16)</b>	<b>24.79 (3.51,175.23)</b>	1.70 (0.36,8.02)	<b>25.40 (3.00,214.74)</b>	11.61 (0.48,279.53)	5.46 (0.97,30.72)	<b>9.53 (1.13,80.44)</b>	LEF

The values in bold are statistically significant.

**Table 4**

**Matrix of the risk of adverse effect incidence.**

CS	0.95 (0.40,2.25)	<b>4.15 (1.56,11.01)</b>	1.13 (0.48,2.65)	0.60 (0.18,2.02)	<b>0.31 (0.14,0.71)</b>	1.77 (0.47,6.73)	2.66 (0.90,7.88)	0.44 (0.15,1.28)	0.51 (0.10,2.71)	0.57 (0.15,2.22)
1.06 (0.45,2.51)	MMF+CS	<b>4.38 (1.66,11.58)</b>	1.19 (0.37,3.84)	0.64 (0.14,2.81)	0.33 (0.10,1.03)	1.87 (0.39,9.00)	2.81 (0.70,11.22)	0.46 (0.14,1.59)	0.54 (0.08,3.44)	0.60 (0.13,2.91)
<b>0.24 (0.09,0.64)</b>	0.23 (0.09,0.60)	3.68 (1.12,12.13)	<b>0.27 (0.08,0.89)</b>	<b>0.15 (0.03,0.69)</b>	<b>0.07 (0.02,0.26)</b>	0.43 (0.08,2.20)	0.64 (0.15,2.76)	<b>0.11 (0.03,0.42)</b>	<b>0.12 (0.02,0.84)</b>	<b>0.14 (0.03,0.72)</b>
0.89 (0.38,2.08)	0.84 (0.26,2.71)	<b>6.89 (1.45,32.75)</b>	1.87 (0.43,8.24)	0.53 (0.12,2.35)	<b>0.28 (0.08,0.90)</b>	1.57 (0.37,6.65)	2.36 (0.59,9.39)	0.39 (0.10,1.51)	0.45 (0.07,2.94)	0.51 (0.10,2.51)
1.66 (0.49,5.58)	1.57 (0.36,6.94)	<b>13.37 (3.79,47.13)</b>	<b>3.63 (1.11,11.85)</b>	CsA+CS	0.52 (0.12,2.22)	2.94 (0.49,17.73)	4.42 (0.87,22.44)	0.73 (0.15,3.67)	0.85 (0.11,6.67)	0.95 (0.15,5.84)
<b>3.22 (1.41,7.33)</b>	3.05 (0.97,9.56)	2.34 (0.46,12.08)	0.64 (0.15,2.70)	1.94 (0.45,8.36)	SC	<b>5.70 (1.20,27.09)</b>	<b>8.58 (2.20,33.38)</b>	1.42 (0.48,4.20)	1.65 (0.38,7.05)	1.84 (0.62,5.42)
0.56 (0.15,2.15)	0.53 (0.11,2.57)	1.56 (0.36,6.72)	0.42 (0.11,1.68)	0.34 (0.06,2.05)	<b>0.18 (0.04,0.83)</b>	TW+CS	1.50 (0.27,8.37)	0.25 (0.05,1.37)	0.29 (0.03,2.45)	0.32 (0.05,2.15)
0.38 (0.13,1.11)	0.36 (0.09,1.42)	1.56 (0.36,6.72)	0.42 (0.11,1.68)	0.23 (0.04,1.15)	<b>0.12 (0.03,0.45)</b>	0.66 (0.12,3.70)	Aza+CS	<b>0.17 (0.04,0.76)</b>	0.19 (0.03,1.40)	0.21 (0.04,1.22)
2.27 (0.78,6.59)	2.15 (0.63,7.36)	<b>9.44 (2.39,37.33)</b>	2.56 (0.66,9.94)	1.37 (0.27,6.87)	0.71 (0.24,2.10)	4.02 (0.73,22.18)	<b>6.05 (1.32,27.68)</b>	TW	1.16 (0.19,7.11)	1.30 (0.28,6.02)
1.96 (0.37,10.34)	1.85 (0.29,11.77)	<b>8.11 (1.20,55.08)</b>	2.20 (0.34,14.30)	1.18 (0.15,9.25)	0.61 (0.14,2.60)	3.46 (0.41,29.32)	5.21 (0.71,38.02)	0.86 (0.14,5.26)	MMF	1.12 (0.18,6.83)
1.75 (0.45,6.81)	1.66 (0.34,7.99)	<b>7.27 (1.38,38.20)</b>	1.97 (0.40,9.79)	1.05 (0.17,6.49)	0.54 (0.18,1.60)	3.10 (0.47,20.64)	4.66 (0.82,26.45)	0.77 (0.17,3.57)	0.90 (0.15,5.48)	LEF

The values in bold are statistically significant.



**Table 5**

**Matrix of the effect of reducing proteinuria.**

CS	-0.64 (-0.97, -0.30)	-0.29 (-0.68, 0.09)	-0.11 (-0.46, 0.25)	-0.27 (-0.69, 0.15)	<b>0.43 (0.16, 0.70)</b>	-0.46 (-0.95, 0.02)	0.21 (-0.28, 0.71)	0.22 (-0.19, 0.62)	0.10 (-0.39, 0.59)	-0.16 (-0.68, 0.36)
MMF+CS	<b>0.64 (0.30, 0.97)</b>	<b>0.34 (0.02, 0.67)</b>	<b>0.53 (0.04, 1.02)</b>	0.37 (-0.17, 0.91)	<b>1.07 (0.65, 1.48)</b>	0.18 (-0.42, 0.77)	<b>0.85 (0.25, 1.45)</b>	<b>0.85 (0.39, 1.32)</b>	<b>0.74 (0.15, 1.32)</b>	0.48 (-0.14, 1.09)
CTX+CS	-0.34 (-0.67, -0.02)	0.19 (-0.34, 0.71)	0.19 (-0.34, 0.71)	0.03 (-0.54, 0.60)	<b>0.72 (0.26, 1.18)</b>	-0.17 (-0.79, 0.45)	0.51 (-0.12, 1.14)	0.51 (-0.01, 1.03)	0.39 (-0.22, 1.01)	0.13 (-0.51, 0.78)
LEF+CS	-0.53 (-1.02, -0.04)	0.16 (-0.39, 0.71)	0.16 (-0.39, 0.71)	-0.16 (-0.71, 0.39)	<b>0.53 (0.09, 0.98)</b>	-0.36 (-0.89, 0.18)	0.32 (-0.30, 0.94)	0.32 (-0.22, 0.87)	0.21 (-0.40, 0.81)	-0.05 (-0.69, 0.58)
CS+CS	-0.27 (-0.15, 0.69)	-0.72 (-1.18, -0.26)	-0.53 (-0.98, -0.09)	-0.70 (-1.19, -0.20)	<b>0.70 (0.20, 1.19)</b>	-0.19 (-0.84, 0.45)	0.48 (-0.17, 1.13)	0.48 (-0.10, 1.07)	0.37 (-0.28, 1.01)	0.11 (-0.56, 0.78)
MMF+CS	-0.34 (-0.67, -0.02)	0.17 (-0.45, 0.79)	0.36 (-0.18, 0.89)	0.19 (-0.45, 0.84)	<b>0.89 (0.34, 1.44)</b>	-0.89 (-1.44, -0.34)	(-0.78, 0.35)	(-0.62, 0.20)	(-0.78, 0.12)	<b>-0.59 (-1.04, -0.14)</b>
LEF+CS	-0.53 (-1.02, -0.04)	-0.51 (-1.03, 0.01)	-0.32 (-0.94, 0.30)	-0.48 (-1.13, 0.17)	0.21 (-0.35, 0.78)	-0.68 (-1.37, 0.02)	0.68 (-0.02, 1.37)	<b>0.68 (0.05, 1.31)</b>	0.56 (-0.13, 1.25)	0.30 (-0.41, 1.01)
MMF	-0.74 (-1.32, -0.15)	-0.39 (-1.01, 0.22)	-0.21 (-0.81, 0.40)	-0.37 (-1.01, 0.28)	0.33 (-0.12, 0.78)	-0.68 (-1.31, -0.05)	-0.00 (-0.65, 0.64)	0.00 (-0.64, 0.65)	-0.11 (-0.81, 0.58)	-0.37 (-1.10, 0.35)
LEF	-0.48 (-1.09, 0.14)	-0.13 (-0.78, 0.51)	0.05 (-0.58, 0.69)	-0.11 (-0.78, 0.56)	<b>0.59 (0.14, 1.04)</b>	-0.30 (-1.01, 0.41)	0.37 (-0.35, 1.10)	0.38 (-0.23, 0.99)	0.26 (-0.38, 0.90)	-0.26 (-0.90, 0.38)

The values in bold are statistically significant.

SUCRA of incidence of adverse events, rate of total remission and incidence of renal composite end point represented safety, short-term efficacy, and long-term efficacy, respectively. Results indicated that MMF+CS and LEF+CS were top two best choice for protecting patients from high-risk IgAN. Despite benefits in short-term efficacy and safety about CsA+CS has been suggested, the long-term efficacy was still unsatisfactory. Moreover, SC showed benefits in safety with poor short- and long-term efficacy, other protocols has displayed no significant benefits in efficacy and safety (Fig. 4A). In addition, we also did cluster analysis for renal composite end point, proteinuria and incidence of adverse events, and found that MMF + CS was still the best treatment (Fig. 4B).

### 3.4. Subgroup and sensitivity analyses

Studies<sup>[52,53]</sup> have reported that races and follow-up duration may affect the effects of immunosuppressants. Therefore, we divided the included studies into Asian subgroup<sup>[9,16-20,22,24,26,28-33,35-37,39-44,46-51]</sup> (China and Japan) and European and American subgroup<sup>[21,23,25,27,34,38,45]</sup> (United States, Italy, Greece, and Belgium). The results showed that the long-term effect and proteinuria were improved in MMF group among Asian population with high-risk IgAN, and the efficacy of other interventions was consistent across ethnic groups.

In addition, we divided the included studies into long-term follow-up subgroup<sup>[20,23,28,34-35,37-38,45]</sup> ( $\geq 3$  years) and short-term follow-up subgroup<sup>[9,16-18,21-22,24,26-27,32-33,42,46]</sup> ( $< 3$  years). Results showed that the long-term effect of MMF increased and that of CTX+CS decreased with the increase of follow-up duration.

Crescentic IgAN is a special type of high-risk IgAN. In order to test the sensitivity of this network meta-analysis, a sensitivity analysis was conducted after removing 3 studies about crescentic<sup>[18,22,32]</sup> IgAN, and the results was consistent except for the decreased efficacy of CTX+CS.

### 3.5. Inconsistency and publication bias

We tested the inconsistency of the closed-loop formed by each outcome index. Our results showed that no significant difference between the closed loops existed, indicating that, the consistency model was reliable (Table 6). Furthermore, based on the node-splitting model, we further tested the inconsistency between the comparisons of each head-to-head treatment schemes. There is no significant difference in outcomes.

The comparison adjusted funnel plot with fitting auxiliary line was made for each outcomes. The results showed that the funnel plots were basically symmetrical, indicating that there was no publication bias in included studies, or publication bias did not affect the results of this network meta-analysis (Fig. 5).

## 4. Discussion

Renin-angiotension-aldosterone system (RAAS) inhibitors are considered as the basic supportive treatment for IgAN recommended by The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.<sup>[54]</sup> However, some patients still manifest as persistent urine protein excretion  $> 1\text{g}/24\text{h}$  after a maximal tolerated or allowed daily dose of RAAS inhibitors for a minimum of 3 months. IgAN is an autoimmune disease and immune complex mediating “Multi-hits” may ultimately lead to

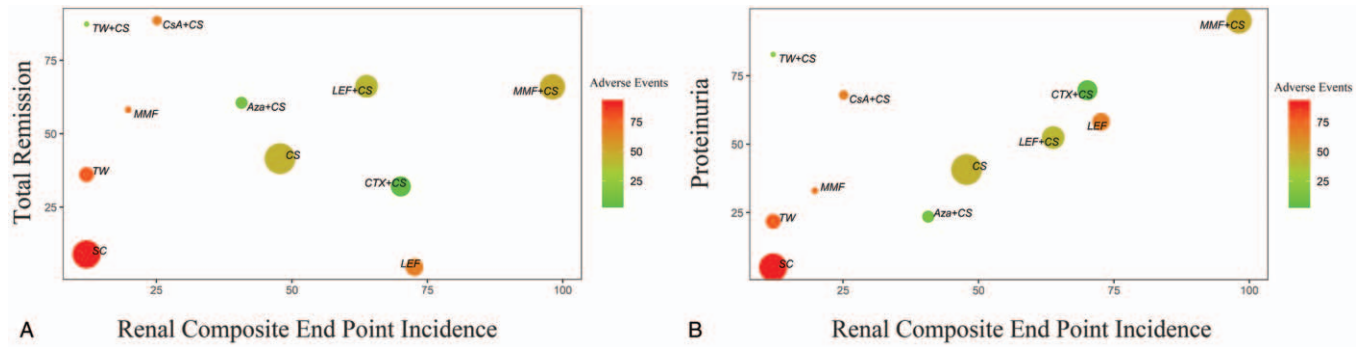


Figure 4. Cluster analysis of efficacy and safety of different treatment schemes (The size of the points represents the number of related studies).

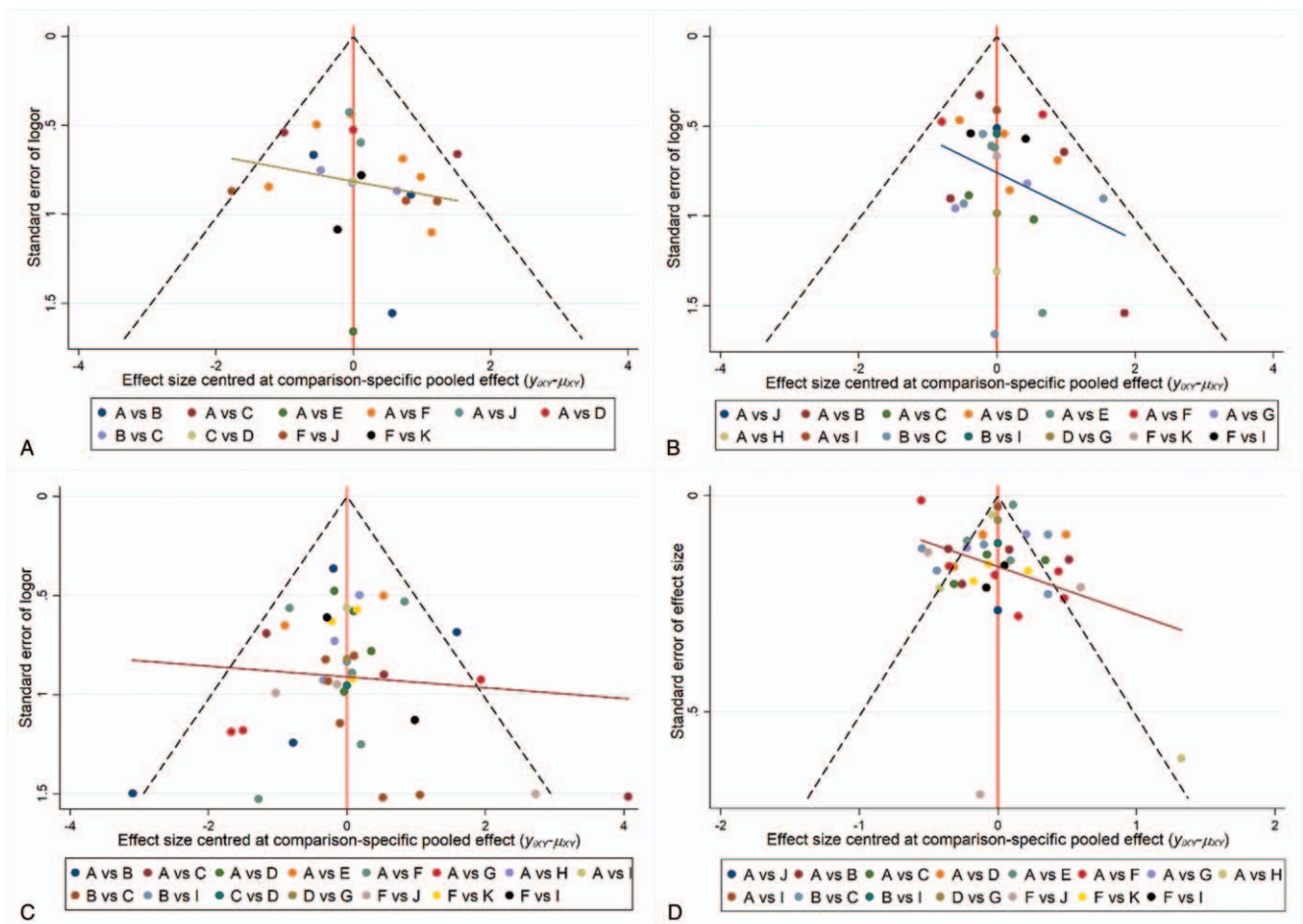
glomerular lesions and interstitial fibrosis,<sup>[55]</sup> indicating the therapeutic potential of immunosuppressants. Evidence obtained from clinical trials has demonstrated the beneficial effects of immunosuppressive therapies in high-risk IgAN,<sup>[9]</sup> and consistent results have been showed by meta-analysis subsequently. Of note, clinical studies mentioned also pointed out that long-term benefits of immunosuppressive drugs was poor due to serious adverse events. The need of seeking a safe and effective immunosuppressive protocol for high-risk IgAN is extremely urgent.

Our network meta-analysis indicated that MMF+CS conferred a lower risk of renal endpoint events in high-risk IgAN indicating a better long-term effect. MMF is a new immunosuppressant with less side effects in the treatment of IgAN. After 6 years follow-up, Tang et al,<sup>[37]</sup> found that MMF could not only reduce the proteinuria level and the eGFR decline of IgAN patients, but also display long-term renal protection. And the results were consistent with a recent meta-analysis reported by Du et al.<sup>[52]</sup> Furthermore, our subgroup analysis showed that the efficacy of MMF was better in Asian population, and the effects increased with the increase of follow-up duration. LEF showed the second best long-term benefits in this study, and the clinical effect was

improved by the combination of LEF and CS. Chen et al found that LEF combined with CS significantly reduced urinary protein, improved albumin and eGFR in patients with IgAN compared with supportive care.<sup>[56]</sup> The similar results has been obtained from a meta-analysis.<sup>[57]</sup> We found that the long-term efficacy of CTX+CS was better, but its safety concerns may restrict the possible benefits, which was in accordance with the study conducted by Woo et al with a minimum 10 years follow-up.<sup>[58]</sup> Our subgroup analysis suggested that CTX+CS showed beneficial effects in crescent IgAN. When the crescent IgAN was removed, the efficacy lost its advantage, and the efficacy became worse with the increase in follow-up duration. In addition, CsA had a significant improvement in rate of total remission in this meta-analysis. Ihm et al,<sup>[59]</sup> found that the long-term efficacy and safety of low-dose CsA combined with CS in IgAN was better than that of high-dose steroid alone. However, clinical evidence on CsA in the treatment of IgAN was few, and more RCTs were needed to further confirm the efficacy and safety of CsA+CS in high-risk IgAN. Our study found that supportive care performed best in safety but worst in the incidence of renal composite end point, total remission rate and adverse events, cluster analysis of different protocols in the treatment of high-risk IgAN showed

**Table 6**  
Inconsistency between closed loops of different indicators.

Outcomes	Closed loops	IF	P	95%CI(truncated)
Renal composite end point incidence	CS-CTX+CS-LEF+CS	0.696	.510	(0.00,2.77)
	CS-MMF+CS-CTX+CS	0.339	.844	(0.00,3.72)
Total remission	CS-MMF+CS-CTX+CS	1.006	.339	(0.00,3.07)
	CS-LEF+CS-TW+CS	0.769	.603	(0.00,3.27)
	CS-SC-TW	0.015	.990	(0.00,2.44)
	CS-MMF+CS-TW	0.038	.973	(0.00,2.23)
Incidence of adverse effect	CS-LEF+CS-TW+CS	2.180	.196	(0.00,5.49)
	CS-SC-TW	1.166	.216	(0.00,3.01)
	CS-MMF+CS-CTX+CS	0.803	.675	(0.00,4.55)
	CS-CTX+CS-LEF+CS	0.068	.970	(0.00,3.59)
Proteinuria	CS-MMF+CS-TW	0.024	.992	(0.00,4.85)
	CS-SC-MMF	1.344	.051	(0.00,2.69)
	CS-MMF+CS-TW	0.770	.124	(0.00,1.75)
	CS-MMF+CS-CTX+CS	0.591	.078	(0.00,1.25)
	CS- LEF+CS-TW+CS	0.455	.069	(0.00,0.95)
	CS-SC-TW	0.358	.542	(0.00,1.51)



**Figure 5.** Funnel chart of different outcome indicators. (A) Renal composite end point incidence; (B) total remission; (C) incidence of adverse effect; (D) proteinuria. (A:CS, B:MMF+CS, C:CTX+CS, D:LEF+CS, E:CsA+CS, F:SC, G:TW+CS, H:Aza+CS, I:TW, J:MMF, K:LEF).

that MMF+CS and LEF+CS displayed better efficacy and safety; The therapeutical effect of CTX+CS in high-risk IgAN accompanied with serious safety concerns, while supportive therapy was safe but had no significant benefit in the long-term course; Other protocols showed no significant benefits in efficacy and safety.

Proteinuria is validated as the prognostic urine biomarker for IgAN.<sup>[5]</sup> Zhao et al,<sup>[60]</sup> confirmed that albumin-to-creatinine ratio(ACR) and 24h-UTP was associated with severe clinical symptoms and pathological lesions of IgAN. Recently, Reich et al<sup>[61]</sup> found that the time-average proteinuria (TAp) (mean value of proteinuria every 6 months) was an important predictor for prognosis of IgAN after average of 6.5 years follow-up. Increase of TAP is related to the decrease of renal function. For patients with IgAN whose TAp > 1g, the risk of ESRD will increase 3 to 10 times. The correlation between TAP and renal survival has also been confirmed in recent studies.<sup>[62,63]</sup> These studies indicated reduction in proteinuria can improve renal prognosis. Our study found that MMF + CS has a great improvement in proteinuria, and the effect of supportive care was the worst.

IgAN at different risks may respond differently to CS and/or immunosuppressants, which previous meta-analyses may not consider. Our study avoided this heterogeneity and only included

high-risk IgAN patients. To the best of our knowledge, our study is the first to evaluate the efficacy and safety of different immunosuppressants in high-risk IgAN. However, there are some limitations in this study. First of all, the sample size of most included RCTs is small, which may limit the accuracy of the results of this study. Second, the dosage and treatment duration of immunosuppressive agents were not considered in this study, which may lead to some deviation in the research results. Third, some studies have found that there are racial differences in the therapeutic effect of some immunosuppressants.<sup>[52]</sup> Given that most of RCTs included were conducted in Asia, the results of this study cannot explain whether racial differences affect the therapeutic effect of immunosuppressants. Finally, some emerging immunosuppressants, such as Budesonide, were not included in this meta-analysis. Thus, the optimal treatment for high-risk IgAN still needs more RCTs and meta-analysis to reach a reliable conclusion.

### 5. Conclusion

In this network meta-analysis, MMF+CS was the best option for high-risk IgAN compared with other immunosuppressive therapies, followed by LEF+CS. However, conclusions need to be explained with caution due to limitations in this study. Well-

design prospective RCTs are still required to further provide strong evidence for the results and guide the clinical use of immunosuppressants in the treatment of high-risk IgAN.

## Author contributions

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