

Comparative efficacy and safety of mycophenolate mofetil and cyclophosphamide in the induction treatment of lupus nephritis

A systematic review and meta-analysis

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Abstract

Background: Lupus nephritis (LN) remains a predominant cause of morbidity and mortality in SLE. Here we performed a meta-analysis to evaluate the efficacy and safety of the induction treatment with mycophenolate mofetil (MMF) and cyclophosphamide (CYC) for LN.

Methods: Relevant literature was searched by computer from the establishment of the database to November 2019. A meta-analysis was conducted to analysis the efficacy and safety between mycophenolate mofetil and cyclophosphamide as induction therapy in LN patients. The primary end-point was response to urine protein, serum creatinine (Scr) and serum complement C3, and the secondary end-points were complete remission and adverse reactions.

Results: Eighteen articles were selected for the final meta-analysis, involving 1989 patients with LN, of which the renal biopsy result could be classified into class III–V according to the standards of WHO/ISN. The results revealed that MMF was superior to CYC in increasing the level of serum complement C3 [SMD=0.475, 95%CI (0.230–0.719)] and complete remission [RR=1.231, 95%CI (1.055–1.437)]. Furthermore, the subgroup analysis showed that it was in Asian patients, rather than in Caucasian patients, that CYC exerted a better effect on lowering the level of urine protein (UPRO) than MMF [SMD=0.405, 95%CI (0.081–0.730)]. Besides, when the initial UPRO level was less than 4 g/day, the effect of CYC was better than MMF [SMD=0.303, 95%CI (0.014–0.591)]. There was no significant difference between MMF and CYC in improving Scr [SMD=0.090, 95%CI (–0.060–0.239)]. When it came to the comparison of safety between MMF and CYC, the meta-analysis showed that MMF was superior to CYC in decreasing infection in Caucasian patients [RR=0.727, 95%CI (0.532–0.993)], reducing the risk of leukopenia and menstrual abnormalities in Asian patients and lowering the frequency of gastrointestinal symptoms [RR=0.639, 95%CI (0.564–0.724)], independent of race.

Conclusions: MMF precedes CYC in improving serum complement C3 and complete remission regardless of race, as well as shows fewer adverse drug reactions in the induction treatment of LN belonging to type III–V. But for Asian patients or those initial UPRO levels are less than 4g/day, CYC may be superior to MMF.

Abbreviations: ADRs = adverse drug reactions, CYC = cyclophosphamide, LN = lupus nephritis, MMF = mycophenolate mofetil, RCTs = randomized controlled trials, Scr = serum creatinine, SLE = systemic lupus erythematosus, UPRO = urine protein.

Keywords: cyclophosphamide, lupus nephritis, meta-analysis, mycophenolate mofetil, urine protein

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Lupus nephritis is a severe, potentially life-threatening disease with a incidence of 60% in adults with SLE.^[1] As one of the most serious manifestations of SLE, it is initiated by the deposition of anti-double stranded DNA antibodies (anti-dsDNA) in glomerular basement membranes, and remains a predominant cause of morbidity and mortality in SLE.^[2–4] Accurately identifying SLE patients destined to develop LN could shift the current management paradigm from treatment to prevention, and various attempts have been made according to comprehensive consideration of the following situations: renal biopsy classification, disease activity, whether combined with other organ damage, and so on.^[5] Up to 26% of patients with diffuse proliferative LN develop into end-stage renal failure, which accounts for the staggering mortality in SLE. It has been a spotlight problem worldwide.^[6] Despite major improvements in treatment strategies over decades, a large proportion of patients display renal damage, and 10% develop renal failure after 10 years.^[7]

The treatment of LN consists of an induction phase to produce remission, and a maintenance phase to prevent relapse and progression to end-stage renal disease (ESRD). The induction phase of treatment usually lasts 3 to 6 months and is followed by a prolonged but less intense maintenance phase, which can last for years.^[8] There is an increased interest in induction therapies, aiming at achieving renal remission while minimizing the serious side effects, especially in the patients whose biopsy stage belongs to type III to V. Large doses of corticosteroids, and combined with CYC or MMF, used for induction therapy in LN of type III/IV–V, are proposed by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR).^[9,10] Although the therapy of glucocorticoid+ CYC has been used in LN for more than 20 years, its efficacy in severe LN is still unsatisfactory,^[11] and there are obvious side effects such as suppression of bone marrow, gonadal function and infection, etc.^[12]

MMF is a hypoxanthine nucleotide dehydrogenase inhibitor, which can selectively inhibit the proliferation of T/B lymphocytes, inhibit the production of antibodies, regulate the immune system, and exert a strong effect on reducing the accumulation of circulating immune complex in renal tissue.^[13] MMF is less toxic to bone marrow cell lines than other immunosuppressive agents because of its preferential target for activated lymphocytes, but its adverse effects, such as infection and diarrhea, should not be ignored.^[14] Therefore, it is still controversial whether the efficacy and safety of MMF is better than CYC or not in the treatment of LN. To evaluate the efficacy and safety of MMF vs CYC as induction therapy for LN, we performed a meta-analysis by pooling the results of all the current randomized controlled trials (RCTs).

2. Materials and methods

2.1. Search strategy

Our study followed the meta-analysis of Observational Studies in Epidemiology Guidelines,^[15] and studies were investigated in the following databases from the time of establishment to Nov. 2019: PubMed, EMBASE, Wiley, Cochrane library. The following medical subject heading (MeSH) words were combined: “lupus glomerulonephritis”, “lupus nephritis”, “lupus nephritides”, “systemic lupus erythematosus”, “mycophenolate mofetil”,

“cellcept”, “mycophenolate sodium”, “myfortic”, “cyclophosphamide” or “randomized controlled trials”. In addition, we searched the references in detail for further research. If necessary, the authors were contacted to obtain information that was not found by the above retrieval strategy.

2.2. Statement

The ethical approval was not necessary. Because this study is about the comparative efficacy and safety of mycophenolate mofetil and cyclophosphamide in the induction treatment of lupus nephritis: a systematic review and meta-analysis. This study is not a clinical trial study, ethical approval, and informed consent are not required. All included articles have passed ethical approval and informed consent.

2.3. Inclusion and exclusion criteria

All articles of the studies were evaluated by two investigators (Jiang and Zhao) independently. Studies that meet the following criteria will be adopted:

1. The literature must be a RCT, written in English.
2. The diagnosis of patients included in the studies should meet with LN set by the American College of Rheumatology (ACR), and the renal biopsy of LN in patients can be classified into stage III–V.
3. Induction treatments for the case and control groups were respectively MMF vs. CYC or MMF/CYC combined with other drugs which were the same in both groups.
4. The study reported at least one of the following outcomes: the primary end-point contains urine protein (UPRO), serum creatinine and serum complement C3.

The secondary end-point contains complete remission, ADRs including infection, leukopenia, menstrual disorders and digestive tract symptoms such as diarrhea, nausea and vomiting.

Studies with the following characteristics were excluded:

1. not associated with the treatment for LN with MMF vs CYC or drugs combined with MMF/CYC in the case group are inconsistent with the control;
2. not a RCT study;
3. The outcomes in literature are incomplete or unclear.

2.4. Data extraction and quality evaluation

The 2 investigators (Jiang and Zhao) sifted through the title and summary of the studies. Then they read the full text for the secondary screening and eliminated the studies that did not meet the above inclusion criteria. If the information provided in this article was not comprehensive and certain, contact the original author by phone, e-mail and other means to obtain relevant information. Cochrane risk-of-bias tool^[16] and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines^[17] were adopted in this meta-analysis, and the evaluation system included adequate generation of randomization, blinding, allocation concealment, incomplete outcome data, selective outcome reporting and possible sources of other bias. These items were judged by using the following criteria: “Yes” (low risk of bias) or adequate if the item was clearly described in detail, “No” (high risk of bias) or inadequate if it was not described adequately, or “Unclear” if a judgment could not

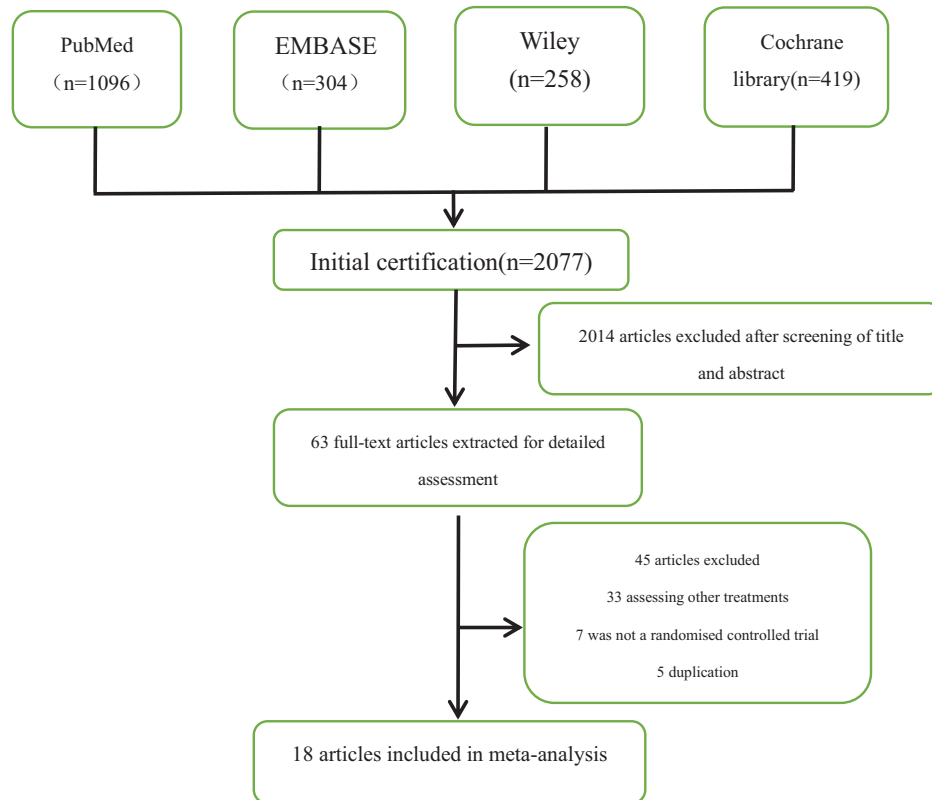


Figure 1. The literature selection process and results.

be made. Organize each article that was included and extract relevant data: the first authors name, years of publication, country or region, combined drug used in the MMF and CYC groups, intervention duration and observational index (Fig. 1).

2.5. Statistical analysis

Statistical analysis was performed with stata12.0 software, and the results of meta-analysis were expressed as risk ratios (RRs) for dichotomous outcomes and standard mean differences (SMDs) for continuous outcomes, both with 95% confidence intervals (CIs). Heterogeneity was analyzed using a Cochrane Q test (n-1, df), with $P < .05$ denoting statistical significance and I^2 measuring the proportion of variation in estimates of effect due to heterogeneity beyond chance. Random effect model was utilized when $I^2 > 50\%$. If not, the fixed effect model was instead (Dersimonian and Laird method). Also, we conducted subgroup analysis to reduce the influence of heterogeneity on the results and performed sensitivity analysis or meta-regression if necessary.

3. Results

3.1. Basic characteristics of the included studies

Overall, a total of 18 out of 2077 articles were selected for the final meta-analysis,^[18-35] involving 19 RCTs studies and 1989 patients (Radhakrishnan et al included 2 studies).^[28] All the 18 papers were published in English before November 2019. Besides, of the 18 articles including 19 RCTs, 10 studied MMF/CYC, 8 related to MMF/CYC combined with glucocorticoids, 1 studied concerning MMF/CYC combined with hydrox-

ychloroquine. All these trials provided efficacy and safety outcomes. Furthermore, LN subjects included in the RCTs were aged 15 to 48, whose pathological stage all belonged to type III-V according to the standards of WHO/ISN. Besides, among all the patients, 825 were Asian and 1164 were Caucasian. Methodological quality assessment was performed according to PRISMA guidelines. All of the articles illustrate random methods, but none use blind methods or assignment concealment. The baseline characteristics and the risk of bias of the studies were respectively shown in Tables 1 and 2.

3.2. Results of the overall meta-analysis in the primary end-point between MMF and CYC treatment groups

3.2.1. Urine protein. A total of 8 studies investigated UPRO in the 2 groups, and the results of meta-analysis showed that there was no difference between MMF and CYC in ameliorating UPRO [SMD=0.183, 95%CI (-0.016 to 0.382)]. Considering that the included articles showed extremely high heterogeneity and reduced the scientific nature of the results ($I^2=87.3\% > 50\%$), we conducted subgroup analysis according to ethnic origin. Among them, 4 studies were from Asian patients and another 4 studies were from Caucasian patients. Subgroup analysis showed that CYC exerted better effects on lowering the level of UPRO than MMF in Asian patients [SMD=0.405, 95% CI (0.081-0.730)], while in Caucasian patients, there is no significant difference between MMF and CYC, as shown in Table 3 and Figure 2(a). Considering that the severity of disease may also influence the action of MMF and CYC, we further performed a subgroup analysis based on the initial levels of proteinuria (≥ 4 g/day vs < 4 g/day). A total of 3 studies of patients

Table 1

Baseline characteristics of the studies.

First author (year)	Nation and race	WHO/ISN Classification	MMF Patients	CYC Patients	MMF group of medication	CYC group of medication	Method of administration, dosage	Intervention Duration	Observed Index	Database source
Ong LM et al (2005)	Malaysia(Asian)	III,IV	17	24	MMF +prednisolone	IVCYC + prednisolone	MMF: 1.0 g orally twice daily intravenous cyclophosphamide (IVC) 0.75–1 g/m ² monthly	6 months	Serum creatinine, Remission, Proteinuria, serum albumin, C3,C4	PubMed, Embase, Wiley, Cochrane library
Bao H et al (2008)	China(Asian)	V,IV	20	20	MMF + intravenous methylprednisolone pulse therapy at the beginning, which was then followed by oral prednisone	IVCYC + intravenous methylprednisolone pulse therapy at the beginning, which was then followed by oral prednisone	MMF:1.0 g/d (0.75 g/d for patients weighing 50 kg) twice daily (every 12 h). CYC:0.75 g/m ² of BSA for the first month and then adjusted between 0.5 and 1.0 g/m ² BSA monthly on the basis of a nadir white cell count of 2.5 × 10 ⁹ /L, 7 to 10 d after the infusion.	9 months	Remission,Negative conversion ratio of Anti-dsDNA,Normalization rate of serum C3, Adverse events	PubMed, Embase, Cochrane library
Rathi M et al (2015)	India(Asian)	III-V	42	41	MMF + HCQ	CYC + HCQ	MMF: 500 mg twice a day and increased every 2 weeks to achieve a target dose of 1.5–3.0 g/day, CYC was administered as 6 fortnightly intravenous infusions at a fixed dose of 500 mg each.	6 months	complete blood counts, renal function tests, uPCR, anti-dsDNA, SLEDAI, glomerular filtration rate	PubMed, Embase, Cochrane library
Chan TM et al (2001)	Hong Kong,China(Asian)	III,IV	21	21	MMF + prednisolone	CYC + prednisolone	MMF:1 g twice a day; CYC:2.5 mg per kilogram per day; prednisolone at 0.8 mg per kilogram per day, and was reduced by 5 mg per day every 2 weeks until the dose was 20 mg per day, after which it was reduced by 2.5 mg per day every 2 weeks for 4 weeks and then by 2.5 mg per day every 4 weeks, until a maintenance dose of 10 mg per day had been reached, at approximately 6 months	6 months	Blood pressure, renal and liver function were evaluated, serum anti-double-stranded DNA antibodies and serum C3. Urinary protein	PubMed, Embase, Cochrane library
Wang J et al (2007)	China(Asian)	III,IV	9	11	MMF	CTX	MMF:1.5–2.0 g/day; CYC: 0.75–1.0 g/m ² ; MMF was commenced at a dose of 0.75 or 1g twice daily unless the white-cell count fell below 3* 10 ⁹ /L. Intravenous CTX was given as monthly pulses at a dose of 0.75–1.0 g/m ² of body-surface area. dosage was modified on the basis of the nadir white-cell count of 2.5 × 10 ⁹ /L or less at 7–10 days after the infusion.	6 months	haematuria, 24-hour urinary protein output, serum creatinine, albumin and liver enzyme levels, haemoglobin, white blood cell and platelet count, anti-dsDNA, ANA, serum C3 and C4.	PubMed, Embase
Elliott JR et al (2006)	USA(Caucasian)	III-V	71	69	MMF	CTX	MMF:starting at 1000 mg/day and increasing to 3000 mg/day, provided the white blood cell count remained ≥3000/mm ³	6 months	complete remission	PubMed, Embase, Wiley, Cochrane library
Chan TM et al (2005)	Hong Kong, China (Asian)	IVy	32	30	MMF + prednisolone	CTX-AZA + prednisolone	MMF was commenced at 1 g twice daily orally; CTX at 2.5 mg/kg per day orally. The dosages of MMF would be halved after 6 mo (to 500 mg twice daily), and after 12 mo the drug would be discontinued and replaced by AZA (1 to 1.5 mg/kg per d). Prednisolone was started at 0.8 mg/kg per d orally and tapered to reach 10 mg/d at approximately 6 mo	12 months	Anti-dsDNA antibodies,C3, Protein-uria was measured by 24-h urine,creatinine clearance	PubMed, Embase, Cochrane library

(continued)

Table 1
(continued).

First author (year)	Nation and race	WHO/ISN Classification	MMF Patients	CYC Patients	MMF group of medication	CYC group of medication	Method of administration, dosage	Intervention Duration	Observed index	Database source
Arun S et al (2018)	Nepal(Asian)	III-V	21	21	MMF	CYC	MMF: 750mg twice daily if the weight was more than 50kg. For those below 50kg of body weight, the dose was started at 500mg twice daily and increased to 750mg twice daily after 30 days. CYC:0.5 to 1 g per m ² of body surface area.	6 months	complete blood count (CBC), renal function test (RFT), blood sugar level, serum calcium and phosphate, serum total protein,serum albumin, and antinuclear antibody (ANA), routine and microscopic examination of urine, 24-h urinary total protein excretion, fasting lipid profile, Serum creatinine	PubMed, Embase, Cochrane library
Feng X et al (2014)	China(Asian)	III-IV	25	28	MMF+prednisone	CYC+prednisone	MMF:2.g per day in two divided doses. CYC intravenously:0.5g every 2 weeks. Prednisone: 0.5mg/kg ⁻¹ d ⁻¹ and tapering down in the course of the study which was based on the patients condition. MZR was given orally at the dose of 300mg every other day.	6 months	Complete blood count, C3, C4, IgG, anti- dsDNA, ANA, and urine routine, 24-hour proteinuria, and 24-hour urine creatinine	PubMed, Embase, Cochrane library
Liu Z et al (2014)	China(Asian)	class III, IV, V	181	181	MMF+prednisone	IVCY+prednisone	The envelopes were opened in sequence and patients were randomly assigned, in a 1:1 ratio, to the multitarget regimen or IVCY. Intravenous methylprednisolone pulse therapy (0.5 g/d) for 3 days, followed by oral prednisone (0.6 mg/kg per day) every morning for 4 weeks. prednisone:5 mg/d every 2 weeks to 20 mg/d and then by 2.5 mg/d every 2 weeks to a maintenance dose of 10 mg/d. MMF (0.5g twice daily) and tacrolimus (2mg twice daily). IVCY: 0.75 g/m ² body surface area and then adjusted to a dose of 0.5 to 1.0 g/m ² body surface area every 4 weeks for 6 doses.	6 months	complete and partial remission, time to overall response, and adverse events.	PubMed, Embase, Cochrane library
Radhakrishnan J et al (2010)	USA(Caucasian)	V.V+ III and V+IV	33; US:8; ALMS:25	32; US:7; ALMS:25	MMF	IVC	MMF: 2653 ±555mg/day in the US study, whereas it was 2828±384 mg/day in the ALMS study. IVC:4574.4±559 mg/m ² of body surface in the US study and 4888.3 ±715 mg/m ² of body surface in the ALMS study, whereas the mean dose per patient per month was 782.4±93 mg/m ² of body surface and 816 ±116 mg/m ² of body surface	6 months	Urine protein(g/24h),Serum creatinine (lmol/l), Serum albumin(g/l), C3 (g/l), C4(g/l), Anti-dsDNA Nephrotic (%)	PubMed, Embase, Cochrane library

(continued)

Table 1
(Continued).

First author (year)	Nation and race	WHO/ISN Classification	MMF Patients	CYC Patients	MMF group of medication	CYC group of medication	Method of administration, dosage	Intervention Duration	Observed Index	Database source
Mendonca S et al (2017)	India(Asian)	III-IV	17	23	MMF	CYC	MMF group: 750 mg twice daily in the 1 st week, and 1.0 g twice daily in the 2 nd week, to a target dosage of 1.5 g twice daily; i.v. Cyc group: 750 mg/m ² of body surface area, which was adjusted to 500–1000 mg/m ² of body surface area every 4weeks to maintain a nadir leukocyte count of 2.5–4.0 × 10 ⁹ /L for a total of 6pulses. MMF: starting dose of 0.5 g twice daily in week 1 and 1.0 g twice daily in week 2 to a target dosage of 1.5 g twice daily; in week 3. Reduction was permitted to 2 g/d in response to adverse events. Cyclophosphamide was given in monthly intravenous pulses of 0.5–1.0 g/m ² . Prednisone: from a maximum starting dosage of 60 mg/d.	6 months	complete blood cell count, urinalysis, 24h urinary protein,Serum anti-double-stranded DNA antibodies, C3, SLEDAI scores.	PubMed, Embase
Walsh M et al. (2013)	Canada(Caucasian)	III-V	20	12	MMF+prednisone	CYC+prednisone	MMF: starting dose of 0.5 g twice daily in week 1 and 1.0 g twice daily in week 2 to a target dosage of 1.5 g twice daily; in week 3. Reduction was permitted to 2 g/d in response to adverse events. Cyclophosphamide was given in monthly intravenous pulses of 0.5–1.0 g/m ² . Prednisone: from a maximum starting dosage of 60 mg/d.	6 months	eGFR (mL/min/1.73m ²), Proteinuria (g/d), Biopsy class	PubMed, Embase
Ginzler EM et al (2006)	USA(Caucasian)	III-IV	71	69	MMF	CYC	Mycophenolate mofetil (initial dose, 1000 mg per day, increased to 3000 mg per day) intravenous cyclophosphamide (0.5g m ² of body-surface area, increased to 1.0g m ²) as induction therapy for active lupus nephritis.	6 months	Serum creatinine,Albumin, Urine protein, Urinalysis, White cells per HPF, Red cells per HPF, Cellular casts,C3,C4, Anti-dsDNA	PubMed, Embase, Wiley, Cochrane library
Appel GB et al (2009)	Canada(Caucasian)	III-V	185	185	MMF	IVC	MMF (target dosage 3 g/d) IVC (0.5 to 1.0g/m ² in monthly pulses)	6 months	Serum creatinine, Urine protein/ creatinine ratio, Range of GFR, anti-dsDNA, C3, C4	PubMed, Embase
Li et al 2012	China(Asian)	III/IV or Combination	20	20	MMF	CYC	MMF-po 1.5–2.0 g/d, Monthly intravenous pulses of 0.5–0.75 g/m ²	6 months	adverse effects,Complete remission	PubMed, Embase
El-Shafey et al 2010	Egypt(Caucasian)	III/IV	24	23	MMF	CYC	MMF-po 2 g/d CYC:Monthly intravenous pulses of 0.5–1g/m ²	6 months	adverse effects,Complete remission	PubMed, Embase, Cochrane library
Ellen M. Ginzler 2010	USA(Caucasian)	III-V	185	185	MMF+prednisone	IVC+prednisone	mycophenolate mofetil (titrated from a dosage of 0.5 gm twice daily in week 1 and 1.0 gm twice daily in week 2, to a target dosage of 3 gm/day in week 3) intravenous cyclophosphamide (0.5–1.0 gm/m ² /month) Prednisone:from a maximum starting dosage of 60 mg/day, which was decreased by 10 mg/day every 2 weeks until a dosage of 40 mg/day was reached, and then decreased by a further 5 mg/day every 2 weeks until a dosage of 10 mg/day was reached. Reductions below 10 mg/day were allowed after 4 weeks of stable response.	6 months	adverse events	PubMed, Embase, Cochrane library

Table 2
Risk of bias of included studies according to the Cochrane Risk of Bias tool.

Author/year	Randomization	Allocation concealment	Blinding of assessor and/or physician (for assessment of objective outcomes)	Blinding of participants (for assessment of subjective outcomes)	Intention to treat	Selective outcome report	Free of other bias
Li et al.(2012)	Yes	Unclear	No	No	Yes	Yes	Yes
El-Shafey et al (2010)	Yes	Unclear	No	No	Yes	Yes	Unclear
Rathi M et al (2015)	Yes	Unclear	No	No	Yes	Yes	Unclear
Chan TM et al (2001)	Yes	Unclear	No	No	Yes	Yes	Unclear
Wang J et al (2007)	Yes	Unclear	No	No	Yes	Yes	Unclear
Elliott JR et al (2006)	Yes	Unclear	No	No	Yes	Yes	Unclear
Chan TM et al (2005)	Yes	Unclear	No	No	Yes	Yes	Unclear
Arun S et al (2018)	Yes	Unclear	No	No	Yes	Yes	Unclear
Feng X et al (2014)	Yes	Unclear	No	No	Yes	Yes	Unclear
Liu Z et al (2014)	Yes	Unclear	No	No	Yes	Yes	Unclear
Radhakrishnan J et al (2010)	Yes	Unclear	No	No	Yes	Yes	Unclear
Mendonca S et al (2017)	Yes	Unclear	No	No	Yes	Yes	Unclear
Walsh M et al (2013)	Yes	Unclear	No	No	Yes	Yes	Unclear
Ginzler EM et al (2006)	Yes	Unclear	No	No	Yes	Yes	Unclear
Appel GB et al (2009)	Yes	Unclear	No	No	Yes	Yes	Unclear
Ginzler EM et al (2010)	Yes	Unclear	No	No	Yes	Yes	Unclear
Ong LM et al (2005)	Yes	Unclear	No	No	Yes	Yes	Unclear
Bao H et al (2008)	Yes	Unclear	No	No	Yes	Yes	Unclear

with initial proteinuria $\geq 4\text{g/day}$, and 5 more studies with proteinuria $< 4\text{g/day}$ were included. Subgroup analysis showed that CYC exerted better effects on lowering the level of UPRO than MMF when the initial level of UPRO $< 4\text{g/day}$ [SMD= 0.303, 95%CI (0.014–0.591)], While there was no significant difference between the 2 drugs when UPRO $\geq 4\text{g/day}$ ($P = .599$), as shown in Table 3 and Figure 2(b).

3.2.2. Serum creatinine (Scr). Seven articles were included in our meta-analysis comparing the efficacy of MMF and CYC in improving Scr. The results showed that there was no significant difference between MMF and CYC treatment in improving Scr [SMD=0.090, 95%CI (-0.060 to 0.239)], with a lower heterogeneity ($I^2 = 18.7\% < 50\%$), as shown in Figure 2(c).

3.2.3. Serum complement C3. Altogether 5 studies observed the changes of serum complement C3, and the results showed that MMF could better increase the level of serum complement C3 [SMD=0.475, 95%CI (0.230–0.719)]. However, the heterogeneity of the articles was comparatively high ($I^2 = 93.4\% > 50\%$), which reduced the credibility of the results. Moreover, sensitivity analysis showed that each article contributed greatly to the heterogeneity, as shown in Figure 2(d).

3.3. Results of the overall meta-analysis in the secondary end-point of MMF and CYC groups

3.3.1. Complete remission. A total of 11 studies examined complete response after treatment in both groups. Meta-analysis showed that MMF could better increase the complete remission [(RR=1.415, 95%CI (1.231–1.626)]. Considering that the value of I^2 was 63.5%, indicating a significant heterogeneity, we conducted sensitivity analysis and found that Lius^[27] paper contributed a lot to the heterogeneity of the paper (Fig. 3). Thus, we excluded this paper and then conducted the meta-analysis again, which showed that the effect of MMF is superior to CYC in terms of complete remission [(RR=1.231, 95% CI (1.055–1.437)], as shown in Table 4 and Figure 2(e).

3.3.2. Adverse drug reaction (ADR). In total, 16 studies examined the incidence of ADRs, including infection, leukopenia, menstrual disorders, and gastrointestinal symptoms such as nausea, vomiting, stomachache, and diarrhea. Considering the heterogeneity, we tried conducting subgroup analysis according to ethnic classification when analyzing ADRs caused by MMF and CYC treatment.

3.3.2.1. Infection. Fourteen articles observed the influence of MMF and CYC on infection, among which 8 articles were about

Table 3
Subgroup analysis of urine protein in MMF and CYC groups.

	I^2	SMD	95%CI		P	Z
Asian	93.8%	0.405	0.081	0.730	<.05	2.45
Caucasian	31.2%	0.049	-0.203	0.301	.705	0.38
Overall	87.3%	0.183	-0.016	0.382	.072	1.80
	I^2	SMD	95%CI		P	Z
Initial proteinuria $< 4\text{ g/day}$	92.0%	0.303	0.014	0.591	<.05	2.06
Initial proteinuria $\geq 4\text{ g/day}$	52.0%	0.074	-0.202	0.349	.599	0.53
Overall	87.3%	0.183	-0.016	0.382	.072	1.80

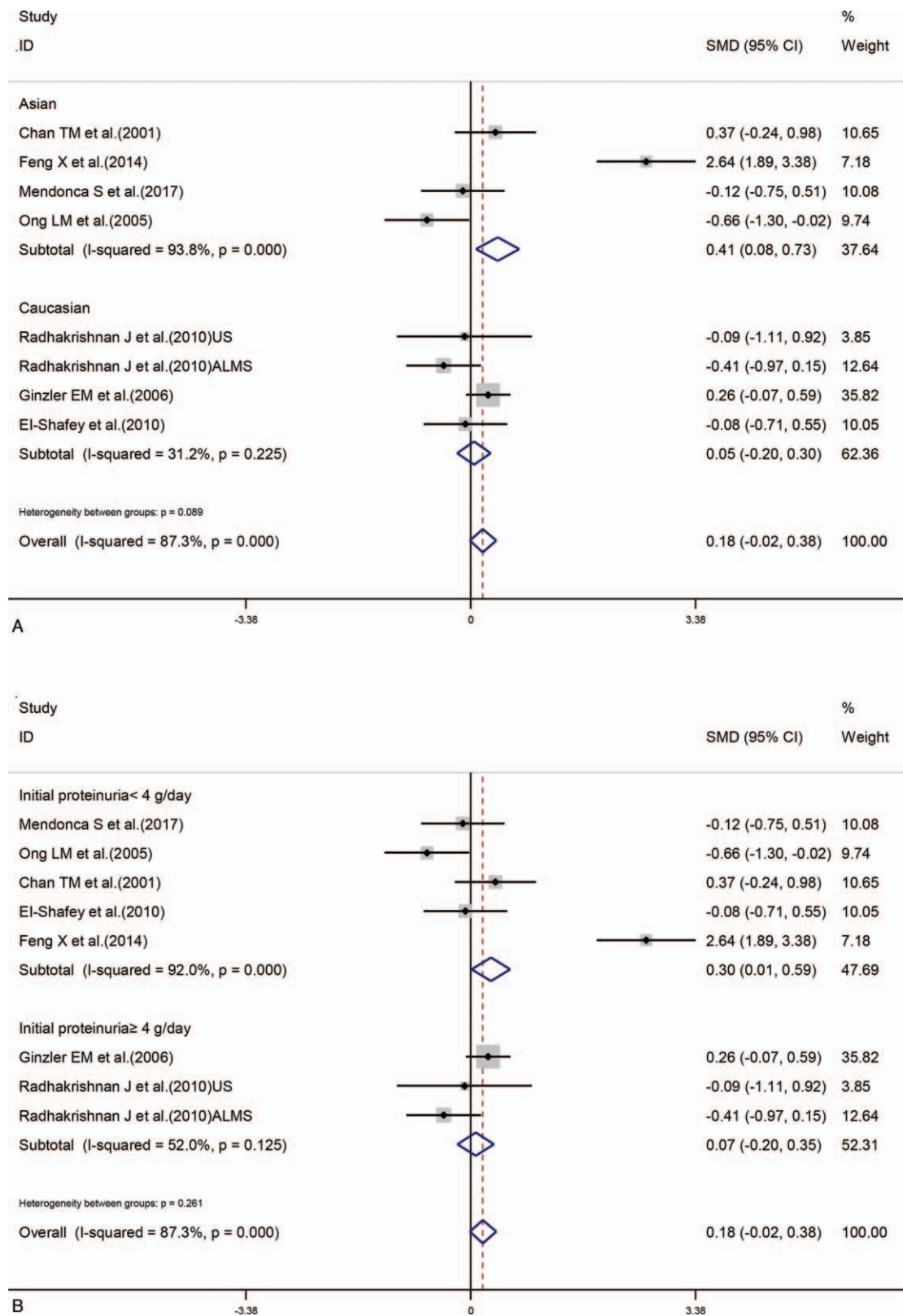


Figure 2. Meta-analysis of randomized controlled trials comparing urine protein, Scr, C3, complete remission and adverse drug reaction between mycophenolate mofetil and cyclophosphamide. Vertical lines indicate “no difference” between compared treatments; horizontal lines indicate 95%CI; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled relative risk plus 95% CI. (a) outcome: urine protein; (b) outcome: urine protein (Subgroup analysis with different initial urine protein); (c)outcome: Scr; (d) outcome: C3; (e) outcome: complete remission; (f) outcome: infection; (g) outcome: leukopenia; (h) outcome: menstrual abnormalities; (i) outcome: gastrointestinal symptoms. SMD = standard mean difference, RR = relative risk.

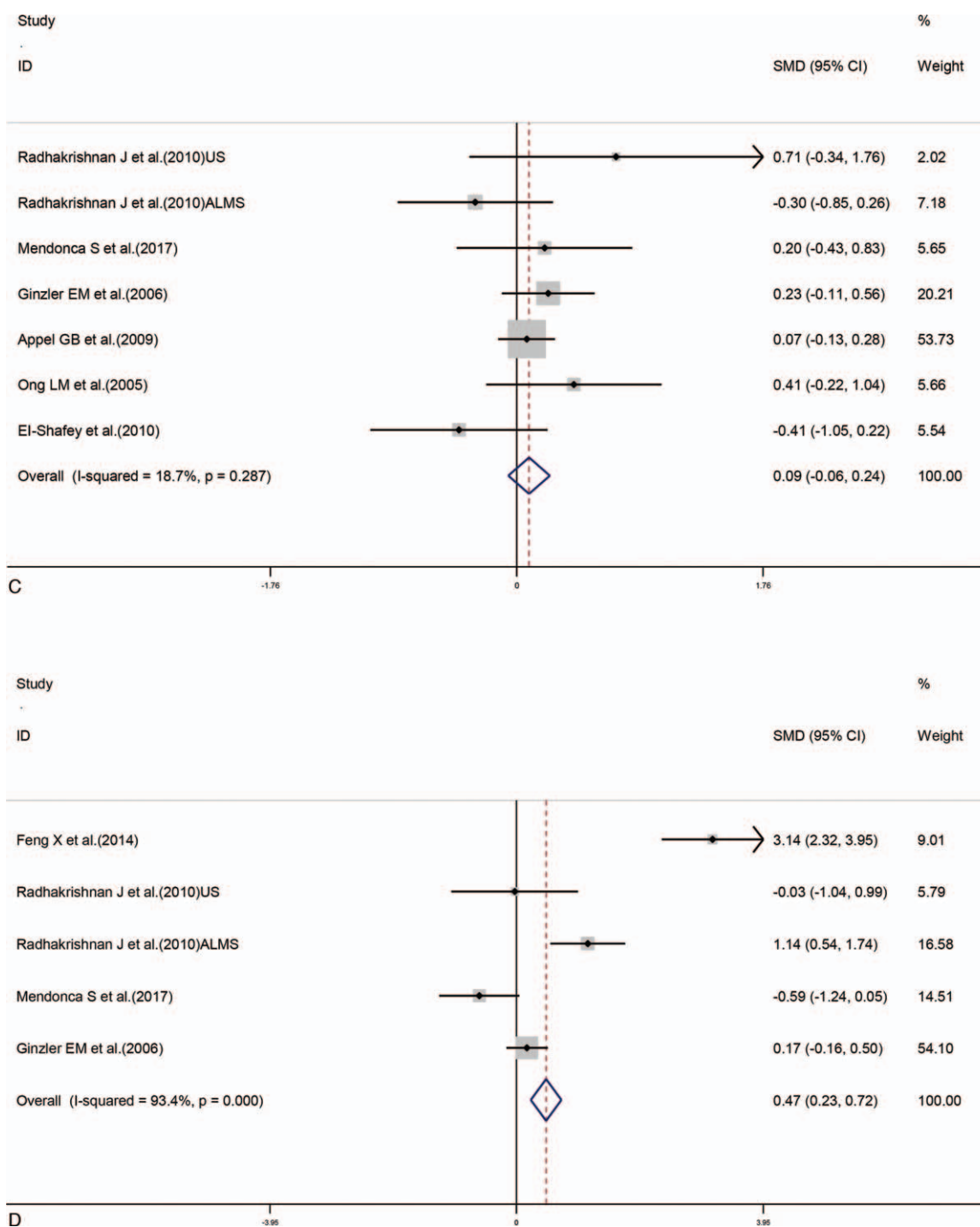


Figure 2. (Continued)

Asian patients, and 6 other articles were conducted in Caucasian patients. Before the subgroup analysis based on ethnic origin, we deleted Radhakrishnans^[28] literature according to sensitivity analysis, and the results showed that the incidence of infection in MMF group was lower than that of CYC in Caucasian patients [RR=0.727, 95%CI (0.532–0.993)] rather than in Asian patients ([RR=0.972, 95%CI (0.753–1.255)], Table 5, Figs. 2(f) and 4).

3.3.2.2. Leukopenia. Totally, 8 articles investigated the occurrence of leukopenia, among which 6 articles were related to Asian patients and the other 2 articles were related to Caucasian patients. The results showed that the incidence of leukopenia in MMF group was significantly decreased in Asian patients [RR=0.187, 95%CI (0.077–0.452)], rather than in Caucasian patients [RR=0.634, 95%CI (0.396–1.014)] when compared with CYC group (P=.057), as was shown in Table 6 and Figure 2(g).

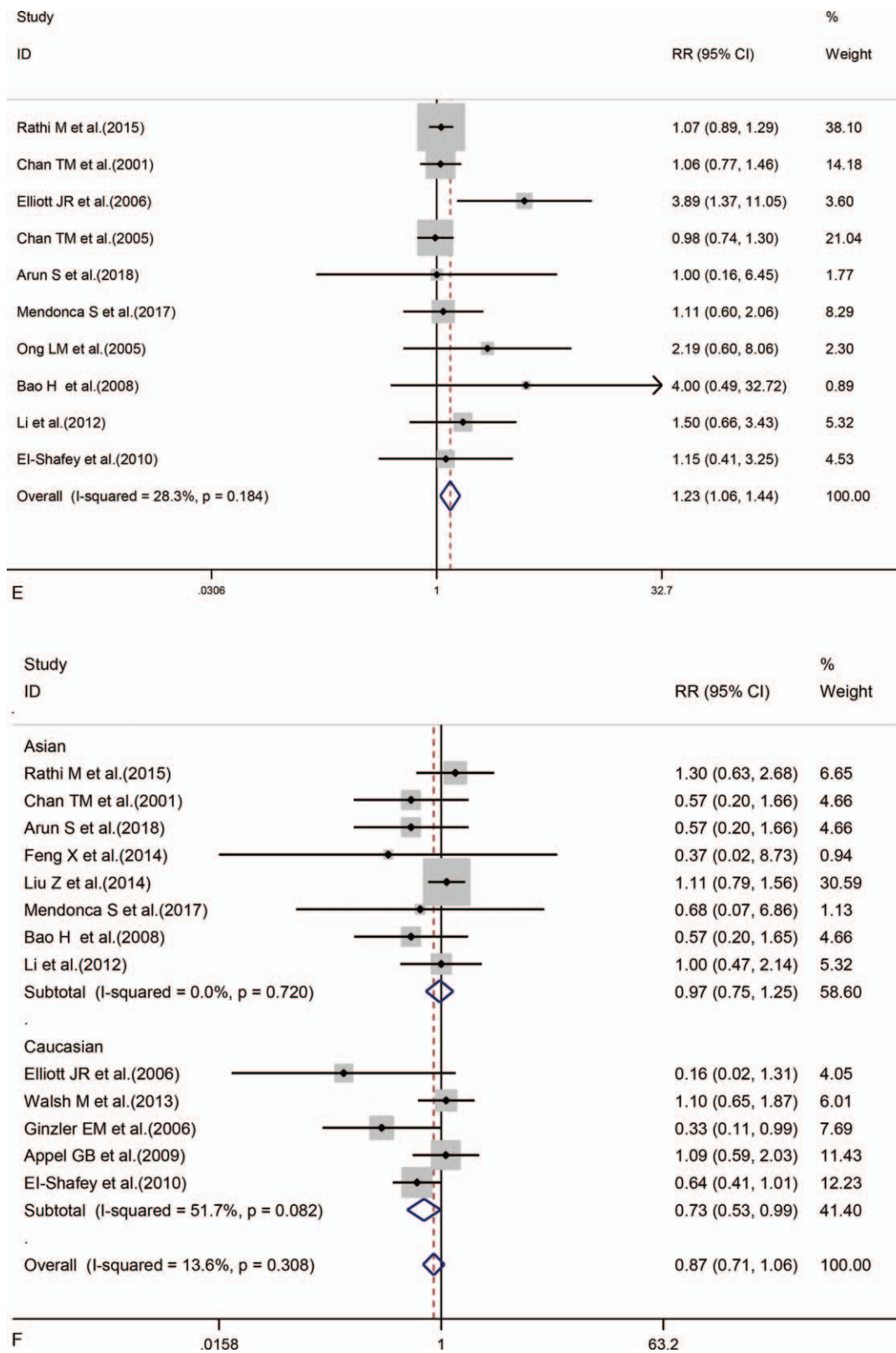
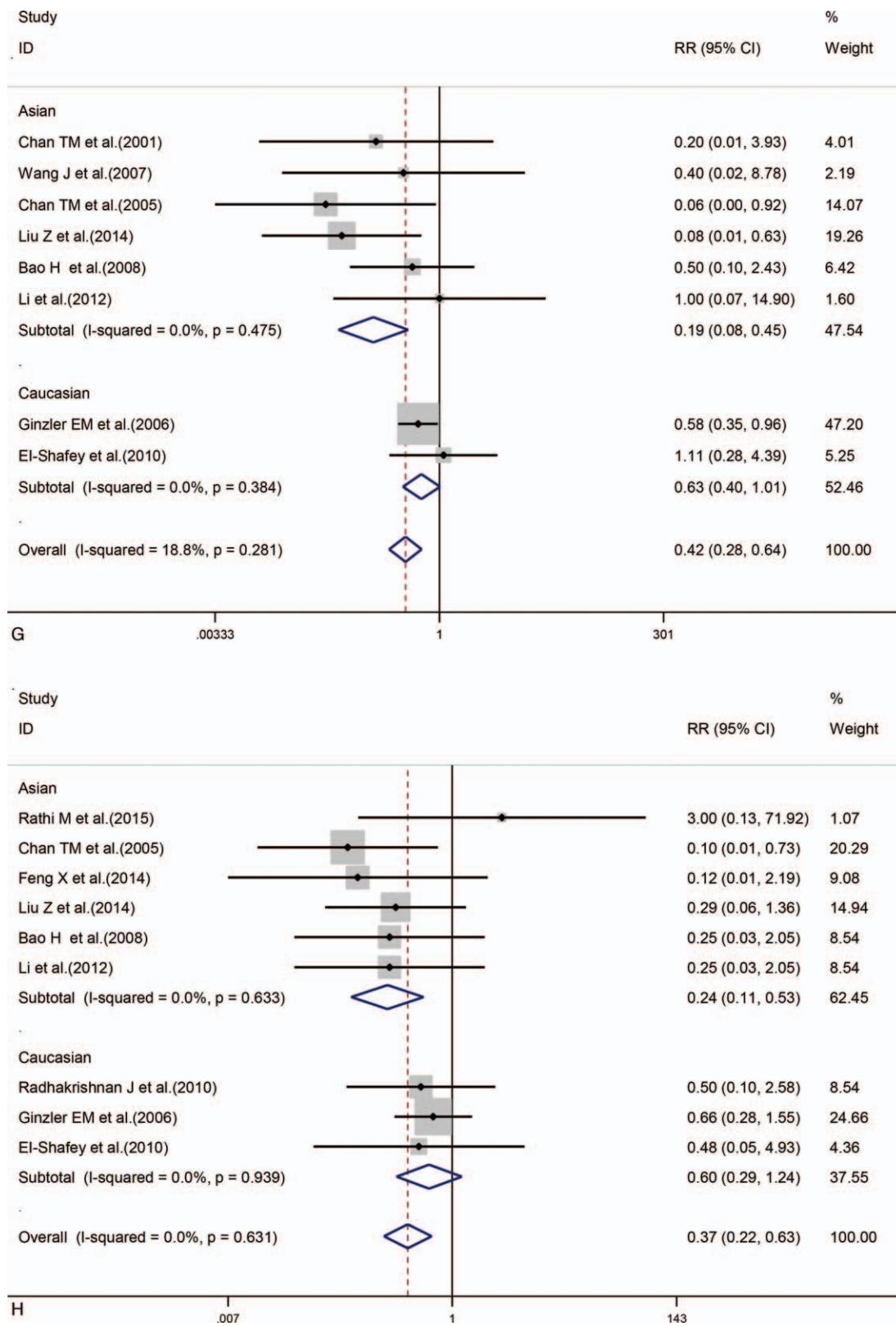


Figure 2. (Continued)



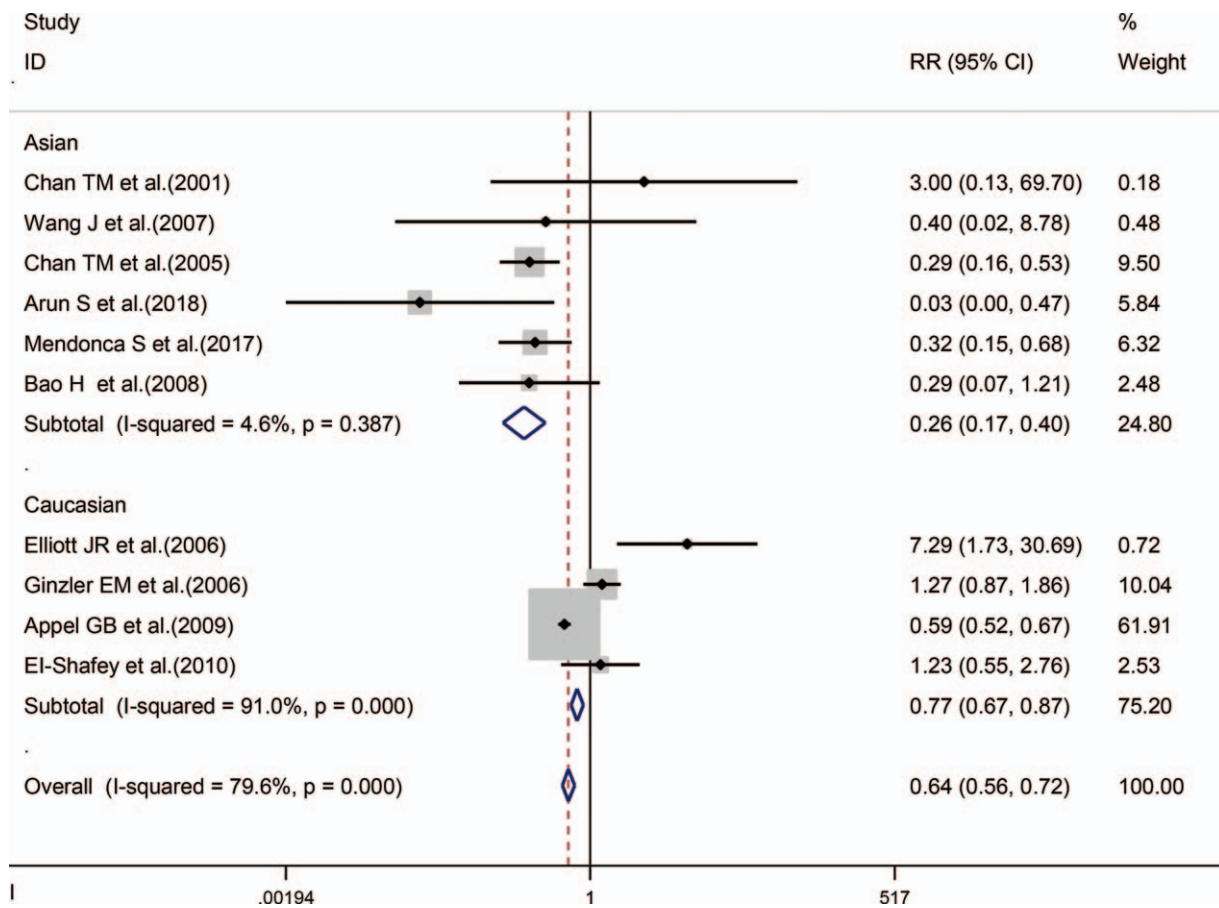


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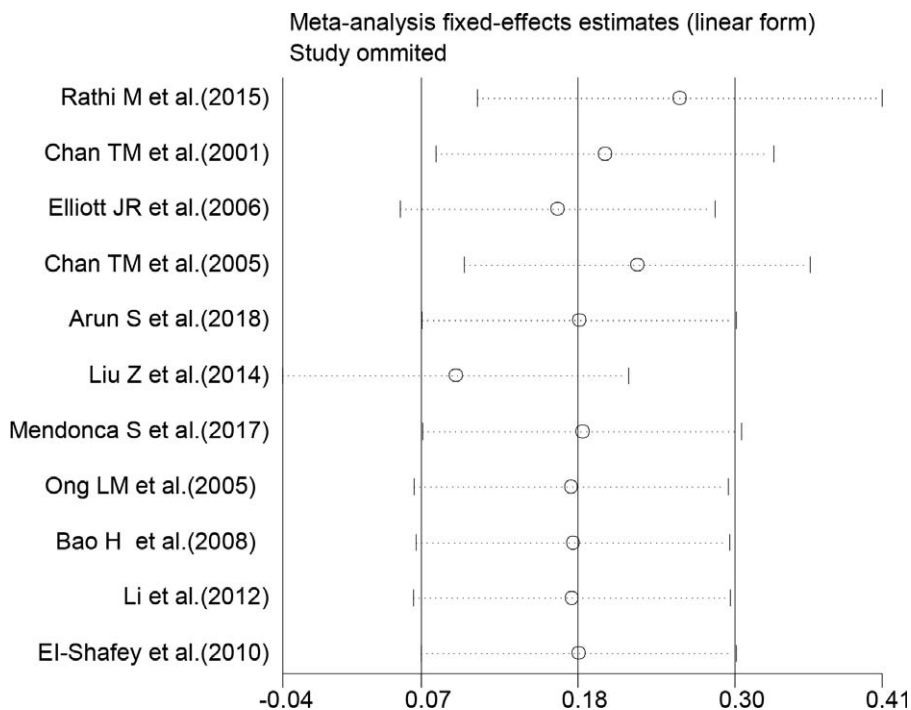


Figure 3. Sensitivity analysis of complete remission.

Table 4
Subgroup analysis of complete remission in MMF and CYC groups.

	I ²	RR	95%CI	P	Z	
Complete remission	63.5%	1.415	1.231	1.626	<.05	4.88
Complete remission without Liu Z	28.3%	1.231	1.055	1.437	<.05	2.64

Table 5
Subgroup analysis of infection in MMF and CYC groups.

	I ²	RR	95%CI	P	Z	
Infections with Asian	0.00%	0.972	0.753	1.255	.829	0.22
Infections with Caucasian	61.7%	0.793	0.645	0.975	.166	2.20
Infections with Caucasian without Radhakrishnan J	51.7%	0.727	0.532	0.993	<.05	2.00
Overall	13.6%	0.871	0.715	1.061	.169	1.38

3.3.2.3. Menstrual abnormalities. In total, 9 studies described the occurrence of abnormal menstruation. There were 6 articles from Asian patients, and 3 from Caucasian patients. The results illustrated that the frequency of abnormal menstruation in MMF group was lower than CYC group in Asian patients [RR = 0.238, 95%CI (0.107–0.531)] rather than in Caucasian patients [RR = 0.601, 95%CI (0.292–1.235)] (*P* = .166), as was shown in Table 7 and Figure 2(h).

3.3.2.4. Gastrointestinal symptoms. A total of 10 articles described the incidence of gastrointestinal symptoms. The result revealed that the incidence of digestive tract symptoms in CYC group was significantly higher than that of MMF group [RR = 0.639, 95%CI (0.564–0.724)] but accompanied with a high heterogeneity (*I*² = 79.6% > 50%). On account of this, we conducted a meta-regression with race as a covariable in order to explore the source of heterogeneity, and the results showed that different races were the main source of heterogeneity. Among them, 6 articles studied patients with LN from the race of Asian,

and 4 articles were from Caucasian. Subgroup analysis showed that the incidence of gastrointestinal symptoms caused by MMF was lower than that of CYC both in Asian patients [RR = 0.257, 95%CI (0.166–0.399)] and Caucasian patients [RR = 0.765, 95%CI (0.674–0.869)], but the former was associated with a lower heterogeneity (*I*² = 4.6%), which made the results more plausible, as was shown in Tables 8 and 9 and Figures 2(i) and 5.

3.4. Publication bias

We analyzed the publication bias of articles on the MMF group and CYC group with LN. The funnel plot analysis of 2 groups showed asymmetry, indicating the possibility of publication bias. The results were shown in Figure 6.

4. Discussion

In the current meta-analysis, we evaluated the efficacy of drugs by the indicators of UPRO, complete remission, Scr and complement

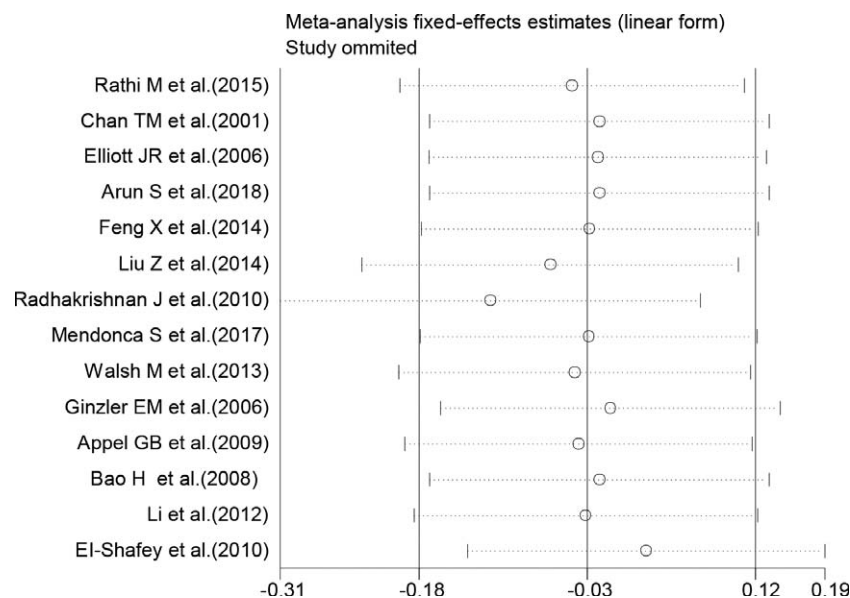


Figure 4. Sensitivity analysis of infection.

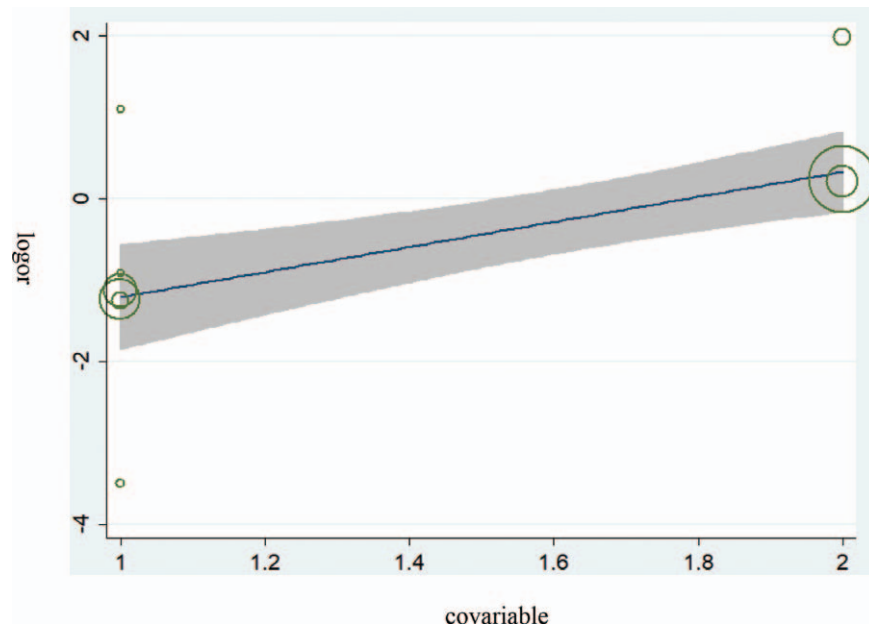


Figure 5. The meta-regression of gastrointestinal symptoms.

Table 6

Subgroup analysis of leukopenia in MMF and CYC groups.

	I^2	RR	95%CI		P	Z
Leukopenia with Asian	0.00%	0.187	0.077	0.452	<.05	3.72
Leukopenia with Caucasian	0.00%	0.634	0.396	1.014	.057	1.90
Overall	18.8%	0.421	0.279	0.636	<.05	4.11

Table 7

Subgroup analysis of menstrual abnormalities in MMF and CYC groups.

	I^2	RR	95%	CI	P	Z
menstrual disorder with Asian	0.00%	0.238	0.107	0.531	<.05	3.51
menstrual disorder with Caucasian	0.00%	0.601	0.292	1.235	.166	1.39
Overall	0.00%	0.374	0.221	0.634	<.05	3.66

Table 8

Subgroup analysis of menstrual abnormalities in MMF and CYC groups.

	I^2	RR	95%	CI	P	Z
digestive symptoms with Asian	4.6%	0.257	0.166	0.399	<.05	6.07
digestive symptoms with Caucasian	91.0%	0.765	0.674	0.869	<.05	4.13
Overall	79.6%	0.639	0.564	0.724	<.05	7.01

C3, and assessed the safety of the drugs with the indicators of infection, leukopenia, menstrual abnormalities, and the digestive tract symptoms. The results revealed that MMF was superior to CYC in increasing the level of serum complement C3 [SMD=0.475, 95%CI (0.230–0.719)] and improving complete remission

[RR=1.231, 95%CI (1.055–1.437)]. The subgroup analysis also showed that it was in Asian patients, rather than Caucasian patients that CYC exerted a better effect on lowering the level of UPRO than MMF [SMD=0.405, 95%CI (0.081–0.730)]. Besides, when the initial UPRO level was less than 4g/day, the effect of CYC was better than MMF [SMD=0.303, 95%CI (0.014–0.591)]. When it came to the comparison of safety between MMF and CYC, the meta-analysis showed that MMF was superior to CYC in decreasing infection in Caucasian patients [RR=0.727, 95%CI (0.532–0.993)], reducing the risk of leukopenia and menstrual abnormalities in Asian patients, and lowering the frequency of gastrointestinal symptoms [RR=0.639, 95%CI (0.564–0.724)], independent of race.

Table 9

Results of meta-regression of gastrointestinal symptoms.

% residual variation due to heterogeneity		$I^2 = 31.44%$
Proportion of between-study variance explained	Adj $R^2 = 100.00%$	
95%CI	2.093647–10.42325	
Standard error (SE)	1.585521	

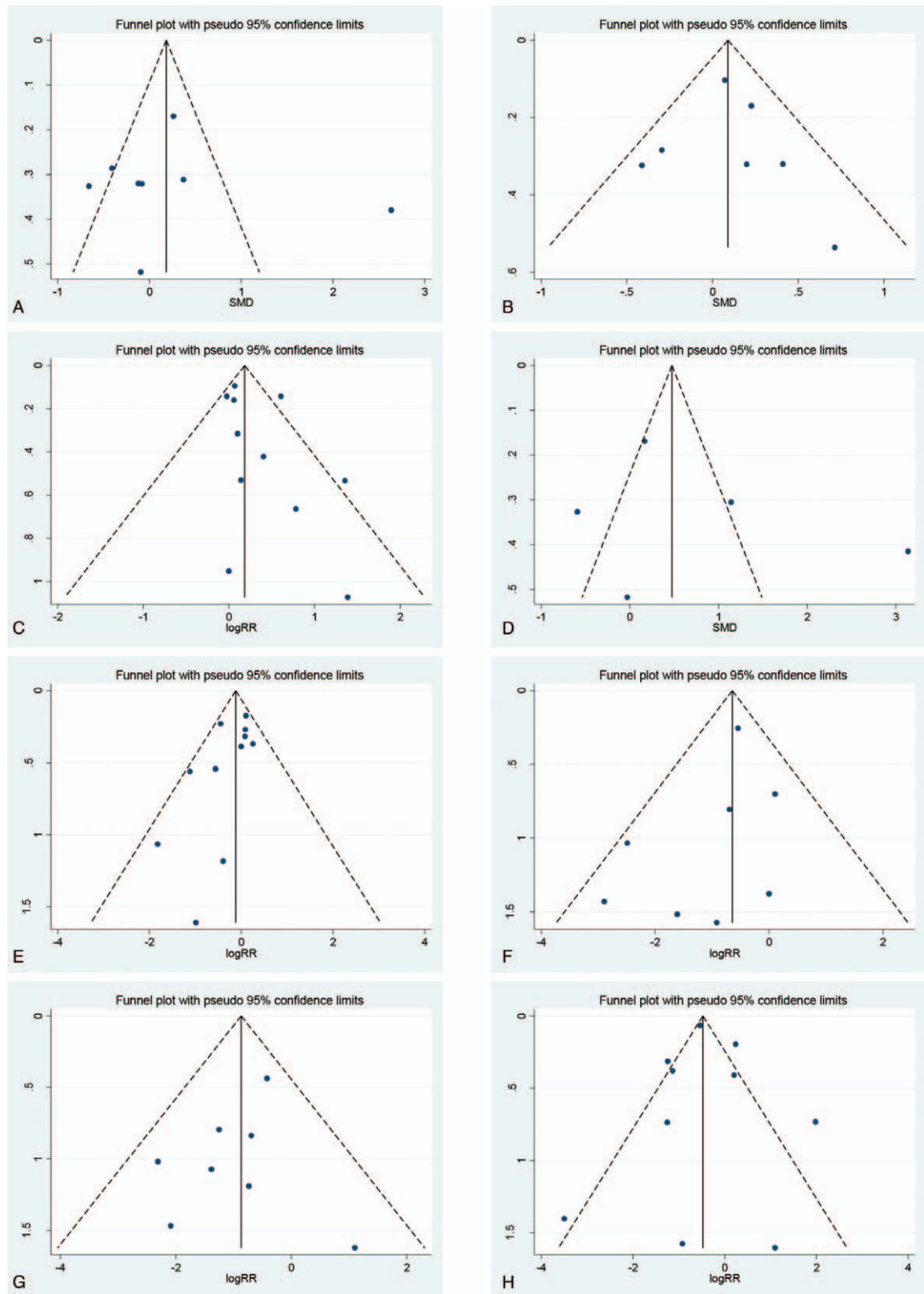


Figure 6. The publication bias of the included articles. (a)funnel plot of urine protein; (b) funnel plot of Scr; (c) funnel plot of C3; (d) funnel plot of complete remission; (e) funnel plot of infection; (f) funnel plot of leukopenia; (g) funnel plot of menstrual abnormalities; (h) funnel plot of gastrointestinal symptoms.

In the present meta-analysis, UPRO, Scr, and serum complement C3 were taken into consideration as primary endpoints of LN. Appel et al followed 56 cases of LN for an average of more than 10 years, and found that UPRO was a risk factor for renal deterioration.^[36] UPRO can not only reflect the presence of glomerular lesions, but also indicate endogenous renal toxicity, such as impairing mesangial cells, renal tubules, and disturbing the function of tubules.^[37] Therefore, we analyzed the effects of MMF and CYC on UPRO with the highest priority. In addition, studies showed that patients with elevated Scr levels or decreased glomerular filtration rate displayed a poor prognosis.^[38] Here, the 2 drugs were equally effective in improving Scr levels in our meta-analysis. Besides, low complement C3 is a vital manifestation of occurrence and activated period of LN. Patients with reduced serum complement C3 are more likely to develop progressive kidney disease.^[39] Baqi et al reported that persistent low complement in the blood was a high risk factor for end-stage renal failure.^[40] So serum complement C3 is also one of the vital endpoints that we should pay close attention to. However, there is still a lack of observation to C3 in the existing RCTs, and only 5 papers are available, with evident contribution to source of heterogeneity. Therefore, more rigorously-designed RCTs are needed to verify the difference between MMF and CYC in improving serum complement C3.

Currently, various RCTs comparing the efficacy and safety of MMF vs CYC for LN has yielded conflicting results, as well as the results from meta-analysis, which can be problematic for clinicians. This inconsistency may be due to the difference of races, baseline characteristics and small sample size, as well as the number of studies that being included were too small to objectively reflect the relevance. The most recent meta-analysis on this topic was published by Henderson^[41] in 2013, of which the retrieval time was before 2012. Accordingly, here we included more available researches in recent years (18 articles were included, involving 1989 patients with LN which can be classified into type III–V according to the standards of WHO/ISN), involving extensive countries and regions, and taking races into consideration. When considering the high heterogeneity associated with the results ($I^2 = 87.3\% > 50\%$), we further performed a subgroup analysis of ethnic origin to increase the objectivity of the results. To our knowledge, this is the first time that different therapies on UPRO are compared between Asian and Caucasian patients, which would be a reference for choosing medication in different ethnic groups in clinic. In addition, our meta-analysis evaluates more extensive outcome indicators so as to make a comprehensive comparison between the 2 drugs, and provide basis for reasonable and targeted selection under different conditions. Lastly, we also applied more adequate methods (such as sensitivity analysis and meta-regression) to ensure the accuracy of our conclusions.

Inevitably, the shortcomings of this meta-analysis are as follows:

1. The limited number of subjects may lead to unstable and reliable results or some conclusions are not universally applicable.
2. At the same time, the sample size of each RCT study varies from 20 to 370, which contribute to some bias when we combine the large sample size with the small because of the better representativeness of large sample data.
3. The difference of characteristics of the study subjects, various therapy plan (stage, dosage and duration), and trial design

plan may lead to greater heterogeneity of some indicators in this meta-analysis, which may have a potential impact on the results.

4. In this paper, we only performed a subgroup analysis of race to reduce the influence of heterogeneity on the meta-results, and more factors should be taken into account if conditions permit.

Taking administration time as an example, a total of 18 literatures were included in this meta-analysis, 16 of which were administered for 6 months. However, too few studies (only 2 papers)^[19,21] were administered for more than 6 months, which would affect the results of the meta-analysis. Such factors hindered our in-depth and comprehensive subgroup analysis. Therefore, more scientific, reasonable and large-scale randomized double-blind controlled trials are needed to further confirm the authenticity of our results, so as to provide an accurate direction for clinical practice.

5. Conclusion

MMF is a better choice for adolescent or reproductive patients of LN with low serum complement C3, susceptibility to infection and poor gastrointestinal function. While CYC tends to be superior for Asian patients and those with a low initial level of UPRO (<4 g/day) when used to reduce UPRO. Besides, from the meta-analysis on side effects, we also infer that race should be taken into consideration with highest priority when choosing medication in clinic, so as to purposefully reduce side effects.

Author contributions

Y-P. J. and X-X. Z. was responsible for the selection of research and literature selection; Y-P. J. and R-R. C. was responsible for meta-analysis; Z-H. X. was in charge of information from literature; C-P. W. took charge of the examination and modification of articles; X-X. Z. and J.Y. wrote the manuscript. J. Y. was responsible for the examination and submission of articles.

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