Title：Efficacy and Safety of Immunosuppressive Treatment in IgA Nephropathy: A Meta-analysis of Randomized Controlled Trials

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Zheng Zhang designed this study and conducted literature retrieval, data extraction, data analysis and article writing.

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Competing interests statement: There is no conflict of interest in this article.

Abstract

Background: There is some controversy regarding the efficacy and safety of immunosuppressive agents for the treatment of kidney diseases. The recent STOP-IgAN and TESTING studies have focused attention on the application of immunosuppressive agents in IgA nephropathy (IgAN). This study investigated the benefits and risks of immunosuppressive agents in IgAN.

Methods: MEDLINE, EMBASE, the Cochrane Library, and article reference lists were searched for randomized controlled trials (RCTs) comparing immunosuppressive agents with any other non-immunosuppressive agents for treating IgAN. A meta-analysis was performed on the outcomes of proteinuria, creatinine (Cr), estimated glomerular filtration rate (eGFR), and adverse events in patients with IgAN, and trial sequential analyses were also performed for outcomes.

Results: Twenty-nine RCTs (1957 patients) that met our inclusion criteria were identified. Steroids (weighted mean difference [WMD] –0.70, 95% confidence interval [CI] –1.2 to –0.20), non-steroidal immunosuppressive agents (NSI) (WMD –0. 43, 95% CI –0.55 to –0.31), and combined steroidal and non-steroidal immunosuppressive agents (S&NSI) (WMD –1.46, 95% CI –2.13 to –0.79) therapy significantly reduced proteinuria levels in patients with IgAN. Steroid treatment significantly reduced the risk for end-stage renal disease (ESRD) (relative risk [RR] 0.39, CI 0.19 to 0.79). The immunosuppressive therapy group showed significant increases in gastrointestinal, hematological, dermatological, and genitourinary side effects, as well as impaired glucose tolerance or diabetes. Hyperkalemia was more common in the control group.

Conclusion: Immunosuppressive therapy can significantly reduce proteinuria and ESRD risk

47 in patients with IgAN, but with a concomitant increase in adverse reactions. Therefore, care
48 is required in the application of immunosuppressive agents in IgAN.
49

50 **Introduction**

51 IgA nephropathy (IgAN) is one of the most common primary glomerular diseases (1). A
52 systematic review demonstrated an overall population incidence of IgAN of 2.5/100000/year
53 (2). There is still no uniform standard of treatment for IgAN. The 2012 Kidney Disease:
54 Improving Global Outcomes (KDIGO) guidelines (3) for IgAN recommend treatment with a
55 renin-angiotensin system (RAS) blocker, such as angiotensin-converting enzyme inhibitors
56 (ACEIs) and angiotensin II receptor blockers (ARBs), in patients with proteinuria with
57 protein excretion > 1 g/day. Corticosteroid therapy can be considered in patients with
58 proteinuria > 1 g/day after 3–6 months of best supportive treatment and without renal failure.
59 Intensive immunosuppression is reserved for patients with crescents in more than half the
60 glomeruli and a rapid decline in renal function.
61 The publication of the Supportive versus Immunosuppressive Therapy of Progressive IgA
62 Nephropathy (STOP-IgAN) trial in 2015 and Therapeutic Evaluation of Steroids in IgA
63 Nephropathy Global (TESTING) trial in 2017 focused attention on the treatment of IgAN
64 with immunosuppressive agents. According to the results of these two large randomized
65 controlled trials (RCTs), there is still no clear evidence that immunosuppressive therapy can
66 improve the prognosis of IgAN. Therefore, we retrieved RCTs on immunosuppressive
67 therapy for IgAN, and performed a meta-analysis of the efficacy and safety of
68 immunosuppressive therapy in this disease.
69 Immunosuppressive agents were divided into three subgroups for this meta-analysis: steroids,

70 non-steroidal immunosuppressive (NSI) agents, and steroids combined with non-steroidal
71 immunosuppressive (S&NSI) agents. Their efficacy and safety were compared relative to
72 controls for the treatment of IgAN.
73 This meta-analysis was performed in accordance with the recommendations of the Cochrane
74 handbook for systematic reviews of interventions (4) and is reported in compliance with the
75 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement
76 guidelines (5). The protocol and registration information are available at
77 http://www.crd.york.ac.uk/PROSPERO/ (CRD42018096197).
78

79 **Inclusion and exclusion criteria**

80 This investigation required studies to meet the following inclusion criteria: the study was an
81 RCT; the study compared different immunosuppressive agents versus
82 non-immunosuppressive agents/placebo/no treatment; and study subjects were adult or
83 pediatric patients with biopsy-proven IgAN.
84 Studies were rejected according to the following exclusion criteria: immunosuppressant not
85 given orally or intravenously; study subjects with secondary IgAN; no data available for this
86 study in the article, data included in other articles, or data repeated in other articles; and
87 article not in English.
88

89 **Data sources and searches**

90 The MEDLINE, EMBASE, and Cochrane Library medical databases were searched to
91 retrieve relevant studies. Searches were performed in English, and each search retrieved
92 studies that were published between establishment of the database and May 2018.

A comprehensive search strategy was established to ensure the comprehensive and accurate retrieval of studies. Specifically, the MEDLINE and Cochrane Library databases were searched using the method described in the Cochrane Policy Manual for optimizing the sensitivity and precision of the search process (6), whereas EMBASE was searched using a sensitivity–specificity filter optimized by the McMaster/Hedges team (7). The following search terms were used: IgAN, steroids, glucocorticoids, immunosuppressive agents, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and placebo. After completing the electronic query of the aforementioned databases, we also searched relevant professional journals manually.

Data extraction and quality assessment

Two investigators (ZZ and YY) independently selected studies from the retrieved literature based on the inclusion criteria and extracted the data and analytical results of these studies. If the two investigators had different opinions regarding the quality of a study, a third investigator (SMJ) examined the disputed study and discussed it with the two aforementioned reviewers. Data were included for consideration only if discussions allowed the three authors to achieve consensus regarding the data.

If necessary, daily proteinuria was recalculated as g/day. Values for eGFR were based on the data provided by the authors of the included studies.

We evaluated treatment-related changes based on changes between the pre-treatment and post-treatment mean values and standard deviations (SDs) of the examined outcome measures. As the standard error of the mean (SEM) was used in some studies, we calculated the SD using the formula: SEM × square root of sample size. In addition, 95% confidence

116 intervals (CIs) were used in some studies; we calculated the SD using the formula: ((upper
117 limit of 95% CI – lower limit of 95% CI)/(2 × 1.96)) × √(n). Publication bias is defined as a
118 condition in which studies with positive results are more likely to be published. Assessment
119 of the risk of bias was performed following the Cochrane handbook.
120
121 **Risk of bias assessment**
122 Two authors (ZZ and YY) independently assessed risk of bias using the Cochrane
123 risk-of-bias tool (8). They reviewed each trial and gave a score of high, low, or unclear risk of
124 bias according to the following criteria: random sequence generation, allocation concealment,
125 blinding of participants and personnel to the study protocol, blinding of outcome assessment,
126 incomplete outcome data, selective reporting, and other bias.
127
128 **Statistical analyses**
129 To compare the effects of immunosuppressive agents and control treatment on proteinuria
130 excretion and serum levels of creatinine, data on eGFR and end-stage renal disease (ESRD)
131 were extracted for meta-analyses. Subgroup analyses were performed for each outcome based
132 on the type of immunosuppressive agent.
133 For continuous outcomes, the differences in means and the 95% CI in mean change between
134 baseline and end of treatment value were calculated for individual trials, and the weighted
135 mean difference (WMD) was used as a summary estimator. Dichotomous outcome data from
136 individual trials were analyzed using the relative risk (RR) measure and 95% CI.
137 Heterogeneity of treatment effects between studies was investigated visually by examination
138 of plots and statistically using the heterogeneity χ^2 and I^2 statistics. In all analyses, $P < 0.05$

was taken to indicate statistical significance. The fixed-effects and random-effects models were used for the meta-analysis of each indicator. Analyses were performed using Review Manager 5.2 (RevMan; Cochrane Collaboration, Oxford, UK).

Trial sequential analyses

To evaluate whether the present meta-analysis had a sufficient sample size to reach firm conclusions about the effects of interventions, we performed trial sequential analyses (TSAs) for outcomes, which involves a cumulative meta-analysis to create a Z curve of the summarized observed effect (the cumulative number of included patients and events) and the monitoring boundaries for benefit and harm and estimate the optimal sample size (9). When the cumulative z curve crosses the trial sequential monitoring boundary, a sufficient level of evidence for the anticipated intervention effect may have been reached. If the z curve crosses none of the boundaries and the required information size has not been reached, there is insufficient evidence to reach a conclusion. These analyses were performed using the software TSA version 0.9 Beta (Copenhagen Trial Unit, Copenhagen, Denmark).

Basic information regarding the included studies

After performing electronic and manual searches, 4,016 potentially relevant papers were obtained. After removing duplicated papers, 2,639 papers remained. After browsing the titles and abstracts, 53 papers were selected. After reading the entire text of these 53 papers, 24 papers were excluded, and 29 papers describing 25 trials with a total of 1957 patients were ultimately included. The literature selection process is illustrated in Figure 1, and detailed information regarding the examined studies is provided in Table 1 (10-38).

Fig. 1. Results of systematic literature search on immunosuppressive treatment for IgAN.

165 **Table 1. Characteristics of RCTs included in the study**

Study	Patient	Sample size	Intervention (treatment)	Intervention (control)	Follow-up
Ballardie 2002	18 to 54 years	38(19/19)	Prednisolone 40mg/d (reduced to 10 mg/d by 2 year) + cyclophosphamide 1.5 mg/kg/day (adjusted down to the nearest 50 mg)	no immunosuppression	24M
Cheng 2015	18-55 years old，hypertension under control，urinary proteins 0.5-3.5 g/24h，Cr <265.2 μmol/L	84(42/42)	leflunomide 20mg/d + Valsartan	Valsartan	24M
Cruzado 2011	18-70 years old, eGFR 30-60ml/min/1.73m^2, proteinuria >1g/d; BP>140/90mmHg with proteinuria 0.3-1g/d	23(14/9)	SRL 1mg/d (initial) +enalapril (or ACEI) +atorvastatin (or other statin)	Enalapril (or ACEI) +atorvastatin (or other statin)	12M
Frisch 2005	18–75 years old, protein>1g/d	32(17/15)	MMF 1000 mg bid +ACEI/ARB	Placebo + ACEI/ARB	12M
Harmankaya 2002	13–63 years, mean Ccr 89.2 ± 10.2 ml/min	43(21/22)	Prednisolone 40mg/day + azathioprine 100mg/day	no specific treatment	60M
Hirai 2017	urinary protein excretion > 0.5 g/day, age > 16 years	42(21/21)	MZR 150 mg once daily orally in the morning for 12 months + Standard treatment	Standard treatment	36M
Hogg 2015	7-70 years old; UPCR > 0.6 g/g (males) or>0.8 g/g (females); eGFR>50 mL/min/1.73 m2 (or>40 mL/min/1.73 m2 in those already receiving ACE or ARB).	52(25/27)	MMF 25 to 36 mg/kg/d (Max dose of 1 g/d) +lisinopril	lisinopril or placebo 25 to 36 mg/kg/d (Max dose of 1 g/d)	12M
Julian 1993	Ccr>25 ml/min/1.73 m^2	35(17/18)	prednisone	no placebo	12M

Yoshikawa 1999[a]	<15 Years old	78(40/38)	Prednisolone 2 mg/kg/d in three divided doses for a total dose of not more than 80 mg/d for 4w, followed by 2 mg/kg /2d, given as a single dose in the morning of every other day for 4w, 1.5 mg/kg/2d for 4w, and 1 mg/kg/2d for 21m + azathioprine 2 mg/kg/d in a single morning dose for 24m +heparin-warfarin + dipyridamole	heparin-warfarin + dipyridamole	24M
Katafuchi 2003	≤60 years old, Cr<1.5mg/dl(132.6umol/L)	90(43/47)	prednisolone orally: 20 mg/d for 1 month, followed by 15 mg/d for 1 month, 10 mg/d for 1 month, 7.5 mg/d for 3 months, and 5 mg/d for 18 months + dipyridamole 150–300 mg/day	Dipyridamole 150–300 mg/day	60M
Kim 2013	18-70 years old，serum creatinine ≤1.5 mg/dL or eGFR ≥45 ml/min/1.73 m^2, UACR 0.3-3g/g creatinine, BP<130/80mmHg	40(20/20)	Tacrolimus 0.1 mg/kg/day, 8weeks (maintain trough levels at 5–10 ng/ml) →0.05 mg/kg/day, 16weeks (maintain the trough level in 5–10 ng/ml) +RASi(9/20)	RASi(11/20), placebo	16W
Koike 2008	NA	48(24/24)	initially treated with 0.4 mg/kg/day of prednisolone (20–30 mg/day) for the first 4 weeks, and the dose was gradually reduced to 10–20 mg on alternate days for the next 12 months, and then 5–10 mg on alternate days for a subsequent year	Dipyridamole or dilazep hydrochloride	24M
Pozzi 1999[b]	15–69 years old, urinary protein excretion of 1.0–3.5 g/d, Cr≤133 umol/L (1.5 mg/dL)	86(43/43)	methylprednisolone intravenously for 3 consecutive days; this course was repeated 2 months and 4 months later. Oral prednisone	Supportive treatment	60M

			was given at a dose of 0.5 mg/kg on alternate days for 6 months.		
Lai 1986	14-42 years old, IgAN & NS	34(17/17)	prednisone/prednisolone 40-60mg/d, reduce by half after 8 weeks	Supportive therapy	38M
Lv 2009	18-65 years old, urinary proteins 1-5 g/d, eGFR>30ml/min	63(33/30)	prednisone: 0.8-1.0 mg/kg/day for 8 weeks, tapered by 5-10 mg every 2 weeks + cilazapril	cilazapril	48M
Lv 2017	proteinuria> 1 g/d, eGFR: 20 -120ml/min/1.73m^2	262(136/126)	oral methylprednisolone (0.6-0.8mg/kg/d; maximum, 48mg/d)	placebo	60M
Maes 2004	>18 years old, inulin clearance 20-70 mL/min/1.73m^2, proteinuria >1 g/day, BP>140/90mmHg,	34(21/13)	MMF: 2g/d + ACEI	Placebo (identical lactose-containing capsules)	36M
Manno 2009	16-70 years old, proteinuria>1g/d, eGFR≥50ml/min/1.73m^2	97(48/49)	prednisone: 1.0 mg/kg/day(Max: 75 mg/day) for 2 months, tapered by 0.2 mg/kg/day every month ramipril	ramipril	5Y
Rauen 2015	proteinuria>0.75g/d after 6 months support treatment	162(82/80)	Supportive Care (100%) + Immunosuppression	RASi (77/80)	36M
Shoji 2000	15-55 years old, proteinuria less than 1.5 g/d, serum creatinine level less than 1.5 mg/dL	19(11/8)	prednisolone 0.8 mg/kg of body weight; this was gradually reduced to a daily dose of 0.4 mg/kg of body weight during the first month of therapy, and then tapered to 10 mg very other day for the remainder of the 1 year of therapy	Dipyridamole 300 mg/day	12M
Tang 2005[c]	urinary proteins>1g/d, BP<125/85mmHg, Cr<300umol/L(3.4mg/dl)	40(20/20)	MMF 2 g/day (weight≥60kg), 1.5g/day(weight<60kg) +ACEI/ARB(16:4)	ACEI/ARB (14:6)	72W

Walker 1990	24h pro>1.0g/d, 120umol/L<Cr<200umol/L one or more	52(25/27)	Cyclophosphamide (1-2 mg/kg/24h - maximum of 100 mg/24h and ajusted according to peripheral white cell counts) +dipyridamole +warfarin	no treatment	2Y
Wu 2016	18–55 years, proteinuria of 0.5–3.5 g/d, serum creatinine <265 μmol/L, blood pressure between 90/60 and 130/80 mmHg	399(100/299)	Leflunomide 20 mg/d + telmisartan + clopidogrel placebo	Telmisartan + Leflunomide placebo + clopidogrel placebo & Telmisartan +clopidogrel + Leflunomide placebo & Telmisartan + clopidogrel	24w
Xie 2011	14-70 years old, urinary protein excretion: 0.5 to 3.5 g/24 h, Cr <353.6 umol/L	64(34/30)	MZR 200mg/d(weight<50kg), 250mg/d(weight>50kg), 150mg/d(Cr>176.8 umol/L) +losartan	Losartan	12M
Woo 1987		48(27/21)	cyclophosphamide 1.5 mg/kg per day+ dipyridamole + warfarin	No treatment	36M

Abbreviations: NA: not applicable; MMF: mycophenolate mofetil; SRL: sirolimus; MZR: mizoribine.

[a]Kamei 2011 and Yoshikawa 1999 describe the same trial, but the available data provided by the articles are different. Here, only the data of Yoshikawa 1999 are listed.

[b]Locatelli 2001 and Pozzi 2004 were follow-up studies of Pozzi 1999, and only the data of Pozzi 1999 are listed here.

[c]Tang 2010 was a follow-up study of Tang 2005, and only the data of Tang 2005 are listed here.

171 **Quality of trials**

172 By current standards, reporting of key indicators of trial quality was suboptimal. Some
173 studies in particular provided few details on the process of randomization and concealment of
174 allocation. Only six studies were double-blinded trials. Seven studies used an open-label
175 design. The bias and overall risk diagrams of the included studies are presented in Figure 2.

176

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

178

179 **Effects on proteinuria**

180 The difference in the means of urinary protein excretion between end of treatment and
181 baseline was significantly lower in the steroid group than in controls (five trials (17, 21-23,
182 31), 222 patients; WMD –0.51, 95% CI –0.73 to –0.28, with a fixed-effects model; WMD
183 –0.70, 95% CI –1.2 to –0.20, with a random-effects model; I^2=58%; Fig. 3). After removing
184 Lai (22), heterogeneity I^2 changed to 0.
185 Patients receiving NSI alone showed a more significant reduction of urinary protein excretion
186 after treatment compared to controls (seven trials (12, 26, 32, 34-37), 660 patients, WMD
187 –0.43, 95% CI –0.55 to 0.31, with a fixed-effects model; WMD –0. 43, 95% CI –0.55 to
188 –0.31, with a random-effects model; I^2=0; Fig. 3).
189 With the S&NSI treatment approach, patients had a more significant reduction of urinary
190 protein excretion after treatment compared to controls (three trials (10, 30, 38), 278 patients,
191 WMD –0.16, 95% CI –1.8 to –1.4, I^2=83%, with a fixed-effects model; WMD –1.42, 95% CI
192 –2.18 to –0.66, I^2=89%, with a random-effects model; Fig. 3). After removing Yoshikawa
193 (38), heterogeneity I^2 changed to 0.

194 TSAs of steroids, NSI, and S&NSI all indicated that the cumulative z curve crossed both the

195 conventional boundary and the trial sequential monitoring boundary (Fig. 4).

196

197 **Fig. 3. Effects of immunosuppressive agents on proteinuria in patients with IgAN.**

198 CI, confidence interval.

199

200 **Fig. 4. Trial sequential analyses of proteinuria.**

201 a) Five comparisons between steroids and controls.

202 b) Seven comparisons between NSI and controls.

203 c) Three comparisons between S&NSI and controls.

204 **Effects on renal function and renal survival**

205 **Creatinine**

206 There were no statistically significant differences in creatinine changes between baseline and
207 end of treatment between immunosuppressive treatment and control groups (nine trials (11,
208 13, 17, 19, 20, 22, 26, 31, 34), 420 patients, WMD –0.03, 95% CI –0.11 to 0.15, with a
209 fixed-effects model; WMD –0.03, 95% CI –0.11 to 0.05, with a random-effects model;
210 I^2=0%; Fig. 5).
211 TSAs of nine comparisons illustrated that the cumulative z curve did not cross the
212 conventional boundary or the line of required information size, indicating that the evidence
213 was insufficient. Therefore, further trials are required.
214

215 **Fig. 5. Effects of immunosuppressive agents on creatinine levels in patients with IgAN.**
216 CI, confidence interval.
217

218 **eGFR**

219 The differences in the means of eGFR between end of treatment and baseline were
220 significantly higher in the NSI group than in controls (five trials (16, 20, 25, 36, 37), 817
221 patients; WMD 5.17, 95% CI 3.18 to 7.16, with a fixed-effects model; WMD 5.17, 95% CI
222 3.18 to 7.16, with a random-effects model; I^2=0%; Fig. 6). TSAs of five comparisons
223 indicated that the cumulative z curve crossed the conventional boundary, but did not cross the
224 trial sequential monitoring boundary.
225 However, when the steroid and S&NSI groups were added, there were no significant
226 differences in eGFR changes in immunosuppressive treatment compared to controls (seven

227 trials (16, 20, 25, 30, 31, 36, 37), 998 patients, WMD 0.26, 95% CI –0.03 to 0.56, with a
228 fixed-effects model; WMD 2.52, 95% CI –0.49 to 0.53, with a random-effects model;
229 I^2=76%; Fig. 6). TSAs of seven comparisons indicated that the cumulative z curve did not
230 cross the conventional boundary or the line of required information size.
231
232 **Fig. 6. Effects of immunosuppressive agents on estimated glomerular filtration rate in**
233 **patients with IgAN.**
234 CI, confidence interval.
235
236 **ESRD**
237 There was a lower risk of reaching ESRD in the immunosuppressive treatment group than in
238 controls (12 trials (13, 17-19, 24-28, 30, 33, 34), 1031 patients; RR 0.51, 95% CI 0.33 to 0.08,
239 with a fixed-effects model; RR 0.55, 95% CI 0.33–0.90, with a random-effects model; I^2=8;
240 Fig. 6). These analyses were dominated by the steroid treatment group (Fig. 7).
241 TSAs of steroids indicated that the cumulative z curve crossed both the conventional
242 boundary and the trial sequential monitoring boundary.
243
244 **Fig. 7. Effects of immunosuppressive agents on end-stage renal disease in patients with**
245 **IgAN.**
246 CI, confidence interval; RR, relative risk.
247
248 **Adverse events of treatment**
249 A total of 20 articles reported adverse events during the observation period. The types of

adverse events varied widely, and included infection, cardiovascular disease, respiratory disease, hepatotoxicity, and many others; the 12 most commonly reported are listed in Table 2. As the number of infections reported in Rauen (30) was greater than the total number, RR could not be calculated for infections. TSAs of infection, gastrointestinal disease, hematological disease, dermatological disease, impaired glucose tolerance or diabetes mellitus, and hyperkalemia indicated that the cumulative z curve crossed the conventional boundary but did not cross the trial sequential monitoring boundary. In addition, TSAs of the other six diseases indicated that the cumulative z curve did not cross the conventional boundary or the line of required information size.

Table 2. Main adverse events reported in the included RCTs

Main adverse events	No. of studies	Immunosuppressive agent group	Control group	RR (95% CI)		*P* value	
				FE	RE	FE	RE
Gastrointestinal	11	38/431	8/606	2.53 [1.15, 5.55]	2.42[1.07, 5.45]	0.02	0.03
Hematologic	9	16/373	6/551	2.17 [1.00, 4.68]	2.0[0.84, 4.77]	0.05	0.12
Dermatologic	7	16/273	3/463	4.09 [1.57, 10.66]	3.88[1.41, 10.64]	0.004	0.009
Hepatotoxicity	7	21/455	19/636	1.26 [0.72, 2.22]	1.26[0.70, 2.24]	0.42	0.44
Respiratory	6	9/371	12/544	0.81 [0.37, 1.74]	0.82[0.37, 1.82]	0.58	0.62
Infection	6	189/373	114/547	Not estimable	Not estimable	Not estimable	Not estimable
Impaired glucose tolerance or diabetes mellitus	5	15/326	5/316	2.61 [1.04, 6.55]	2.16[0.77, 6.05]	0.04	0.14
BP↑	4	14/193	16/389	0.96 [0.52, 1.79]	0.97[0.43, 2.22]	0.9	0.95
Malignant	4	4/167	2/157	1.40 [0.39, 4.98]	1.33[0.30, 5.93]	0.61	0.71
Musculoskeletal	3	5/238	3/226	1.47 [0.44, 4.93]	1.37[0.40, 4.71]	0.53	0.62
Hyperkalemia	3	2/156	11/350	0.23 [0.07, 0.71]	0.3[0.05, 1.98]	0.01	0.21
Genitourinary	3	6/59	0/56	4.59 [0.85, 24.85]	4.07[0.71, 23.39]	0.08	0.12

RR: Relative Risk; CI: Confidence Intervals; FE: Fixed Effect Model; RE: Random Effect Model

Conclusions

Farnsworth (39) and Barnett (40) first used corticotropin between 1949 and 1950 for the treatment of lipoid nephrosis, which is now known as minimal change disease or childhood nephrotic syndrome. Chasis *et al*. (41) used nitrogen mustard to treat chronic glomerulonephritis and achieved good initial results, thus pioneering the use of immunosuppressive agents for the treatment of nephropathy. Immunosuppressive agents have been used for the treatment of kidney diseases for about 70 years. However, the outcomes immunosuppressive therapy for IgAN are controversial. Therefore, we included 29 reports published between 1986 and 2017 in a meta-analysis of the efficacy and safety of immunosuppressive treatment and control treatment in IgAN.

Alleviation of proteinuria

Previous studies have suggested that treatment with steroids or alkylating agents can significantly reduce proteinuria levels in patients with IgAN (42-44). Our meta-analysis also showed that immunosuppressive agents can significantly reduce the level of proteinuria. The levels of proteinuria in groups treated with steroids, NSI, or S&NSI were significantly reduced compared to controls. The heterogeneity of the steroid group was mainly derived from Lai (22), in which the inclusion criterion included nephrotic syndrome. In addition, the heterogeneity of the S&NSI group was mainly derived from Yoshikawa (38), in which the inclusion criterion included age < 15 years. Sequential analyses showed that immunosuppressive agents were effective for relieving proteinuria, and no additional sample size was required.

306 **Reducing the risk for ESRD**

307 Our results suggest that non-steroidal immunosuppressive therapy may have a positive effect
308 on eGFR. However, sequential analyses suggested that this is still inconclusive and further
309 studies are required for confirmation. In addition, the treatment group showed a greater
310 reduction in the risk for ESRD than the control group, and this effect was mainly due to the
311 steroid treatment group. Sequential analyses showed that steroids could reduce the risk for
312 ESRD without the need for a larger sample size. A relevant study (43) also suggested that
313 high-dose short-course steroid therapy has a significant protective effect on renal function,
314 while a low-dose long-course of steroids does not. Further studies are required to determine
315 whether NSI or S&NSI can reduce the risk for ESRD.

316

317 **More adverse events**

318 The use of immunosuppressive agents is often accompanied by side effects. The
319 immunosuppressive therapy group showed significant increases in gastrointestinal,
320 hematological, dermatological, and genitourinary side effects, as well as impaired glucose
321 tolerance or diabetes in this meta-analysis. As the number of infection events reported in the
322 STOP study was too high, even exceeding the total number of patients, it was not possible to
323 calculate the RR value. However, across all studies, the proportion of infections reported was
324 still higher in the immunosuppressive therapy group than in controls. In addition, the
325 TESTING study had to be discontinued because of the excessive number of serious adverse
326 events, mostly infections. By contrast, hyperkalemia was more common in the control group,
327 which may have been related to the application of ACEI and ARB. However, it should be
328 noted that sequential analyses indicated that the statistical results of the above adverse events

329 should be verified by further experiments.

330

331 **Strengths and limitations**

332 Our study had several limitations that should be taken into consideration. The results of bias
333 analyses indicated that nearly half of the studies did not explicitly report the methods used for
334 randomization. In addition, few studies used blinded methodologies. The quality of the
335 reports in the literature is unsatisfactory. In addition, there were some differences in the
336 inclusion criteria between each study, such as age, proteinuria level, and renal function, and
337 these confounding factors led to a high degree of data heterogeneity.

338

339 In conclusion, immunosuppressants significantly reduce proteinuria and decrease the risk for
340 ESRD but also increase the risk for serious adverse reactions. Therefore, if it is necessary to
341 use immunosuppressive agents, clinicians should evaluate the patient on an individual basis
342 according to their own conditions before treatment. In the course of using
343 immunosuppressive agents, close observation should be carried out to prevent and control
344 complications. In addition, further well-designed and high-quality RCTs are needed to
345 explore the applicability and optimal methods of immunosuppressant treatment.

346

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350 http://www.textcheck.com/certificate/gC26x1

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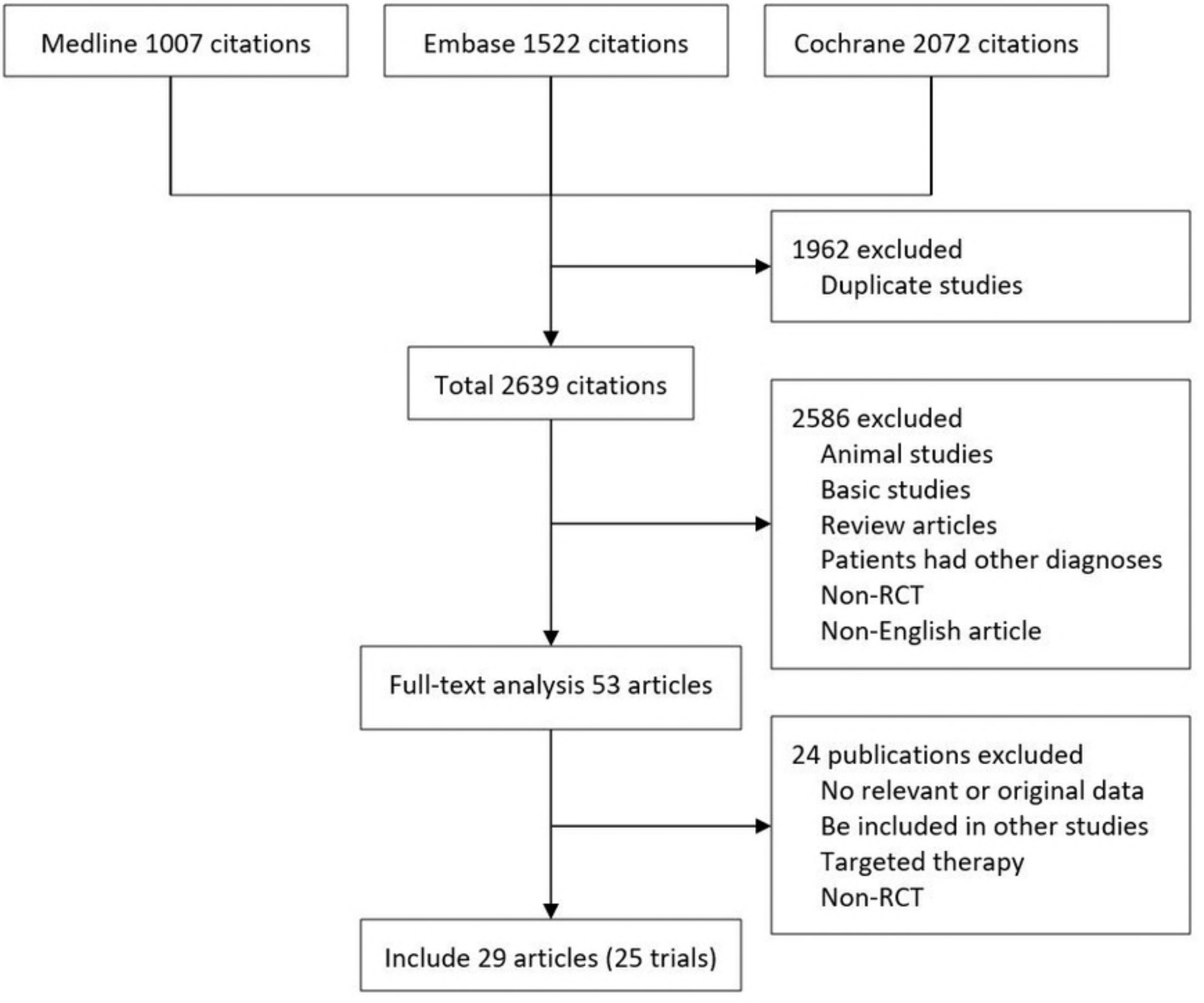
Medline 1007 citations
Embase 1522 citations
Cochrane 2072 citations
1962 excluded
Duplicate studies
Total 2639 citations
2586 excluded
Animal studies
Basic studies
Review articles
Patients had other diagnoses
Non-RCT
Non-English article
Full-text analysis 53 articles
24 publications excluded
No relevant or original data
Be included in other studies
Targeted therapy
Non-RCT
Include 29 articles (25 trials)

Fig.1

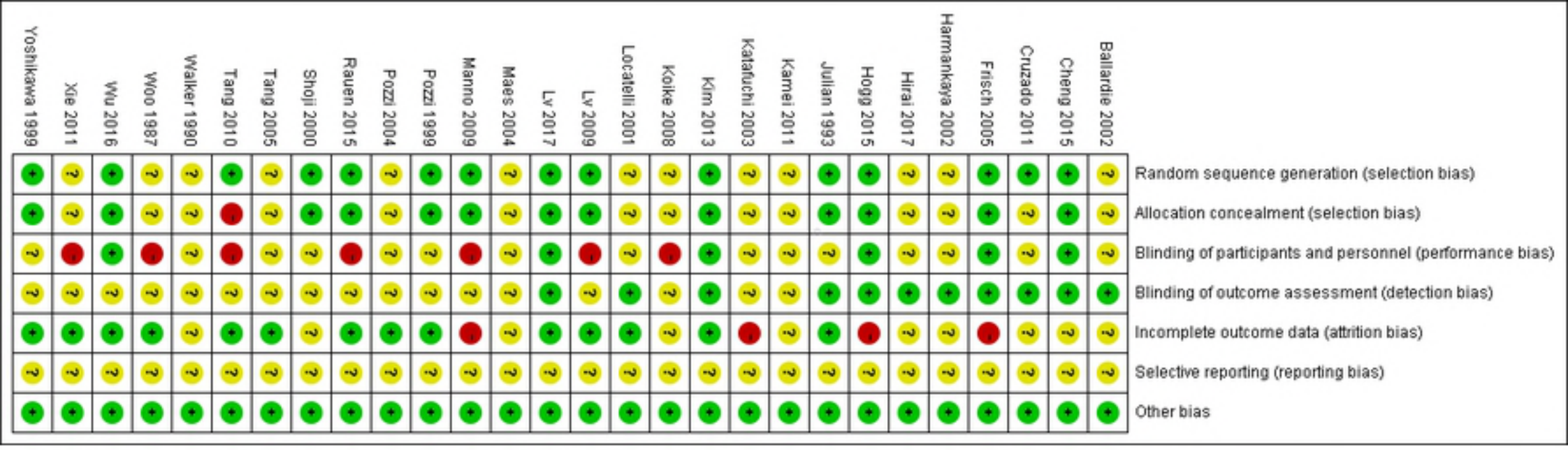
Ballardie 2002
Cheng 2015
Cruzado 2011
Frisch 2005
Harmankaya 2002
Hirai 2017
Hogg 2015
Julian 1993
Kamei 2011
Katafuchi 2003
Kim 2013
Koike 2008
Locatelli 2001
Lv 2009
Lv 2017
Maes 2004
Manno 2009
Pozzi 1999
Pozzi 2004
Rauen 2015
Shoji 2000
Tang 2005
Tang 2010
Walker 1990
Woo 1987
Wu 2016
Xie 2011
Yoshikawa 1999
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

Fig.2

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Steroids								
Julian 1993	-2.2	2.148	17	-1.4	2.583	18	0.4%	-0.80 [-2.37, 0.77]
Koike 2008	-0.66	0.663	24	-0.21	0.615	24	6.8%	-0.45 [-0.81, -0.09]
Lai 1986	-4.2	2.553	17	-1.4	1.852	17	0.4%	-2.80 [-4.30, -1.30]
Locatelli 2001	-1.33	3.585	43	-0.42	9.77	43	0.1%	-0.91 [-4.02, 2.20]
Shoji 2000	-0.465	0.258	11	-0.02	0.371	8	9.9%	-0.45 [-0.74, -0.15]
Subtotal (95% CI)			**112**			**110**	**17.6%**	**-0.51 [-0.73, -0.28]**
Heterogeneity: Chi² = 9.44, df = 4 (P = 0.05); I² = 58%								
Test for overall effect: Z = 4.44 (P < 0.00001)								
Non-steroidal immunosuppressive agents								
Cruzado 2011	-0.9	1.559	14	-0.9	1.51	9	0.5%	0.00 [-1.28, 1.28]
Maes 2004	-0.3	2.381	21	-0.3	1.908	13	0.4%	0.00 [-1.45, 1.45]
Tang 2005	-0.66	0.987	20	0.53	1.59	20	1.3%	-1.19 [-2.01, -0.37]
Walker 1990	-0.53	1.15	25	0.13	1.767	27	1.4%	-0.66 [-1.46, 0.14]
Woo 1987	1.02	0.91	27	1.82	1.84	21	1.2%	-0.80 [-1.66, 0.06]
Wu 2016	-0.59	0.51	100	-0.17	0.838	299	46.7%	-0.42 [-0.56, -0.28]
Xie 2011	-0.61	0.23	34	-0.25	0.83	30	9.4%	-0.36 [-0.67, -0.05]
Subtotal (95% CI)			**241**			**419**	**60.9%**	**-0.43 [-0.55, -0.31]**
Heterogeneity: Chi² = 5.31, df = 6 (P = 0.50); I² = 0%								
Test for overall effect: Z = 7.04 (P < 0.00001)								
Combined steriodal and non-steroidal immunosuppressive agents								
Ballardie 2002	-2.05	3.045	19	-0.4	11.433	19	0.0%	-1.65 [-6.97, 3.67]
Rauen 2015	-1.04	0.854	82	0.77	0.665	80	16.0%	-1.81 [-2.05, -1.57]
Yoshikawa 1999	-1.13	0.402	40	-0.14	1.206	38	5.5%	-0.99 [-1.39, -0.59]
Subtotal (95% CI)			**141**			**137**	**21.5%**	**-1.60 [-1.80, -1.40]**
Heterogeneity: Chi² = 11.85, df = 2 (P = 0.003); I² = 83%								
Test for overall effect: Z = 15.45 (P < 0.00001)								

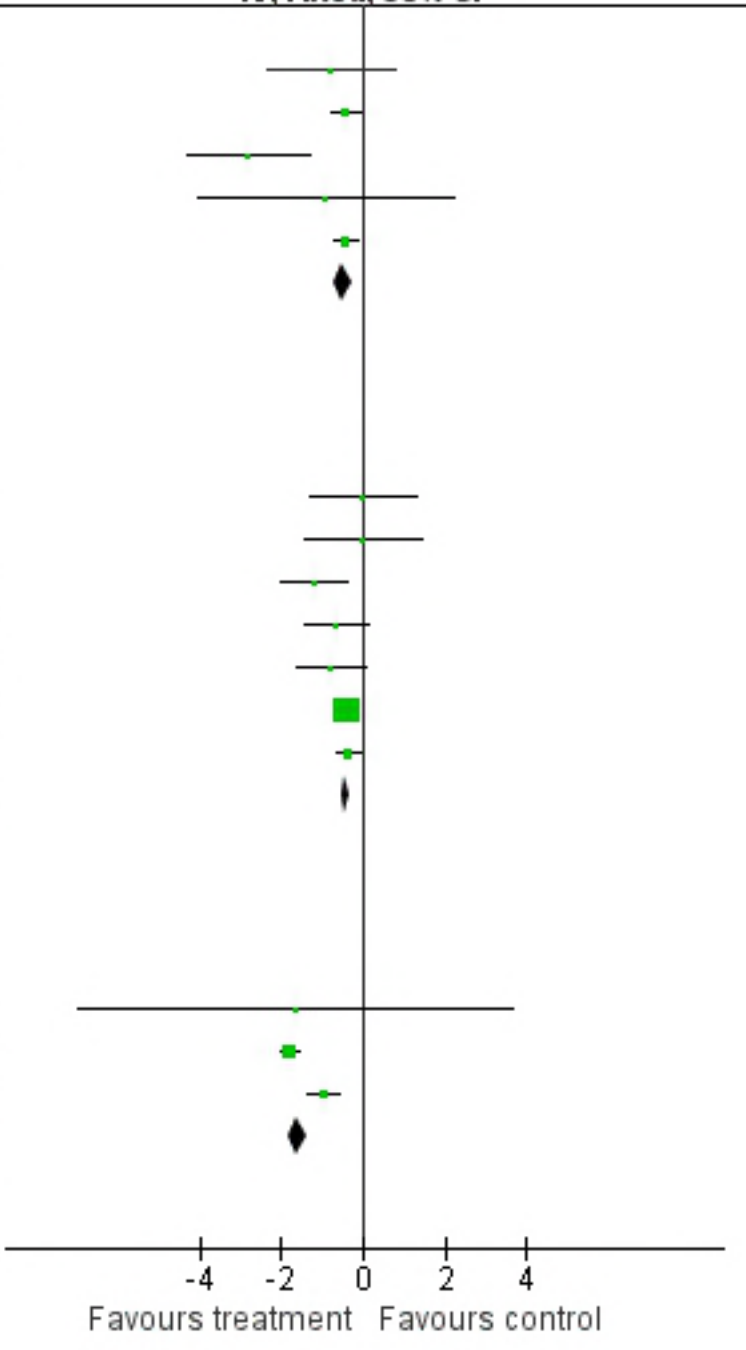

Fig.3

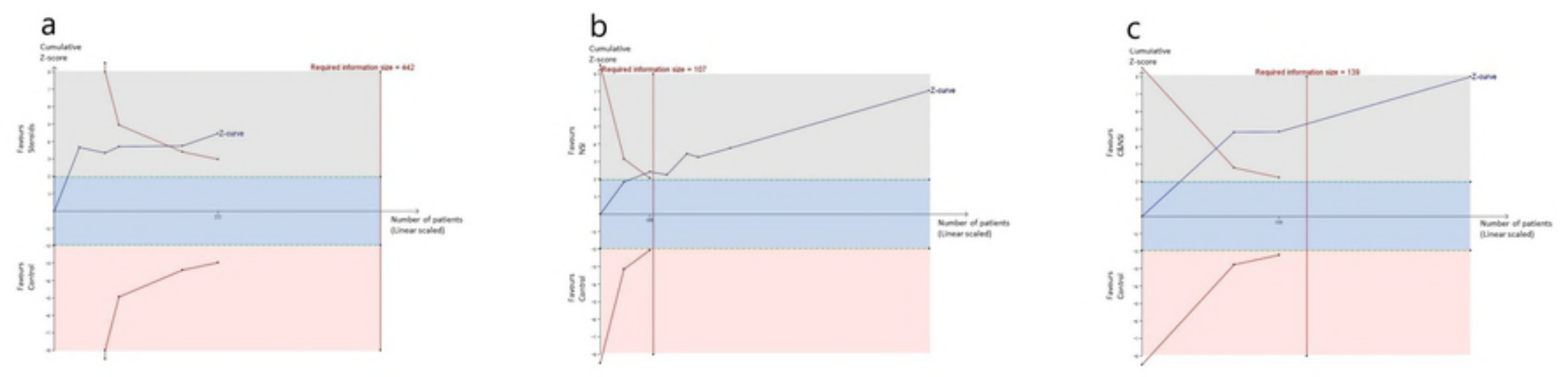
a
Cumulative
Z-score
Required information size = 442
Z-curve
Favours
Steroids
Favours
Control
Number of patients
(Linear scaled)
b
Cumulative
Z-score
Required information size = 107
Z-curve
Favours
NS
Favours
Control
Number of patients
(Linear scaled)
c
Cumulative
Z-score
Required information size = 139
Z-curve
Favours
CBVSI
Favours
Control
Number of patients
(Linear scaled)

Fig.4

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Steroids								
Julian 1993	-0.452	0.6887	17	0.215	1.5062	18	1.0%	-0.67 [-1.44, 0.10]
Katafuchi 2003	0.04	0.5786	43	0.06	0.04	47	19.0%	-0.02 [-0.19, 0.15]
Lai 1986	0.1312	0.771	17	0.059	0.6166	17	2.6%	0.07 [-0.40, 0.54]
Shoji 2000	0.01	0.1868	11	0.05	0.25	8	13.5%	-0.04 [-0.25, 0.17]
Subtotal (95% CI)			**88**			**90**	**36.1%**	**-0.04 [-0.16, 0.09]**
Heterogeneity: $Chi^2 = 2.82$, df = 3 (P = 0.42); $I^2 = 0\%$								
Test for overall effect: Z = 0.60 (P = 0.55)								
Non-steroidal immunosuppressive agents								
Cheng 2015	0.1643	0.2554	42	0.247	0.3088	42	38.8%	-0.08 [-0.20, 0.04]
Frisch 2005	1.4	2.5239	17	0.8	1.5692	15	0.3%	0.60 [-0.84, 2.04]
Kim 2013	0.04	0.3105	20	0.01	0.2651	20	17.8%	0.03 [-0.15, 0.21]
Maes 2004	0.26	1.4556	21	0.09	0.5048	13	1.2%	0.17 [-0.51, 0.85]
Walker 1990	0.2262	0.5656	25	0.113	0.5878	27	5.8%	0.11 [-0.20, 0.43]
Subtotal (95% CI)			**125**			**117**	**63.9%**	**-0.03 [-0.12, 0.07]**
Heterogeneity: $Chi^2 = 3.02$, df = 4 (P = 0.55); $I^2 = 0\%$								
Test for overall effect: Z = 0.53 (P = 0.59)								
Total (95% CI)			**213**			**207**	**100.0%**	**-0.03 [-0.11, 0.05]**
Heterogeneity: $Chi^2 = 5.87$, df = 8 (P = 0.66); $I^2 = 0\%$								
Test for overall effect: Z = 0.78 (P = 0.43)								
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$								

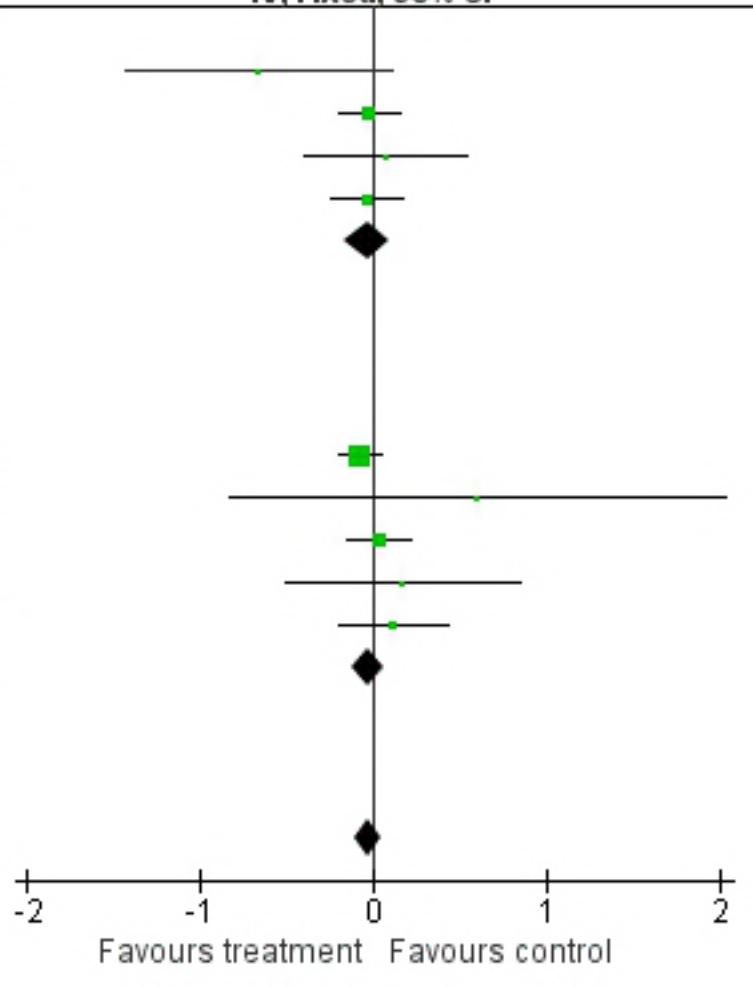

Fig.5

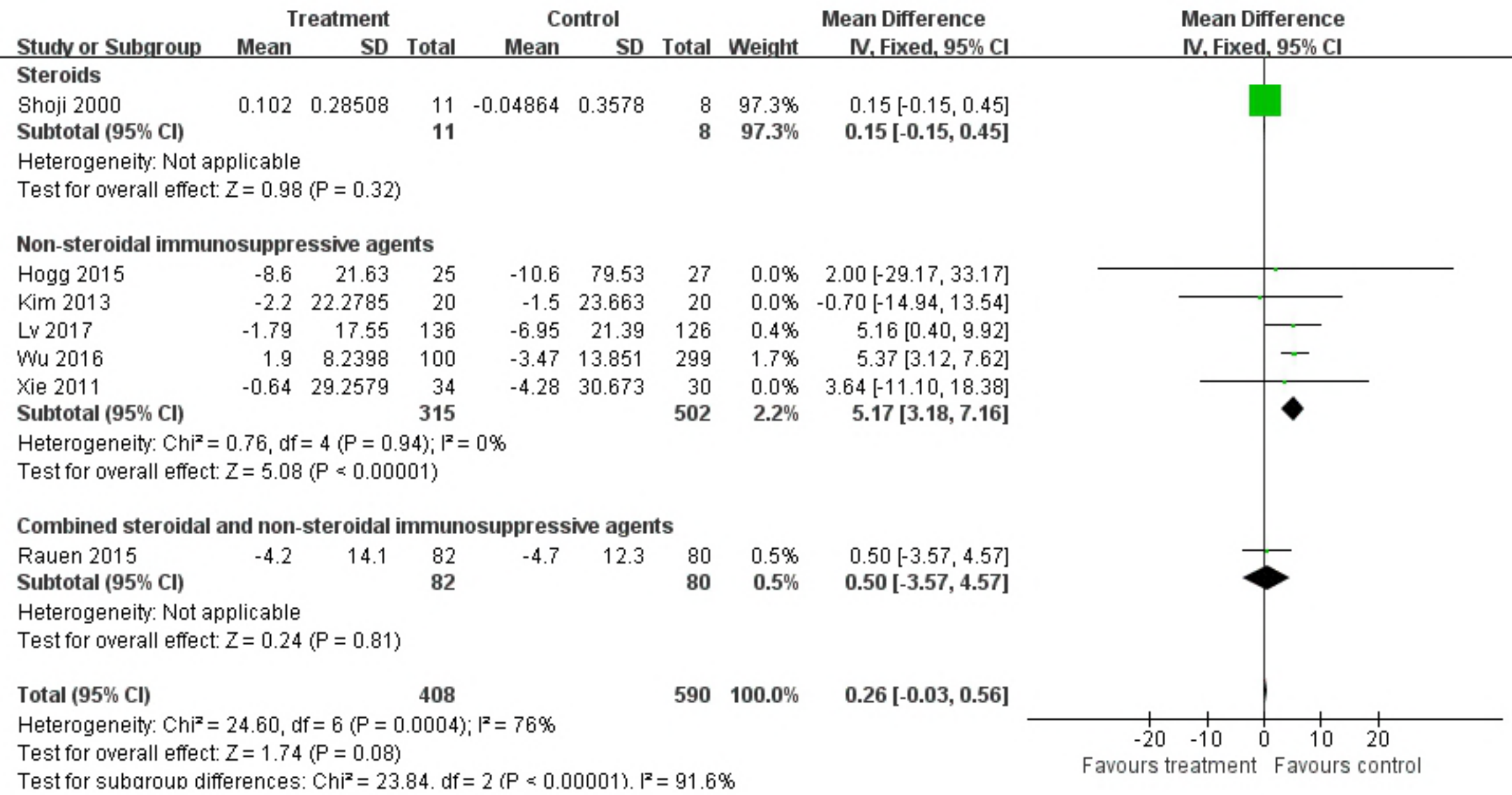
Treatment
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Steroids
Shoji 2000 0.102 0.28508 11 -0.04864 0.3578 8 97.3% 0.15 [-0.15, 0.45]
Subtotal (95% CI) 11 8 97.3% 0.15 [-0.15, 0.45]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.32)
Non-steroidal immunosuppressive agents
Hogg 2015 -8.6 21.63 25 -10.6 79.53 27 0.0% 2.00 [-29.17, 33.17]
Kim 2013 -2.2 22.2785 20 -1.5 23.663 20 0.0% -0.70 [-14.94, 13.54]
Lv 2017 -1.79 17.55 136 -6.95 21.39 126 0.4% 5.16 [0.40, 9.92]
Wu 2016 1.9 8.2398 100 -3.47 13.851 299 1.7% 5.37 [3.12, 7.62]
Xie 2011 -0.64 29.2579 34 -4.28 30.673 30 0.0% 3.64 [-11.10, 18.38]
Subtotal (95% CI) 315 502 2.2% 5.17 [3.18, 7.16]
Heterogeneity: Chi² = 0.76, df = 4 (P = 0.94); I² = 0%
Test for overall effect: Z = 5.08 (P < 0.00001)
Combined steroidal and non-steroidal immunosuppressive agents
Rauen 2015 -4.2 14.1 82 -4.7 12.3 80 0.5% 0.50 [-3.57, 4.57]
Subtotal (95% CI) 82 80 0.5% 0.50 [-3.57, 4.57]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Total (95% CI) 408 590 100.0% 0.26 [-0.03, 0.56]
Heterogeneity: Chi² = 24.60, df = 6 (P = 0.0004); I² = 76%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Chi² = 23.84, df = 2 (P < 0.00001), I² = 91.6%
-20 -10 0 10 20
Favours treatment Favours control

Fig.6

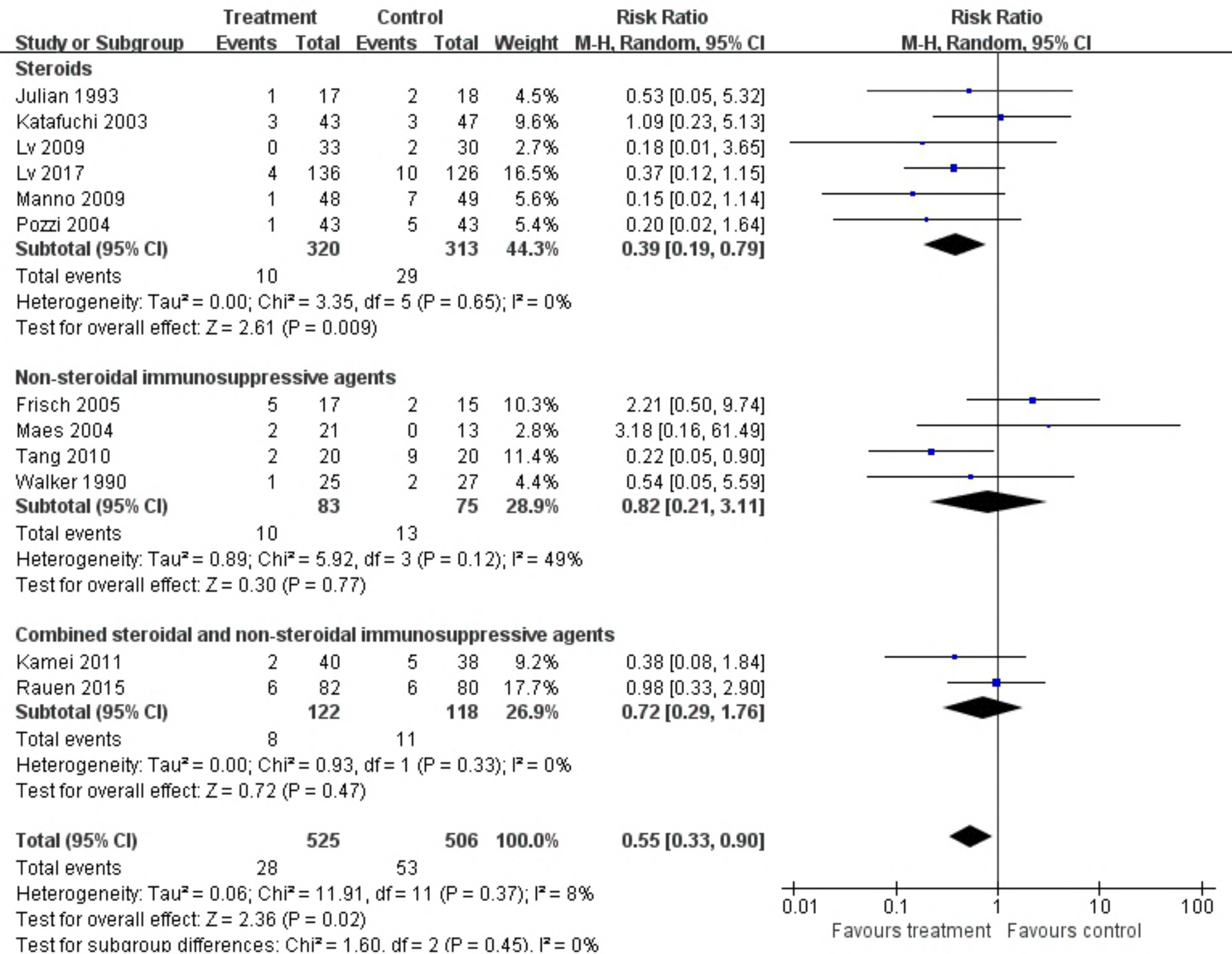
Treatment
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Steroids
Julian 1993 1 17 2 18 4.5% 0.53 [0.05, 5.32]
Katafuchi 2003 3 43 3 47 9.6% 1.09 [0.23, 5.13]
Lv 2009 0 33 2 30 2.7% 0.18 [0.01, 3.65]
Lv 2017 4 136 10 126 16.5% 0.37 [0.12, 1.15]
Manno 2009 1 48 7 49 5.6% 0.15 [0.02, 1.14]
Pozzi 2004 1 43 5 43 5.4% 0.20 [0.02, 1.64]
Subtotal (95% CI) 320 313 44.3% 0.39 [0.19, 0.79]
Total events 10 29
Heterogeneity: Tau² = 0.00; Chi² = 3.35, df = 5 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.61 (P = 0.009)
Non-steroidal immunosuppressive agents
Frisch 2005 5 17 2 15 10.3% 2.21 [0.50, 9.74]
Maes 2004 2 21 0 13 2.8% 3.18 [0.16, 61.49]
Tang 2010 2 20 9 20 11.4% 0.22 [0.05, 0.90]
Walker 1990 1 25 2 27 4.4% 0.54 [0.05, 5.59]
Subtotal (95% CI) 83 75 28.9% 0.82 [0.21, 3.11]
Total events 10 13
Heterogeneity: Tau² = 0.89; Chi² = 5.92, df = 3 (P = 0.12); I² = 49%
Test for overall effect: Z = 0.30 (P = 0.77)
Combined steroidal and non-steroidal immunosuppressive agents
Kamei 2011 2 40 5 38 9.2% 0.38 [0.08, 1.84]
Rauen 2015 6 82 6 80 17.7% 0.98 [0.33, 2.90]
Subtotal (95% CI) 122 118 26.9% 0.72 [0.29, 1.76]
Total events 8 11
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Total (95% CI) 525 506 100.0% 0.55 [0.33, 0.90]
Total events 28 53
Heterogeneity: Tau² = 0.06; Chi² = 11.91, df = 11 (P = 0.37); I² = 8%
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroup differences: Chi² = 1.60, df = 2 (P = 0.45), I² = 0%
0.01
0.1
1
10
100
Favours treatment
Favours control

Fig.7