

SUPPLEMENTARY MATERIAL

Efficacy and Safety of Agents in IgA Nephropathy: An Update Network Meta-Analysis

Pingping Yang^{a,b} Qi Wang^a Chen Xie^a Gaosi Xu^a Qinghua Wu^b

^aDepartment of Nephrology, the Second Affiliated Hospital of Nanchang University, Nanchang,

^bDepartment of Cardiovascular Medicine, the Second Affiliated Hospital of Nanchang University,
Nanchang, China

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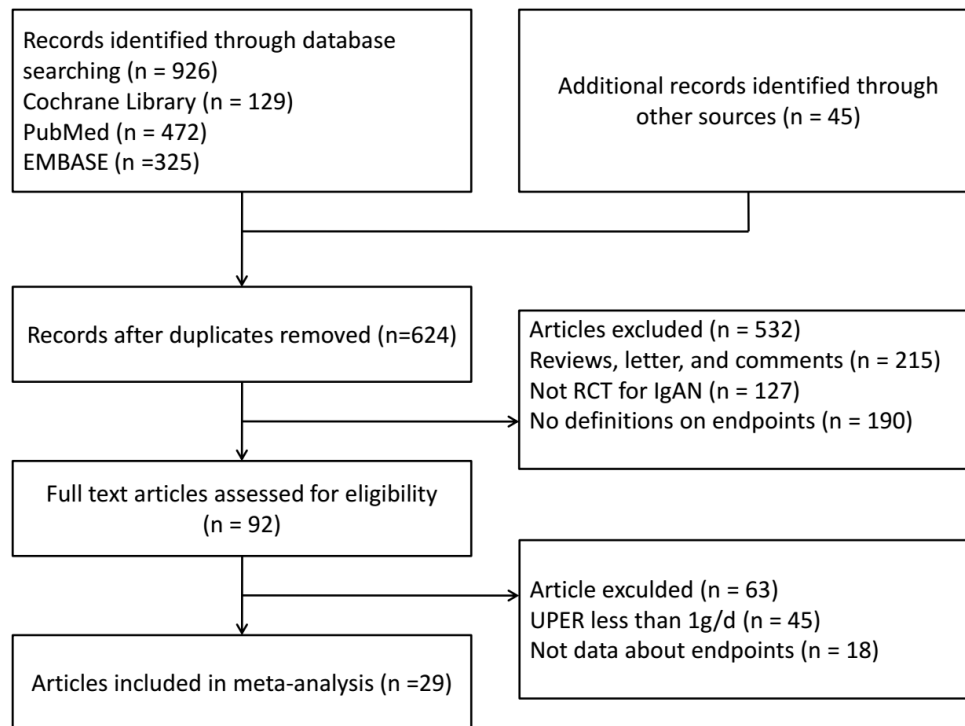
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S1: Table 1 Electronic search strategies determined on August 2018

Search	Query
The Cochrane library	
#1	RASi OR ACEi OR ARB OR Enalapril OR Losartan OR Benazepril OR Cilazapril OR Ramipril OR steroid OR Methylprednisolone OR prednisone OR Mycophenolate mofetil OR azathioprine OR cyclosporine A CsA OR tonsillectomy OR TSP
#2	IgAN OR IgA nephropathy OR immunoglobulin A nephropathy OR IgA nephritis
#3	#1 and #2
PubMed	
#1	RASi [Mesh] ACEi [Mesh] OR ARB [Mesh] OR Enalapril [Text Word] OR Losartan [Text Word] OR Benazepril [Text Word] OR Cilazapril [Text Word] OR Ramipril [Text Word] OR steroid [Mesh] OR Methylprednisolone [Mesh] OR prednisone [Text Word] OR Mycophenolate mofetil [Mesh] OR azathioprine [Text Word] OR cyclosporine A [Mesh] OR tonsillectomy [Mesh] OR TSP [Text Word]
#2	IgAN [Mesh] OR IgA nephropathy [Text Word] OR immunoglobulin A nephropathy [Text Word] OR IgA nephritis [Mesh]
#3	#1 and #2
EMBASE	
#1	' RASi '/exp OR 'ACEi'/exp OR ' ARB '/exp OR ' Enalapril '/exp OR ' Losartan '/exp OR ' Benazepril '/exp OR ' Cilazapril '/exp OR ' Ramipril '/exp OR 'steroid '/exp OR ' Mycophenolate mofetil '/exp OR ' azathioprine '/exp OR ' cyclosporine A '/exp OR ' tonsillectomy '/exp OR ' TSP'/exp
#2	' IgAN '/exp OR ' IgA nephropathy '/exp OR ' immunoglobulin A nephropathy '/exp OR ' IgA nephritis '/exp
#3	#1 and #2



S2. PRISMA diagram of the study selection process for the meta-analysis

S3: Table 2 Characteristics of RCTs involved in the study

Study	Patients	Renal function	Proteinuria UPE(g/d)	Sample size	Treatment	Control	Follow up	Outcome
Woo 2000	UPE > 1 g/d, Scr > 1.4 mg/dL	Scr (mg/dl) T: 2.0 ± 0.8 C: 1.8 ± 0.8	T: 2.2 ± 1.2 C: 2.1 ± 1.1	41(21/20)	Enalapril or/and Losartan	Placebo	13±5	Serum creatinine, proteinuria
Locatelli 2001	UPE 1 - 3.5 g/d, serum creatinine ≤ 1.5 mg/dL	NA	T: 2.0 ± 0.60 C: 1.9 ± 0.70	86(43/43)	Methylprednisolone: 1.0 g×3 d; prednisone: 0.5 mg/kg every other day;	supportive therapy	72	Renal function, severe adverse events
Chen 2002	Lee's IV- V, UPE > 2.0 g/d Scr < 4 mg/dL	NA	T: 3.2 ± 1.7 C: 2.9 ± 1.5	62(31/31)	MMF	prednisone	18	Clinical remission, severe adverse events
Pozzi 2004	Scr < 1.5 mg/dl, UPE 1-3.5 g/d	Scr (mg/dl) T: 1.10 (0.90 - 1.30) C: 0.98 (0.81 - 1.27)	T: 2.0 (1.6 - 2.4) C: 1.8 (1.4 - 2.4)	86(43/43)	Methylprednisolone: 1.0 g×3 d; prednisone: 0.5 mg/kg every other day;	Placebo	120	Kidney survival, proteinuria, BP
Maes 2004	UPE > 1.0 g/d, GFR 20-70 ml/min per 1.73 m ²	GFR T: 73 ± 5 C: 69 ± 7	T: 1.9 ± 0.3 C: 1.3 ± 0.4	34(21/13)	MMF: 2g/day	placebo	36	Kidney survival, proteinuria, BP
Frisch 2005	UPE > 1.0 g/d, GFR 20-70 ml/min per 1.73 m ²	GFR 38 ± 22.2 41 ± 26.3	T: 2.7 ± 1.6 C: 2.7 ± 1.4	32(17/15)	MMF: 2g/day RAS	RAS	24	Clinical remission, eGFR, ESRD, adverse events
Li 2006	UPE > 1 g/d, Scr < 2.8 mg/dL	GFR T: 87 ± 36 C: 78 ± 38	T: 1.8 ± 1.2 C: 2.3 ± 1.7	109(54/55)	RAS	Placebo	24	Increase ≥50% in serum creatinine, adverse events
Coppo 2007	UPE 1 - 3.5 g/d, GFR > 50 ml/min per 1.73 m ²	GFR T: 116.0 ± 24.3 C: 109.2 ± 18.0	T: 1.61 ± 0.70 C: 1.87 ± 0.74	174(86/88)	Benazepril	Placebo	38	Clinical remission loss of 30% of initial creatinine clearance [CrCl

Woo 2007	UPE > 1 g/d, Scr > 1.6 mg/dl	Scr (mg/dL) 1.84 ± 0.26	2.3 ± 0.8	75(37/38)	Enalapril or/and Losartan	Placebo	60	Clinical remission, Renal function
Horita 2007	UPE 1.0 - 2.6 g/d, Ccr >50 mL/min/1.73m ²	GFR 38 ± 22.2 41 ± 26.3	1.6 ± 0.5	38(20/18)	Prednisolone, 30 mg/dL for two months, then tapered; losatan	Prednisolone	24	Increase ≥50% in serum creatinine, decrease ≥50% in proteinuria
Lv 2009	Proteinuria 1 - 5 g/d, GFR > 30 ml/min per 1.73 m ²	Scr (mg/dL) 1.1 ± 0.3	2.26 ± 0.85	63(33/30)	Prednisone: 0.8–1 mg/kg per day for 8 wk, then tapered; cilazapril	Cilazapril	28	Kidney survival, 25% decrease in eGFR or 50% proteinuria reduction
Huang 2009	UPE 1.0 - 3.0 g/d, Scr ≤ 353.6 umol/L	Scr (umol/L) T: 99.34 ± 12.33 C: 97.34 ± 12.25	T: 1.78 ± 1.11 C: 1.82 ± 1.23	36(20/16)	Azathioprine + benazepril	Benazepril	9	Clinical remission, adverse events
Manno 2009	Proteinuria > 1 g/d, GFR > 50 ml/min per 1.73 m ²	Scr (mg/dL) 1.07 ± 0.29	T: 1.7 (1.2 - 2.5) C: 1.5 (1.4 - 2.3)	97 (48/49)	Prednisone: initial, 1 mg/kg per day for 2 mo, then tapered; ramipril	Ramipril	96	Doubleline of serum creatine or ESRD, 24-h proteinuria < 1g/d, BP
Tang 2010	Proteinuria > 1.0 g/d, Scr < 300 umol/L	GFR T: 52.5 ± 4.40 C: 50.0 ± 4.51	T: 1.8 ± 0.21 C: 1.87 ± 0.28	40	MMF 2g/day or 1.5 g/day for 6 months	Control	72	Reduction of proteinuria by 50%
Kuang 2010	Proteinuria 1 - 3.5 g/d Scr ≤ 135 mg/dL	Scr (umol/L) T: 78.02 ± 11.05 C: 78.04 ± 12.05	T: 0.39 ± 0.09 C: 0.38 ± 0.09	64 (32/32)	Azathioprine + benazepril	Benazepril	6	Clinical remission
Pozzi 2011	Proteinuria ≥ 1 g/d, Scr ≤ 2.0 mg/dL	GFR T: 72 (53 - 88) C: 63 (44 - 85)	T: 2.1 (1.5 - 3.5) C: 2.0 (1.5 - 2.7)	207(101/10 7)	Azathioprine + methylprednisolone	Methylpredni solone	60	Kidney survival, Clinical remission, adverse events
Stangou 2011	Proteinuria > 1 g/d, GFR ≥ 30 ml/min per 1.73 m ²	GFR T: 57.4 ± 28.7 C: 52.0 ± 26.7	T: 1.41 ± 1.29 C: 2.4 ± 0.9	22(12/10)	Azathioprine + methylprednisolone	Methylpredni solone	18	Clinical remission, adverse events

Li 2011	Proteinuria 1 - 3.5 g/d Scr ≤ 135 mg/dL	Scr (umol/L) T: 94.11 ± 11.52 C: 92.56 ± 9.53	T: 2.4 ± 1 C: 2.4 ± 0.9	42(21/21)	Azathioprine + benazepril	benazepril	12	Kidney survival, proteinuria, BP
Kamei 2011	Proteinuria 1 - 3.5 g/d	CCr (ml/min) T: 144 ± 52 C: 152 ± 47	T: 2.09 ± 1.78 C: 1.35 ± 1.26	74(40/34)	Prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 24 months	Heparin-warfarin, and dipyridamole	120	Kidney survival, proteinuria, BP
Pozzi 2013	Proteinuria ≥ 1 g/d, Scr > 2.0 mg/dL	GFR T: 28 (22 - 32) C: 25 (20 - 23)	T: 3.2 (1.7 - 5.5) C: 2.0 (1.5 - 3.2)	46(26/20)	Azathioprine + methylprednisolone	Methylprednisolone	60	Kidney survival, Clinical remission, adverse events
Liu 2014	Proteinuria > 1 g/d, GFR > 30 ml/min per 1.73 m ²	GFR T: 78.9 ± 23.1 C: 81.6 ± 18.4	T: 3.2 ± 3.3 C: 2.6 ± 2.0	48(23/25)	Cyclosporine A + methylprednisolone	methylprednisolone	12	Kidney survival, Clinical remission, adverse events
Kawamura 2014	Proteinuria 1 - 3.5 g/d, Scr ≤ 1.5 mg/dL	GFR T: 75 ± 24 C: 69 ± 22	T: 1.6 ± 0.5 C: 1.6 ± 0.6	72(33/39)	TSP	methylprednisolone	24	Disappearance of proteinuria, clinical remission, eGFR
Xu 2014	UPE 1 - 3.5 g/d, eGFR ≥ 60 ml/min per 1.73 m ²	GFR T: 75.1 ± 24 C: 76.7 ± 23.8	T: 2.07 ± 0.9 C: 2.01 ± 0.8	96(48/48)	Cyclosporine A (3 mg/kg/d) + prednisolone (0.6-0.8 mg/kg/d; maximum, 40 mg/d),	prednisolone(maximum, 60 mg/d)	12	Clinical remission, adverse events
Rauen 2015	UPE 0.75 - 3.5 g/d, eGFR ≥ 30 ml/min per 1.73 m ²	GFR T: 61.1 ± 29.0 C: 57.4 ± 24.9	T: 1.8 ± 0.8 C: 1.6 ± 0.7	162(82/80)	methylprednisolone + cyclophosphamide + azathioprine + RAS;	RAS	36	Clinical remission, eGFR, ESRD, adverse events
Lu 2016	UPE > 2 g/d,, Scr ≤ 135 mg/dL	Scr (umol/L) T: 92.86 ± 1.28 C: 92.78 ± 1.77	T: 4.36 ± 1.26 C: 4.38 ± 1.24	154(77/77)	Cyclosporine A + methylprednisolone	methylprednisolone	6	Clinical remission, adverse events
Katafuchi 2016	UPE 1 - 3.5 g/d, Scr ≤ 1.5 mg/dL	GFR T: 74 ± 26	T: 1.7 ± 1.1 C: 1.7 ± 1.0	59(27/32)	TSP	SP	58	Clinical remission

		C: 67 ± 22						
Yang 2016	UPE 1 - 3.5 g/d, Scr ≤ 1.5 mg/dL	GFR T: 95.00 ± 32.14 C: 89.02 ± 37.29	T: 0.94 ± 1.03 C: 1.36 ± 1.05	98(49/49)	TSP	SP	48	Clinical remission
Hou 2017	UPE ≥ 1.0 g/d, eGFR > 30 mL/min/1.73 m ²	GFR 90.2 (64.4 - 109.6) 94.3 (72.2 - 111.4)	2.37 ± 1.23 2.47 ± 2.01	174(86/88)	MMF, 1.5 g/d, prednisone, 0.4 - 0.6 mg/kg/d.	prednisone, 0.8 - 1.0 mg/kg/d	6	complete remission rate, ESRD, doubling of serum creatinine level, severe adverse events
Lv 2017	UPE ≥ 1 g/d, eGFR 20 - 120 mL/min/1.73 m ²	GFR 59.4 ± 25.0	2.40 ± 1.94	262(136/12 6)	methylprednisolone (0.6-0.8 mg/kg/d; maximum, 48 mg/d), RAS	RAS	60	Clinical remission, ESRD, death due to kidney failure, severe adverse events

Abbreviations: UPE, urinary protein excretion; Scr, serum creatinine; T, treatment group; C, control group; Ccr, creatinine clearance rate; UPCR, urinary protein-creatinine ratio; GFR, glomerular filtration rate; MMF, Mycophenolate mofetil; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; TSP, tonsillectomy with steroid pulse therapy; SP, Steroid pulse.

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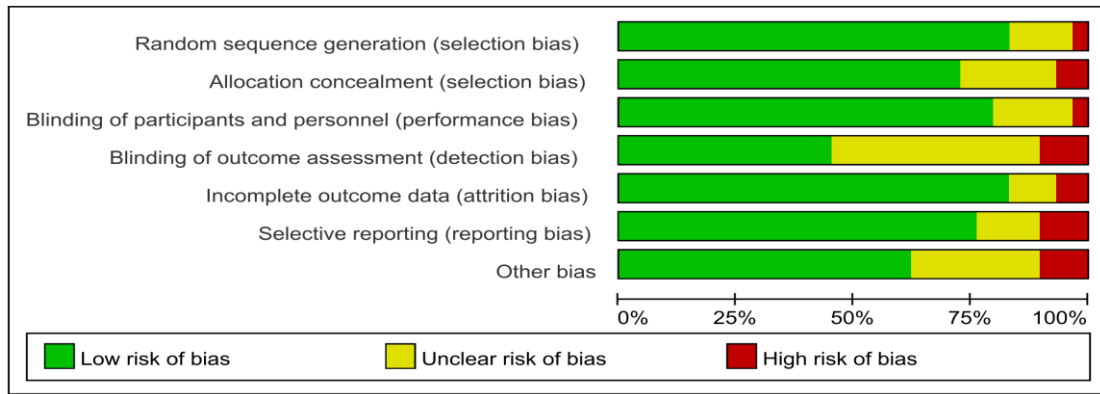
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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen 2002	+	+	+	?	+	?	+
Coppo 2007	+	+	+	?	+	+	+
Frisch 2005	+	+	?	+	+	+	?
Horita 2007	+	?	+	+	?	+	+
Hou 2017	+	+	+	+	+	+	+
Huang 2009	?	+	+	+	+	?	?
Kamei 2011	?	+	+	+	+	+	+
Katafuchi 2016	+	+	?	+	+	+	+
Kawamura 2014	+	?	+	+	+	+	+
Kuang 2010	+	+	+	?	?	+	+
Li 2006	+	+	+	?	?	+	+
Li 2011	+	+	+	?	+	+	+
Liu 2014	+	+	?	+	+	+	+
Locatelli 2001	+	+	+	?	+	+	+
Lu 2016	?	+	+	+	+	+	?
Lv 2009	+	+	+	?	+	+	?
Lv 2017	+	+	+	+	+	+	+
Maes 2004	?	+	+	+	+	+	+
Manno 2009	+	+	+	?	+	+	?
Pozzi 2004	+	+	+	?	+	?	+
Pozzi 2011	+	?	+	+	+	+	?
Pozzi 2013	+	+	?	+	+	+	?
Rauen 2015	+	+	+	?	+	+	+
Stangou 2011	+	+	+	+	+	+	+
Tang 2010	+	?	+	?	+	+	+
Woo 2000	+	?	?	+	+	+	+
Woo 2007	+	+	+	?	+	+	?
Xu 2014	+	?	+	+	+	+	+
Yang 2016	+	+	+	?	+	?	+

S4. Risk of bias of included studies.

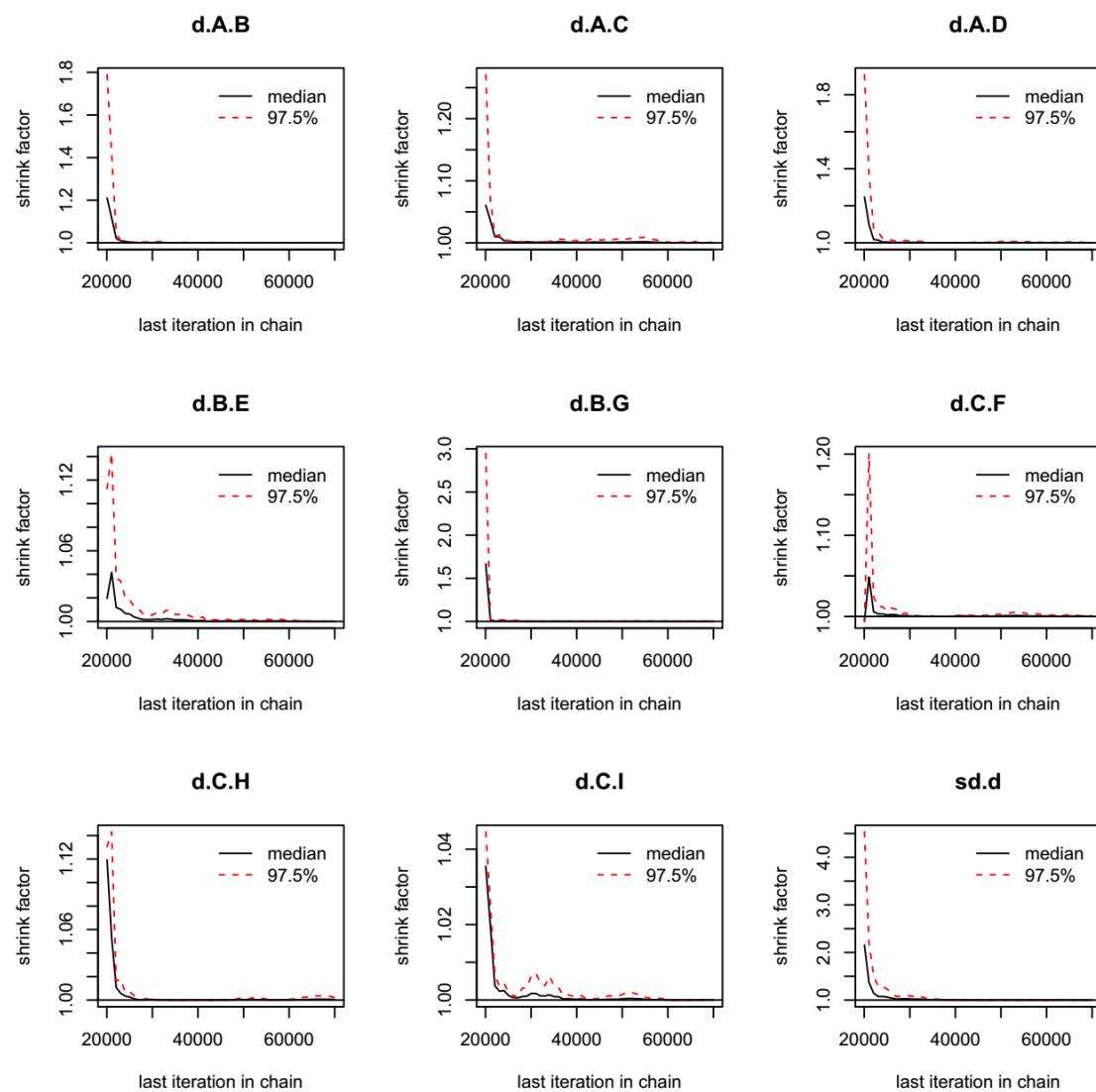
Placebo	0.17 (0.04, 0.66)	0.24 (0.06, 0.84)	0.6 (0.1, 4.4)		
0.14 (0.039, 0.43)	RASi		3.1 (0.18, 70)	0.34 (0.09, 0.94)	
0.39 (0.12, 1.6)	2.8 (0.61, 18)	Steroid	6.7e-16 (1.2e-38, 0.05)	2.6e-11 (1.5e-32, 0.055)	
0.39 (0.084, 1.6)	2.8 (0.52, 15)	1.0 (0.14, 5.3)	MMF		
0.041 (0.006, 0.17)	0.29 (0.08, 0.82)	0.11 (0.01, 0.57)	0.10 (0.01, 0.69)	RASi+ steroid	
0.37 (0.05, 3.2)	2.6 (0.31, 32)	0.95 (0.19, 4.5)	0.94 (0.10, 13)	8.9 (0.99, 160)	AZA + steroid

S5. Table 3a. Summary of results from network meta-analysis (on the lower triangle) and traditional pairwise meta-analysis (on the upper triangle) on ESRD and doubling of serum creatinine level. On the lower triangle, the column-defining treatment is compared to the row-defining treatment, and odds ratios (OR) > 1 favor the column-defining treatment. On the upper triangle, the row-defining treatment is compared to the column-defining treatment, and OR > 1 favor the row-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold. Direct comparisons within 2 inconsistent loops are underlined. Abbreviations: RASi, renin-angiotensin system inhibitors; MMF, mycophenolate mofetil; AZA, azathioprine.

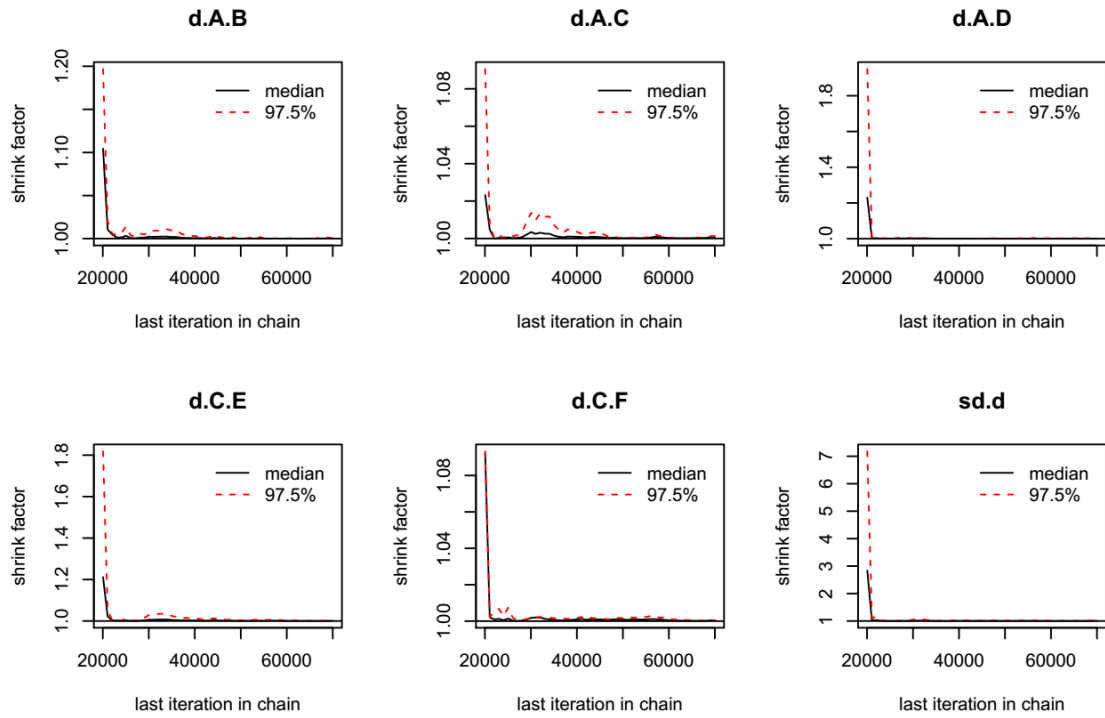
Placebo	0.86 (0.11, 8.1)	1.5 (0.29, 9.3)	3.3 (0.42, 43)					
1.6 (0.33, 11)	RASi		0.49 (0.03, 6.9)					
1.2 (0.32, 4.5)	0.71 (0.09, 3.0)	Steroid	2.6 (0.54, 24)					
2.3 (0.65, 11)	1.4 (0.22, 8.7)	2.0 (0.59, 9)	MMF					
3.8 (0.60, 38)	2.3 (0.88, 7.4)	3.3 (0.41, 40)	1.6 (0.21, 15)	RASi + steroid				
0.31 (0.007, 7.4)	0.19 (0.003, 5.8)	0.27 (0.007, 4.7)	0.13 (0.003, 3)	0.08 (0.001, 2.8)	TSP			
13 (0.93, 240)	7.4 (0.93, 76)	11 (0.65, 240)	5.4 (0.13, 100)	3.2 (0.28, 39)	41 (0.74, 4500)	AZA + RASi		
1.9 (0.36, 13)	1.2 (0.11, 11)	1.7 (0.55, 5.9)	0.85 (0.13, 4.7)	0.52 (0.03, 5.6)	6.3 (0.29, 290)	0.16 (0.006, 3.4)	AZA + steroid	
1.3 (0.24, 7.8)	0.82 (0.07, 7.1)	1.2 (0.37, 3.6)	0.59 (0.08, 3.0)	0.36 (0.02, 3.7)	4.3 (0.20, 190)	0.11 (0.004, 2.2)	0.69 (0.13, 3.4)	CyA+ steroid

S5. Table 3b. Summary of results from NMA (on the lower triangle) and traditional pairwise meta-analysis (on the upper triangle) on serious adverse events. On the lower triangle, the column-defining treatment is compared to the row-defining treatment, and odds ratios (OR) > 1 favor the column-defining treatment. On the upper triangle, the row-defining treatment is compared to the column-defining treatment, and OR > 1 favor the row-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold. Direct comparisons within 2 inconsistent loops are underlined. Abbreviations: RASi, renin-angiotensin system inhibitors; MMF, mycophenolate mofetil; TSP, tonsillectomy combined with steroid pulse therapy; AZA, azathioprine; CyA, cyclosporine A.

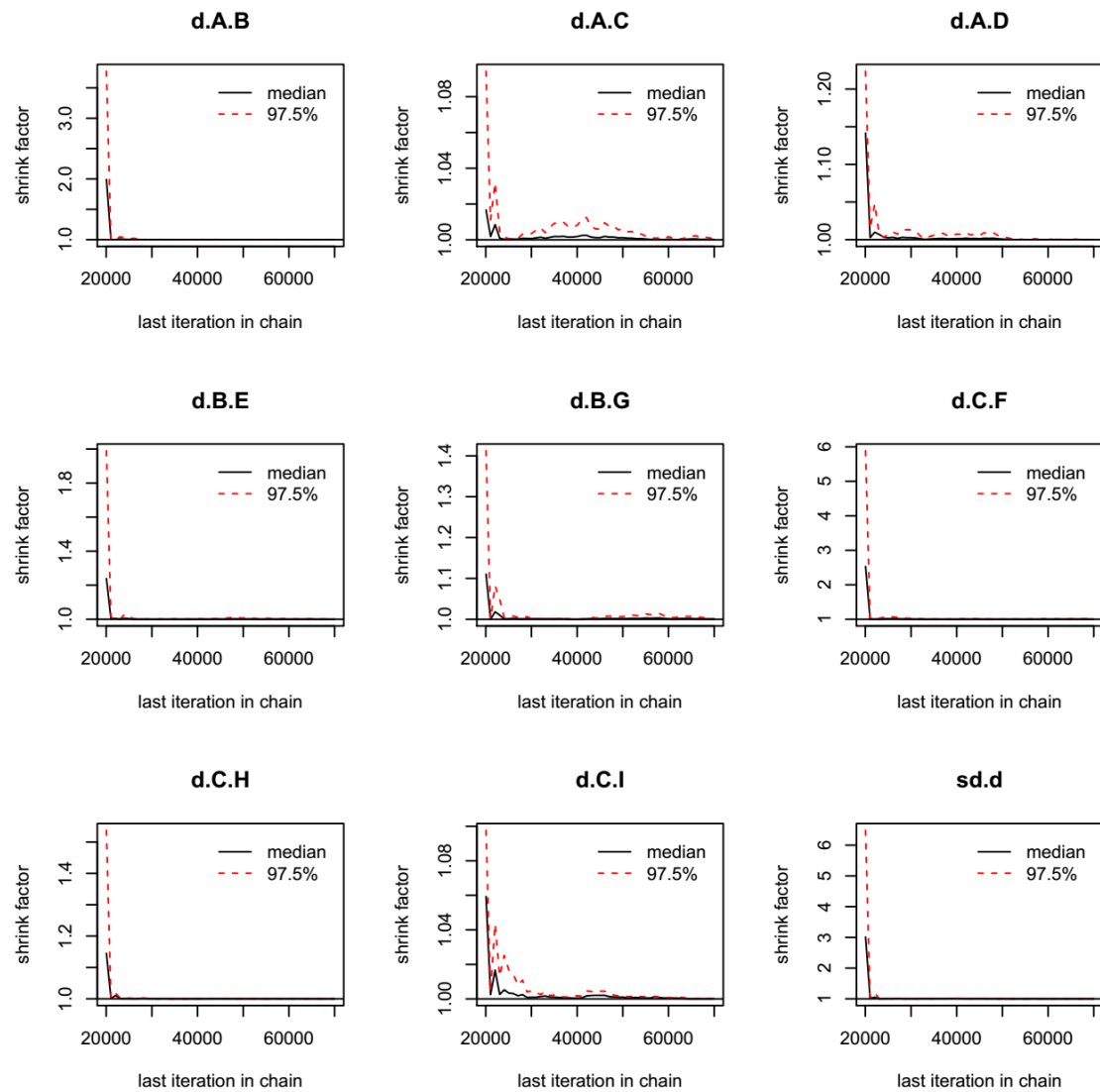
S6. Diagnostic and trace plots



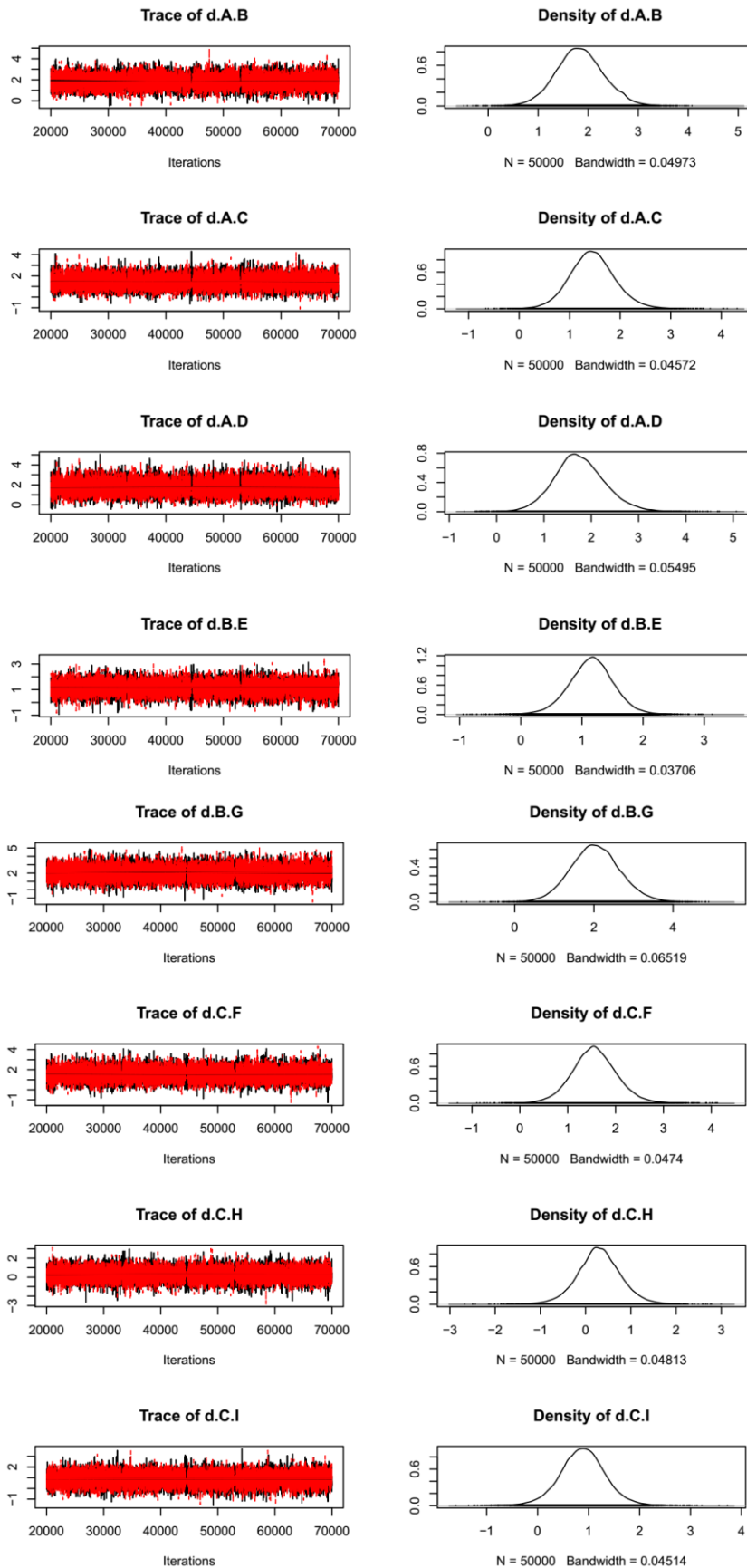
S6-a. Diagnostic plot for clinical remission. (A, placebo; B, RASi; C, steroid; D, MMF; E, steroid + RASi; F, TSP; G, AZA + RASi; H, AZA + steroid; I, CyA + steroid)



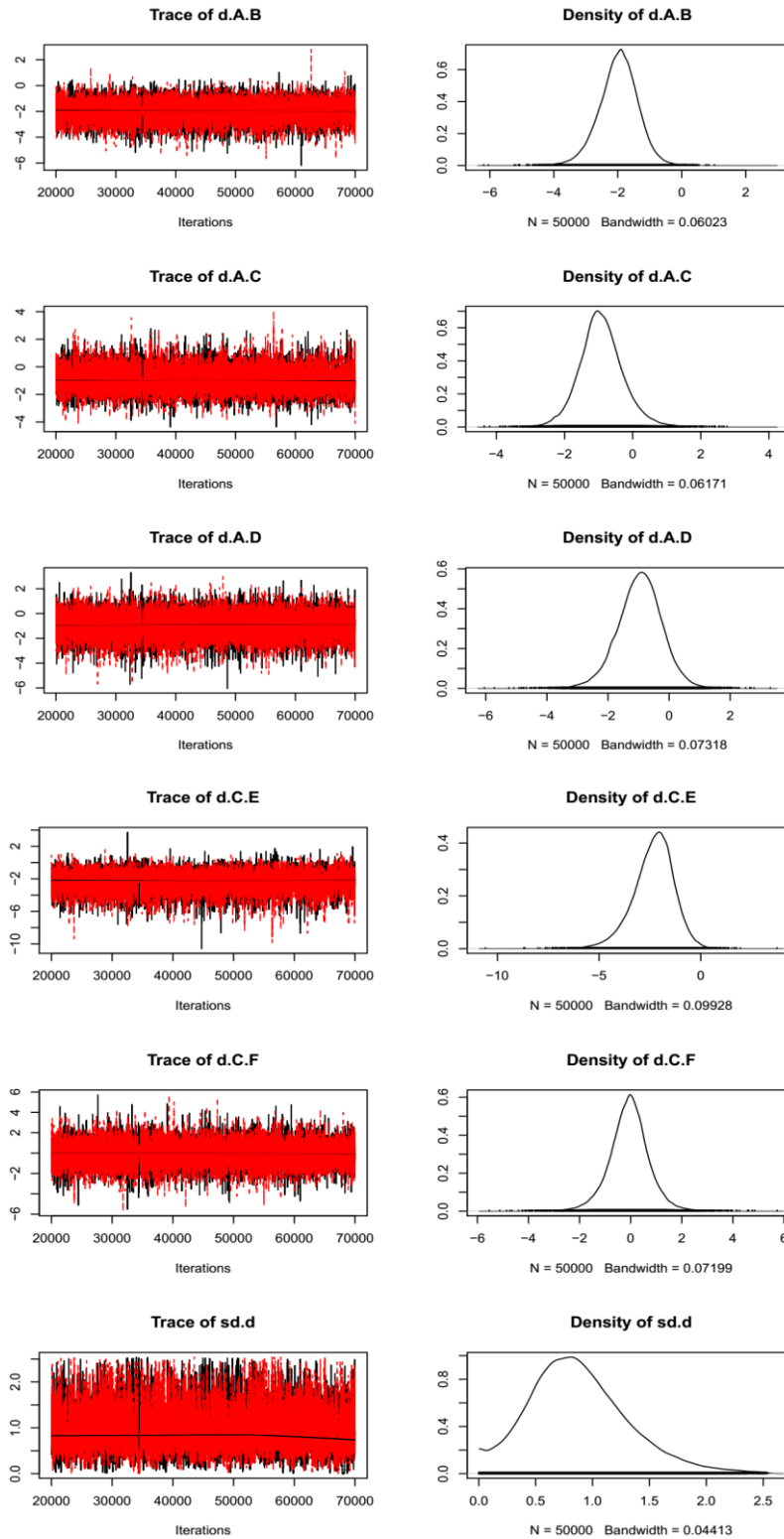
S6-b. Diagnostic plot for ESRD or doubling of serum creatinine level. (A, placebo; B, RASi; C, steroid; D, MMF; E, RASi + steroid; F, AZA + steroid)



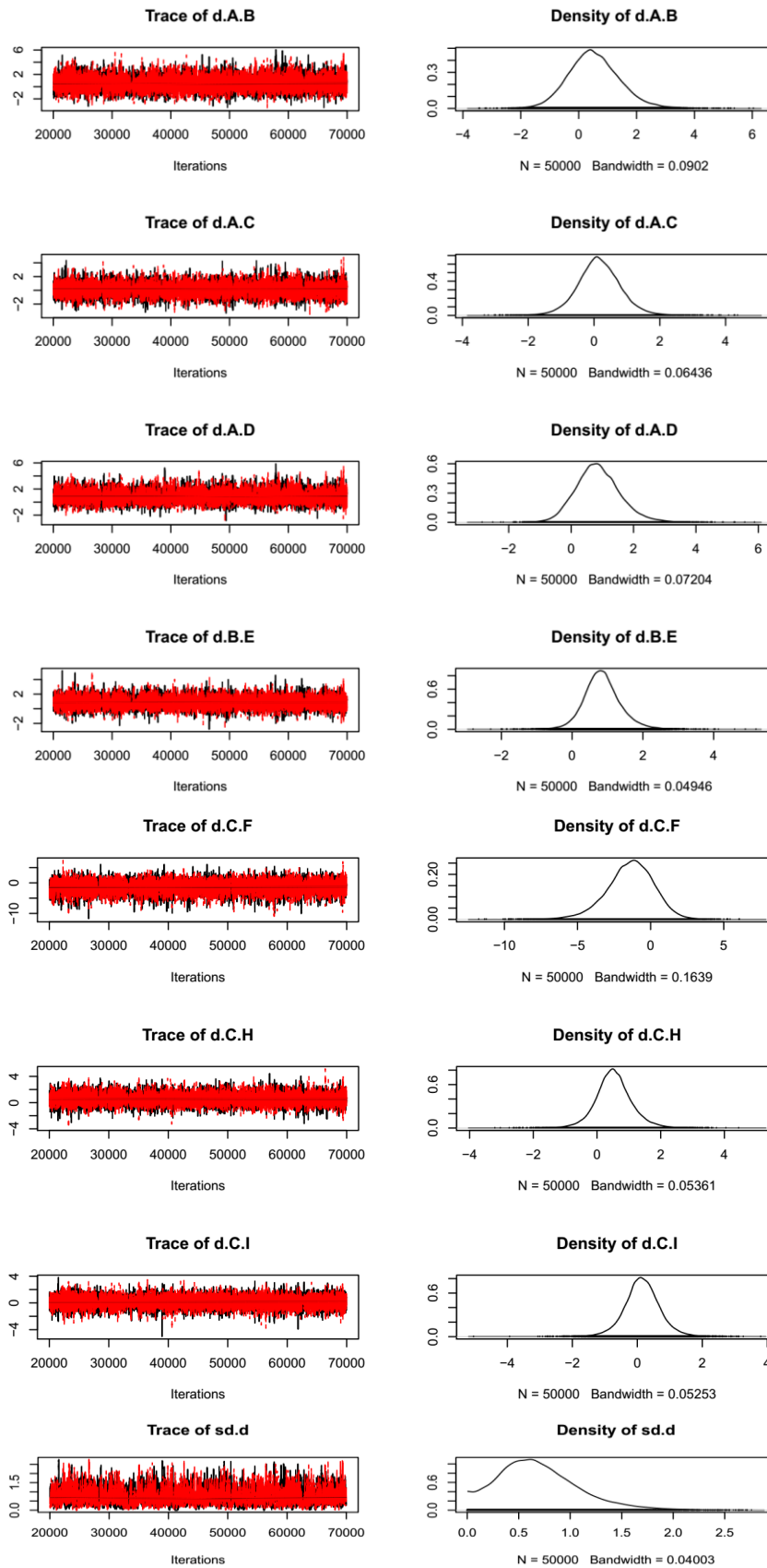
S6-c. Diagnostic plot for severe adverse events. (A, placebo; B, RASi; C, steroid; D, MMF; E, steroid + RASi; F, TSP; G, AZA + RASi; H, AZA + steroid; I, CyA + steroid)



S6-A. Trace plots for clinical remission. (A, placebo; B, RASi; C, steroid; D, MMF; E, steroid + RASi; F, TSP; G, AZA + RASi; H, AZA + steroid; I, CyA + steroid)

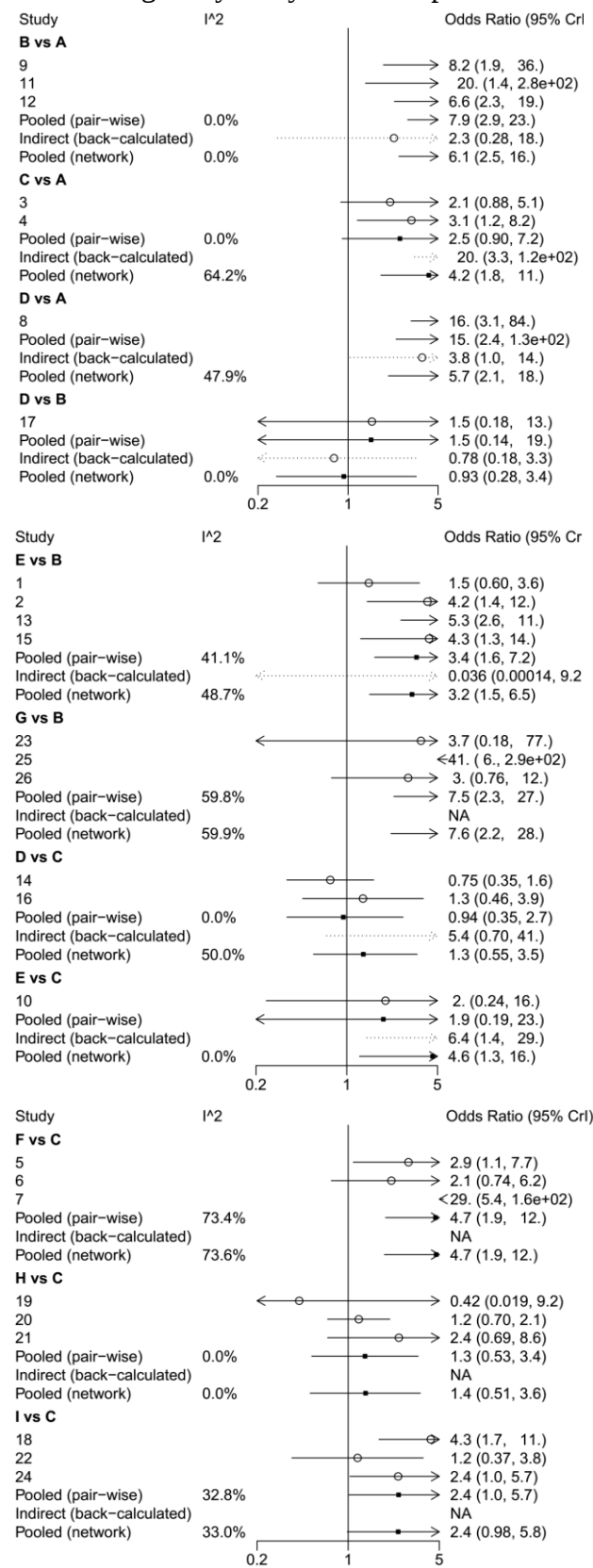


S6-B. Trace plots for ESRD or doubling of serum creatinine level. (A, placebo; B, RASi; C, steroid; D, MMF; E, RASi + steroid; F, AZA + steroid)

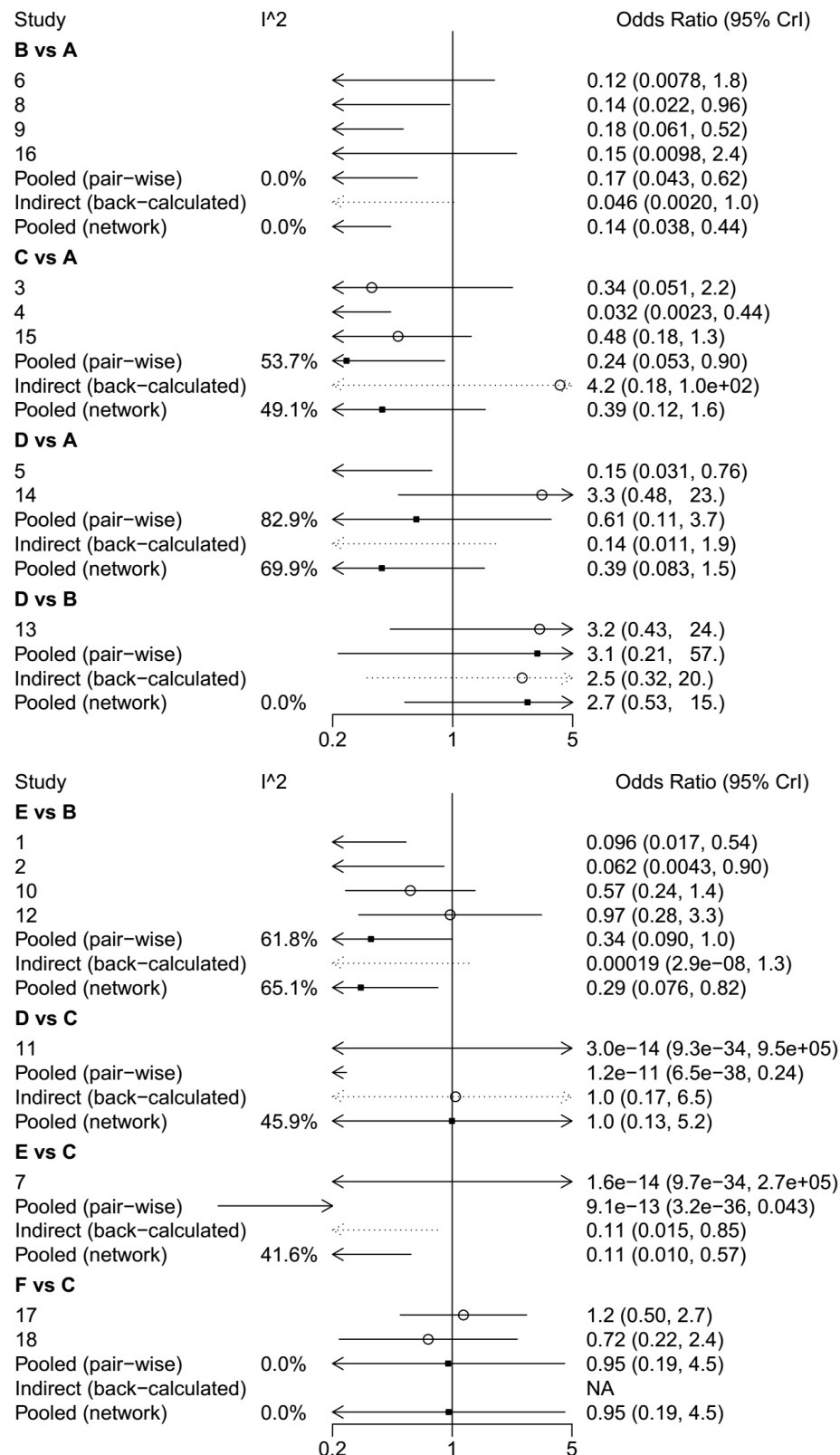


S6-C. Trace plots for severe adverse events. (A, placebo; B, RASi; C, steroid; D, MMF; E, steroid + RASi; F, TSP; G, AZA + RASi; H, AZA + steroid; I, CyA + steroid)

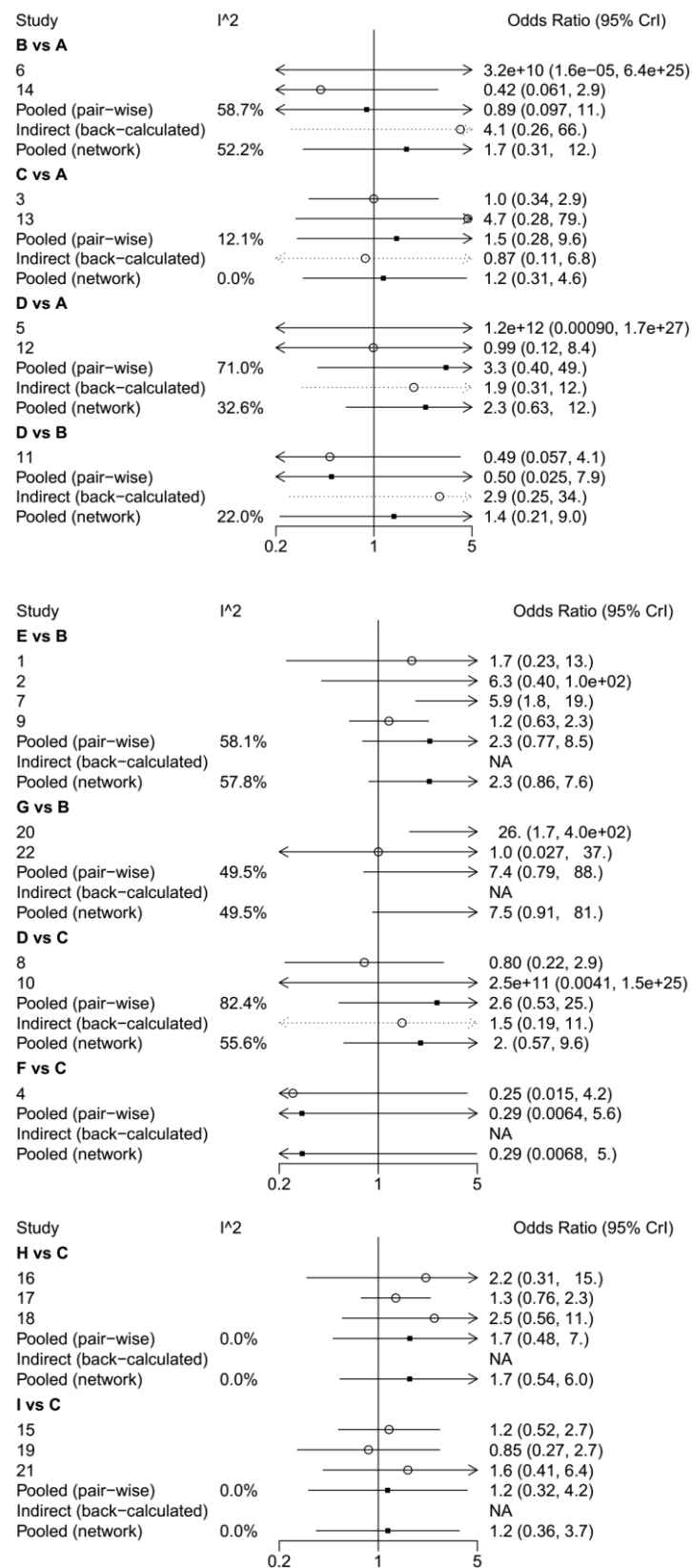
S7. Heterogeneity analysis on end points



S7-A. Heterogeneity analysis on clinical remission. (A, placebo; B, RASi; C, steroid; D, MMF; E, RASi + steroid; F, RASi + antiplatelet; G, TSP)

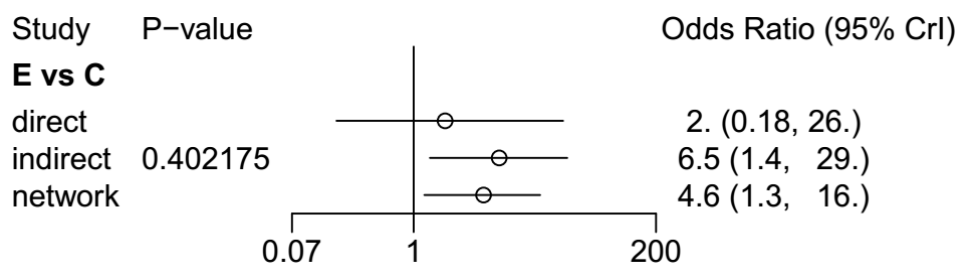
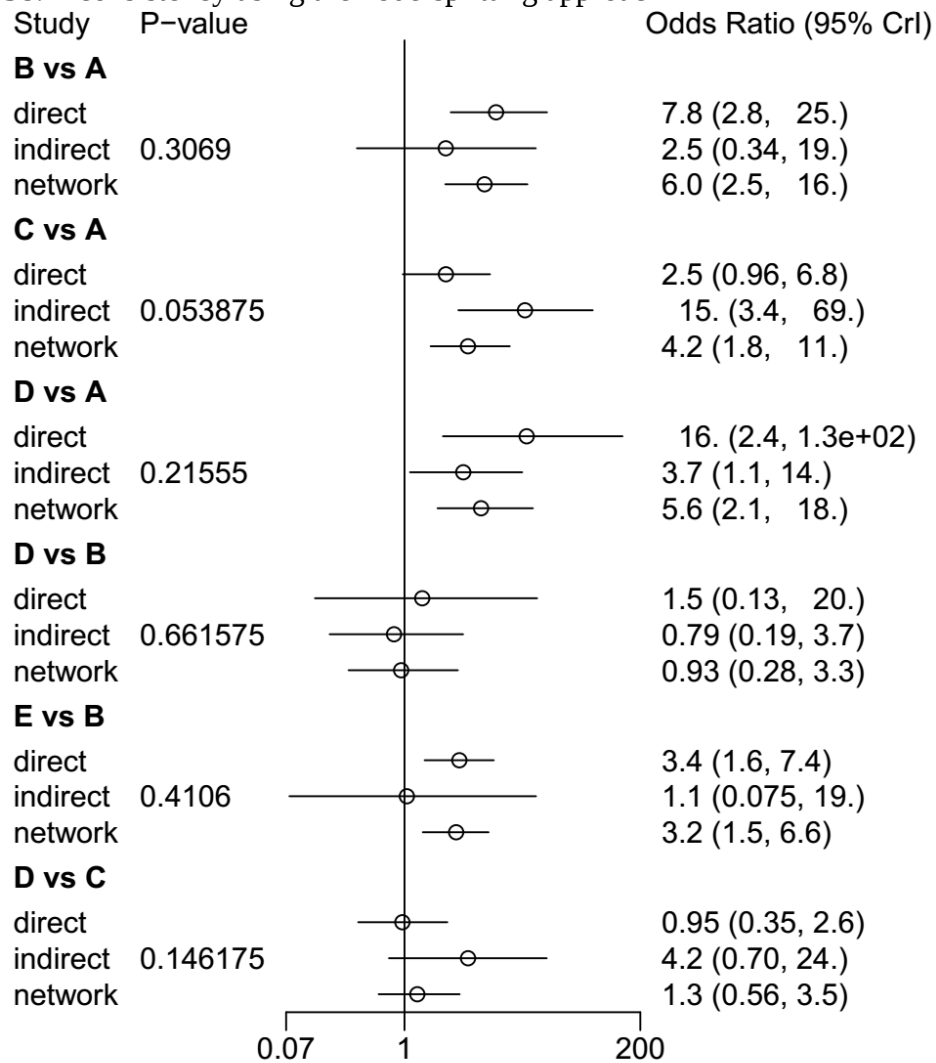


S7-B. Heterogeneity analysis on ESRD or doubling of serum creatinine level. (A, placebo; B, RASi; C, steroid; D, MMF; E, RASi + steroid; F, AZA + steroid)

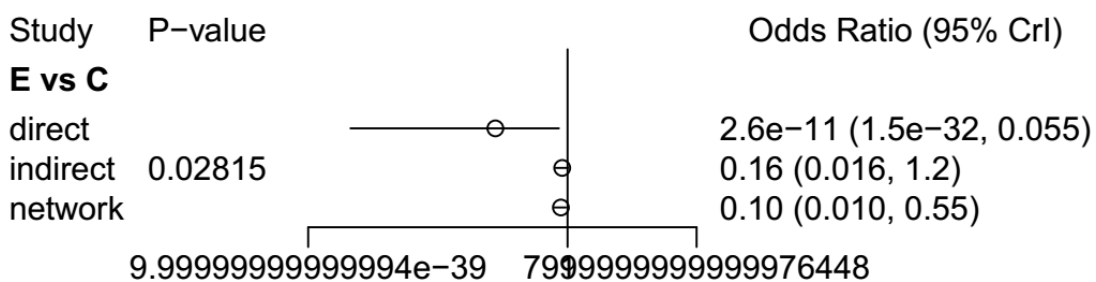
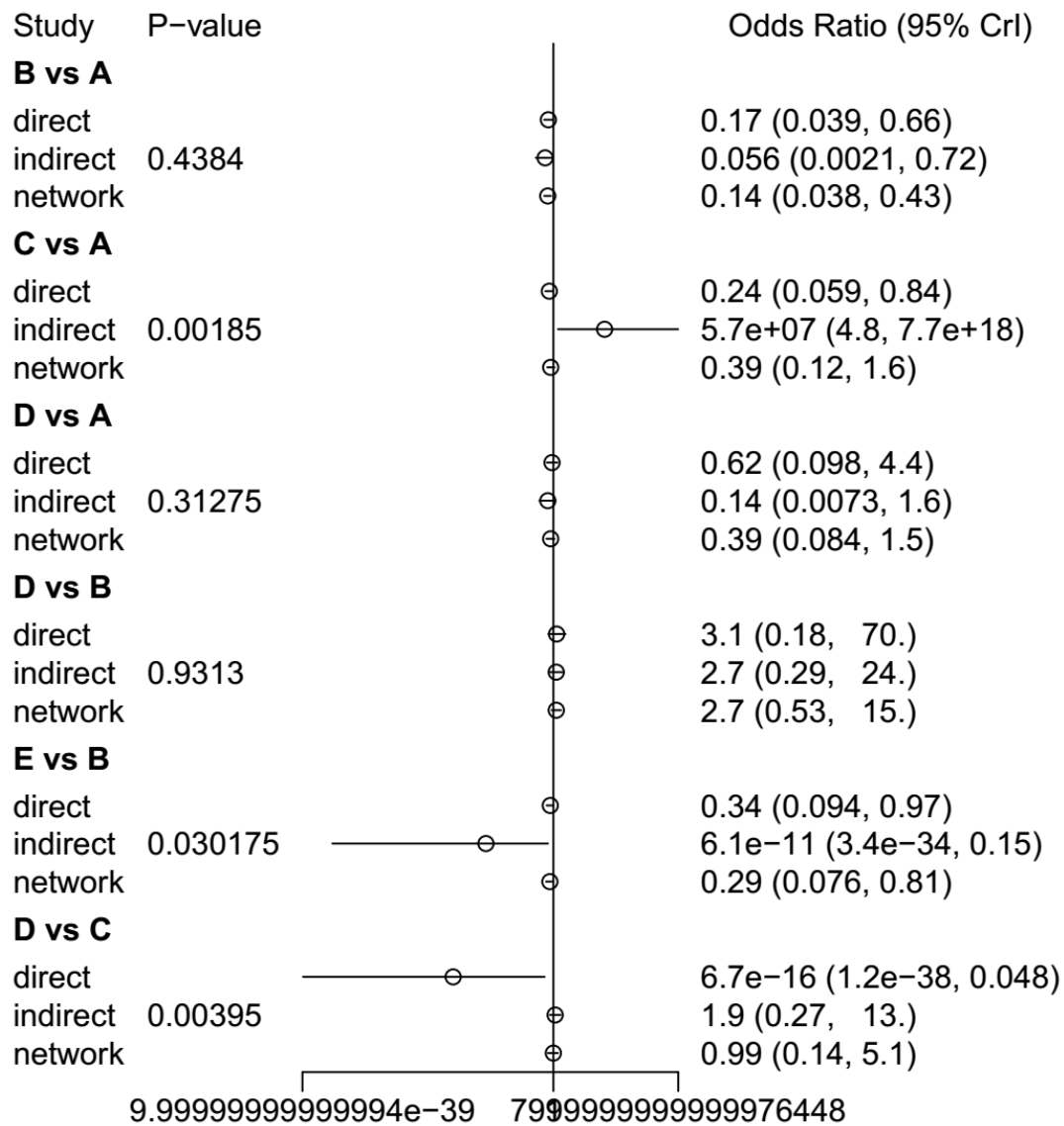


S7-C. Heterogeneity analysis on severe adverse events. (A, placebo; B, RASi; C, steroid; D, MMF; E, steroid + RASi; F, TSP; G, AZA + RASi; H, AZA + steroid; I, CyA + steroid)

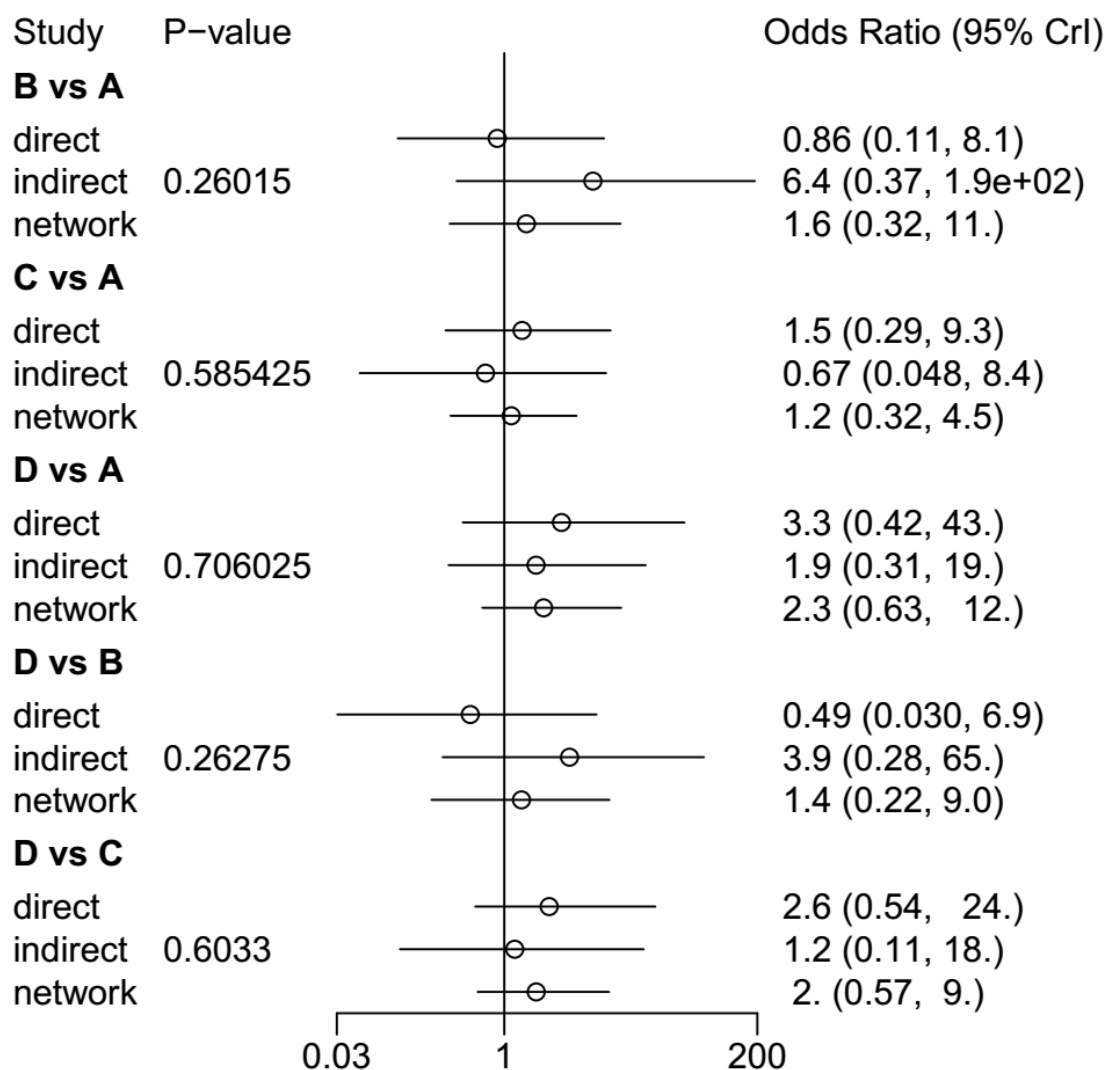
S8. Inconsistency using the node-splitting approach



S8-A. Inconsistency using the node-splitting approach for clinical remission. (A, placebo; B, RASi; C, steroid; D, MMF; E, steroid + RASi; F, TSP; G, AZA + RASi; H, AZA + steroid; I, CyA + steroid)

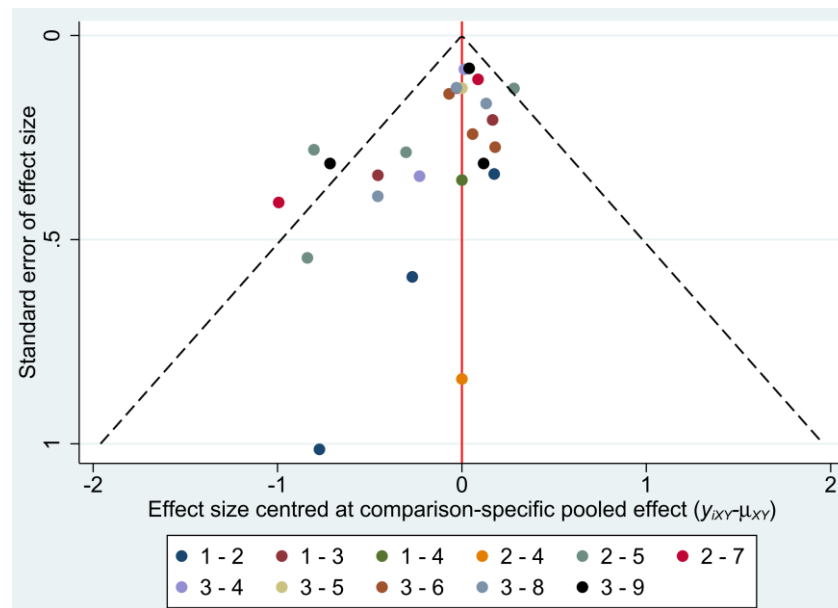


S8-B. Inconsistency using the node-splitting approach for ESRD or doubling of serum creatinine level. (A, placebo; B, RASi; C, steroid; D, MMF; E, RASi + steroid; F, AZA + steroid)



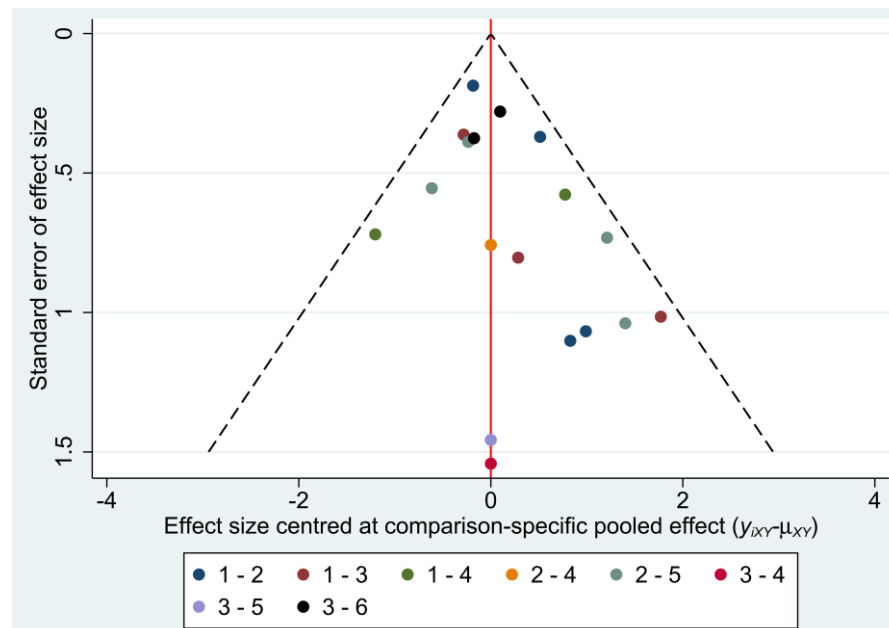
S8-C. Inconsistency using the node-splitting approach for severe adverse events. (A, placebo; B, RASi; C, steroid; D, MMF; E, steroid + RASi; F, TSP; G, AZA + RASi; H, AZA + steroid; I, CyA + steroid)

S9. Publication bias of funnel plot



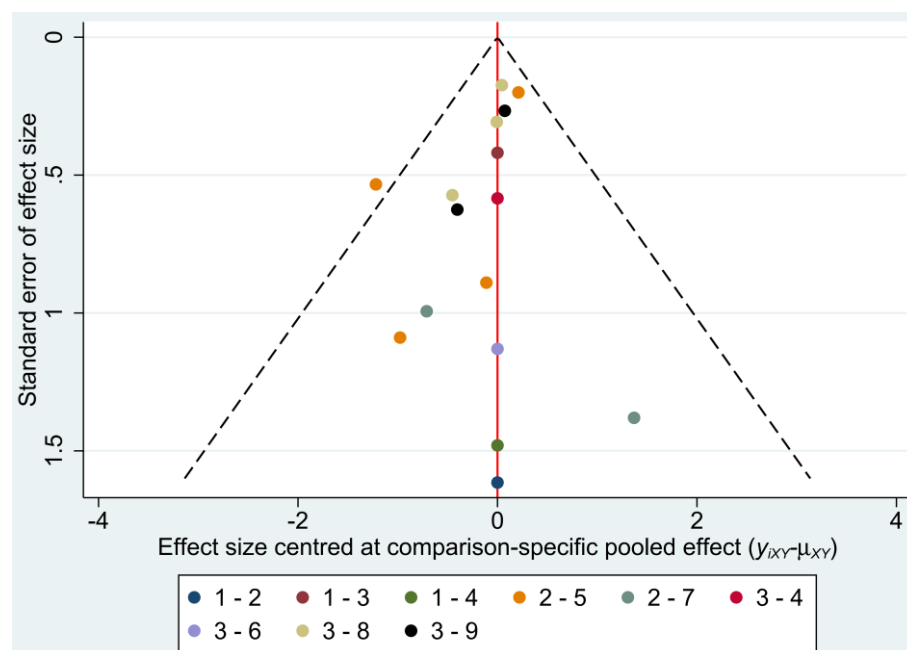
S9-A. Funnel plot for clinical remission.

(1, placebo; 2, RASi; 3, steroid; 4, MMF; 5, RAS + steroid; 6, TSP; 7, AZA + RASi; 8, AZA + steroid; 9, CyA + steroid)



S9-B. Funnel plot for ESRD or doubling of serum creatinine level

(1, placebo; 2, RASi; 3, steroid; 4, MMF; 5, RAS + steroid; 6, AZA + steroid)



S9-C. Funnel plot for severe adverse events.

(1, placebo; 2, RASi; 3, steroid; 4, MMF; 5, RAS + steroid; 6, TSP; 7, AZA + RASi; 8, AZA + steroid; 9, CyA + steroid)