

Supplementary Table S1: Criteria converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)

Good quality	3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality	2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality	0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Supplementary Table S2: Characteristics of studies included in the systematic review and meta-analysis.

No.	Author [year]	Country	Original study design	N	Age (years)	% Female	% Race (Caucasian/Asian/African/unknown)	Pathologic classification					Serum Cr (mg/dL)	Induction (I) or Maintenance (M) phase	Type of MPA	Initial dose of MPA (g/day)	Mean \pm SD AUC (mg.h/L)	Mean \pm SD C ₀ (mg/L)	Steroid	% response	Definition of clinical response	Aim of study	Main findings	Recommended MPA parameter level
								I or II	III or IV	V	mixed	unknown												
1	Roland et al. ¹⁸ [2009]	France	Cross sectional (single measurement)	20	41 \pm 15	65	N/A	-	9	1	-	-	1.02 \pm 0.36	I, M	MMF 100%	1.6 \pm 0.45	AUC ₀₋₄ 28.4 \pm 13.6 (30.8 \pm 29.5 months after treatment)	N/A	N/A	N/A	No definition	Evaluate variations in PK for MPA and relationship between MPA-AUC and disease activity	- There was a significant relationship between MPA trough levels and complement level. - High inter-individual variability of MPA-AUC ₀₋₄ in patients was found.	N/A
2	Lertdumrongluk et al. ²¹ [2010]	Thailand	Prospective cohort (single measurement)	18	33 \pm 7.7	88.9	0/100/0/0	-	13	-	5	-	1.26 \pm 0.56	I	MMF 67%, EC-MPS 33%	1.42 \pm 0.19 1.26 \pm 0.20	AUC ₀₋₁₂ 52.8 \pm 25.4 (1 month after treatment)	2.37 \pm 1.34	Prednisolone 0.7 mg/kg/day then reduce by 5 mg/day every 2 weeks until 5 mg/day (cumulative = 3400 \pm 461 mg)	61.1	Treatment response = 1. normal or increased eGFR \geq 25% 2. no active urine sediments (RBC $<$ 5/HPF), and 3. 50% reduction of 24-h urine protein and $<$ 2g/day)	Determine the correlation between MPA levels of MMF/EC-MPS and response in patients with proliferative LN	- Mean MPA-AUC was significantly higher in responding patients than those not responding. - Successful treatment was seen in patients with AUC $>$ 45 mg.h/L. - AUC was correlated with C ₀ and C ₁ .	AUC ₀₋₁₂ \geq 45 mg.h/L
3	Zahr et al. ²⁰ [2010]	France	Cross sectional (single measurement)	71	34.1 \pm 10.0	85.9	62/11/27/0	-	-	-	-	N/A	N/A	N/A	MMF 100%	1.87 \pm 0.53	AUC ₀₋₁₂ 39.3 \pm 18.0 (at least 10 months after treatment)	N/A	Prednisolone in active SLE group 18.8 \pm 10.8 mg/day vs inactive SLE 14.8 \pm 8.5 mg/day	63.4	Active SLE = SLEDAI \geq 6, BILAG A or B Inactive SLE = SLEDAI $<$ 6	Study correlations between MPA-AUC ₀₋₁₂ and SLE activity	- Mean \pm SD AUC ₀₋₁₂ in active SLE group was significantly lower than that in the inactive SLE group (26.8 \pm 13.6 vs 46.5 \pm 16.3 mg.h/L). - MPA AUC ₀₋₁₂ threshold value of 35 mg.h/L was associated with lowest risk of active SLE	AUC ₀₋₁₂ \geq 35 mg.h/L
4	Sagecal-Gironella et al. ³¹ [2011]	US	Prospective cohort (single measurement)	19	16.9 \pm 4.0	94.7	42/0/58/0	-	-	-	-	N/A	N/A	N/A	MMF 100%	1.97 \pm 0.63	AUC ₀₋₁₂ 32 \pm 18.1 (1.5 \pm 1.4 years after treatment)	N/A	At first visit: Prednisolone (18/19) Dose 17.2 \pm 10.4 mg/day Methylprednisolone (3/19) Dose not mentioned	78.9	Response = reduction in Mean time adjusted BILAG scores	Characterize PK and PD of MPA and explore relationship between MPA-PK and childhood SLE disease activity	- Large inter-patient variability in AUC was observed. - AUC ₀₋₁₂ \geq 30 mg.h/L associated with decreased BILAG scores.	AUC ₀₋₁₂ \geq 30 mg.h/L
5	Daleboudt et al. ¹² [2013]	Netherlands	Retrospective cohort (two measurements)	16	33.2 \pm 12.1	93.8	75/0/0/25	-	16	-	-	-	69.3 \pm 19.4	M	MMF 100%	1.9 \pm 0.29	AUC ₀₋₁₂ 69.3 \pm 19.4 (6.6 \pm 7.2 months after treatment)	N/A	N/A	87.5	Complete response (CR) = proteinuria $<$ 0.5 g/day and stable serum Cr or $<$ 25% higher than prior to treatment Partial response (PR) = $>$ 50% reduction in proteinuria and no increase in serum Cr Failure = not reaching PR criteria	Investigate the effect of concentration-controlled treatment of MPA exposure and renal outcome with target AUC ₀₋₁₂ 60-90 mg.h/L.	- Individualized dose adjustment with a target AUC ₀₋₁₂ 60-90 mg.h/L resulted in significantly higher MPA-AUC and 87.5% of patients achieved CR or PR at 12 months.	AUC ₀₋₁₂ 60-90 mg.h/L
6	Kittanamongkolchai et al. ²² [2013]	Thailand	Prospective cohort (multiple measurements)	19	30.5 \pm 10.4	94.7	0/100/0/0	-	14	-	5	-	66.4 \pm 25.3	I	MMF 100%	1.8 \pm 0.29	AUC ₀₋₁₂ 66.4 \pm 25.3 (12 weeks after treatment)	N/A	Prednisolone 0.5 mg/kg/day then reduce by 5 mg/day every 2 weeks for 2 times then every 4 weeks until 5 mg/day (average dose 12.08 \pm 5.87 mg/day)	89	CR = normal or \leq 25% decline of eGFR + UPCR $<$ 0.2 and inactive urine sediment PR = normal or \leq 25% decline of eGFR and \geq 50% reduction of proteinuria with 0.2-2.0 g/day Non-responders =not meet CR/PR criteria	Explore the efficacy and safety of MPA concentration-controlled therapy based on MPA-C ₁ level $>$ 13 mg/L	- 89% of patients responded to therapy at week 24, and no renal relapsed at week 48. - No association between MPA concentrations and adverse reactions of infection was found.	C ₁ $>$ 13 mg/L

7	Alexander et al. ²³ [2014]	India	Prospective cohort (multiple measurements)	34	29.7 ± 12.4	88.2	N/A	-	34	-	-	-	1.0 ± 0.36	I, M	MMF 100%	1.5 ± 0.3	AUC ₀₋₁₂ 31.96 ± 13.6 (7.7 ± 3.1 days after treatment)	1.55 ± 0.87	Oral steroids 1 mg/kg on alternate days then reduced to 0.125-0.25 mg/kg on alternate days over 4-6 months	79.4	Renal response = 24-h urine protein < 3.5 g/day (baseline nephrotic range proteinuria) or ≥50% decrease in proteinuria (baseline subnephrotic proteinuria < 3.5 g/day) and stabilization (±25%) or improvement in Cr CR = improvement Cr to baseline and a decline in the 24-hour urine protein to < 0.5 g/day	Assess the relationship between clinical and PK parameters of MPA in proliferative LN	- 61.8% of patients had MPA-AUC < 30 mg/L with an empiric starting dose of 30 mg/kg. - Patients with an AUC ≥ 30 mg/L had greater renal response at 1 year, 79.4% of patients achieved renal response by 1 year. - MMF dose/BW had a weak correlation with AUC and did not correlate with trough concentrations.	AUC ₀₋₁₂ ≥ 30 mg.h/L
8	Zabotti et al. ¹¹ [2015]	Italy	Prospective cohort (single measurement)	5	34.2 ± 10.3	80	N/A	-	5	-	-	-	GFR 87.6 ± 34.4 ml/min	I, M	MMF 100%	2.8 ± 0.4	AUC ₀₋₁₂ 98.7 ± 24.6 (induction) 56.74 ± 2.9 (maintenance) (overall mean, timing not mentioned)	N/A	IVMP 1 g/day total 3 days then prednisone starting 1 mg/kg/day and discontinued after 7.4 ± 2.1 months	100	CR = proteinuria < 0.5 g/day and normal/near-normal renal function (GFR change < 10%) PR = ≥50% reduction in proteinuria to subnephrotic levels and normal/near-normal renal function	Investigate TDM of MPA to optimize the MMF dose in the maintenance phase of LN.	- CR was found in all 5 patients. No renal flares were observed. - Mean AUC ₀₋₁₂ at the last visit (56.74 ± 2.9 mg.h/L) was significantly lower than baseline (98.7 ± 24.6 mg.h/L) since the dose of MMF was significantly reduced in all the patients [from 2.8 g/day (±0.4) to 1.9 g/day (±0.4)].	AUC ₀₋₁₂ 45-60 mg.h/L
9	Abd Rahman et al. ²⁴ [2015]	Malaysia	Cross sectional (single measurement)	25	33.5 ± 18.2	80	N/A	-	9	1	15	-	0.86 ± 0.33	I, M	MMF 100%	1.5 ± 0.78 (average dose)	AUC ₀₋₁₂ 26.2 ± 26.07 (11.2 ± 12.3 months after treatment)	1.54 ± 2.87	Prednisolone in responders 10 ± 1 mg/day vs non-responders 11.7 ± 4.1 mg/day	60	Treatment response = all the following criteria 1. ≥50% decrease in proteinuria from a baseline to ≤ 2 g/day 2. Inactive urinary sediments: • RBC ≤ 5/HPF and • WBC ≤ 5/HPF and • absence of RBC casts. 3. Normal or increased eGFR by ≥ 25%	Examine relationships between total and unbound MPA and prednisolone exposure and clinical outcomes in patients with LN.	- Median values of total AUC ₀₋₈ and C _{max} were significantly higher in responders than non-responders. - Poorer treatment response was observed in patients with lowest tertile exposure to both total MPA and prednisolone as compared with patients with middle and higher tertile exposure.	AUC ₀₋₁₂ > 30 mg.h/L
10	Hui-Yuen et al. ³⁰ [2016]	US	Retrospective cohort (single measurement)	17	N/A	70.6	47/6/47/0	-	5	3	9	-	N/A	I, M	MMF 100%	1.2 ± 0 *(g/m2)	Glucuronidated MPA AUC ₀₋₁₂ 39.14 ± 25.42 (45.6 ± 85 months after treatment)	N/A	Prednisone in responders 23.75 ± 14.2 vs non-responders 63 ± 33.1 mg/day	64.7	Renal remission = < 500 mg/24 h urinary protein excretion, inactive sediment, and normal serum Cr.	Evaluate the relationship between plasma MPA and MPA-G levels and response to treatment in pediatric LN	- The mean MPA level for patients in CR was 3.26 ± 2.02 mg/L compared with 3.02 ± 1.76 mg/L for patients not in CR. Three patients in CR did not have detectable levels of MPA. - Glucuronidated MPA levels were therapeutic (44.2 ± 26.7 mg/L) in patients in CR, but low (29.88 ± 22 mg/L) in patients not in CR.	N/A
11	Katsuno et al. ²⁵ [2018]	Japan	Retrospective cohort (multiple measurements)	20	31.7 ± 22.3	90	N/A	1	6	-	10	3	0.61 ± 0.29	I, M	MMF 100%	1 ± 0	AUC ₀₋₁₂ 48.74 ± 5.64 (various times)	N/A	Prednisolone in responders 10 ± 0 mg/day vs non-responders 11.7 ± 4.1 mg/day	70	CR = the return of serum creatinine to baseline, plus a decline in the UPCr to < 0.5 g/g Cr	Assess the therapeutic benefits and safety of MMF and to investigate the utility of TDM in the treatment of Japanese patients with LN.	- The ratio of maintaining CR after MMF therapy was as high as 85.7%. - The relationship between AUC and MMF dose was low, and AUC correlated with trough level (r = 0.73). - AUC tended to be high in the treatment responder but did not correlate with adverse events of infection.	AUC ₀₋₁₂ > 45 mg.h/L
12	Kiyokawa et al. ²⁶ [2020]	Japan	Prospective cohort (multiple measurements)	10	42.3 ± 6.0	90	0/100/0/0	-	8	-	2	-	0.82 ± 0.11	I	MMF 100%	2 ± 0	AUC ₀₋₁₂ 45.4 ± 16.32 at week 4 after treatment AUC ₀₋₁₂ 57.02 ± 8.53 at week 12 after treatment	4.15 ± 1.21	Prednisolone dose 40 ± 16 mg/day at baseline decreased to 8.8 ± 2.4 mg/day at 12 months	60	CR = UPCr < 0.5 g/gCr and normal/near-normal renal function (within 10% of the normal eGFR if previously abnormal)	To identify the prognostic predictive factor of complete renal response at week 12 by focusing on the plasma MPA concentration in induction therapy in LN.	- A significantly higher MPA-AUC ₀₋₁₂ at the early phase was observed in the patients with CR at week 12 than in those without. - All the patients with high MPA-AUC ₀₋₁₂ (> 40 mg.h/L) at the early phase achieved CR at week 12, but no association was found at the middle phase.	AUC ₀₋₁₂ > 40 mg.h/L at week 4

13	Yap et al. ²⁷ [2020]	Hongkong	Prospective cohort (multiple measurements)	88	43.8 ± 12.2	87.5	0/100/0/0	-	84	4	-	-	0.98 ± 0.75	I, M	MMF 100%	1.04 ± 0.36	N/A	2.34 ± 1.20	Prednisolone 0.8 mg/kg/day then reduced to 7.5 mg/day at 6 months and 5-7.5 mg/day at 12 months	100% (CR 56.8%, PR 43.2%)	CR = urine protein excretion <0.3 g/day with normal urinary sediment and serum albumin and with improved/stable serum Cr ≤ 25% of the baseline PR = urinary protein excretion 0.3-2.9 g/day with a serum albumin ≥ 3.0 g/dL and stable renal function	Investigate MMF pharmacokinetics and pharmacogenomics and the relationship between MPA exposure and clinical outcomes in LN patients on maintenance immunosuppression	- Multivariate analysis revealed that MPA-AUC ₀₋₁₂ was selected as an independent predictive factor of CR at week 12. - C ₁ , C ₂ and C ₁₂ were all correlated with the 12-hour AUC of MPA and is related to renal flare, infection, and anemia. - SNP rs2273697 A/G is associated with lower MPA exposure.	C ₀ 2.0-2.4 mg/L
14	Godron-Dubrasquet et al. ¹⁹ [2021]	France	Retrospective cohort (multiple measurements)	27	12.5 ± 1.4	88.9	100/0/0/0	8	17	2	-	-	N/A	I, M	MMF 100%	1.21 ± 0.13 *(g/m2)	AUC ₀₋₃ 43.67 ± 15.94 (overall mean, all 27 patients had one MPA-AUC median time 2 month, 78% had two MPA-AUC median time 12 month, 48% had three or more MPA-AUC, median time 30 months)	N/A	IVMP 3 days then oral prednisone 0.5-1 mg/kg/day then reduced to 5-10 mg/day at 6 months and consider discontinuation at 12 months	56	Response = normal or improved GFR by 25% over baseline, 50% reduction of proteinuria until < 0.5 g/day or 50 mg/mmol, and no hematuria (RBC < 10,000/mL or ≤ 1+ by urine dipstick) at 6 months of MMF treatment.	Determine whether TDM of MMF therapy in childhood LN is associated with dose adaptation of MMF and therapeutic response.	- Patients with MPA-AUC levels > 45, 30-45, and < 30 mg.h/L had 6-month response rates of 89% (8/9), 60% (6/10), and 0% (0/6), respectively. - In a logistic regression model, an MPA-AUC > 45 mg.h/L was significantly associated with therapeutic response.	AUC > 45 mg.h/L in childhood LN
15	Kirubakaran et al. ²⁸ [2022]	India	Cross sectional (single measurement)	25	14.9 ± 2.0	80	0/100/0/0	-	25	-	-	-	0.78 ± 0.12	I, M	MMF 100%	1.78 ± 0.325	AUC ₀₋₁₂ 42.17 ± 22.75 (at least 1 month after treatment)	N/A	Prednisolone (13/25), dose not mentioned	64.7	Disease activity is assessed with SLEDAI system. SLEDAI score of ≥ 6 is considered an active disease	Determine whether MPA-AUC _{0-12h} concentrations correlate with the disease activity in children with LN	- Mean AUC ₀₋₁₂ was significantly lower in patients with active disease (38.46 ± 14.3 mg.h/L) than patients with inactive disease (69 ± 19.24 mg.h/L) - Daily MMF doses were recognized as independent variables influencing the MPA AUC ₀₋₁₂	N/A
16	Chariyavilas kul et al. ²⁹ [2023]	Thailand	Prospective cohort (multiple measurements)	19	31.3 ± 16.8	100	0/100/0/0	-	-	-	-	-	0.99 ± 0.40	I	EC-MPS 100%	1.440	AUC ₀₋₁₂ 58.9 ± 45.3 (24 month after treatment)	N/A	Prednisolone 0.7 mg/kg/day then reduced by 5 mg every 2-4 weeks, reaching 20 mg/day at 12 week and 5 mg/day at 24 week.	N/A	Remission = stabilization or improvement of renal function, resolution of urine sediment or cast CR = proteinuria <0.5 g/day PR = proteinuria <1.5 g/day or >50% decrease from baseline and <3g/day	Assess PK and PD of EC-MPS in resistant or relapsed LN, investigate an optimal single time point of plasma MPA	- C _{0.5} cutoff of 2.03 mg/L yielded the highest sensitivity of 85% and specificity of 88.2% in predicting AUC ₀₋₁₂ ≥ 45 mg.h/L.	C _{0.5} 2.03 mg/L

Abbreviation: AUC; Area Under Curve, BILAG; British Isles Lupus Assessment Group index, BW; Body weight, C₀; predose concentration, C_{0.5}; Concentration at 30 minutes, C₁;

Concentration at 1 hour, C₂; Concentration at 2 hour, C₁₂; Concentration at 12 hours, C_{max}; Maximum concentration at steady state, CR; Complete remission, Cr; Creatinine, EC-MPS; Enteric-

coated mycophenolate sodium, eGFR; estimated glomerular filtration rate, g; gram, GFR; Glomerular filtration rate, h; hour, HPF; High power field, IVMP; intravenous methylprednisolone, L;

Liters, LN; Lupus nephritis, mg; milligram, mL; milliliters, MMF; Mycophenolate Mofetil, MPA; Mycophenolic acid, PD; Pharmacodynamic, PK; Pharmacokinetic, PR; Partial remission,

RBC; Red blood cell, SLEDAI; Systemic lupus erythematosus disease activity index, SD; Standard Deviation, TDM; Therapeutic drug monitoring, WBC; White blood cell, UPCR; Urine

protein creatinine ratio

Supplementary Table S3: Quality assessment according to Newcastle-Ottawa scale

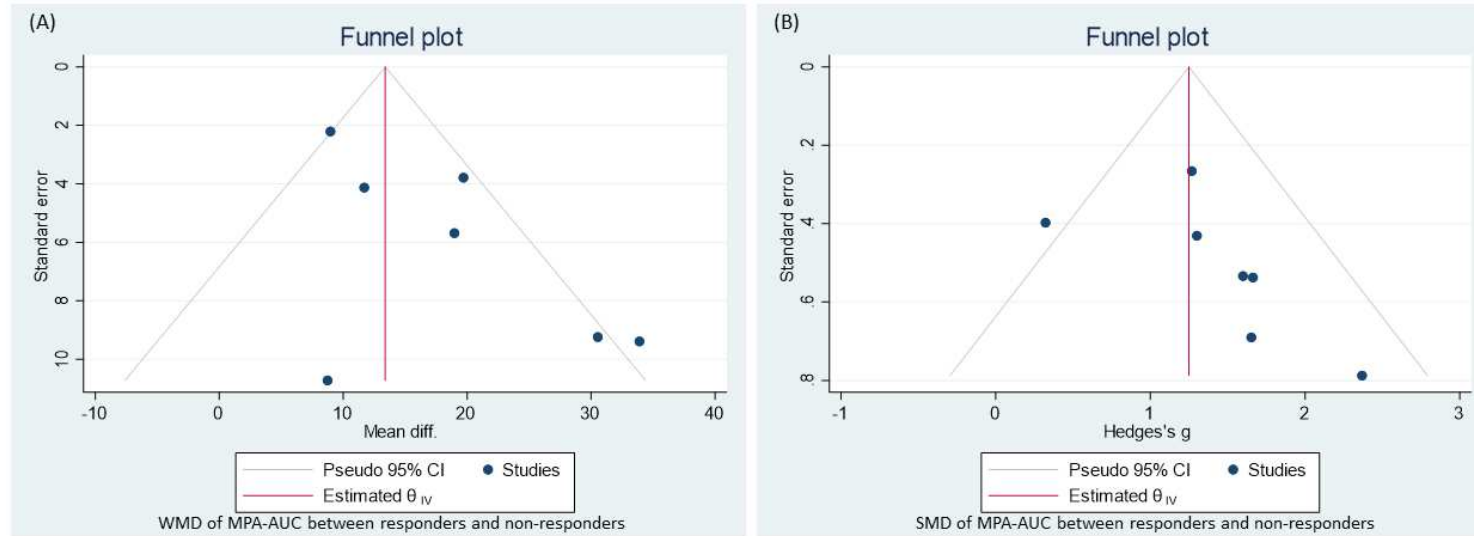
No.	Author	Year	Selection				Comparability	Outcome			Total	
			Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study		Assessment of outcome	Follow-up long enough ^a	Adequacy of follow up ^b		
1	Roland et al.	2009	*	-	*	*	**	*	*	*	8	Good
2	Lertdumrongluk et al.	2010	*	-	*	*	**	*	*	*	8	Good
3	Zahr et al.	2010	*	-	*	*	**	*	N/A	*	7	Good
4	Sagcal-Gironella et al.	2011	*	-	*	*	*	*	*	N/A	6	Good
5	Dalaboudt et al.	2013	*	-	*	*	**	*	*	*	8	Good
6	Kittanamongkolchai et al.	2013	*	-	*	*	**	*	*	*	8	Good
7	Alexander et al,	2014	*	*	*	*	*	*	*	*	8	Good
8	Zabotti et al.	2015	*	-	*	*	-	*	*	*	6	Good
9	Rahman et al.	2015	*	*	*	*	*	*	-	-	6	Poor
10	Hui-Yuen et al.	2016	*	*	*	*	*	*	*	*	8	Good
11	Katsuno et al.	2018	*	*	*	*	-	*	*	*	7	Poor
12	Kiyokawa et al.	2020	*	*	*	*	*	*	*	*	8	Good
13	Yap et al.	2020	*	*	*	*	-	*	*	*	7	Good
14	Godron-Dubrasquet et al.	2021	*	*	*	*	*	*	*	*	8	Good
15	Kirubakaran et al.	2022	*	*	*	*	**	*	-	*	8	Good
16	Chariyavilaskul et al.	2022	*	-	*	*	-	*	*	*	6	Poor

^aFollow-up time enough = at least 6 months^bAdequate follow-up rate = at least 80% of total participants

Supplementary Figure S1:

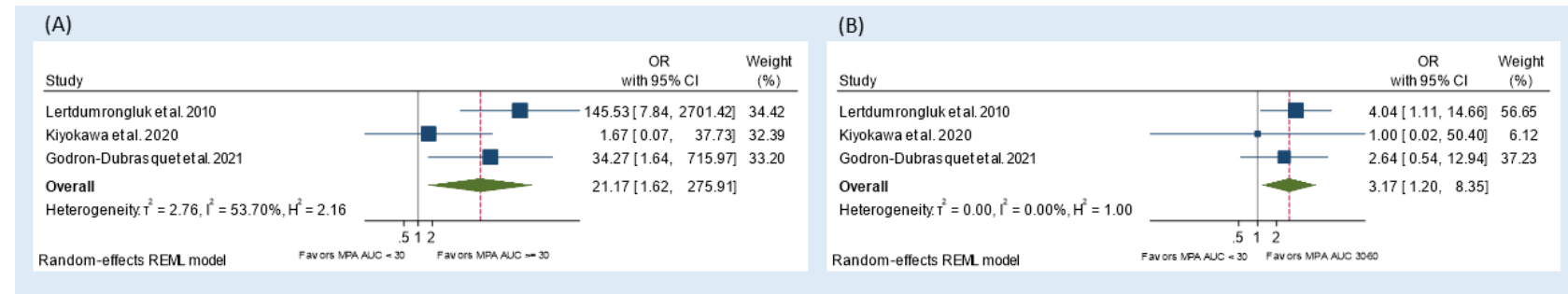
(A) Funnel plot of studies investigating WMD of MPA-AUC and the renal response

(B) Funnel plot of studies investigating SMD of MPA-AUC and the renal response



Supplementary Figure S2:(A) Comparison of the renal response in patients with MPA-AUC < 30 and ≥ 30 mg.h/L

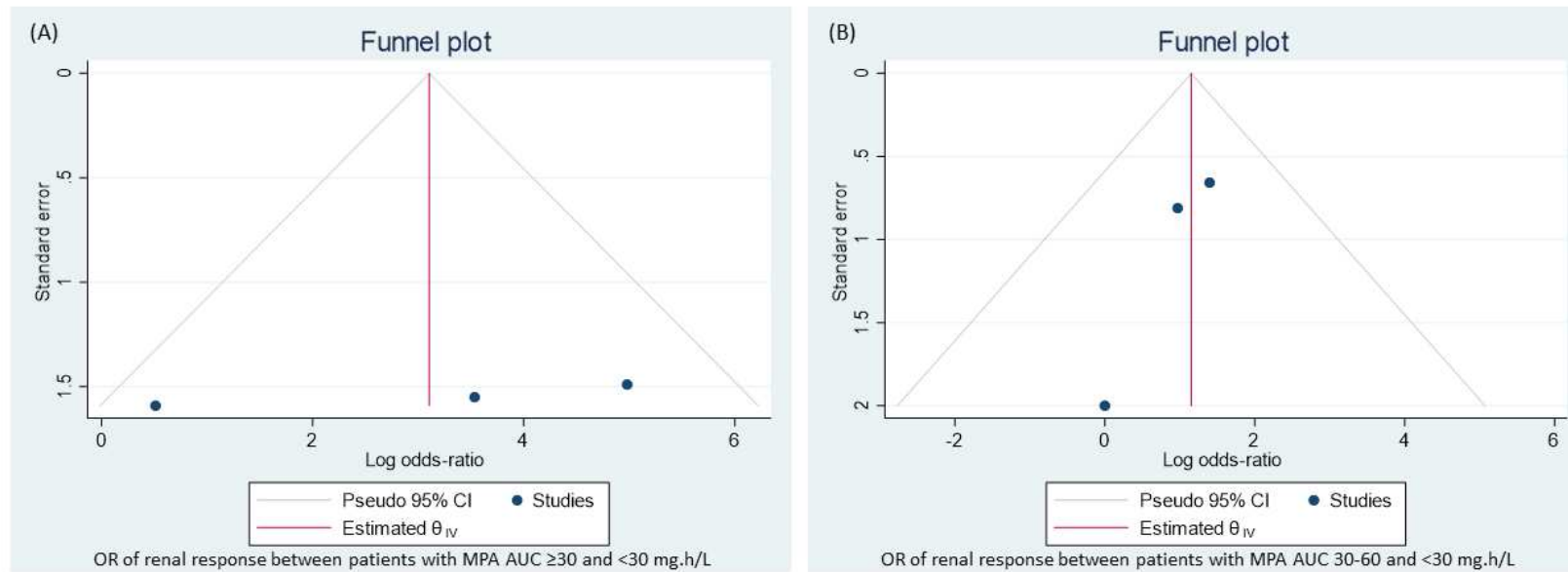
(B) Comparison of the renal response in patients with MPA-AUC < 30 and 30-60 mg.h/L



Supplementary Figure S3:

(A) Funnel plot of studies investigating odd ratio for the renal response in patients with MPA-AUC < 30 and ≥ 30 mg.h/L

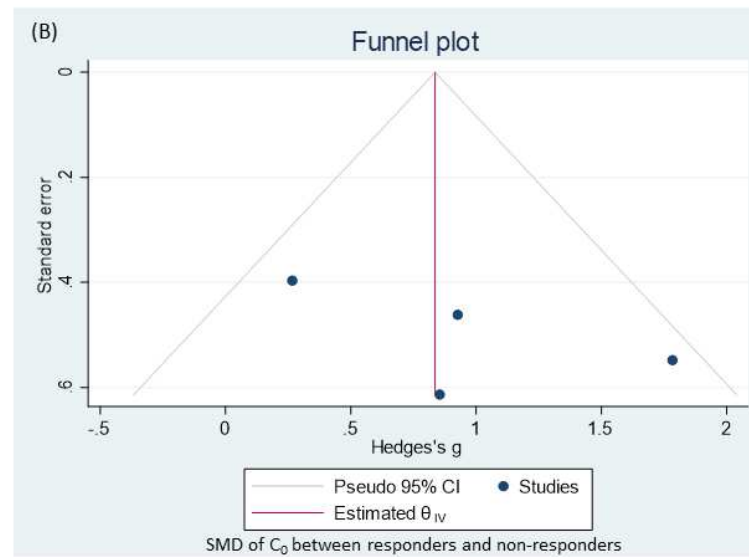
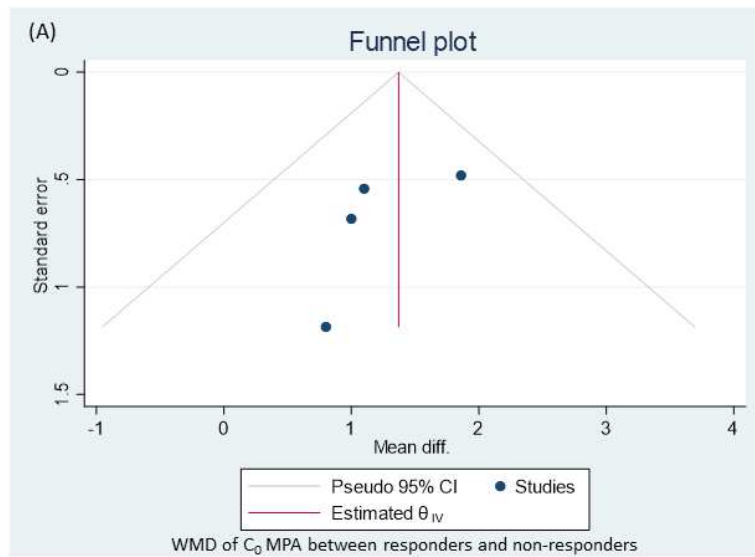
(B) Funnel plot of studies investigating odd ratio for the renal response in patients with MPA-AUC < 30 and 30-60 mg.h/L



Supplementary Figure S4:

(A) Funnel plot of studies investigating WMD of C_0 and the renal response

(B) Funnel plot of studies investigating SMD of C_0 and the renal response



Supplementary Figure S5:

(A) Funnel plot of studies investigating WMD of MPA-AUC and the adverse events

(B) Funnel plot of studies investigating SMD of MPA-AUC and the adverse events

