

Comparison: Tocilizumab versus placebo or standard care

Outcome	No. of studies	No. Of participants	Statistical method	Effect size
Clinical improvement D28	7	5585	Risk Ratio (M-H, Random, 95% CI)	1.06 (1.00 to 1.13)
WHO progression score (level 7 or above) D28	3	712	Risk Ratio (M-H, Random, 95% CI)	0.99 (0.56 to 1.74)
All-cause mortality D28	8	6363	Risk Ratio (M-H, Random, 95% CI)	0.89 (0.82 to 0.97)
All-cause mortality D60	2	519	Risk Ratio (M-H, Random, 95% CI)	0.86 (0.53 to 1.40)
Adverse events	7	1534	Risk Ratio (M-H, Random, 95% CI)	1.23 (0.87 to 1.72)
Serious adverse events	8	2312	Risk Ratio (M-H, Random, 95% CI)	0.89 (0.75 to 1.06)
Time to clinical improvement	6	2118	Hazard Ratio (95% CI)	1.23 (1.08 to 1.39)
Time to WHO progression score (level 7 and above)	3	762	Hazard Ratio (95% CI)	0.62 (0.42 to 0.91)
Time to death	3	1152	Hazard Ratio (95% CI)	0.65 (0.51 to 0.83)

Analysis 1.1.1 Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28

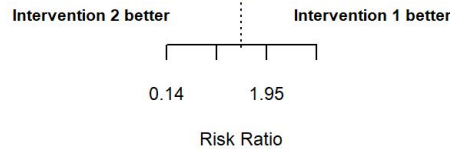
Pharmacological treatments
Clinical improvement D28

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]			
						A	B	C	D	E					
Mild to severe															
Salama C,EMPACTA, 2020	28	Tocilizumab 8 mg/kg	Placebo	218/259	107/129	■	■	■	■	■	■	19.84%	1.01	[0.92, 1.12]	
Mild to severe															
Stone JH, 2020	28	Tocilizumab 8mg/kg	Placebo	147/161	72/82	■	■	■	■	■	■	19.98%	1.04	[0.95, 1.14]	
Moderate/severe															
Hermine O,CORIMUNO-19, 2020	28	Tocilizumab 8mg/kg	Standard care	52/64	49/67	■	■	■	■	■	■	8.12%	1.11	[0.92, 1.34]	
Mild to critical															
Rosas I,COVACTA, 2021	28	Tocilizumab 8mg/kg	Placebo	103/301	41/151	■	■	■	■	■	■	3.51%	1.26	[0.93, 1.71]	
Moderate to critical															
Horby P,RECOVERY, 2021	28	Tocilizumab maximum 800 mg	Standard care	1093/2022	990/2094	■	■	■	■	■	■	27.98%	1.14	[1.08, 1.21]	
Moderate to critical															
Veiga VC,TOCIBRAS, 2021	29	Tocilizumab 8 mg/kg	Standard care	42/65	48/64	■	■	■	■	■	■	5.82%	0.86	[0.69, 1.08]	
Severe															
Salvarani C, 2020	30	Tocilizumab 8mg/kg	Standard care	54/60	58/66	■	■	■	■	■	■	14.74%	1.02	[0.91, 1.16]	

Heterogeneity: Q = 11.24, p = 0.08; I² = 40.9%; τ² = 0.00

Risk of bias ratings:
■ Low Risk of Bias
■ Some Concerns
■ High Risk of Bias

Risk of Bias Domains:
 A: Bias due to randomization
 B: Bias due to deviation from intended intervention
 C: Bias due to missing data
 D: Bias due to outcome measurement
 E: Bias due to selection of reported result



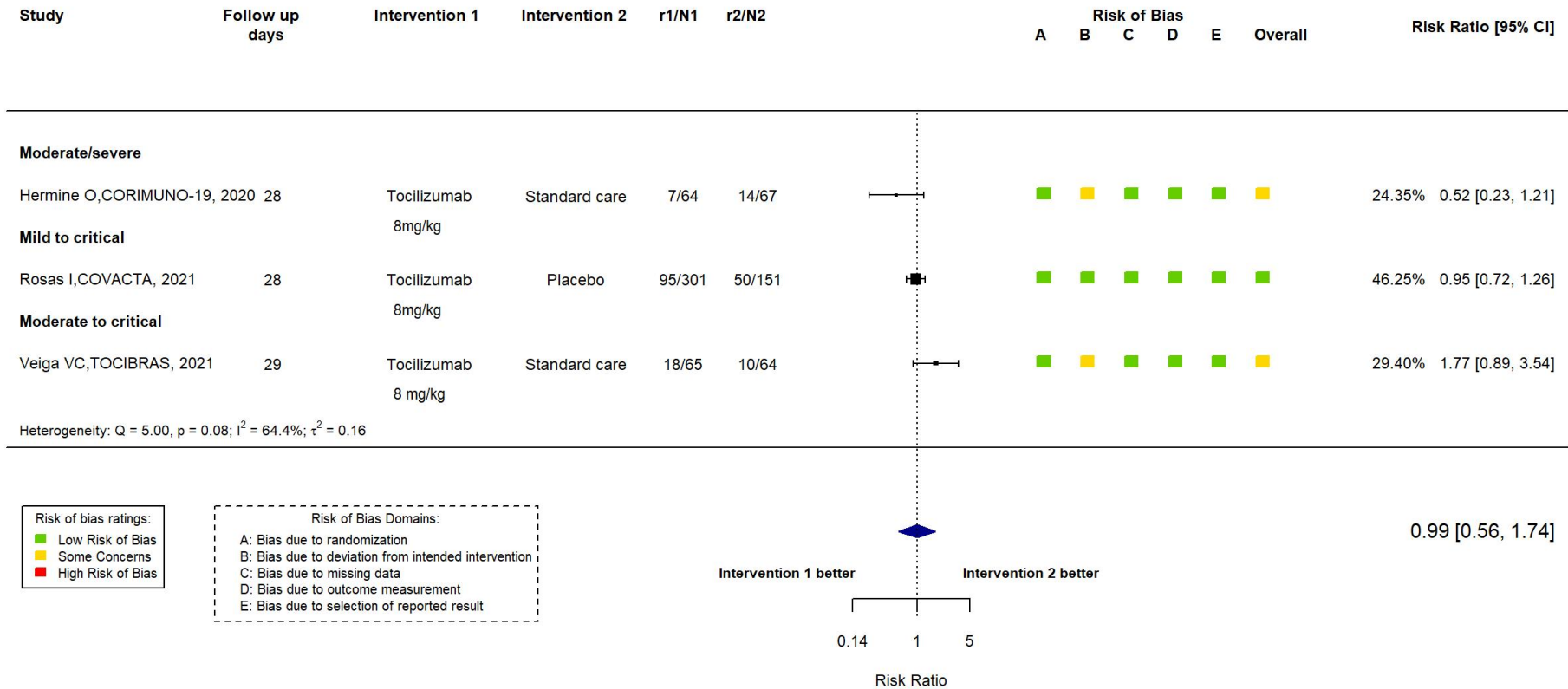
1.06 [1.00, 1.13]

Analysis 1.1.2 Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

Pharmacological treatments

WHO progression score level 7 or above D28

[mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death]



Analysis 1.1.3 Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28

Pharmacological treatments All-cause mortality D28

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]		
						A	B	C	D	E				
Mild to severe														
Salama C,EMPACTA, 2020	28	Tocilizumab 8 mg/kg	Placebo	26/259	11/129		■	■	■	■	■	■	1.43%	1.18 [0.60, 2.31]
Mild to severe														
Stone JH, 2020	28	Tocilizumab 8mg/kg	Placebo	9/161	3/82		■	■	■	■	■	■	0.40%	1.53 [0.43, 5.49]
Moderate/severe														
Hermine O,CORIMUNO-19, 2020	28	Tocilizumab 8mg/kg	Standard care	7/64	8/67		■	■	■	■	■	■	0.71%	0.92 [0.35, 2.38]
Mild to critical														
Rosas I,COVACTA, 2021	28	Tocilizumab 8mg/kg	Placebo	58/301	28/151		■	■	■	■	■	■	3.92%	1.04 [0.69, 1.56]
Moderate to critical														
Horby P,RECOVERY, 2021	28	Tocilizumab maximum 800 mg	Standard care	596/2022	694/2094	■	■	■	■	■	■	■	78.64%	0.89 [0.81, 0.97]
Moderate to critical														
Veiga VC,TOCIBRAS, 2021	29	Tocilizumab 8 mg/kg	Standard care	14/65	6/64		■	■	■	■	■	■	0.82%	2.30 [0.94, 5.61]
Severe														
Salvarani C, 2020	30	Tocilizumab 8mg/kg	Standard care	2/60	1/66		■	■	■	■	■	■	0.11%	2.20 [0.20, 23.65]
Severe/critical														
Gordon AC,REMAP-CAP, 2021	21	Tocilizumab 8 mg/kg	Standard care	98/366	142/412		■	■	■	■	■	■	13.97%	0.78 [0.63, 0.96]

Heterogeneity: Q = 8.34, p = 0.30; I² = 0.0%; τ² = 0.00

Risk of bias ratings:
 ■ Low Risk of Bias
 ■ Some Concerns
 ■ High Risk of Bias

Risk of Bias Domains:
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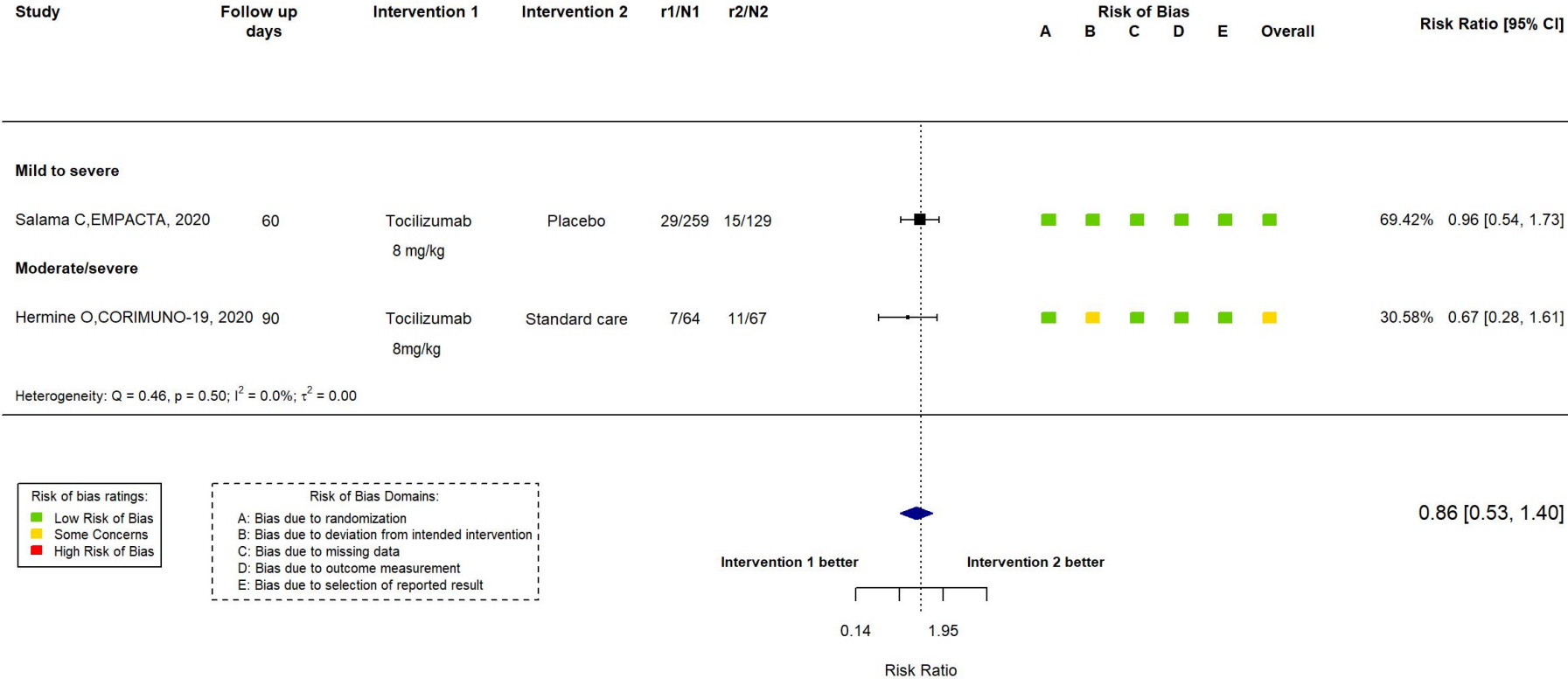


0.89 [0.82, 0.97]

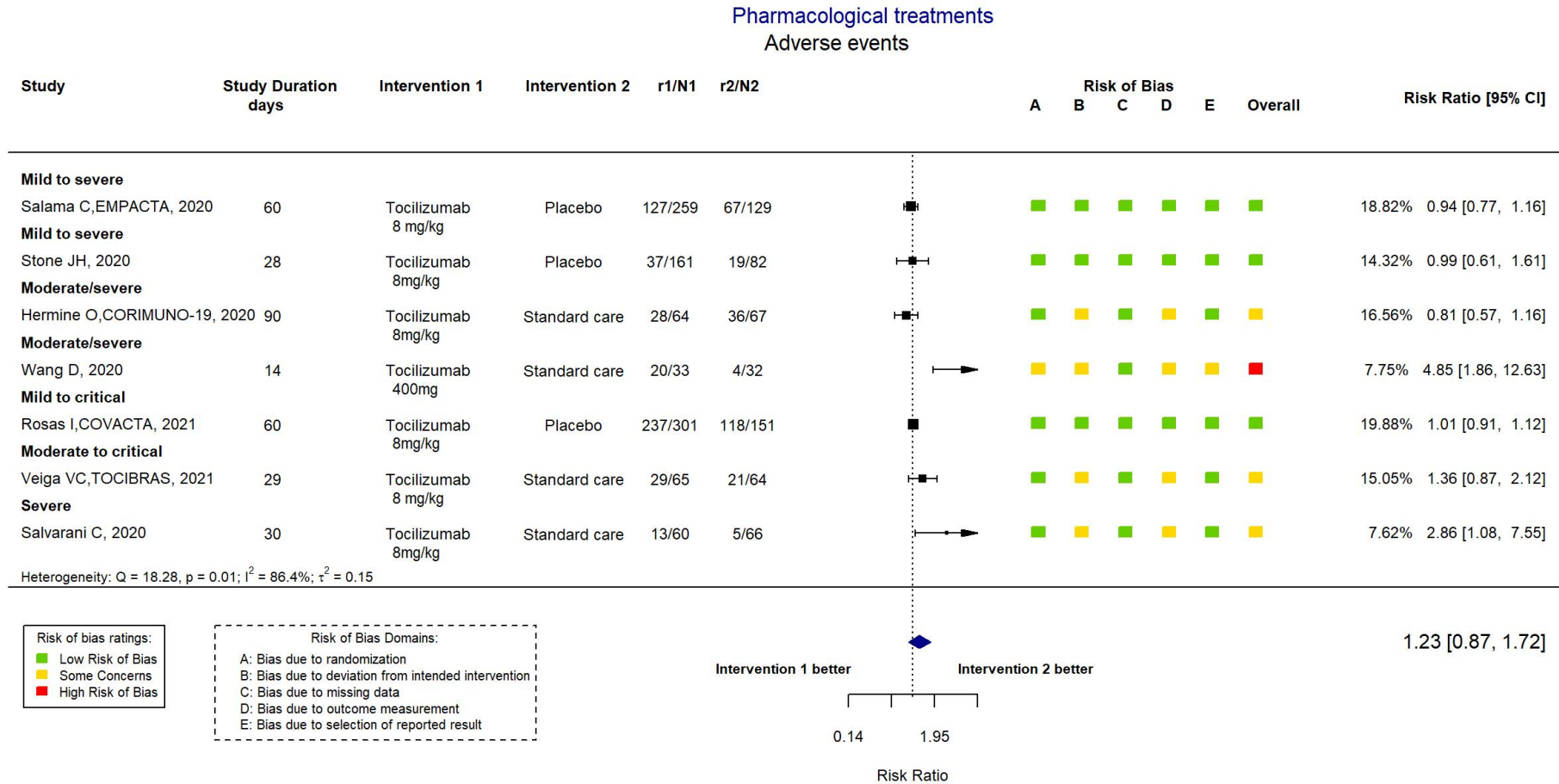
Analysis 1.1.4 Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

Pharmacological treatments

All-cause mortality D60 or above



Analysis 1.1.5 Tocilizumab versus placebo or standard care. Outcome: Adverse events

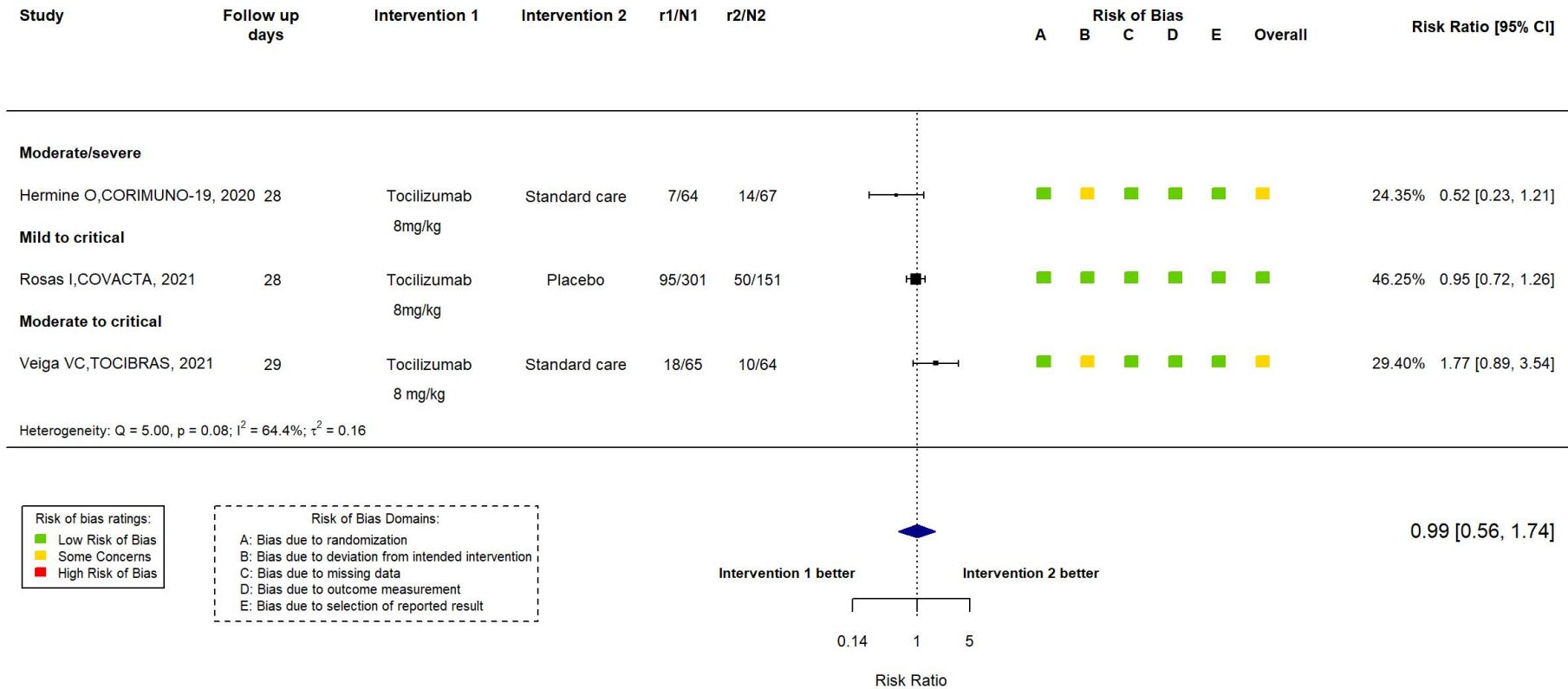


Analysis 1.1.6 Tocilizumab versus placebo or standard care. Outcome: Serious adverse events

Pharmacological treatments

WHO progression score level 7 or above D28

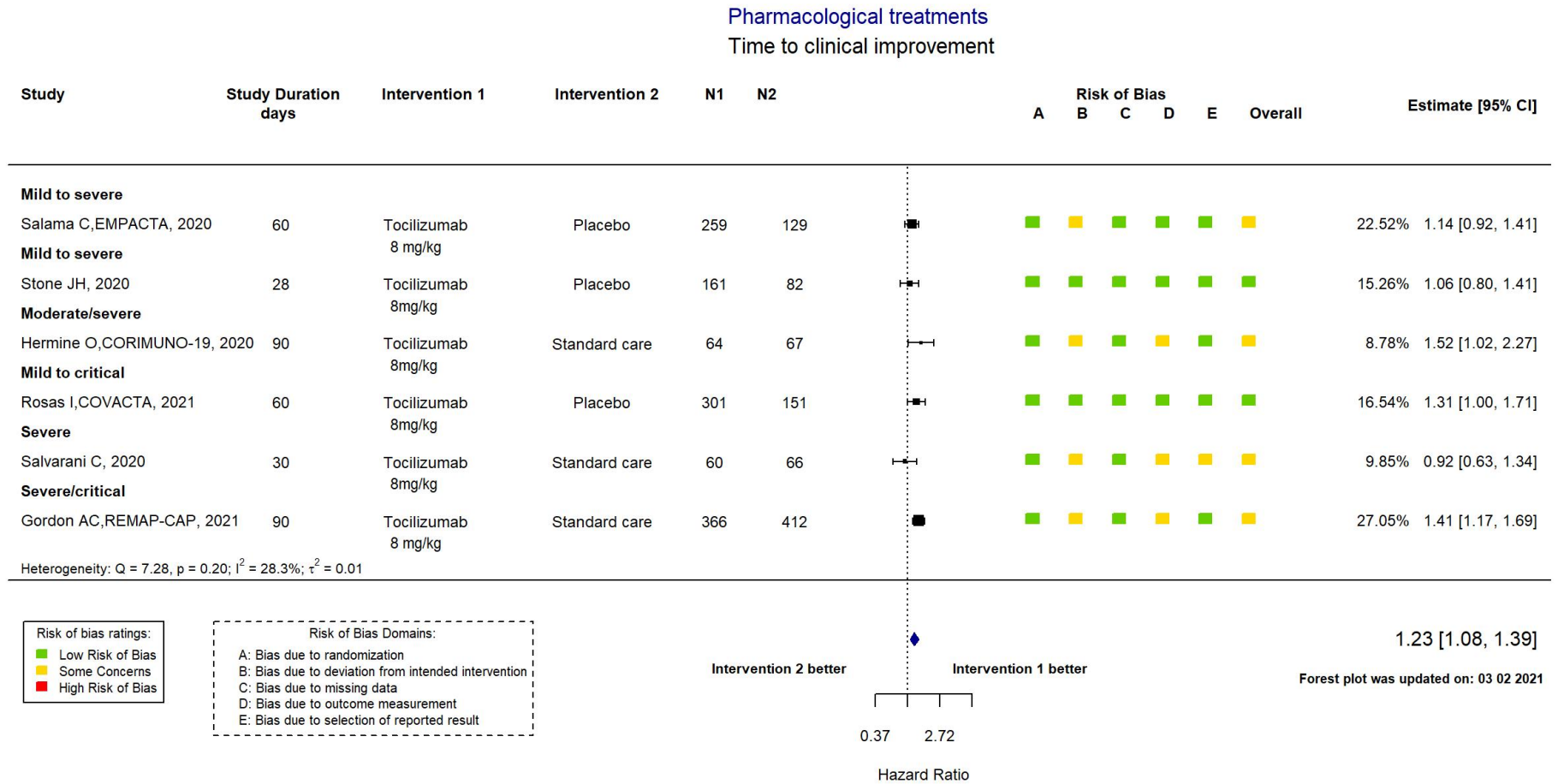
[mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death]



Analysis 1.2.1 Tocilizumab versus placebo or standard care. Outcome: Time to clinical improvement

N1: Number of participants randomized to intervention 1

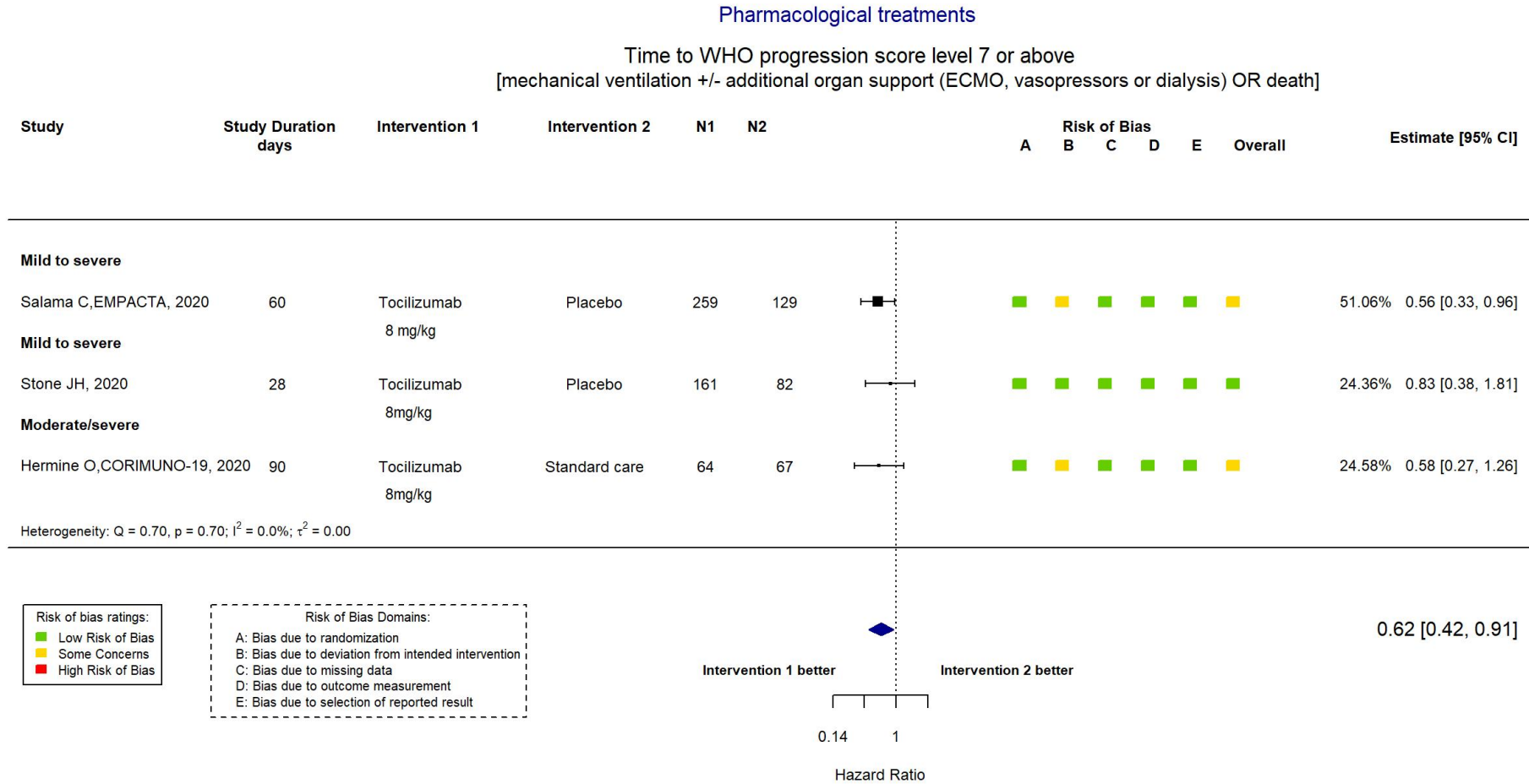
N2: Number of participants randomized to intervention 2



Analysis 1.2.2 Tocilizumab versus placebo or standard care. Outcome: Time to WHO progression score (level 7 and above)

N1: Number of participants randomized to intervention 1

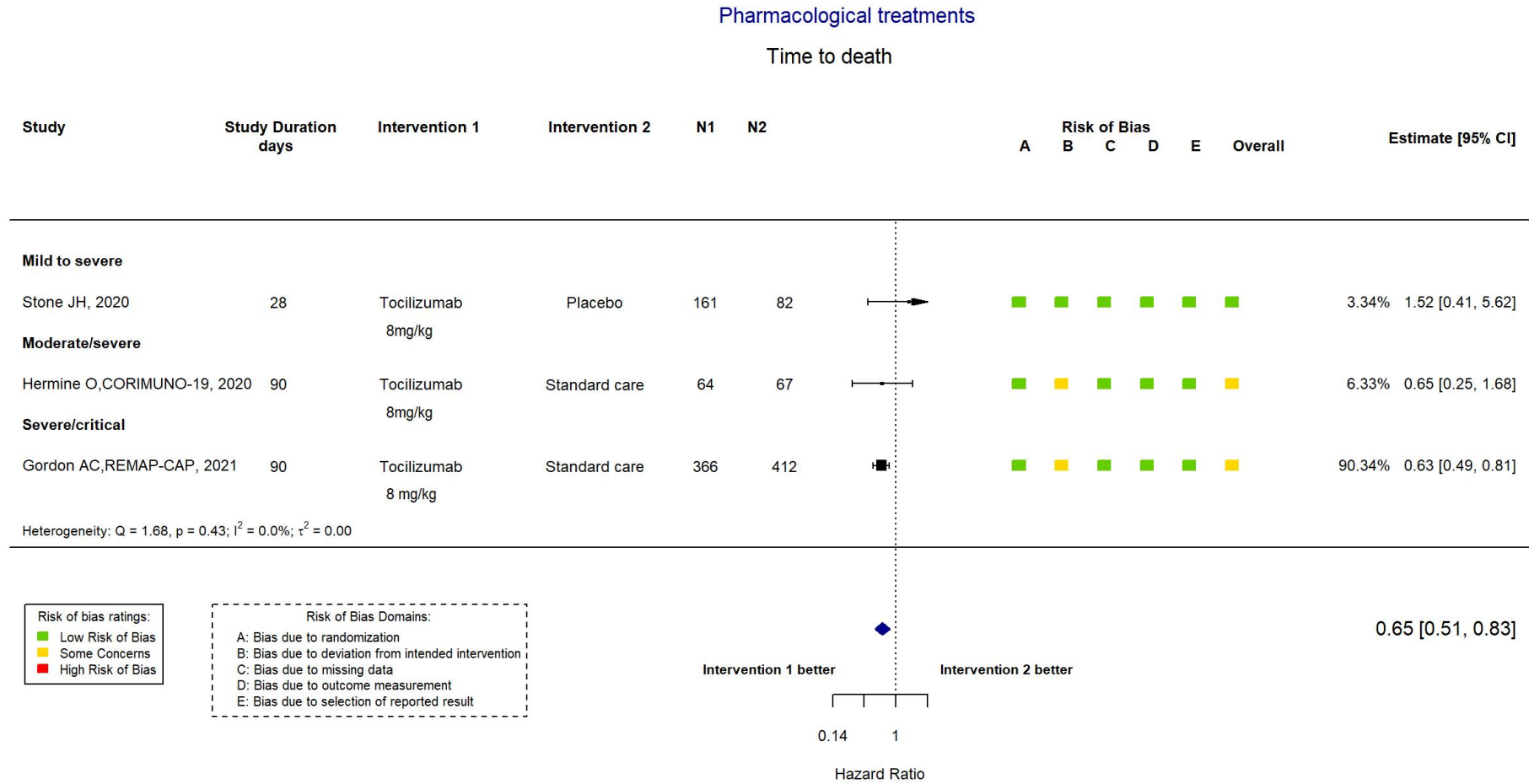
N2: Number of participants randomized to intervention 2



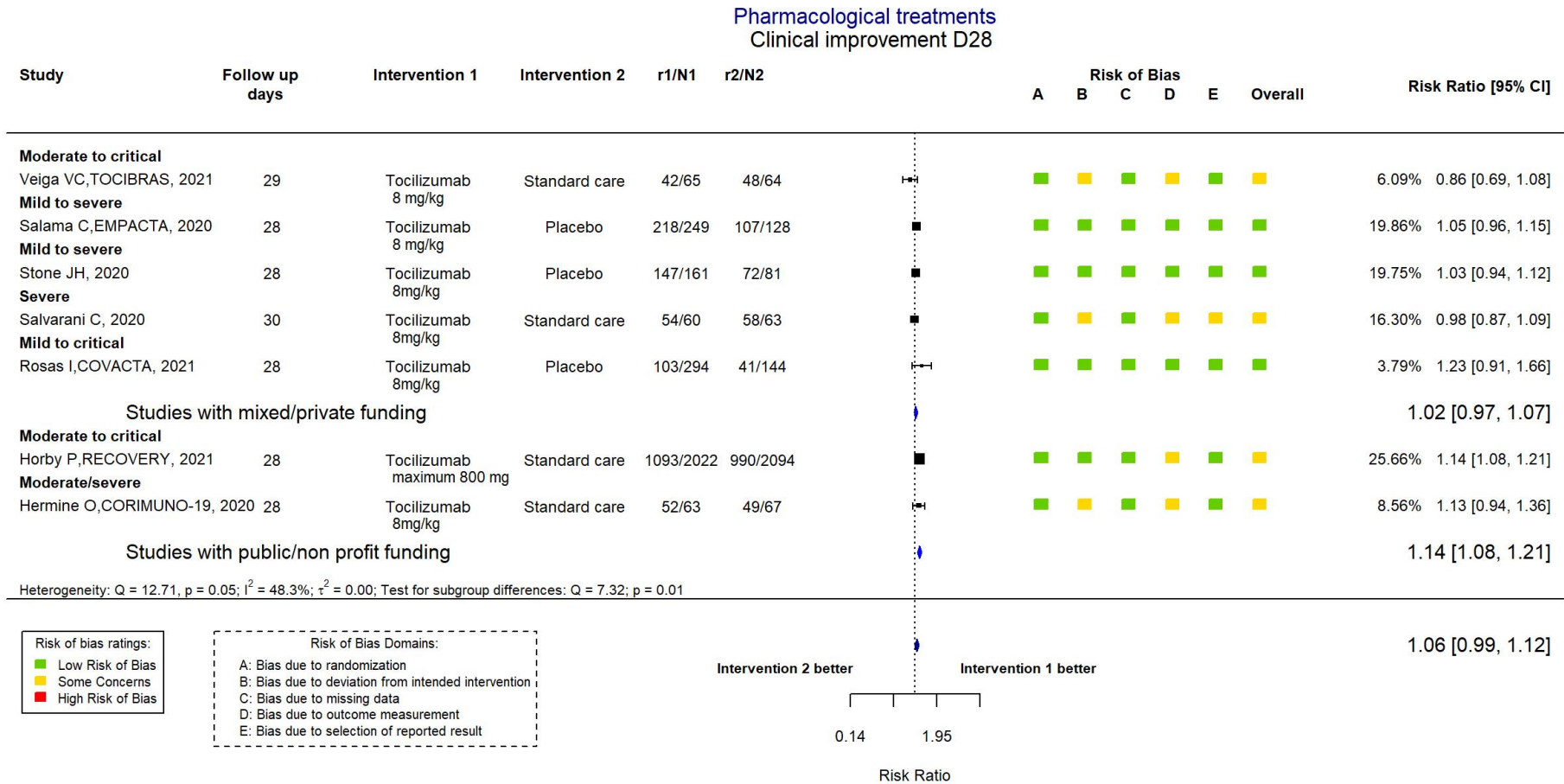
Analysis 1.2.3 Tocilizumab versus placebo or standard care. Outcome: Time to death

N1: Number of participants randomized to intervention 1

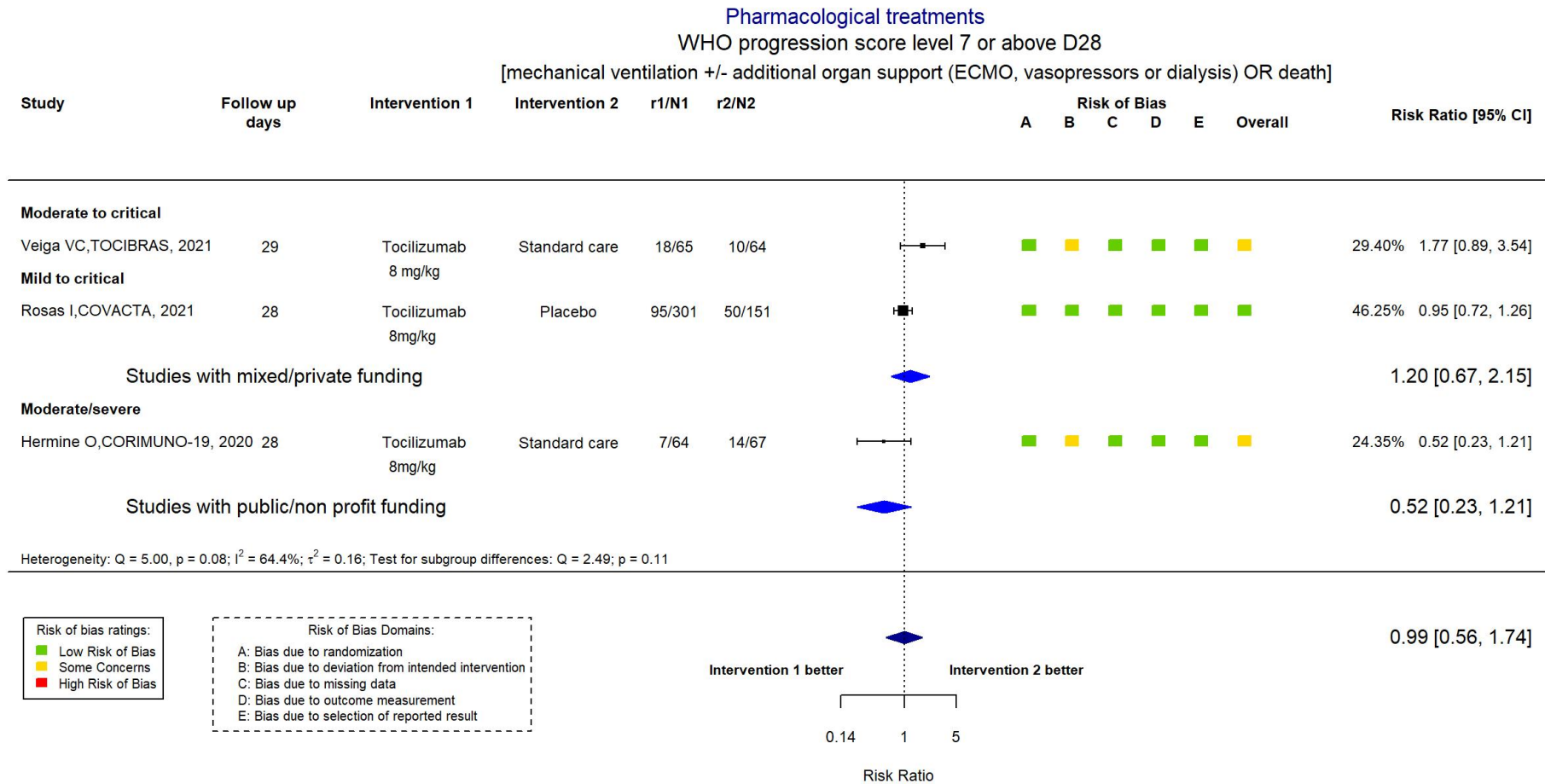
N2: Number of participants randomized to intervention 2



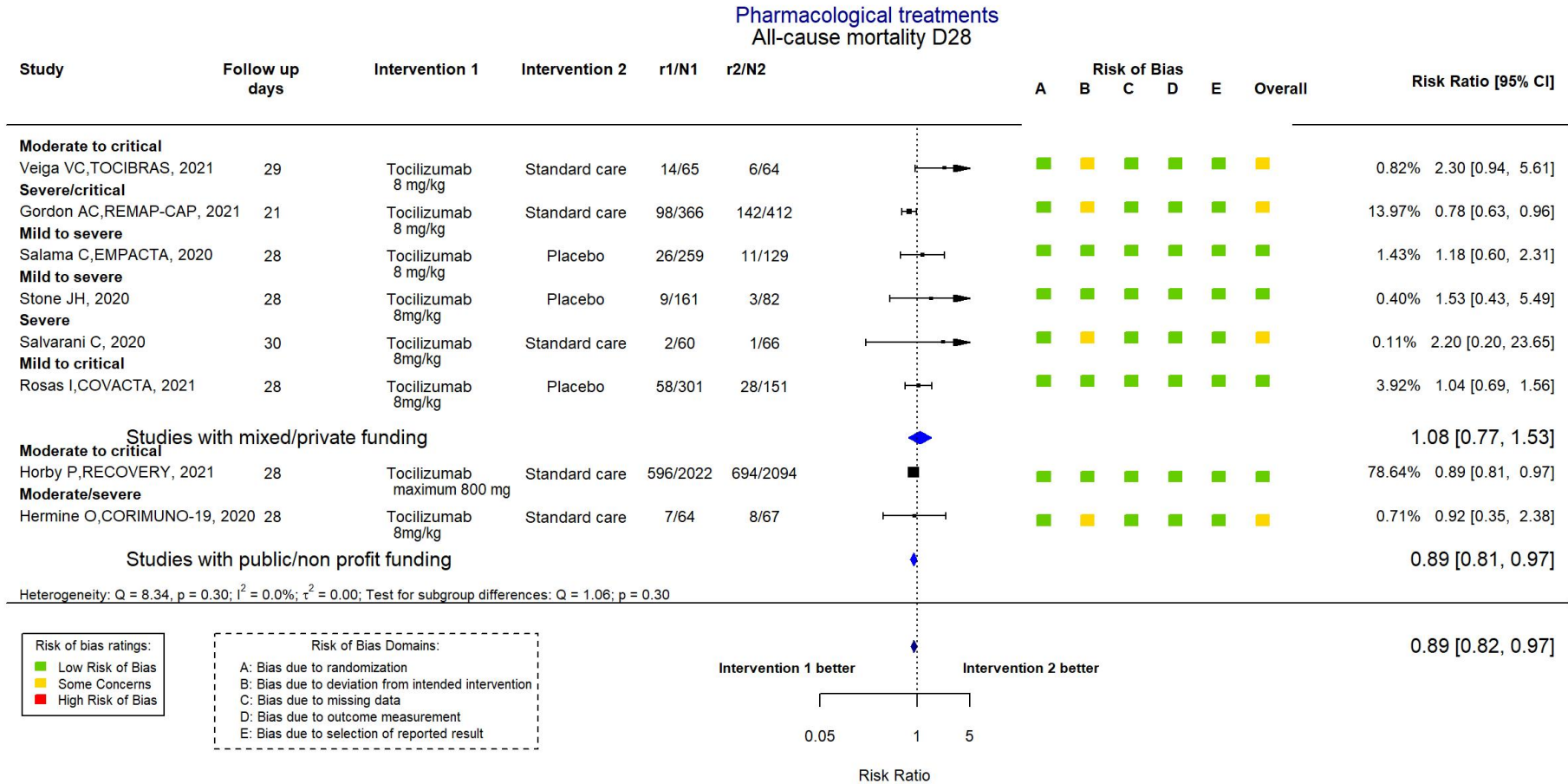
Subgroup analysis. 1.3.1 Funding. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28



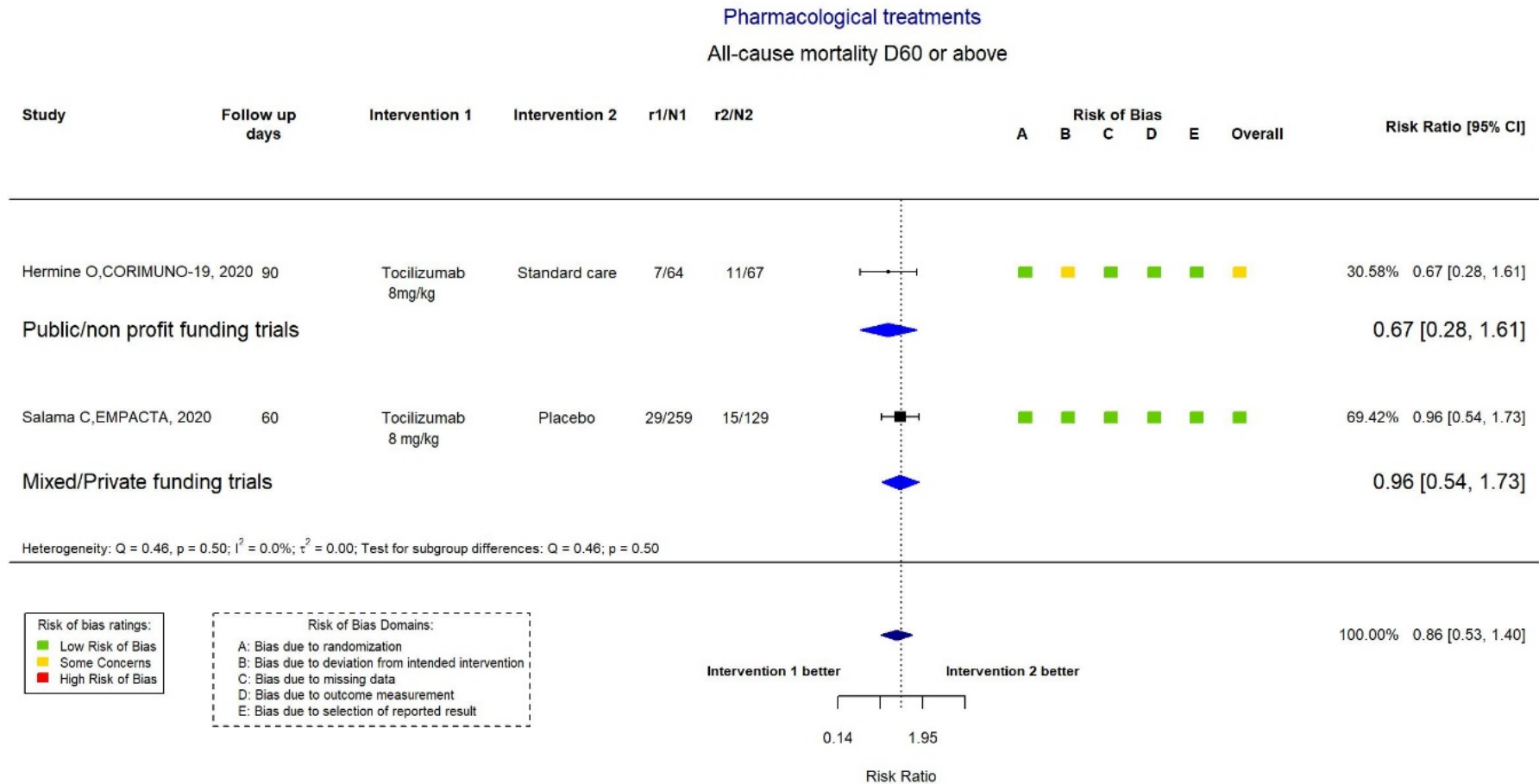
Subgroup analysis.1.3.2 Funding. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



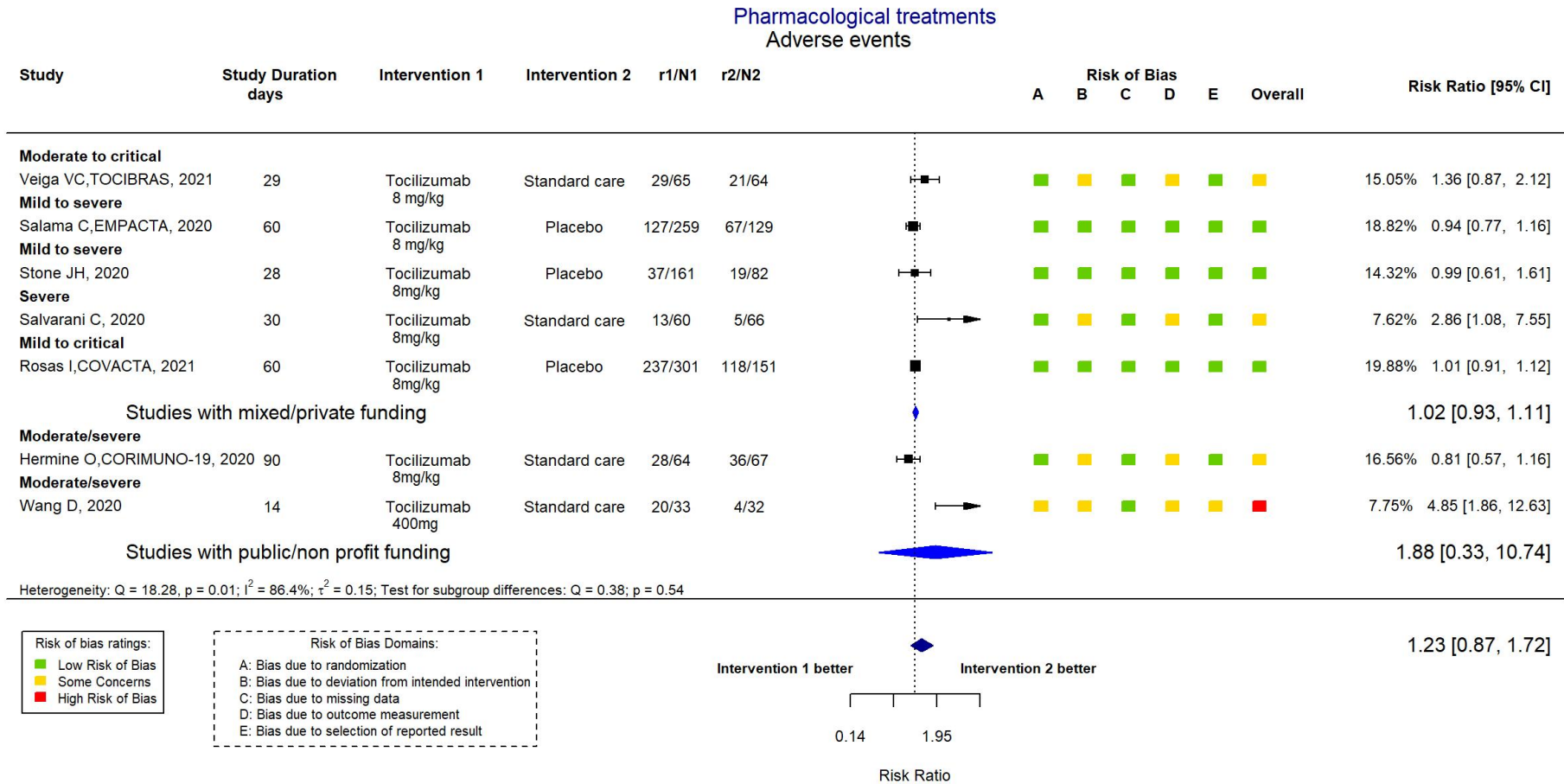
Subgroup analysis.1.3.3 Funding. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



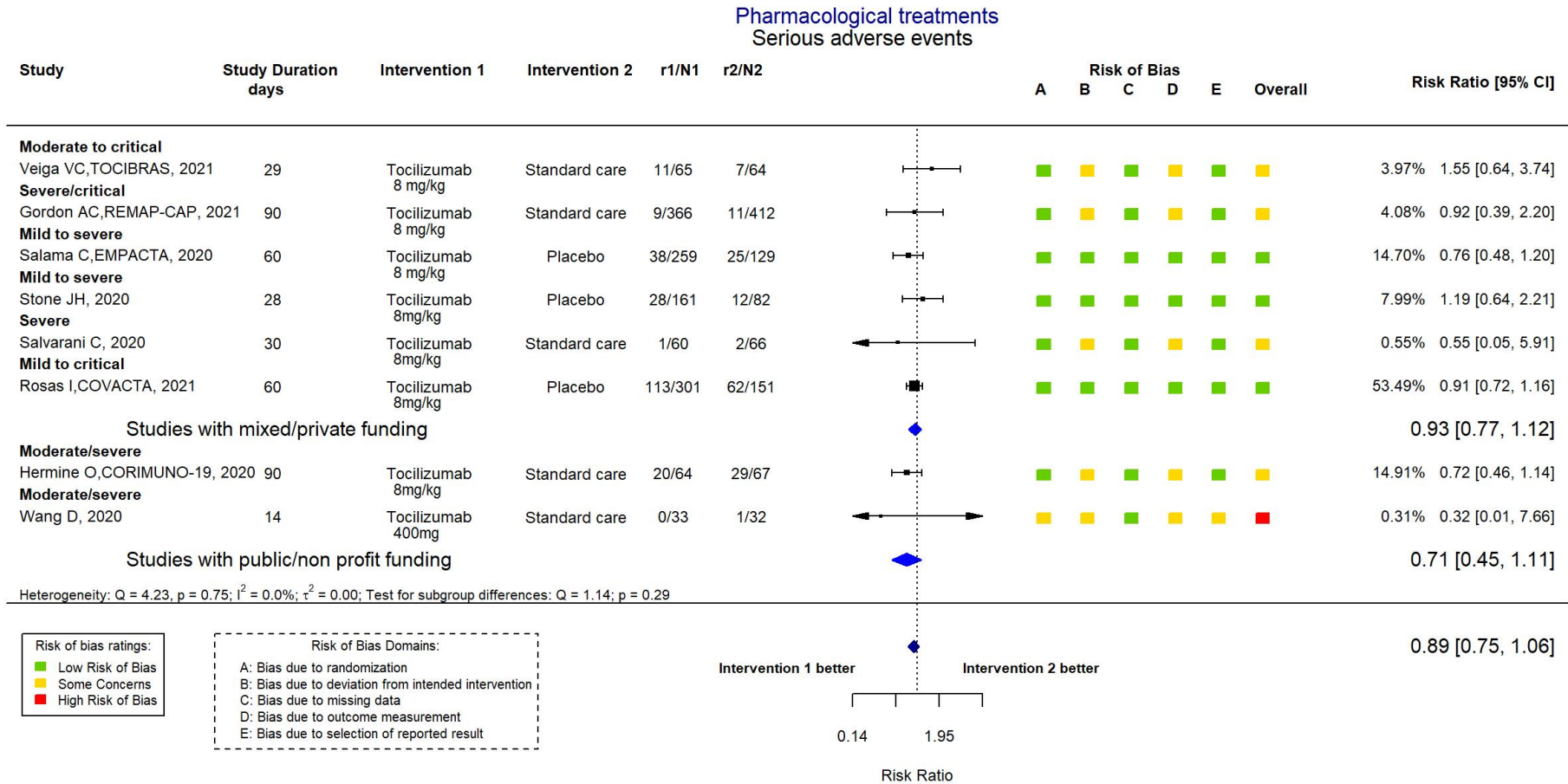
Subgroup analysis. 1.3.4 Funding. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60



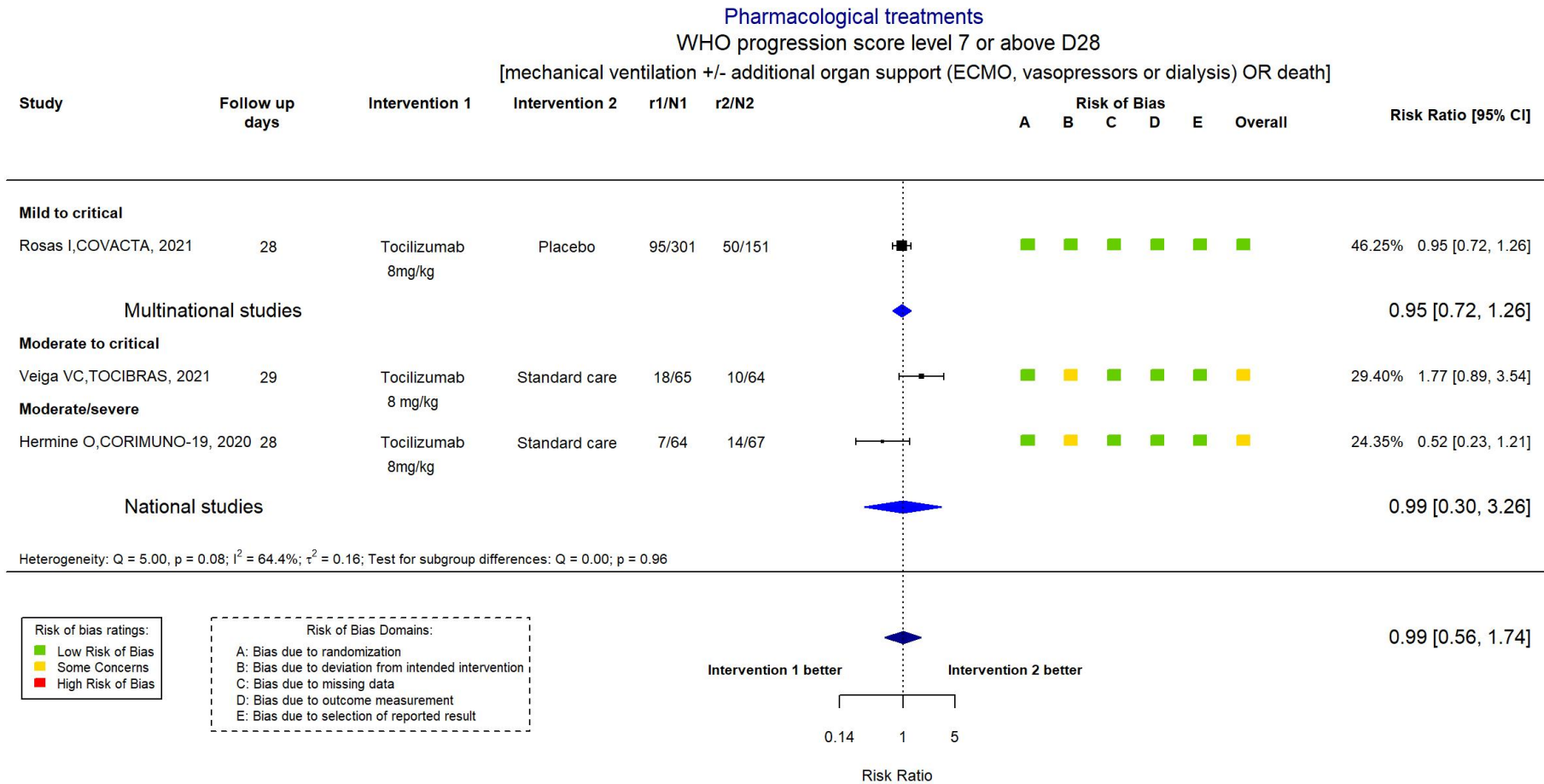
Subgroup analysis. 1.3.5 Funding. Tocilizumab versus placebo or standard care. Outcome: Adverse events



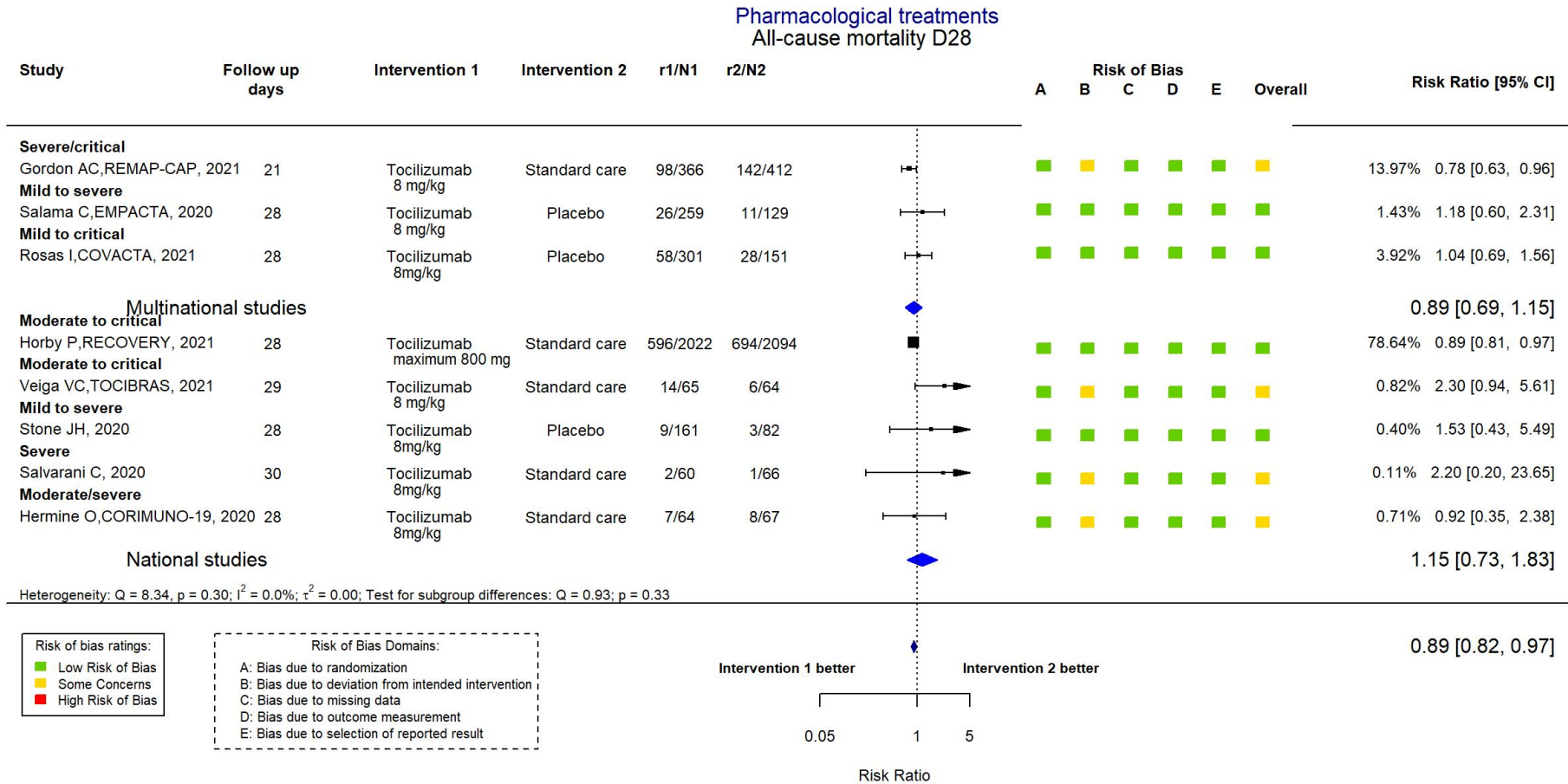
Subgroup analysis. 1.3.6 Funding. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events



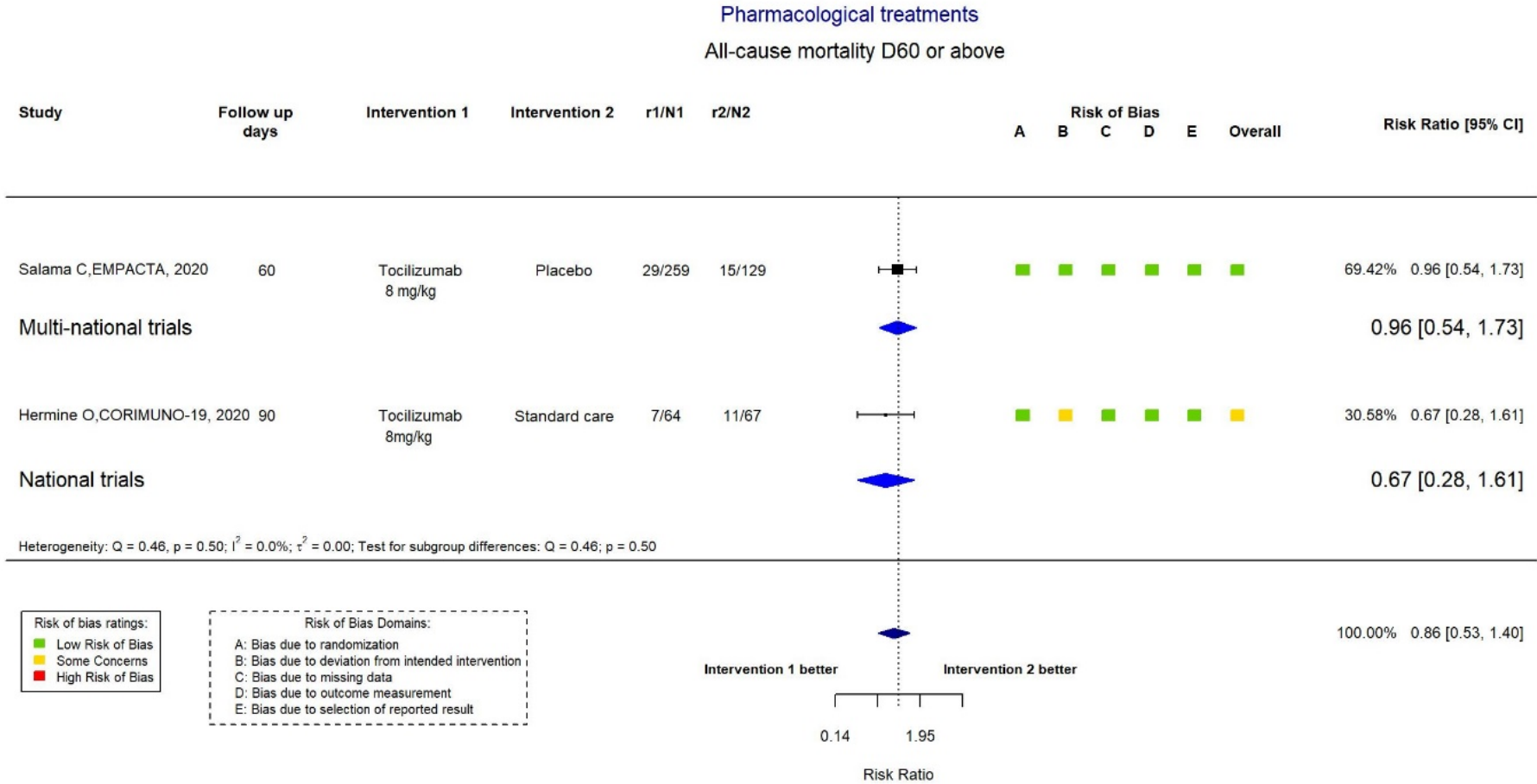
Subgroup analysis. 1.4.2 Location. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



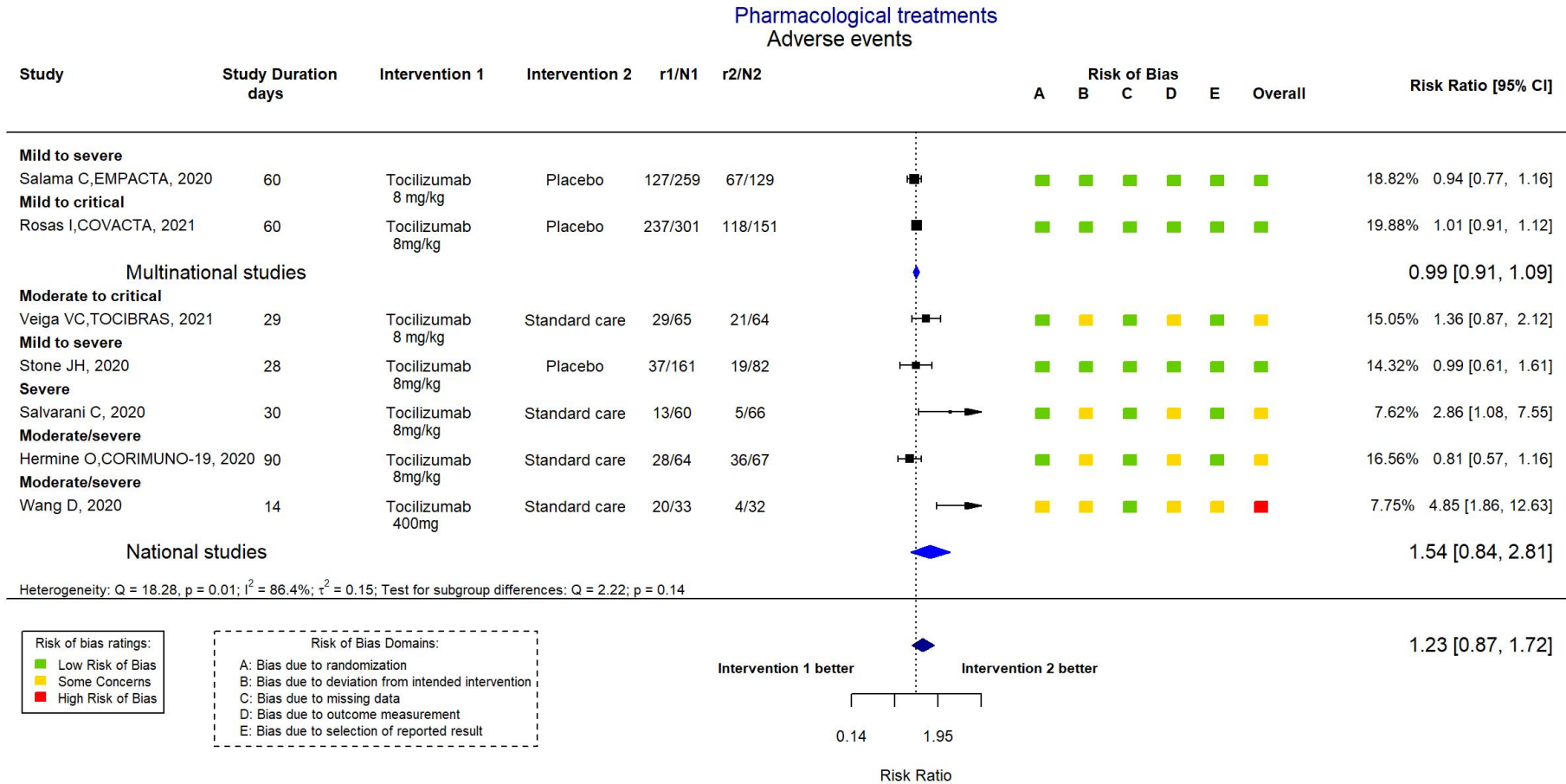
Subgroup analysis.1.4.3 Location. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



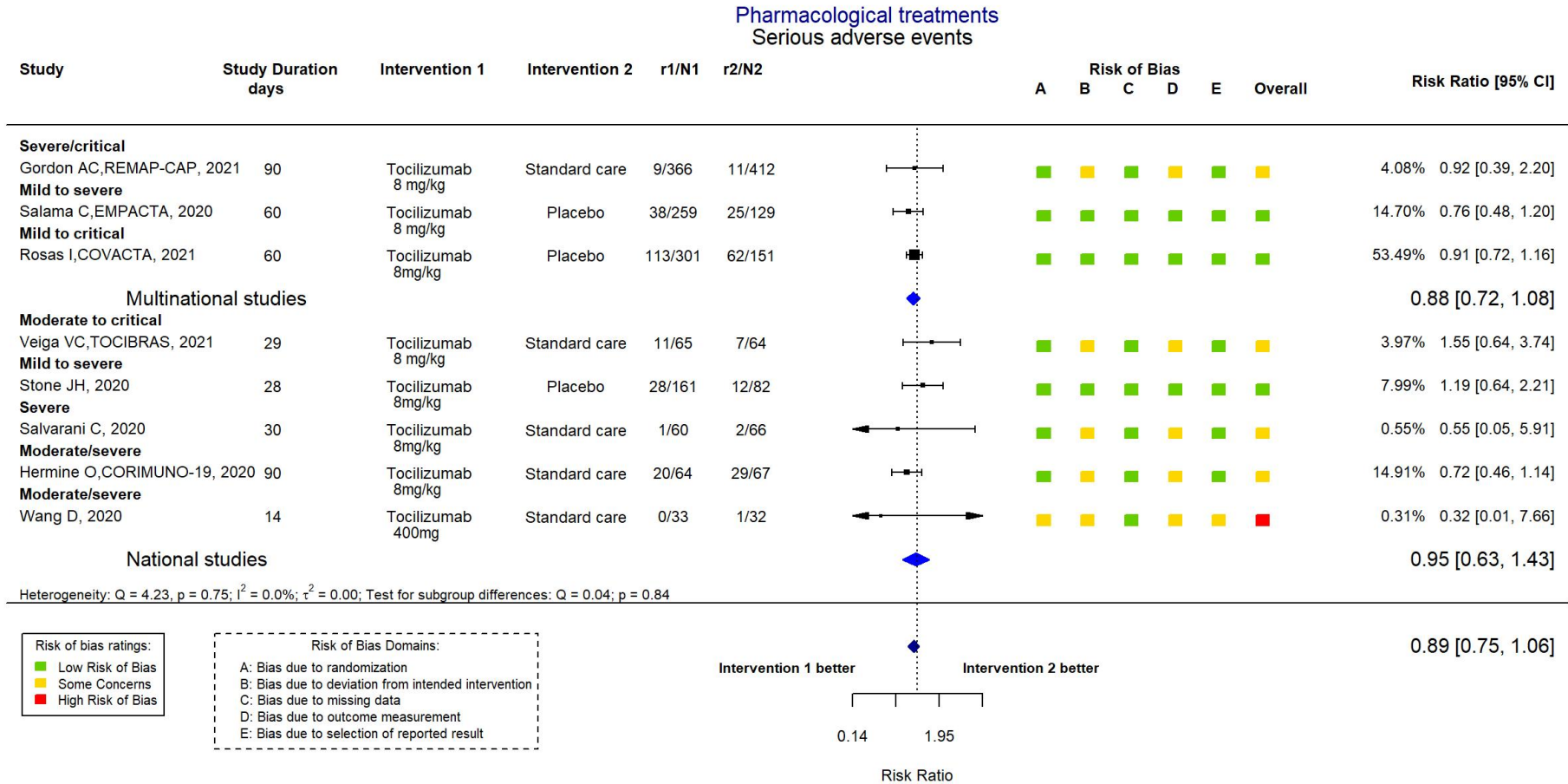
Subgroup analysis. 1.4.4 Location. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60



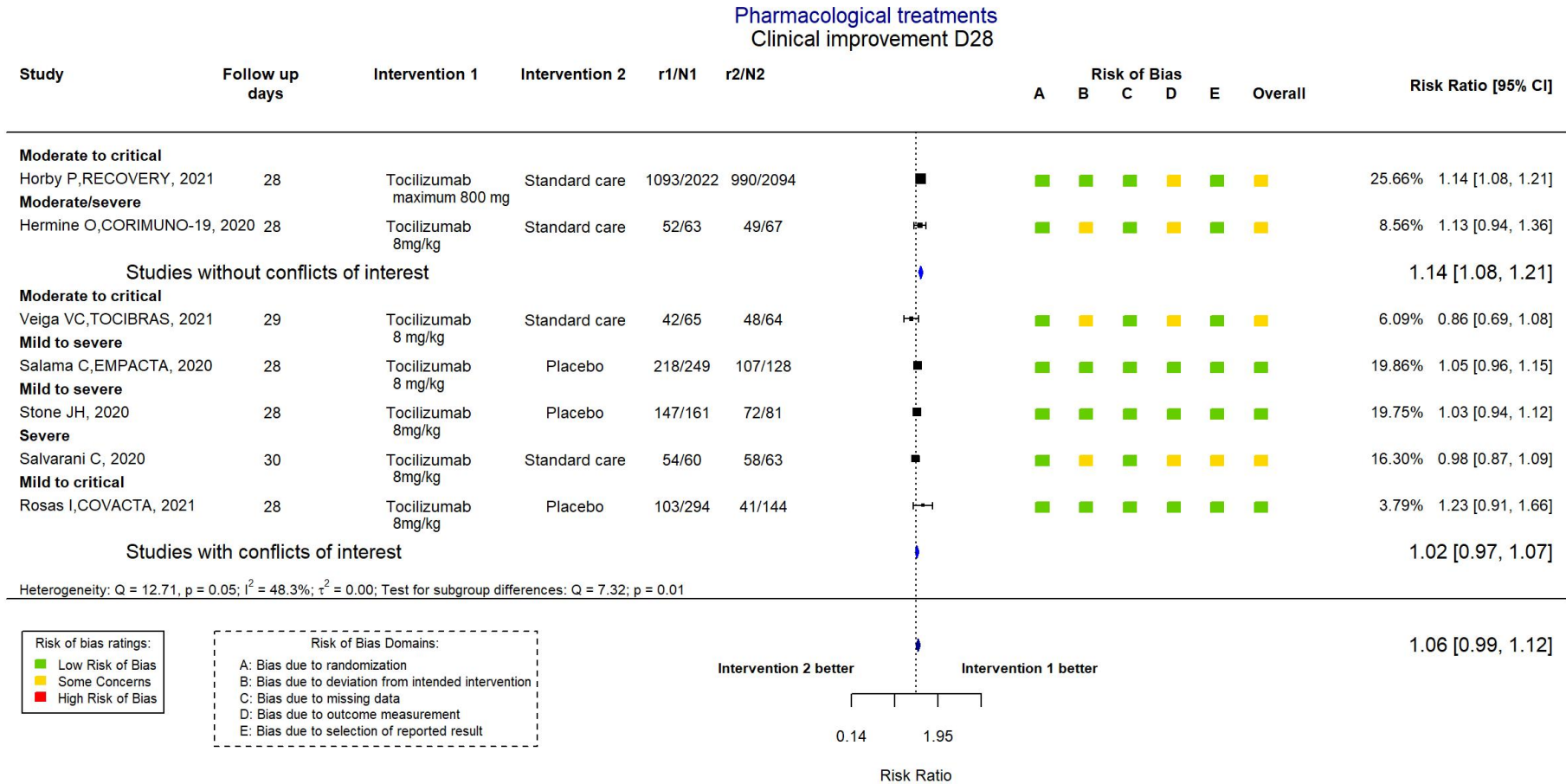
Subgroup analysis. 1.4.5 Location. Tocilizumab versus placebo or standard care. Outcome: Adverse events



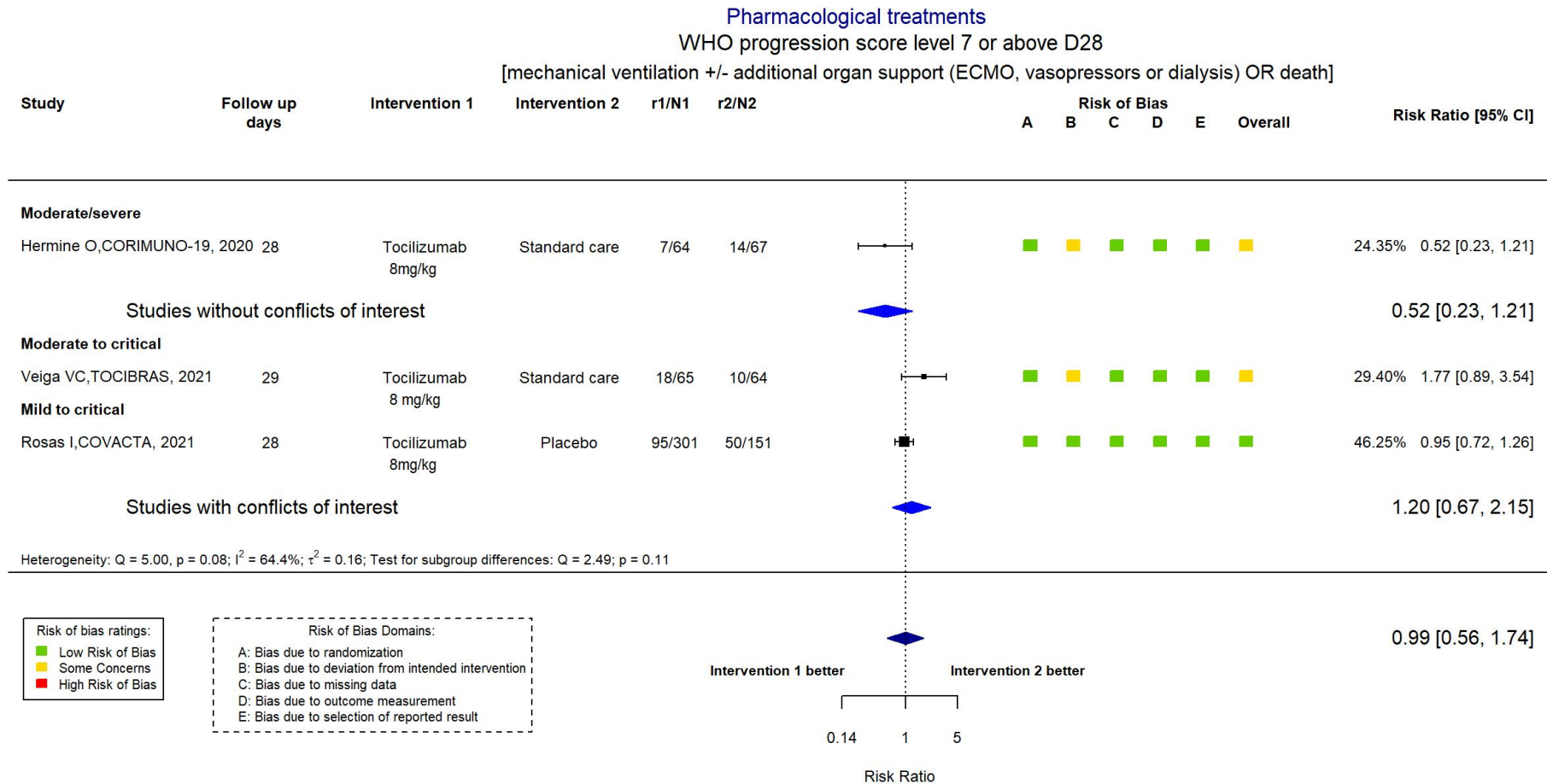
Subgroup analysis. 1.4.6 Location. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events



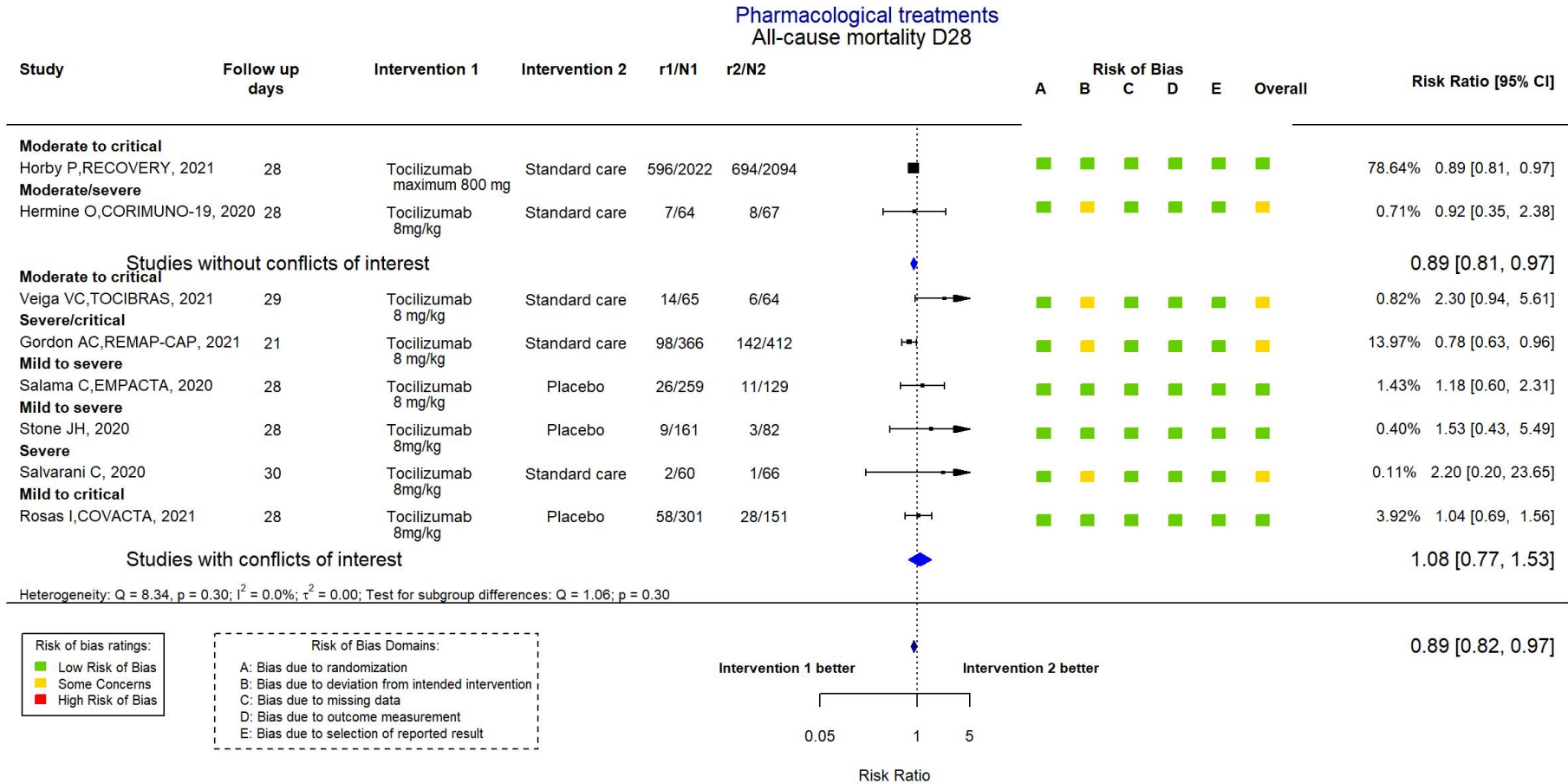
Subgroup analysis. 1.5.1 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28



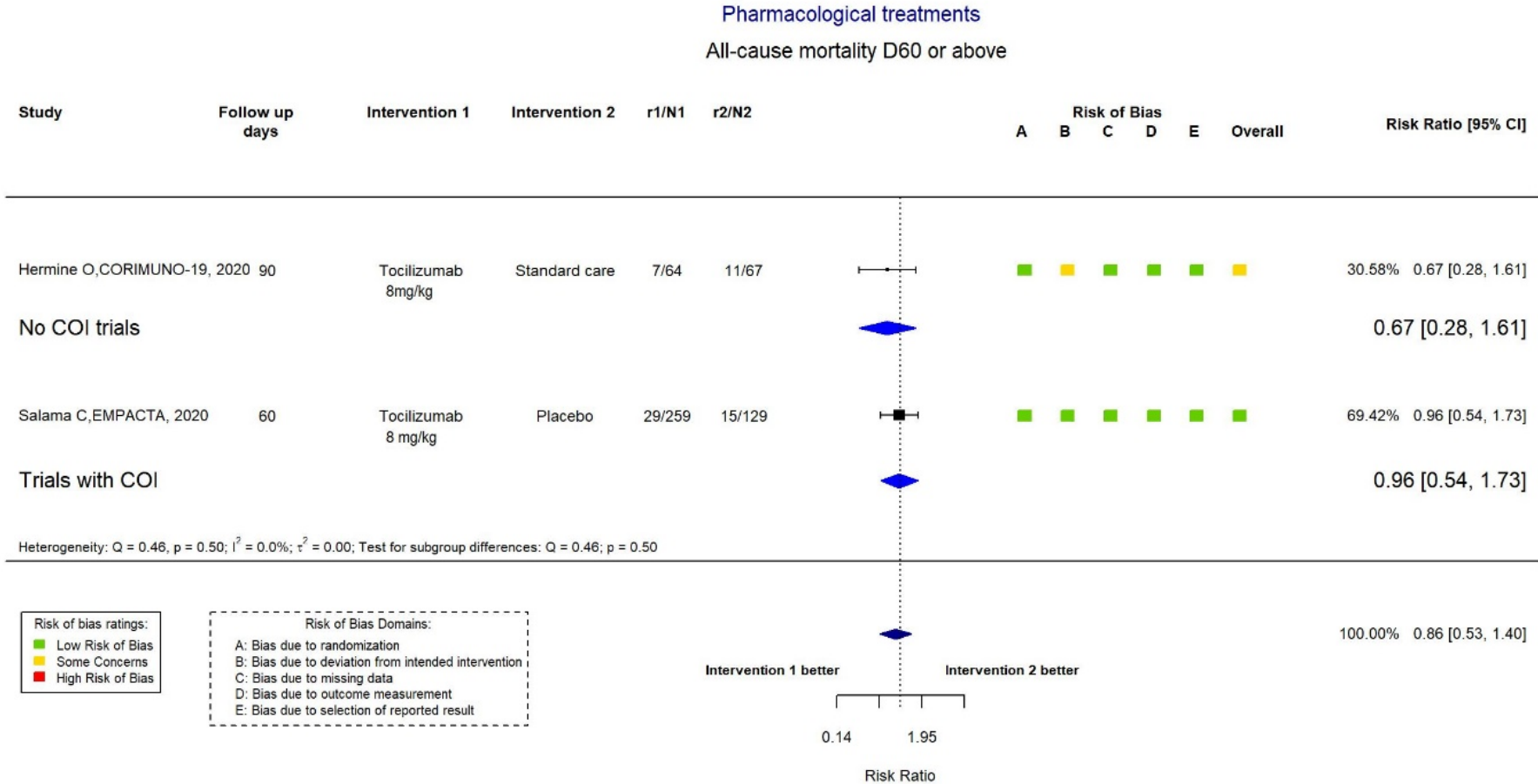
Subgroup analysis. 1.5.2 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



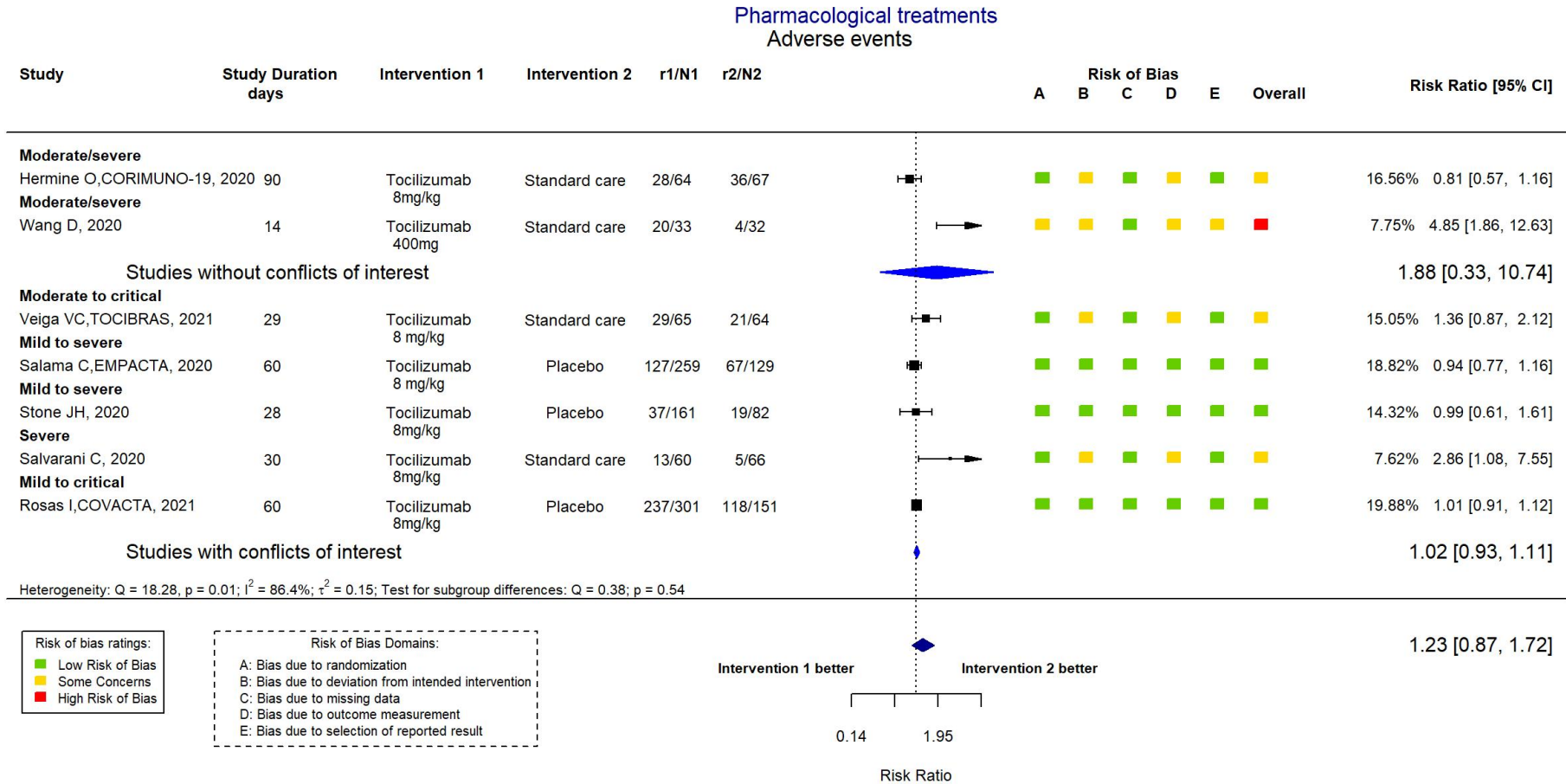
Subgroup analysis. 1.5.3 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



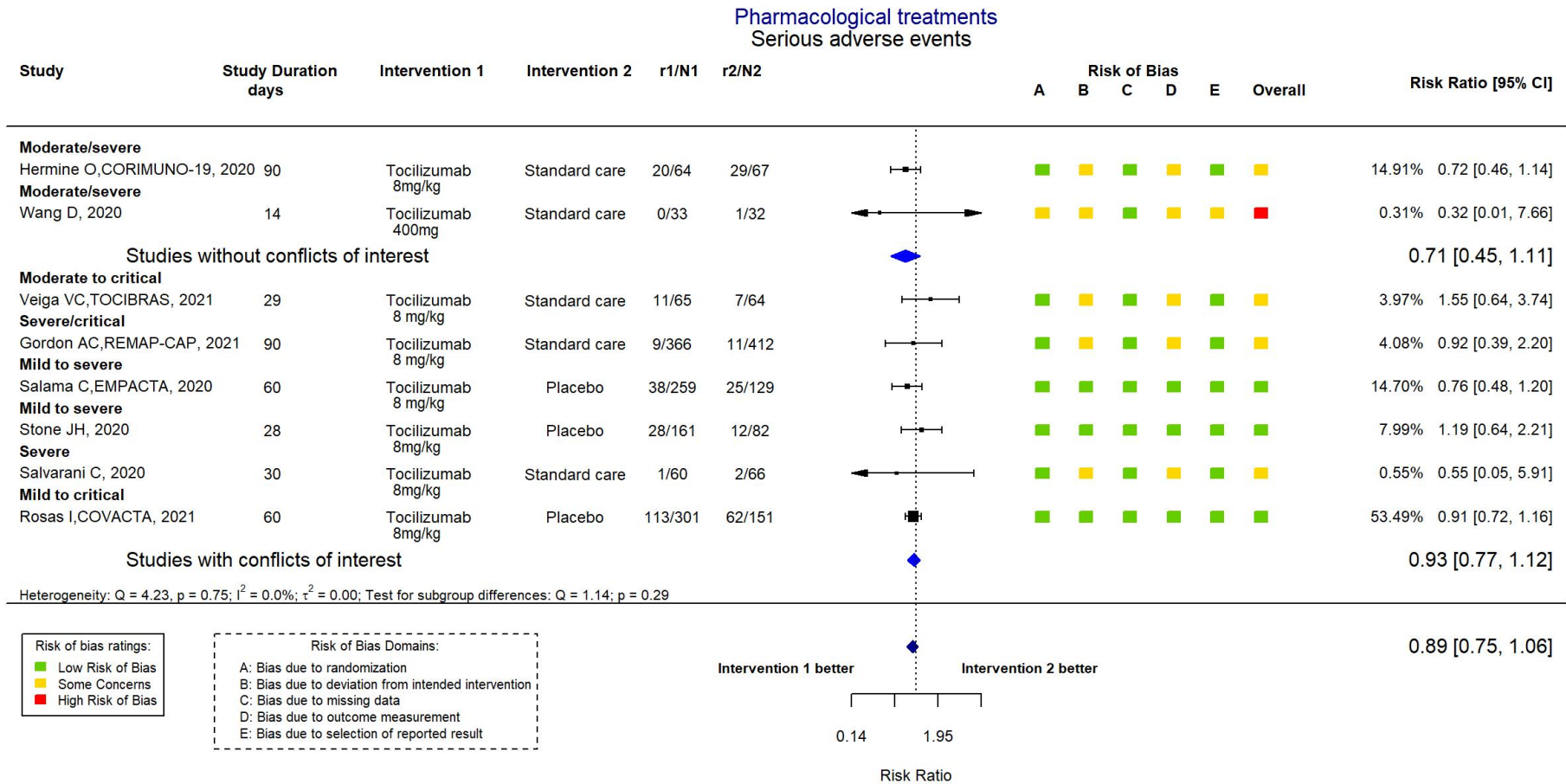
Subgroup analysis. 1.5.4 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60



Subgroup analysis. 1.5.5 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Adverse events

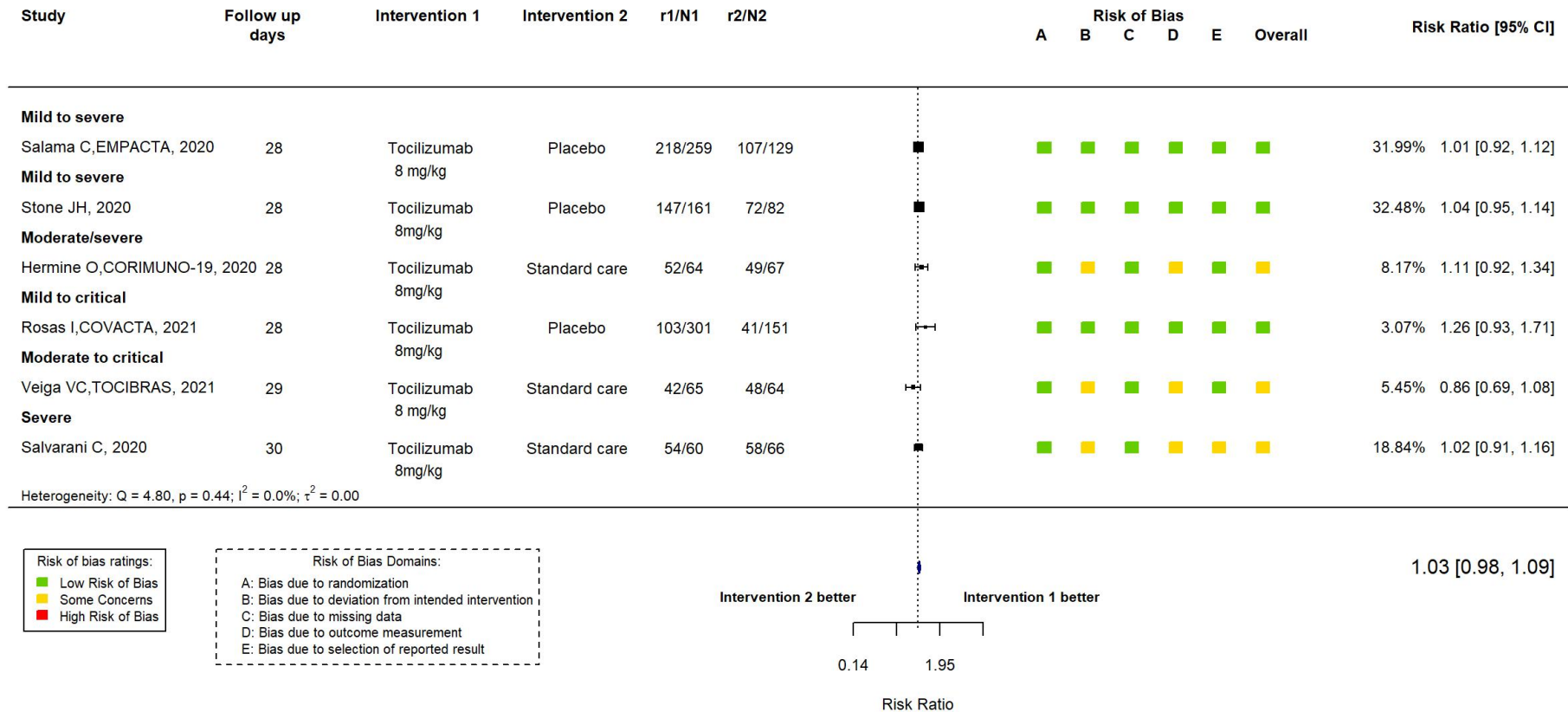


Subgroup analysis. 1.5.6 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Serious Adverse events

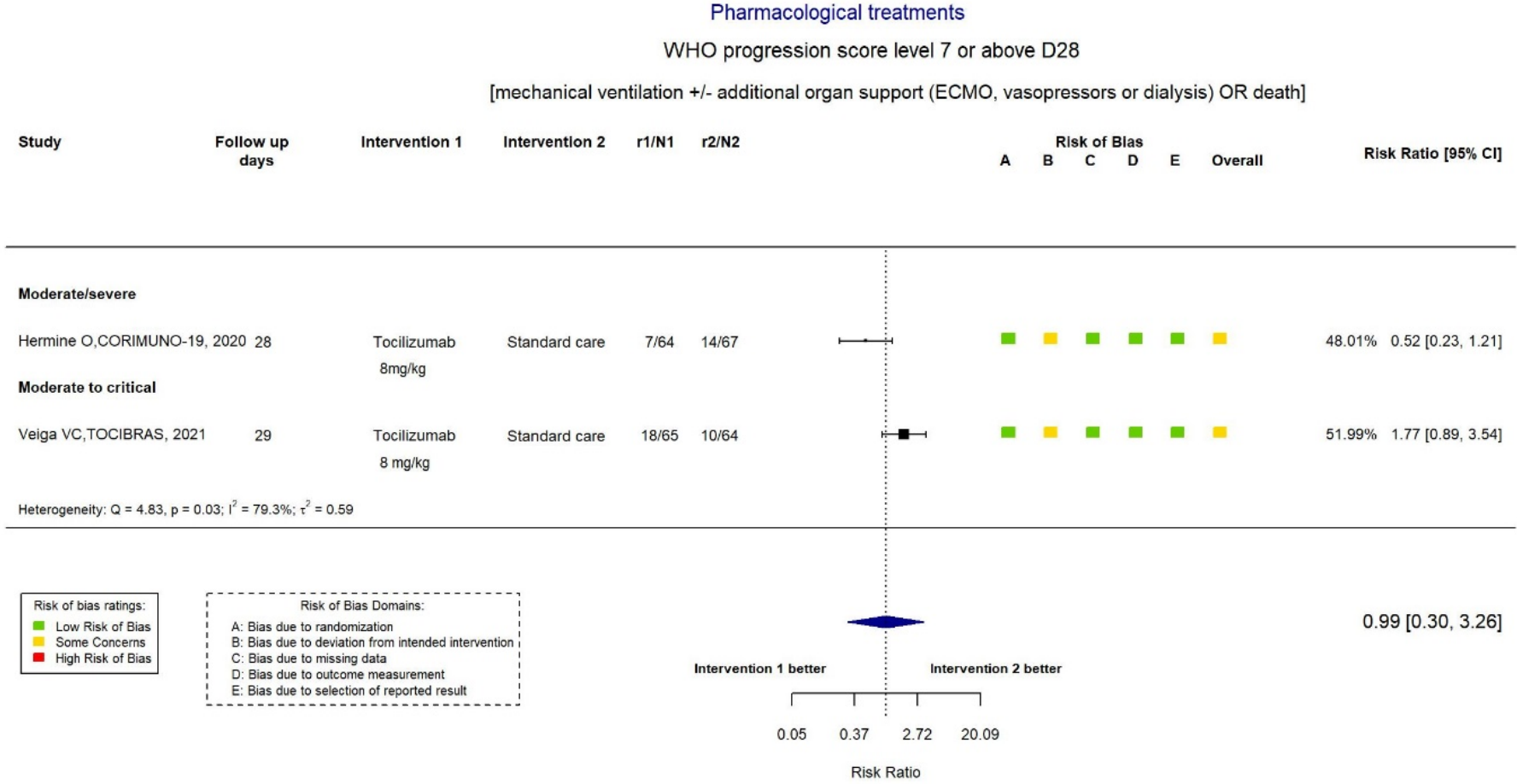


Sensitivity analysis 1.6.1 Published studies. Tocilizumab versus placebo or standard care. Outcome: Clinical Improvement D28. Published studies.

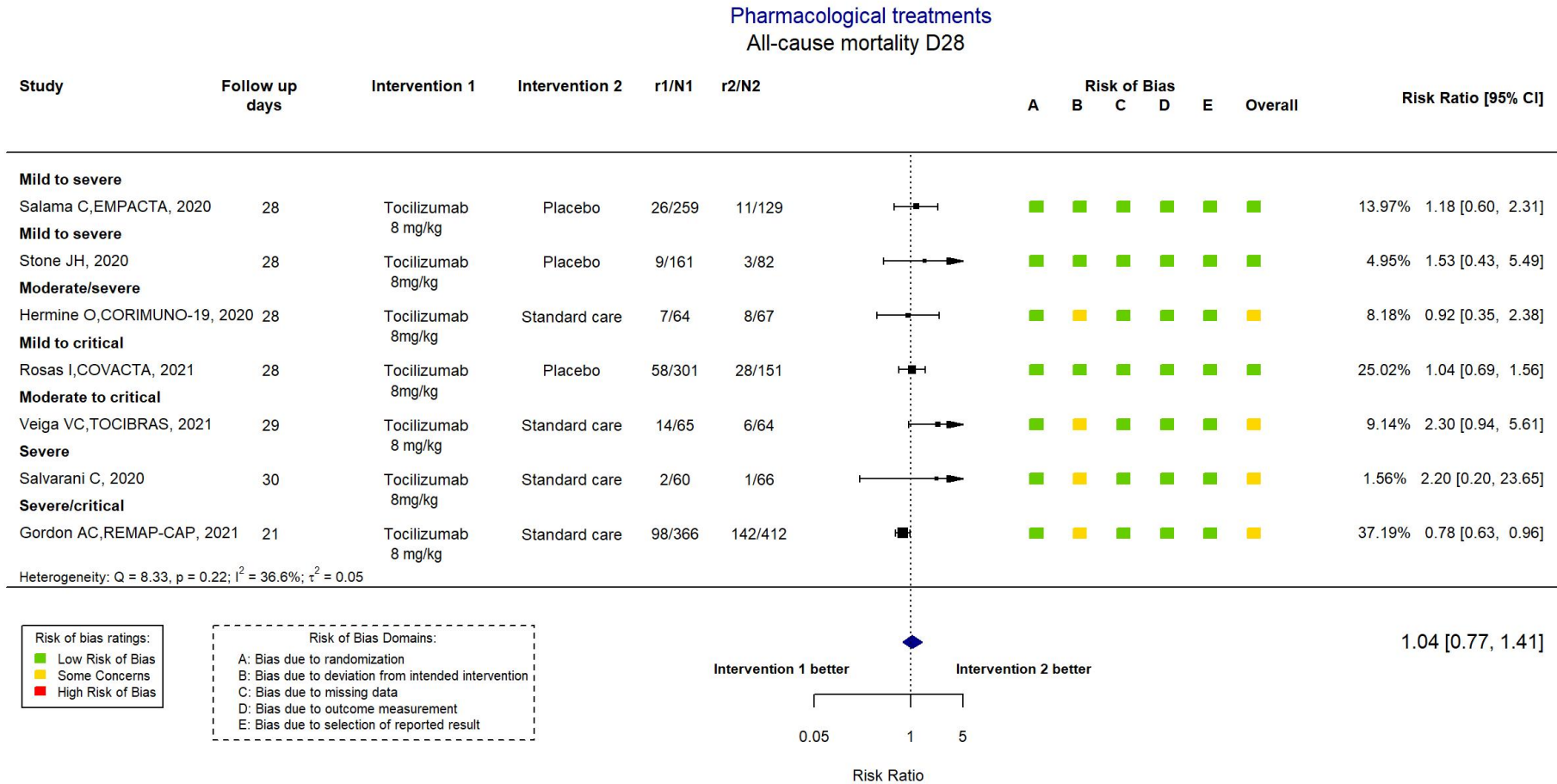
Pharmacological treatments
Clinical improvement D28



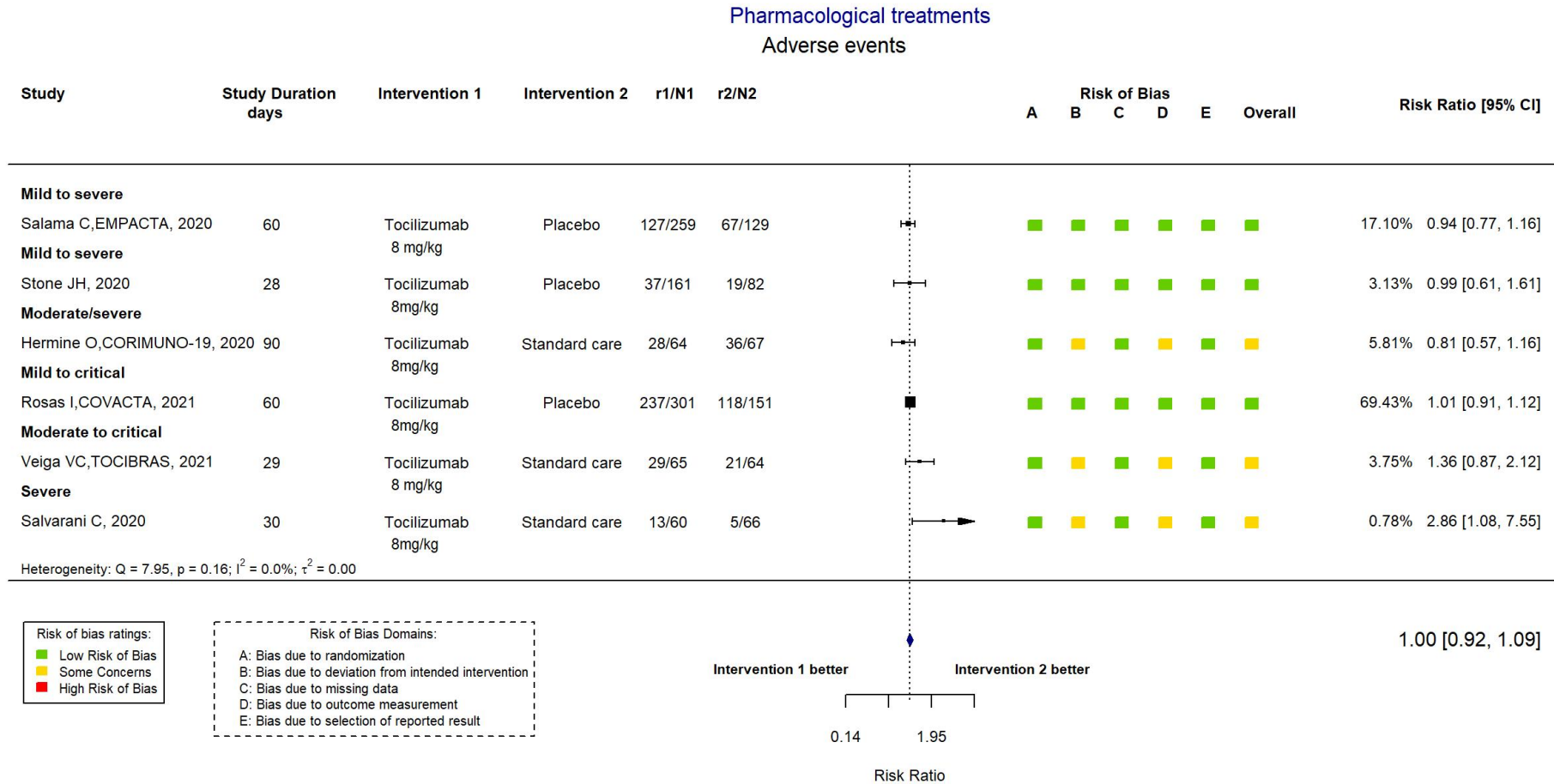
Sensitivity analysis 1.6.2 Published studies. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28.



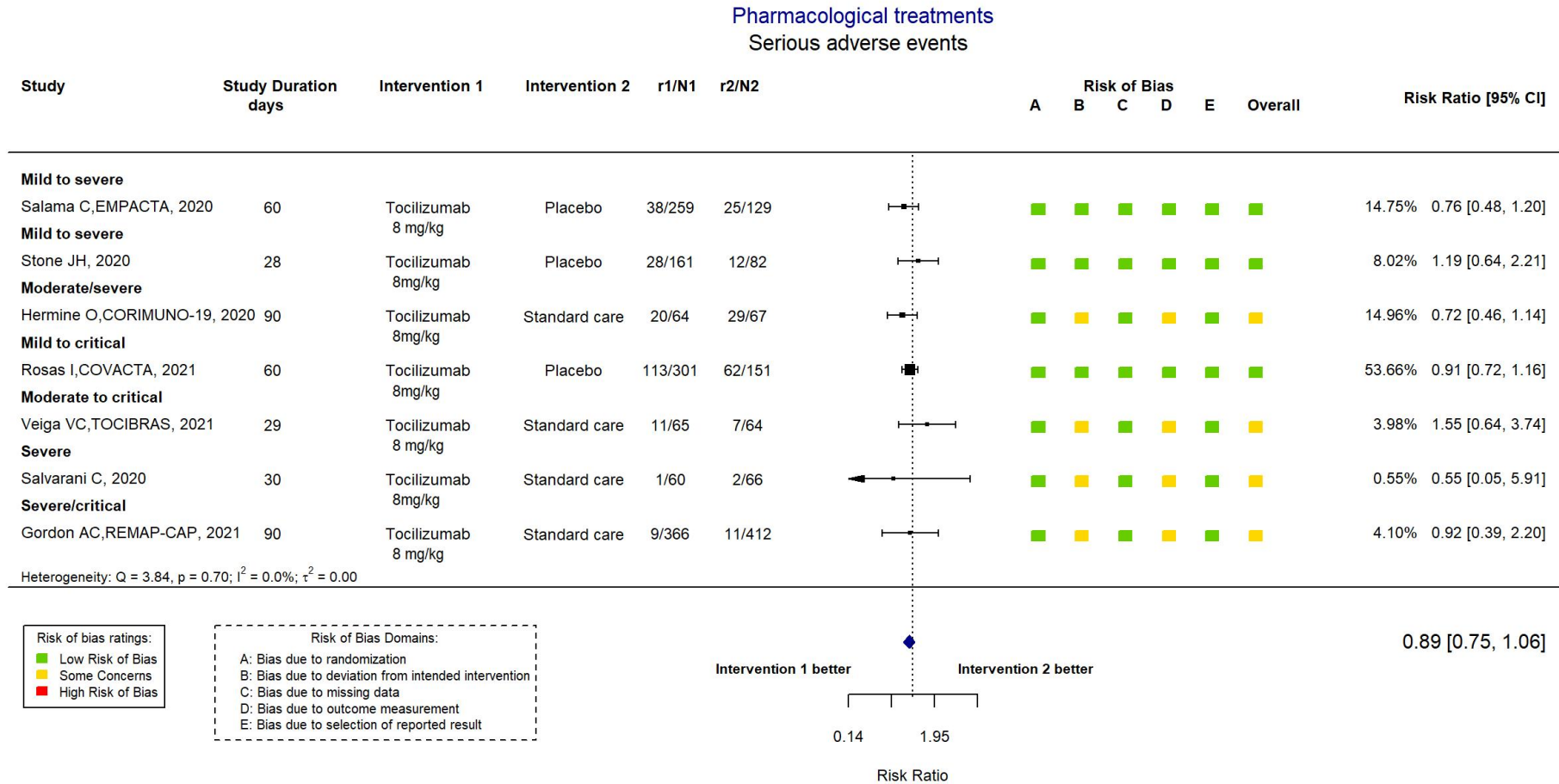
Sensitivity analysis 1.6.3 Published studies. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28.



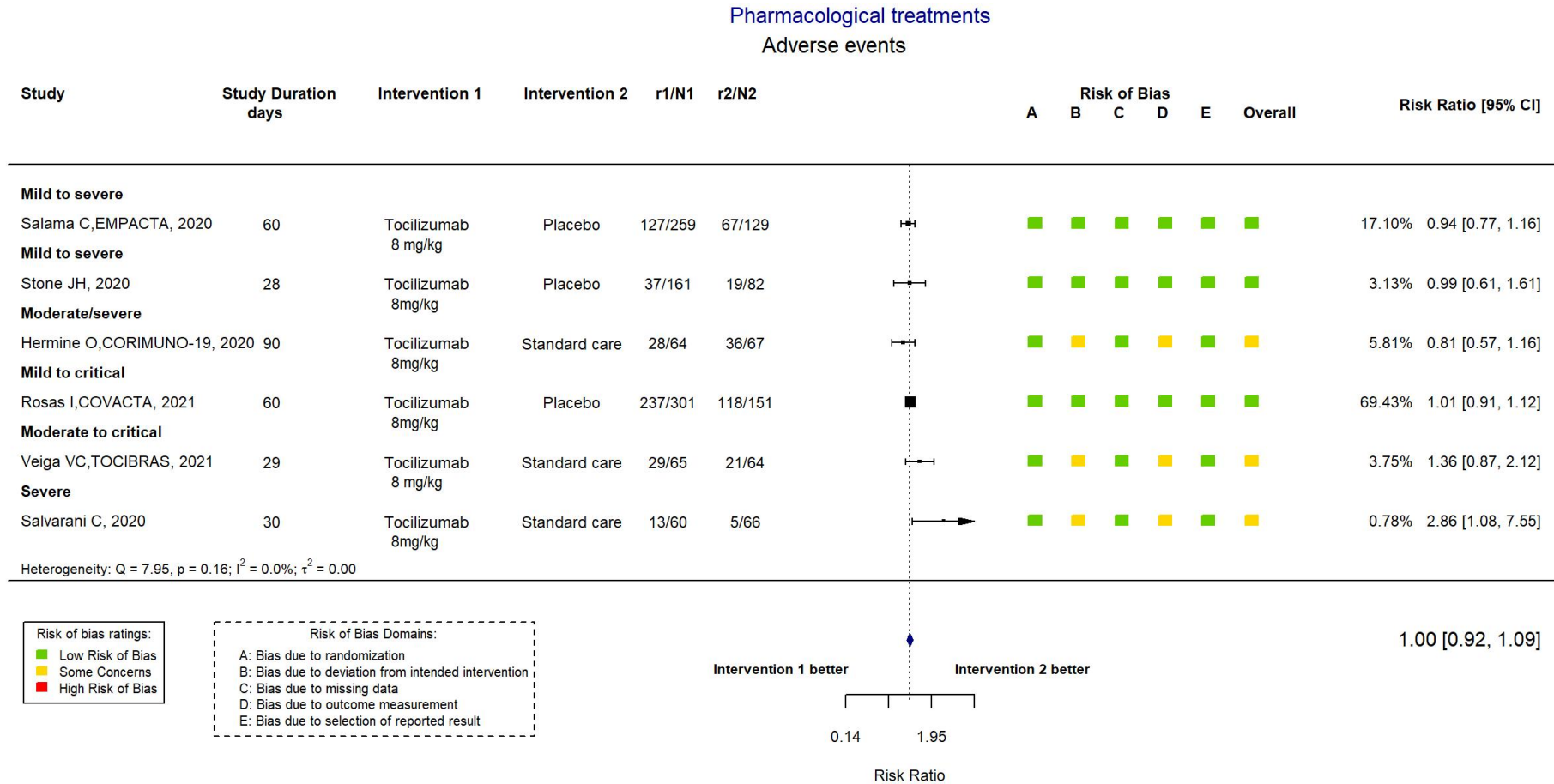
Sensitivity analysis 1.6.4 Published studies. Tocilizumab versus placebo or standard care. Outcome: Adverse events.



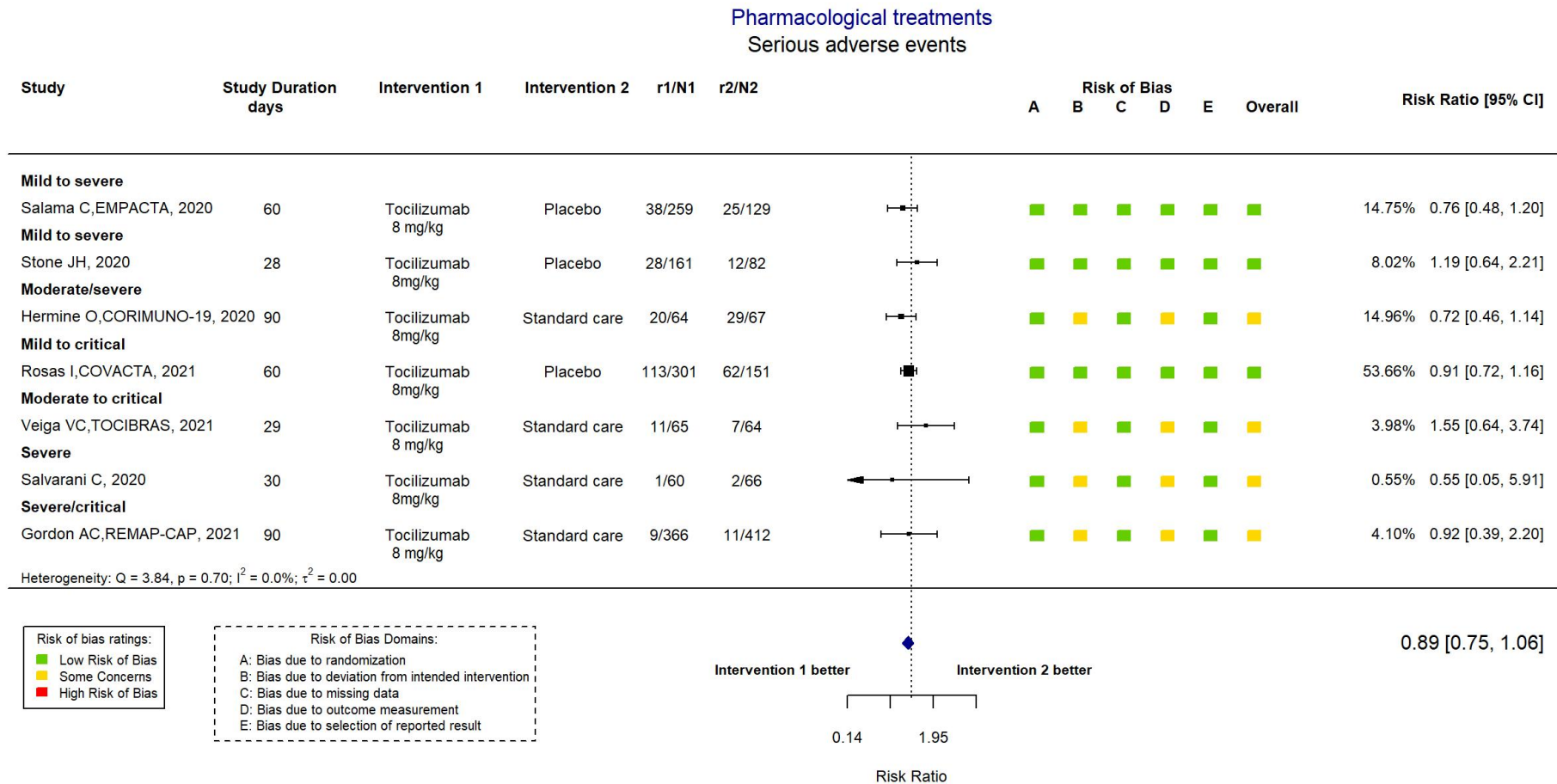
Sensitivity analysis 1.6.5 Published studies. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events.



Sensitivity analysis 1.7.1 Without studies at High risk of Bias. Tocilizumab versus placebo or standard care. Outcome: Adverse events.



Sensitivity analysis 1.7.2 Without studies at High risk of Bias. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events.



Sensitivity analysis 1.8.1 Severity. Tocilizumab versus placebo or standard care. Outcome: Clinical Improvement D28.

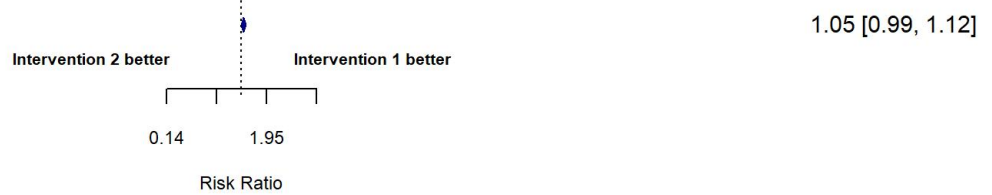
Pharmacological treatments
Clinical improvement D28

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]	
						A	B	C	D	E			
Mild to severe													
Salama C, EMPACTA, 2020	28	Tocilizumab 8 mg/kg	Placebo	218/259	107/129	■	■	■	■	■	■	20.55%	1.01 [0.92, 1.12]
Mild to severe													
Stone JH, 2020	28	Tocilizumab 8mg/kg	Placebo	147/161	72/82	■	■	■	■	■	■	20.69%	1.04 [0.95, 1.14]
Moderate/severe													
Hermine O, CORIMUNO-19, 2020	28	Tocilizumab 8mg/kg	Standard care	52/64	49/67	■	■	■	■	■	■	8.62%	1.11 [0.92, 1.34]
Moderate to critical													
Horby P, RECOVERY, 2021	28	Tocilizumab maximum 800 mg	Standard care	1093/2022	990/2094	■	■	■	■	■	■	28.52%	1.14 [1.08, 1.21]
Moderate to critical													
Veiga VC, TOCIBRAS, 2021	29	Tocilizumab 8 mg/kg	Standard care	42/65	48/64	■	■	■	■	■	■	6.20%	0.86 [0.69, 1.08]
Severe													
Salvarani C, 2020	30	Tocilizumab 8mg/kg	Standard care	54/60	58/66	■	■	■	■	■	■	15.43%	1.02 [0.91, 1.16]

Heterogeneity: Q = 10.21, p = 0.07; I² = 46.5%; τ² = 0.00

Risk of bias ratings:
 ■ Low Risk of Bias
 ■ Some Concerns
 ■ High Risk of Bias

Risk of Bias Domains:
 A: Bias due to randomization
 B: Bias due to deviation from intended intervention
 C: Bias due to missing data
 D: Bias due to outcome measurement
 E: Bias due to selection of reported result



Sensitivity analysis 1.8.2 Severity. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28.

Pharmacological treatments

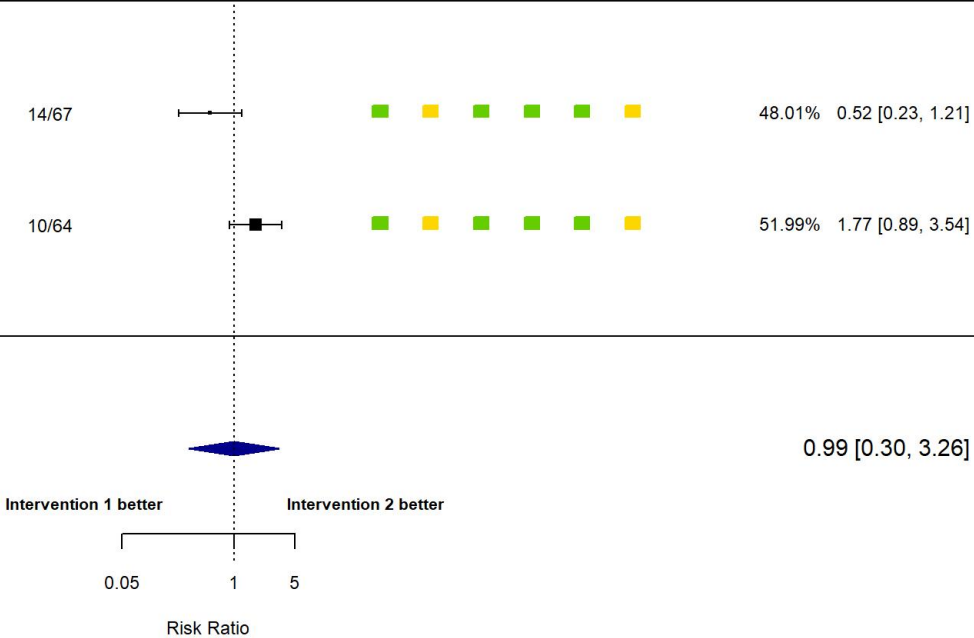
WHO progression score level 7 or above D28

[mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death]

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]	
						A	B	C	D	E			
Moderate/severe													
Hermine O,CORIMUNO-19, 2020	28	Tocilizumab 8mg/kg	Standard care	7/64	14/67	Low	Some	Low	Low	Low	Some	48.01%	0.52 [0.23, 1.21]
Moderate to critical													
Veiga VC,TOCIBRAS, 2021	29	Tocilizumab 8 mg/kg	Standard care	18/65	10/64	Low	Some	Low	Low	Low	Some	51.99%	1.77 [0.89, 3.54]
Heterogeneity: Q = 4.83, p = 0.03; I ² = 79.3%; τ ² = 0.59													

Risk of bias ratings:
 Low Risk of Bias
 Some Concerns
 High Risk of Bias

Risk of Bias Domains:
 A: Bias due to randomization
 B: Bias due to deviation from intended intervention
 C: Bias due to missing data
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Sensitivity analysis 1.8.3 Severity. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28.

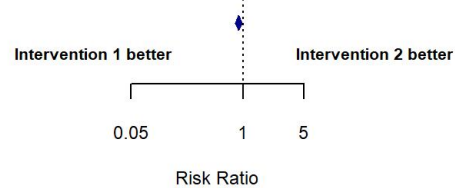
Pharmacological treatments
All-cause mortality D28

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]			
						A	B	C	D	E					
Mild to severe															
Salama C, EMPACTA, 2020	28	Tocilizumab 8 mg/kg	Placebo	26/259	11/129							1.49%	1.18 [0.60, 2.31]		
Mild to severe															
Stone JH, 2020	28	Tocilizumab 8mg/kg	Placebo	9/161	3/82							0.41%	1.53 [0.43, 5.49]		
Moderate/severe															
Hermine O, CORIMUNO-19, 2020	28	Tocilizumab 8mg/kg	Standard care	7/64	8/67							0.74%	0.92 [0.35, 2.38]		
Moderate to critical															
Horby P, RECOVERY, 2021	28	Tocilizumab maximum 800 mg	Standard care	596/2022	694/2094							81.85%	0.89 [0.81, 0.97]		
Moderate to critical															
Veiga VC, TOCIBRAS, 2021	29	Tocilizumab 8 mg/kg	Standard care	14/65	6/64							0.85%	2.30 [0.94, 5.61]		
Severe															
Salvarani C, 2020	30	Tocilizumab 8mg/kg	Standard care	2/60	1/66							0.12%	2.20 [0.20, 23.65]		
Severe/critical															
Gordon AC, REMAP-CAP, 2021	21	Tocilizumab 8 mg/kg	Standard care	98/366	142/412							14.54%	0.78 [0.63, 0.96]		

Heterogeneity: Q = 7.77, p = 0.26; I² = 0.0%; τ² = 0.00

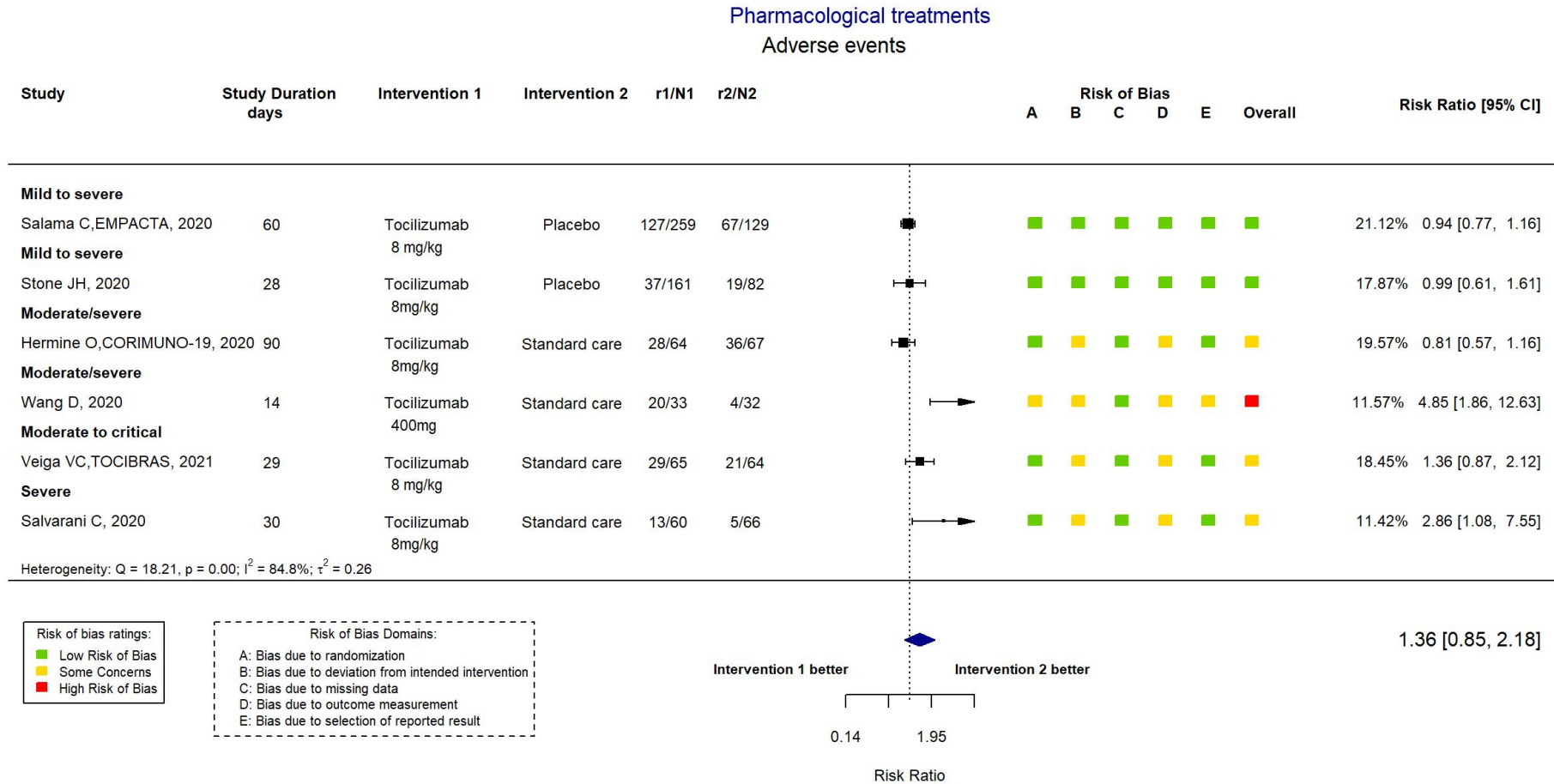
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Risk of Bias Domains:
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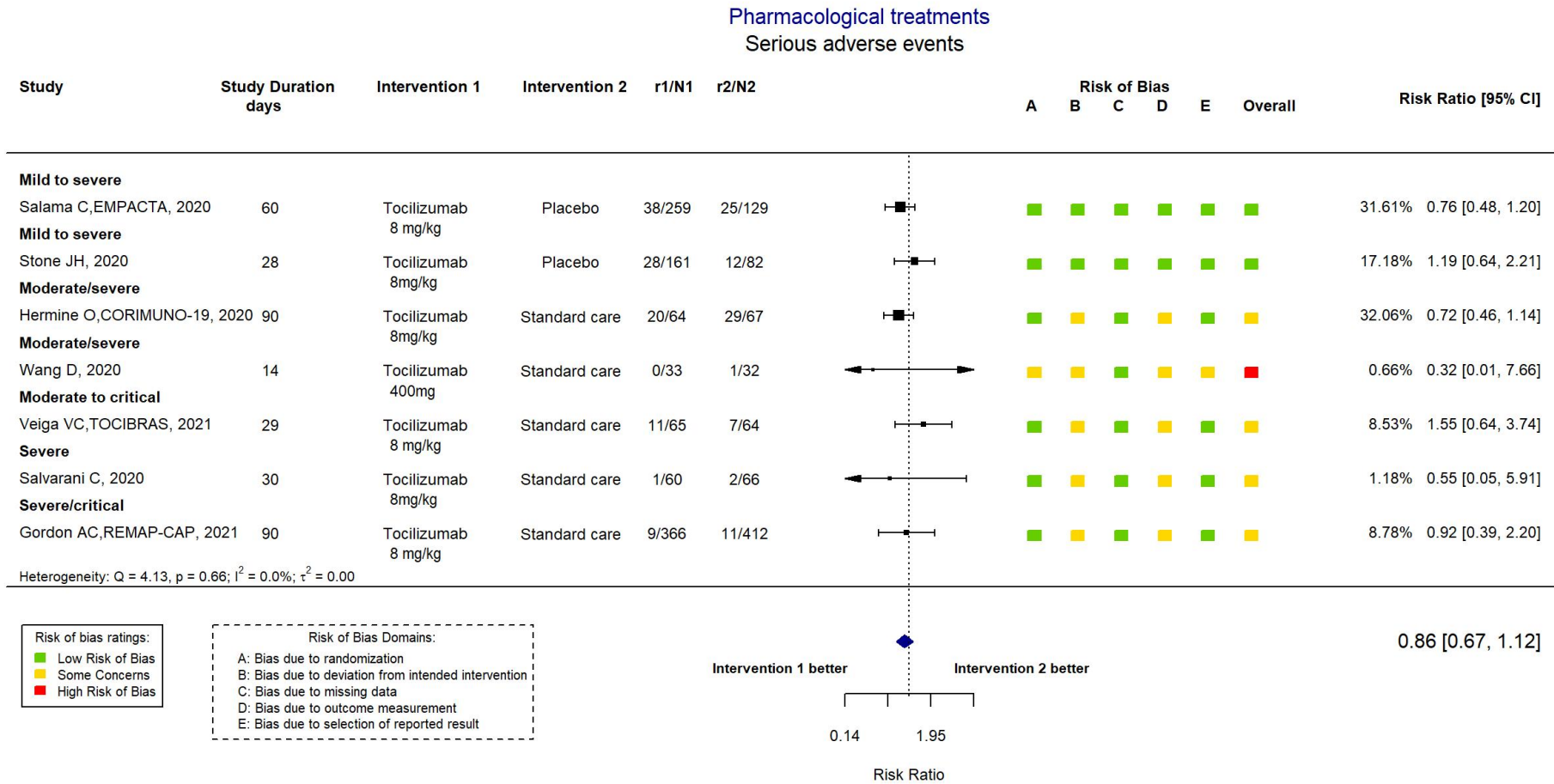


0.89 [0.82, 0.96]

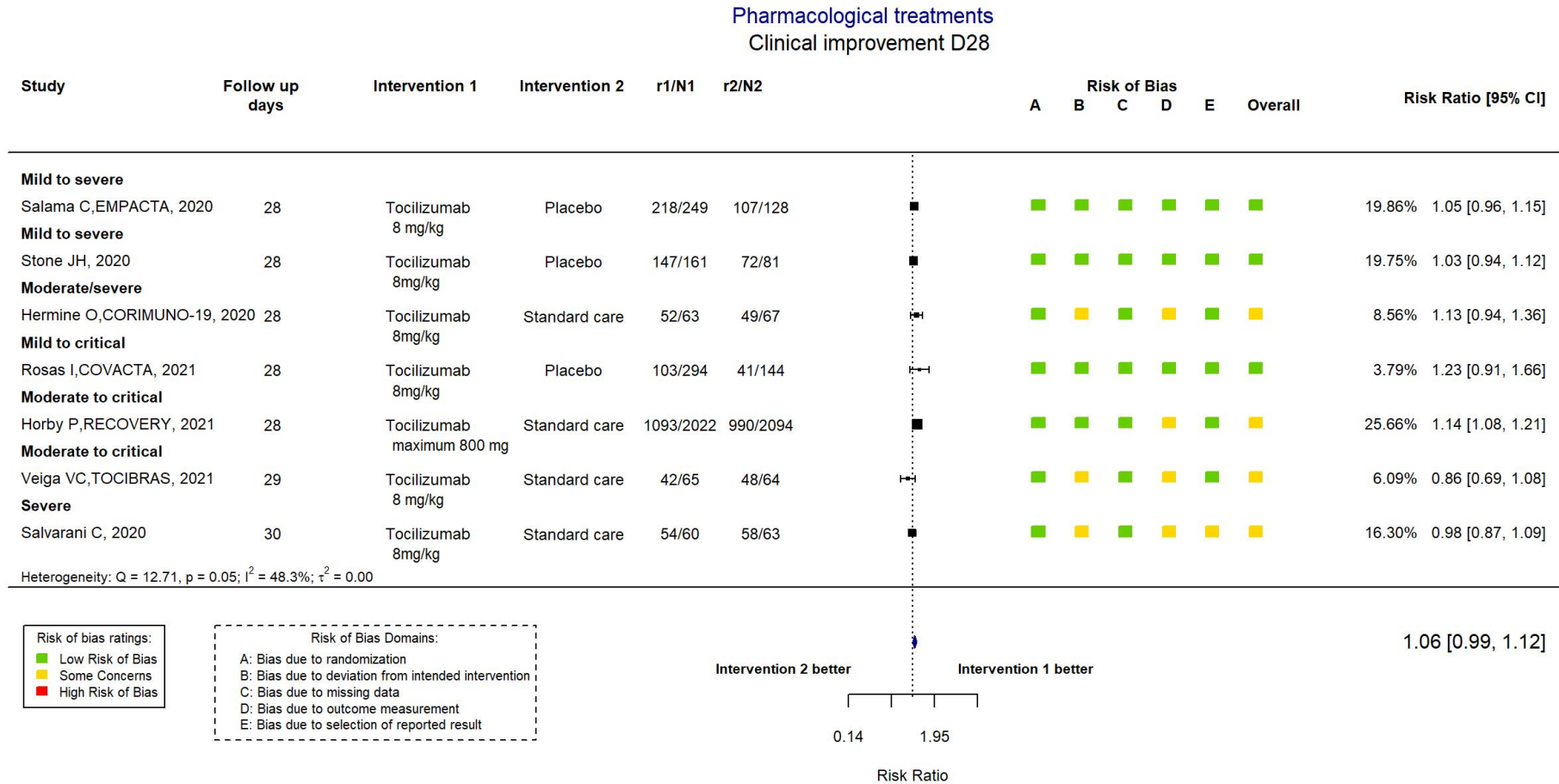
Sensitivity analysis 1.8.4 Severity. Tocilizumab versus placebo or standard care. Outcome: Adverse events.



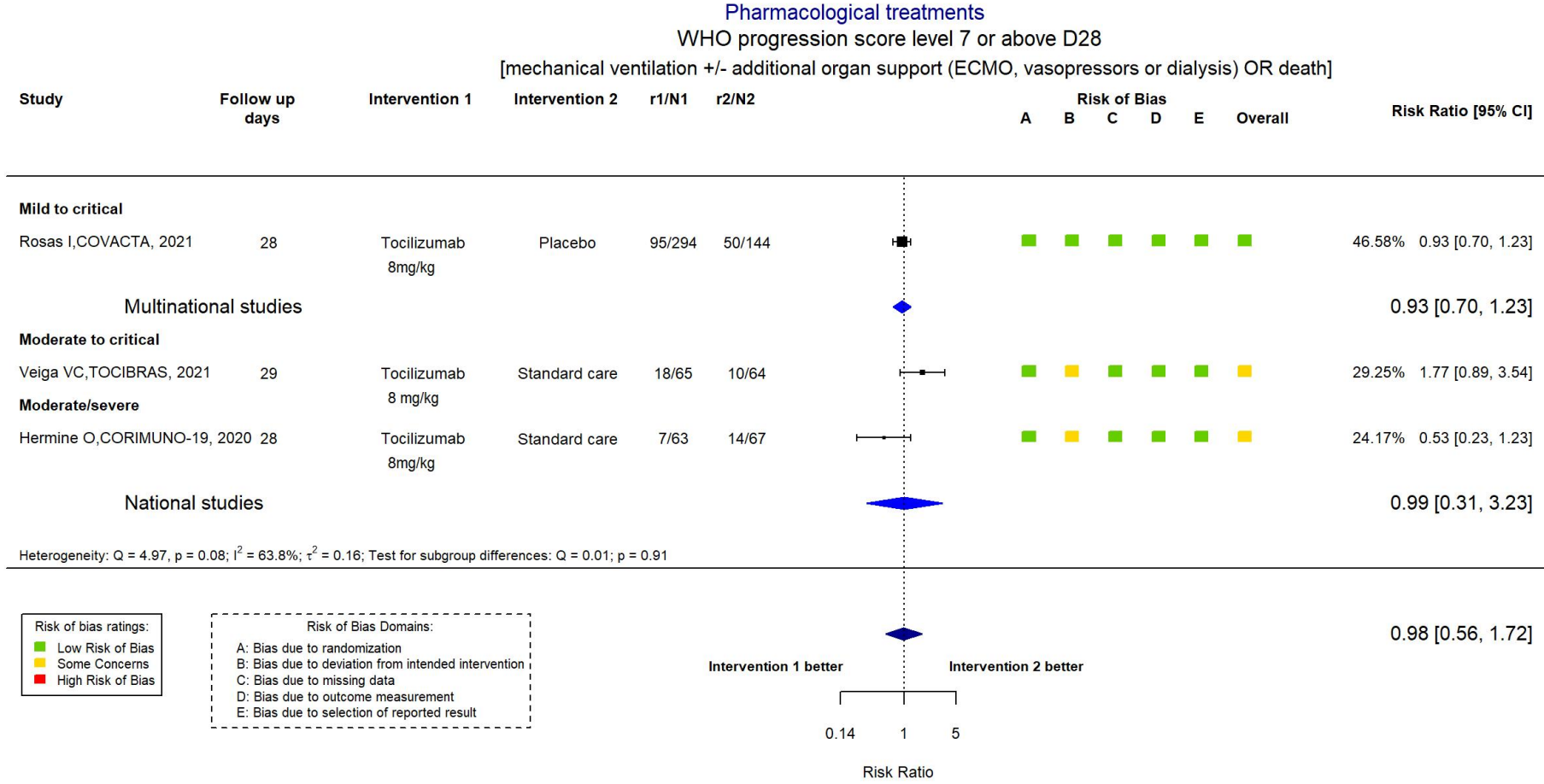
Sensitivity analysis 1.8.5 Severity. Tocilizumab versus placebo or standard care. Outcome: Serious Adverse events.



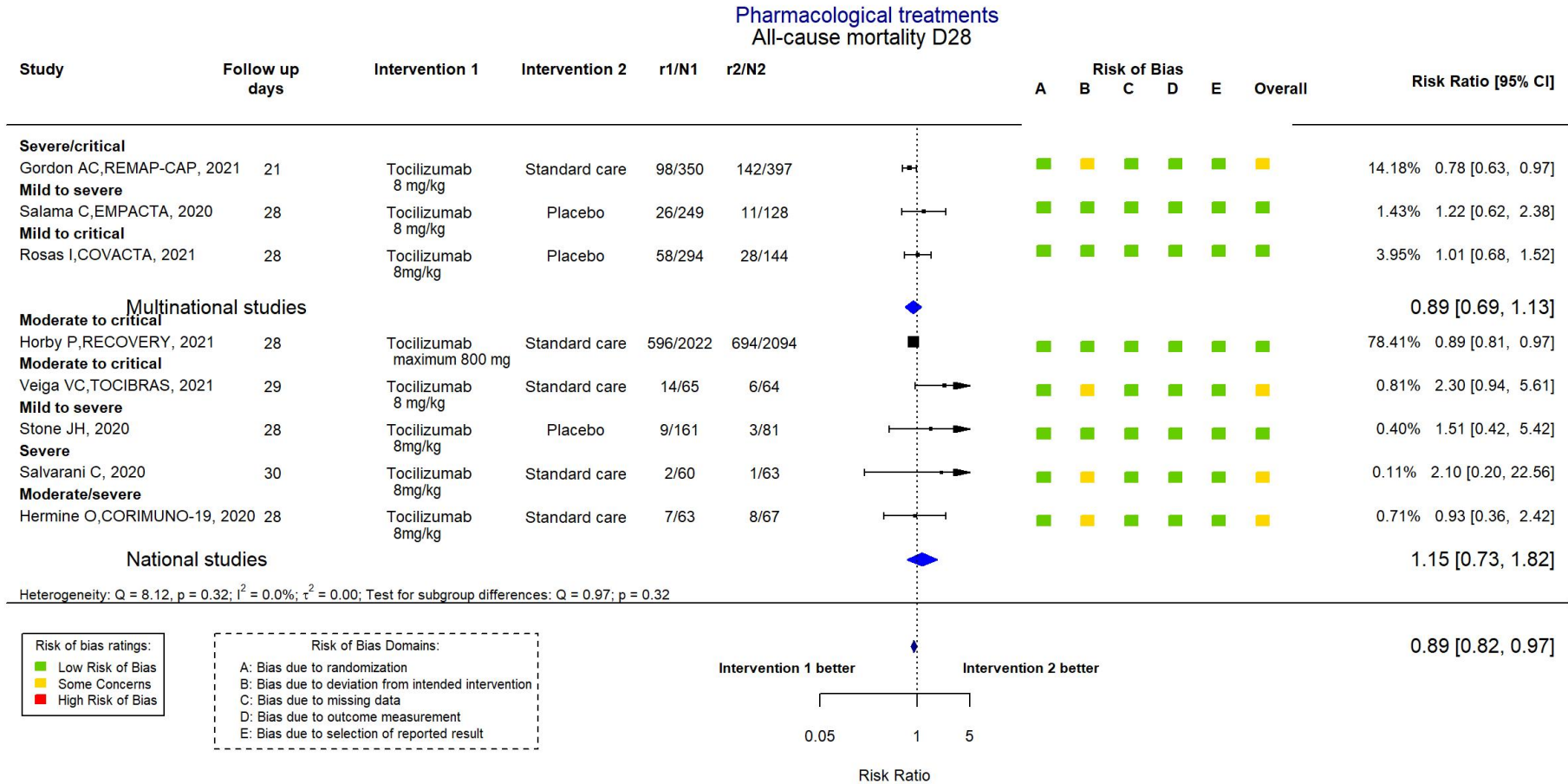
Sensitivity analysis 1.9.1 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: Clinical Improvement D28.



Sensitivity analysis 1.9.2 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28.



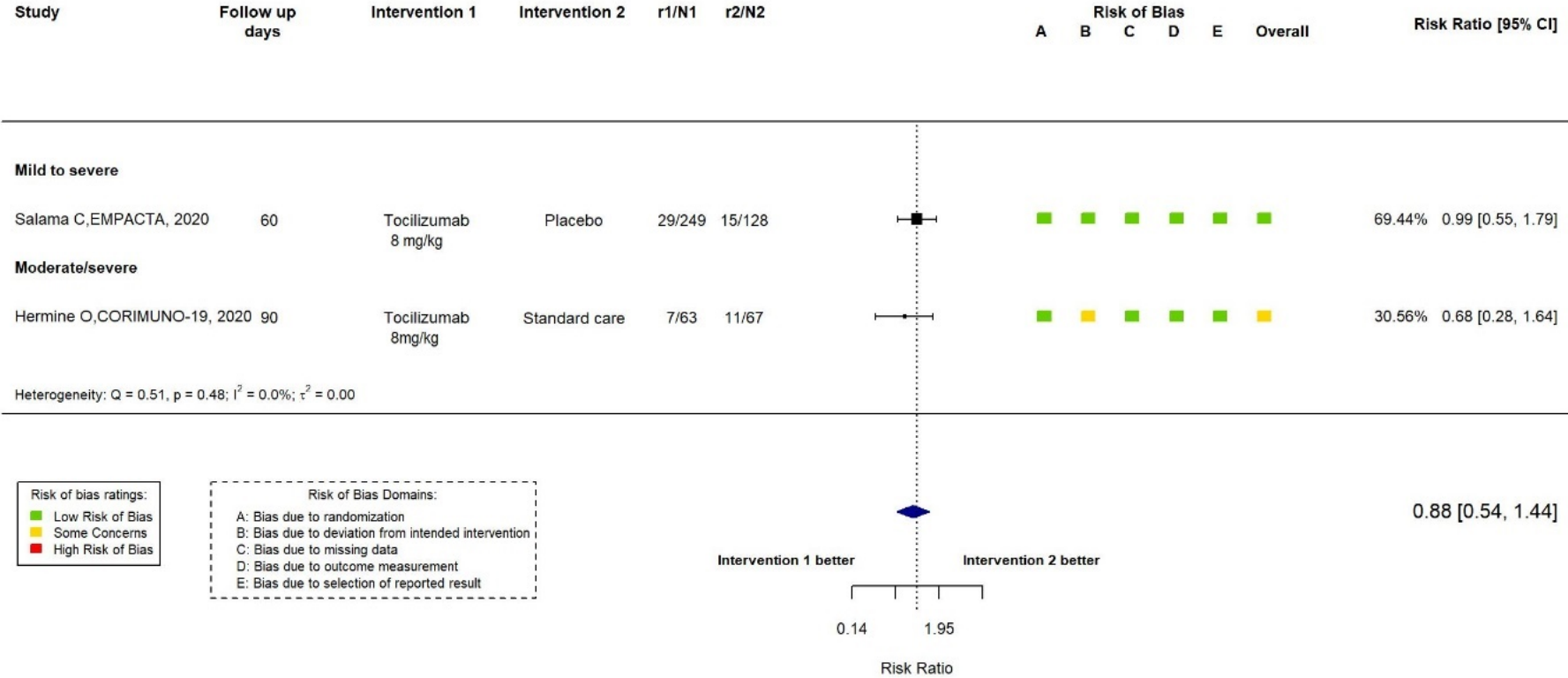
Sensitivity analysis 1.9.3 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28.



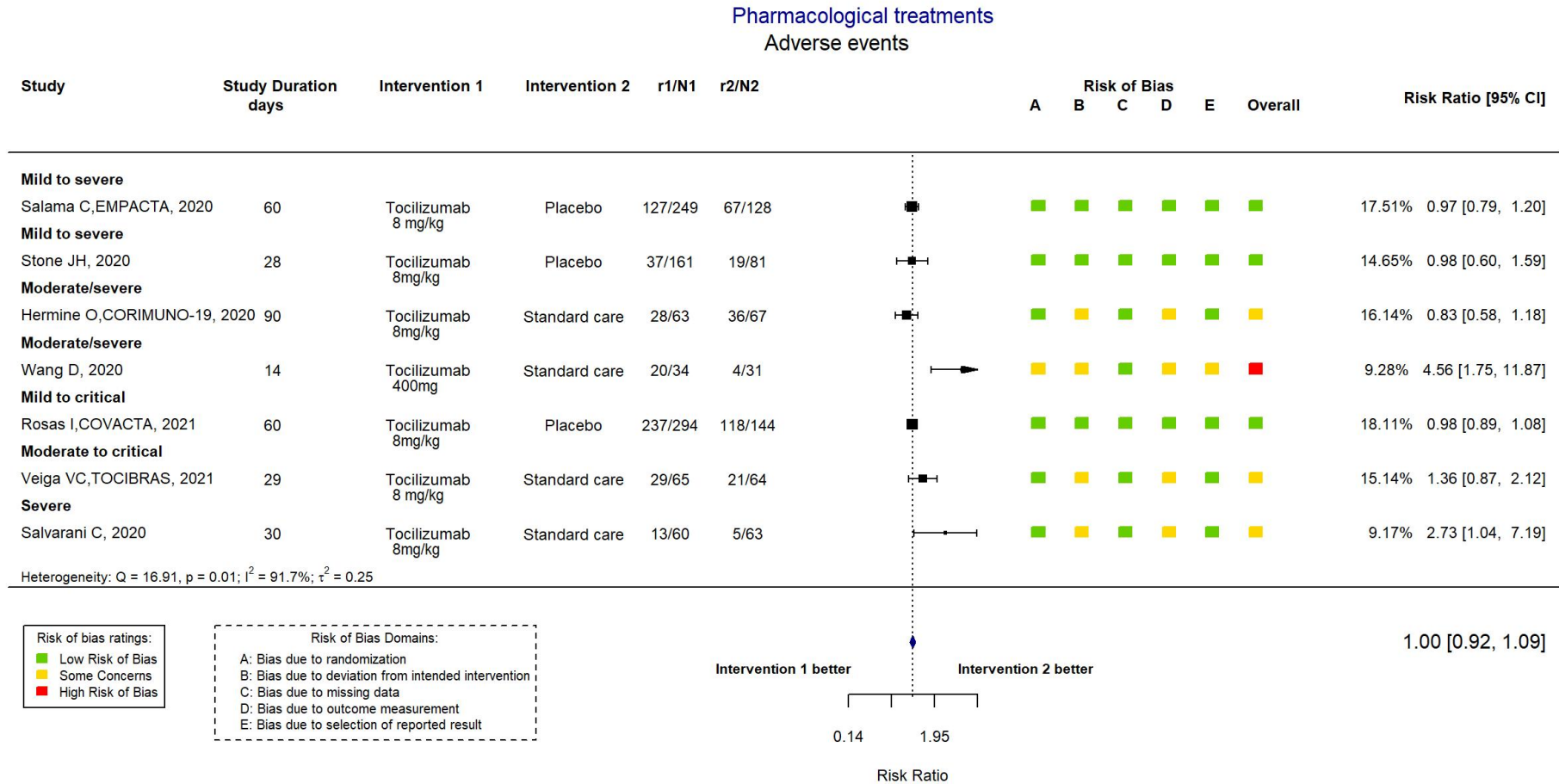
Sensitivity analysis 1.9.4 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60.

Pharmacological treatments

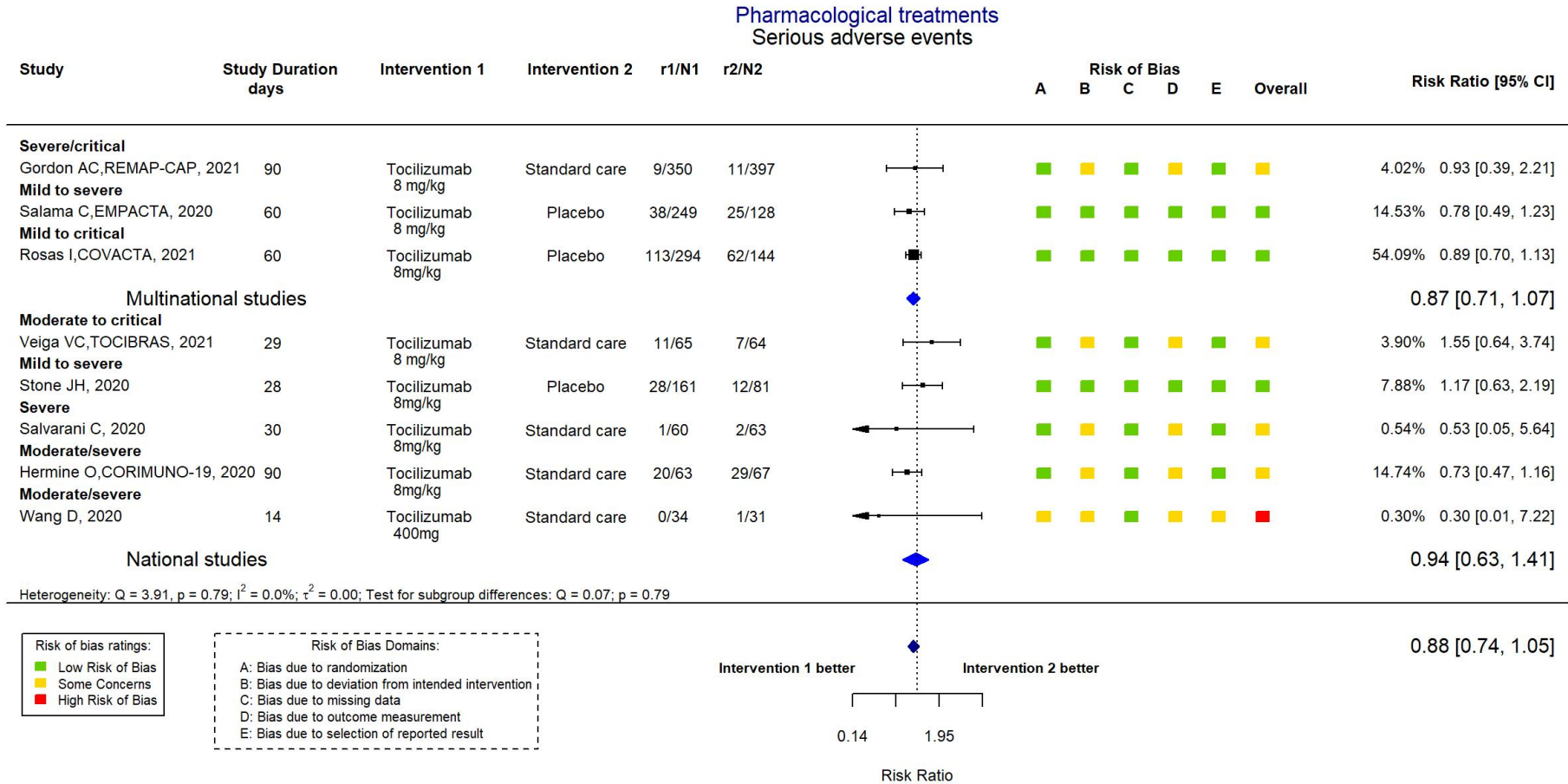
All-cause mortality D60 or above



Sensitivity analysis 1.9.5 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: Adverse events.



Sensitivity analysis 1.9.6 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: Serious Adverse events.



Comparison: Sarilumab versus placebo or standard care

Outcome	No. of studies	No. Of participants	Statistical method	Effect size
All-cause mortality D28	2	880	Risk Ratio (M-H, Random, 95% CI)	0.77 (0.43 to 1.36)
All-cause mortality D60	1	420	Risk Ratio (M-H, Random, 95% CI)	1.00 (0.50 to 2.00)
Adverse events	1	420	Risk Ratio (M-H, Random, 95% CI)	1.05 (0.88 to 1.25)
Serious adverse events	2	880	Risk Ratio (M-H, Random, 95% CI)	1.17 (0.77 to 1.77)
Time to clinical improvement	2	880	Hazard Ratio (95% CI)	1.28 (0.88 to 1.87)
Time to death	1	460	Hazard Ratio (95% CI)	0.55 (0.33 to 0.91)

Analysis 2.1.1 Sarilumab versus placebo or standard care. Outcome: All-cause mortality D28

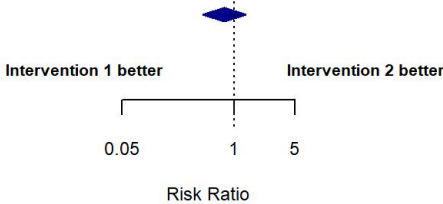
Pharmacological treatments

All-cause mortality D28

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]	
						A	B	C	D	E			
Moderate to critical													
Lescure FX, 2021	28	Sarilumab	Placebo	30/334	7/86							39.26%	1.10 [0.50, 2.43]
		2 arms merged (200mg and 400mg)											
Severe/critical													
Gordon AC,REMAP-CAP, 2021	21	Sarilumab	Standard care	10/48	142/412							60.74%	0.60 [0.34, 1.07]
		400 mg											
Heterogeneity: Q = 1.48, p = 0.22; I ² = 32.3%; τ ² = 0.06													

Risk of bias ratings:
■ Low Risk of Bias
■ Some Concerns
■ High Risk of Bias

Risk of Bias Domains:
 A: Bias due to randomization
 B: Bias due to deviation from intended intervention
 C: Bias due to missing data
 D: Bias due to outcome measurement
 E: Bias due to selection of reported result



0.77 [0.43, 1.36]

Analysis 2.1.2 Sarilumab versus placebo or standard care. Outcome: All-cause mortality D60

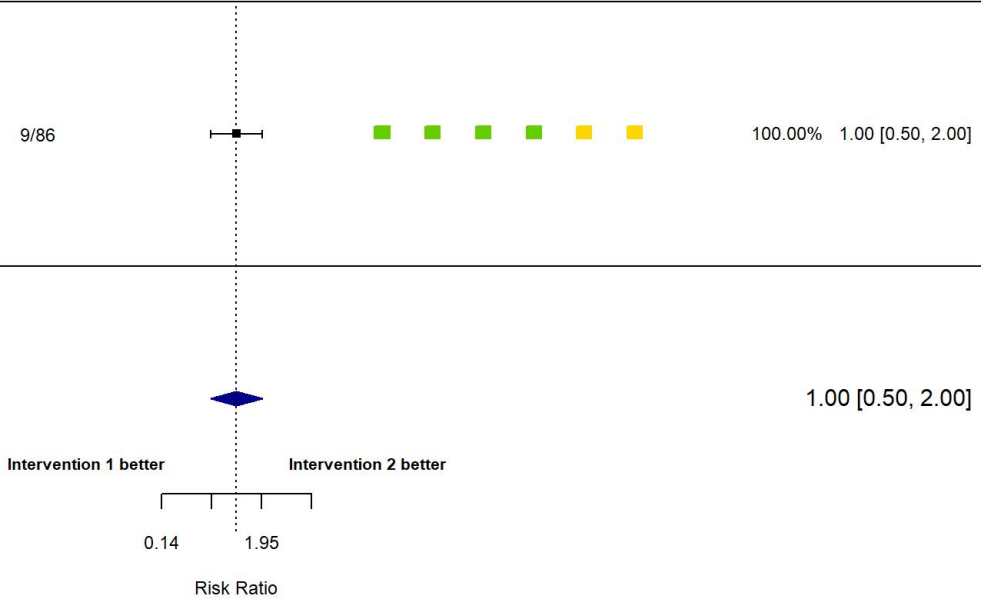
Pharmacological treatments

All-cause mortality D60 or above

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]	
						A	B	C	D	E			
Moderate to critical													
Lescure FX, 2021	60	Sarilumab	Placebo	35/334	9/86							100.00%	1.00 [0.50, 2.00]
		2 arms merged (200mg and 400mg)											

Risk of bias ratings:
■ Low Risk of Bias
■ Some Concerns
■ High Risk of Bias

Risk of Bias Domains:
 A: Bias due to randomization
 B: Bias due to deviation from intended intervention
 C: Bias due to missing data
 D: Bias due to outcome measurement
 E: Bias due to selection of reported result



Analysis 2.1.3 Sarilumab versus placebo or standard care. Outcome: Adverse events

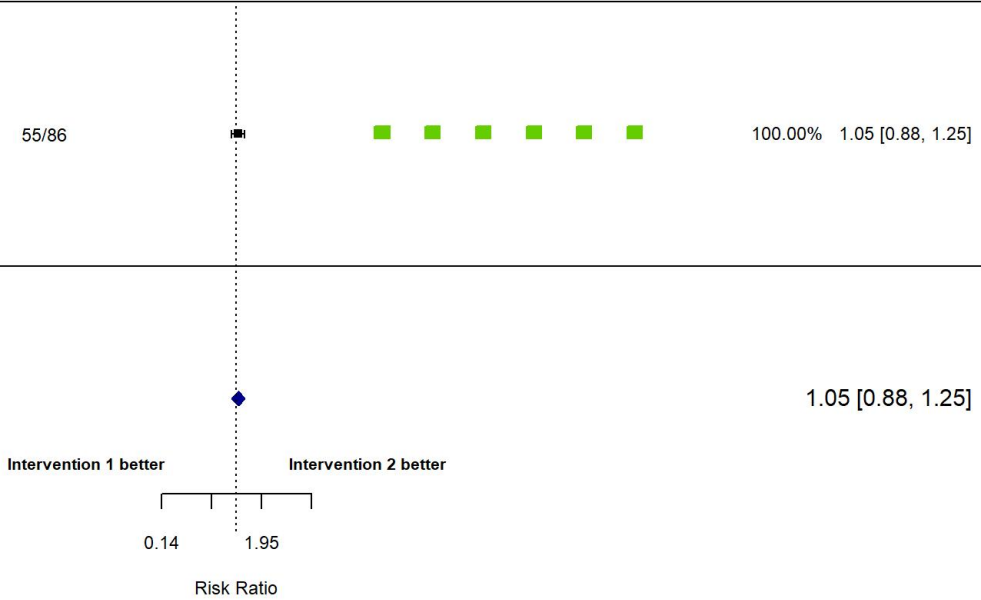
Pharmacological treatments

Adverse events

Study	Study Duration days	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of Bias					Overall	Risk Ratio [95% CI]	
						A	B	C	D	E			
Moderate to critical													
Lescure FX, 2021	60	Sarilumab	Placebo	224/334	55/86							100.00%	1.05 [0.88, 1.25]
		2 arms merged (200mg and 400mg)											

Risk of bias ratings:
■ Low Risk of Bias
■ Some Concerns
■ High Risk of Bias

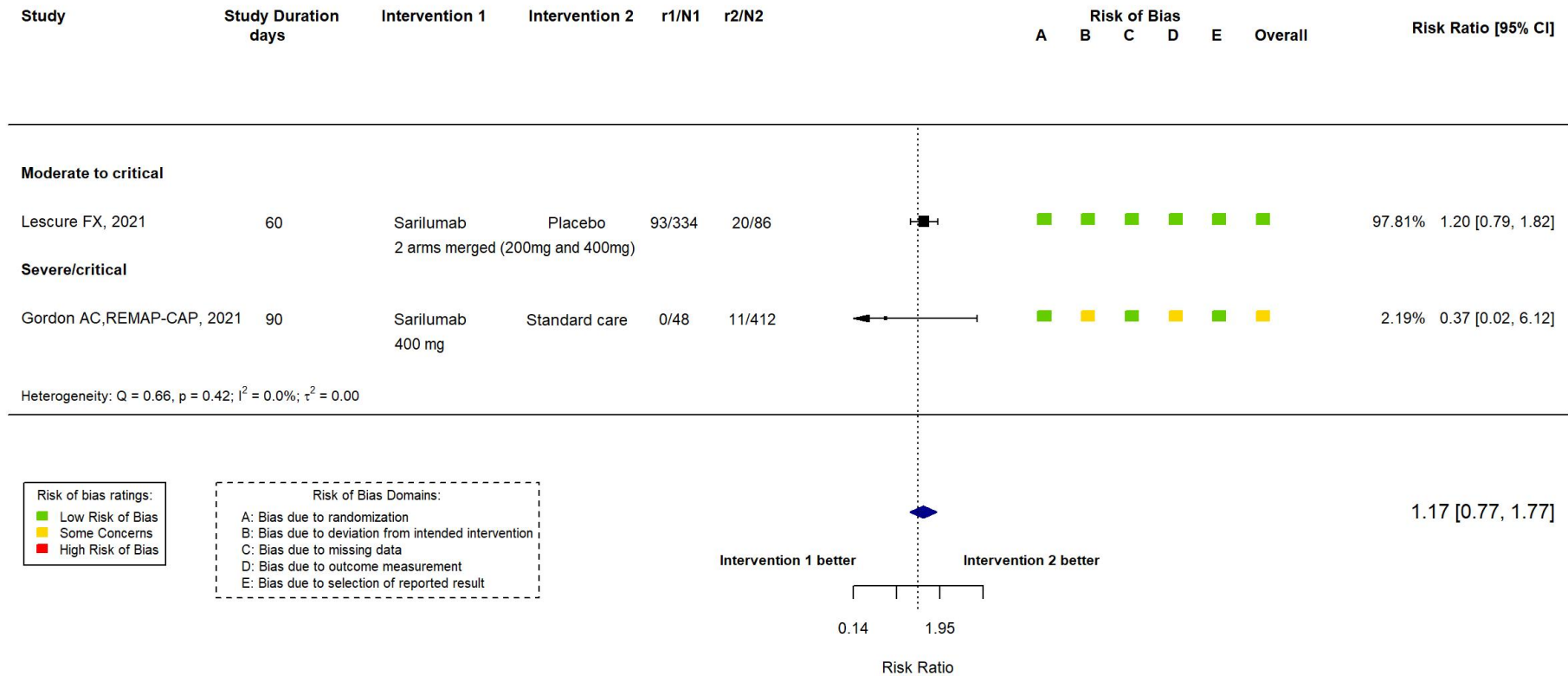
Risk of Bias Domains:
 A: Bias due to randomization
 B: Bias due to deviation from intended intervention
 C: Bias due to missing data
 D: Bias due to outcome measurement
 E: Bias due to selection of reported result



Analysis 2.1.4 Sarilumab versus placebo or standard care. Outcome: Serious adverse events

Pharmacological treatments

Serious adverse events



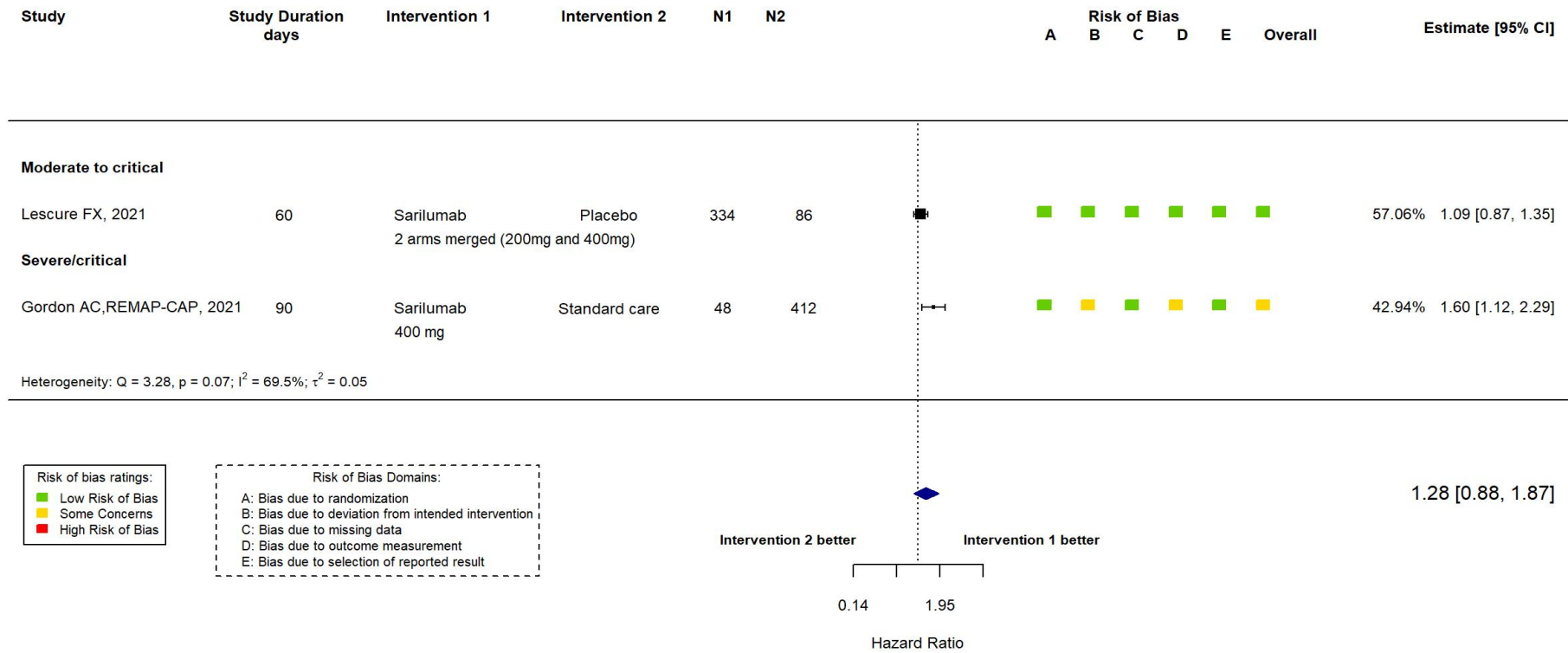
Analysis 2.2.1 Sarilumab versus placebo or standard care. Outcome: Time to clinical improvement

N1: Number of participants randomized to intervention 1

N2: Number of participants randomized to intervention 2

Pharmacological treatments

Time to clinical improvement



Analysis 2.2.2 Sarilumab versus placebo or standard care. Outcome: Time to death

N1: Number of participants randomized to intervention 1

N2: Number of participants randomized to intervention 2

