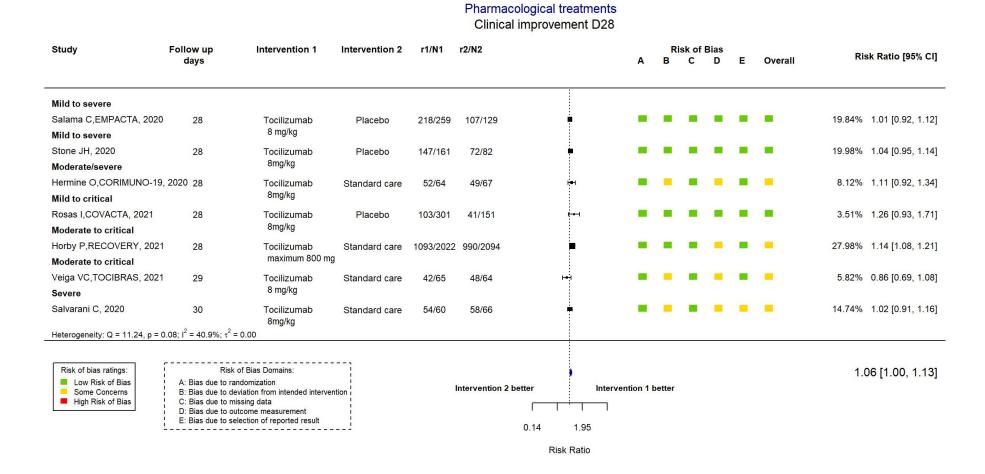
Comparison: Tocilizumab versus placebo or standard care

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 28

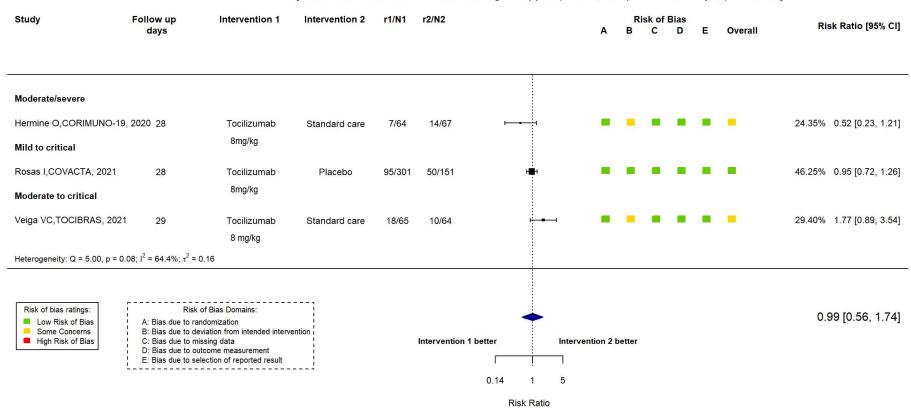


Analysis 1.1.2 Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

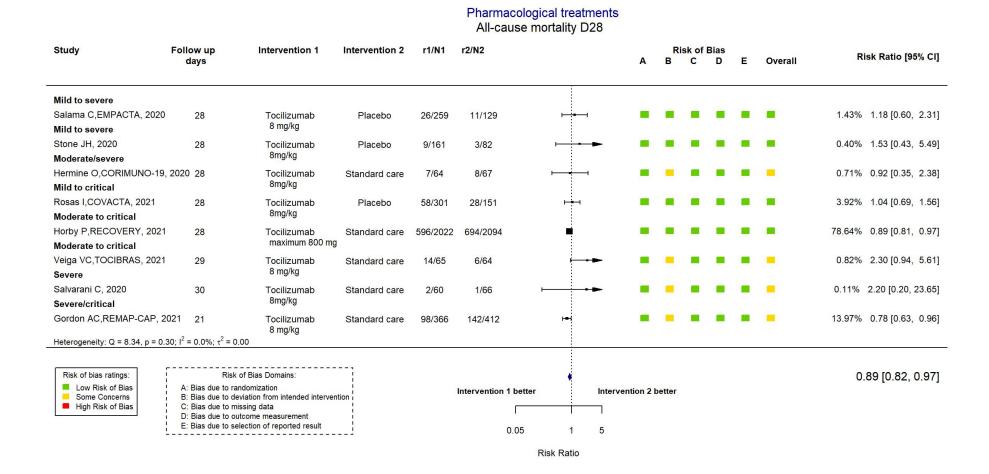
Pharmacological treatments

WHO progression score level 7 or above D28

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



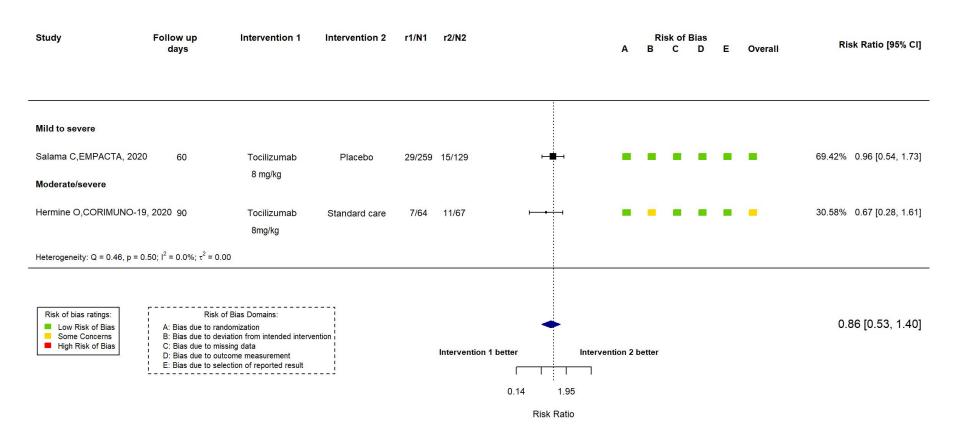
Analysis 1.1.3 Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



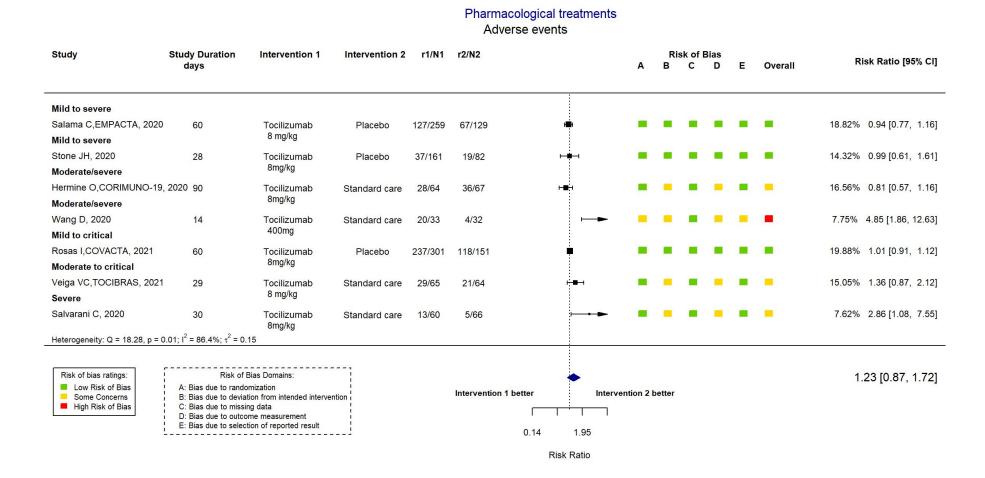
Analysis 1.1.4 Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

Pharmacological treatments

All-cause mortality D60 or above



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

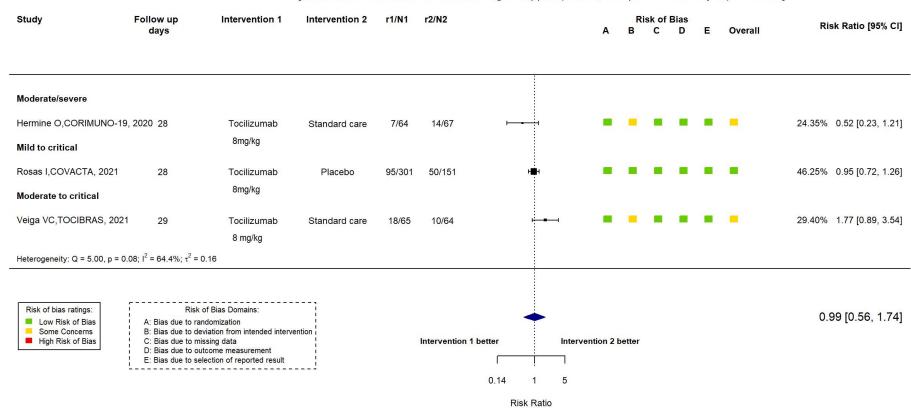


Analysis 1.1.6 Tocilizumab versus placebo or standard care. Outcome: Serious adverse events

Pharmacological treatments

WHO progression score level 7 or above D28

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

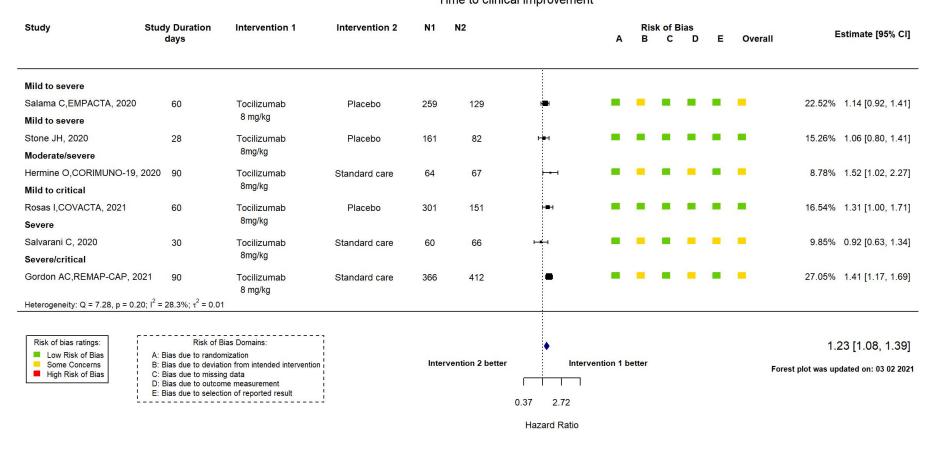


Analysis 1.2.1 Tocilizumab versus placebo or standard care. Outcome: Time to clinical improvement

N1: Number of participants randomized to intervention 1

N2: Number of participants randomized to intervention 2

Pharmacological treatments Time to clinical improvement



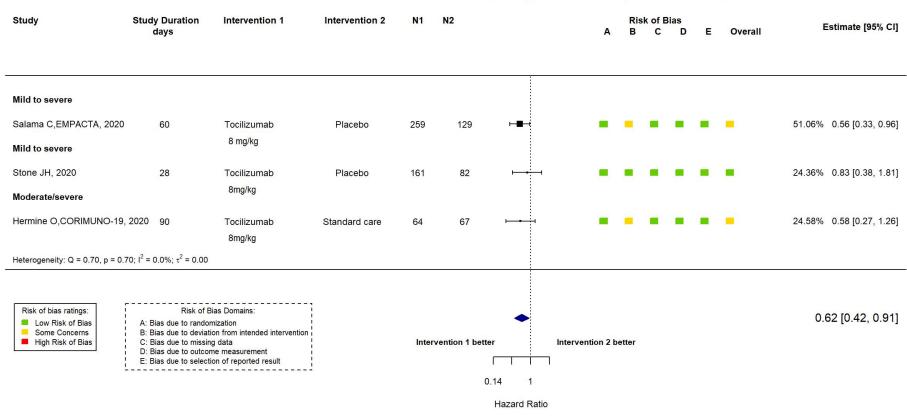
Analysis 1.2.2 Tocilizumab versus placebo or standard care. Outcome: Time to WHO progression score (level 7 and above)

N1: Number of participants randomized to intervention 1

N2: Number of participants randomized to intervention 2

Pharmacological treatments

Time to WHO progression score level 7 or above [mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death]



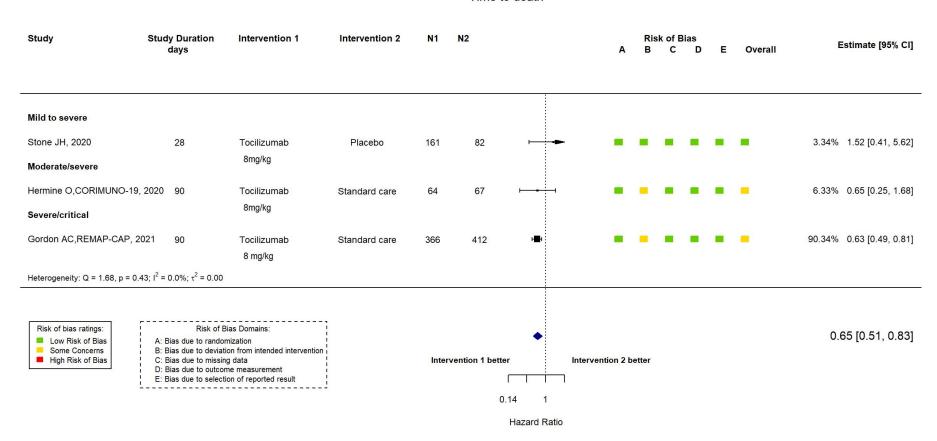
Analysis 1.2.3 Tocilizumab versus placebo or standard care. Outcome: Time to death

N1: Number of participants randomized to intervention 1

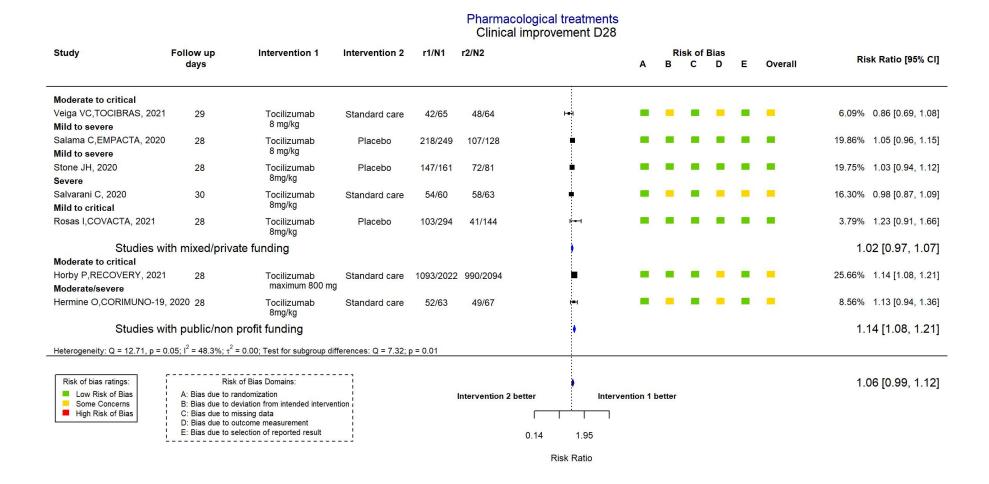
N2: Number of participants randomized to intervention 2

Pharmacological treatments

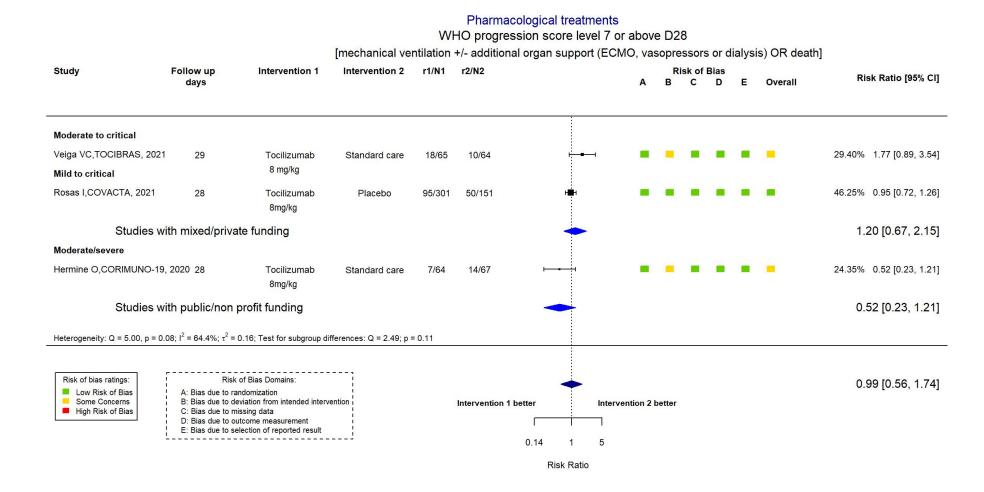
Time to death



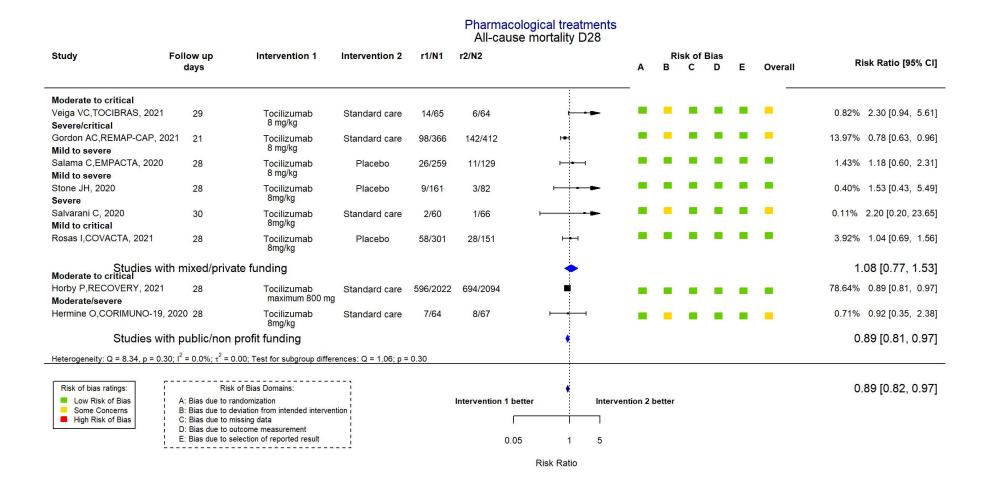
Subgroup analysis. 1.3.1 Funding. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28



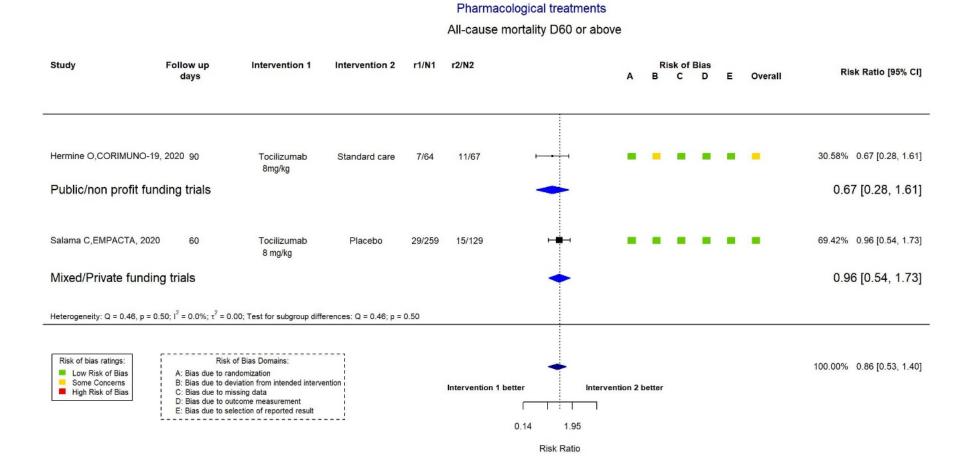
Subgroup analysis.1.3.2 Funding. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



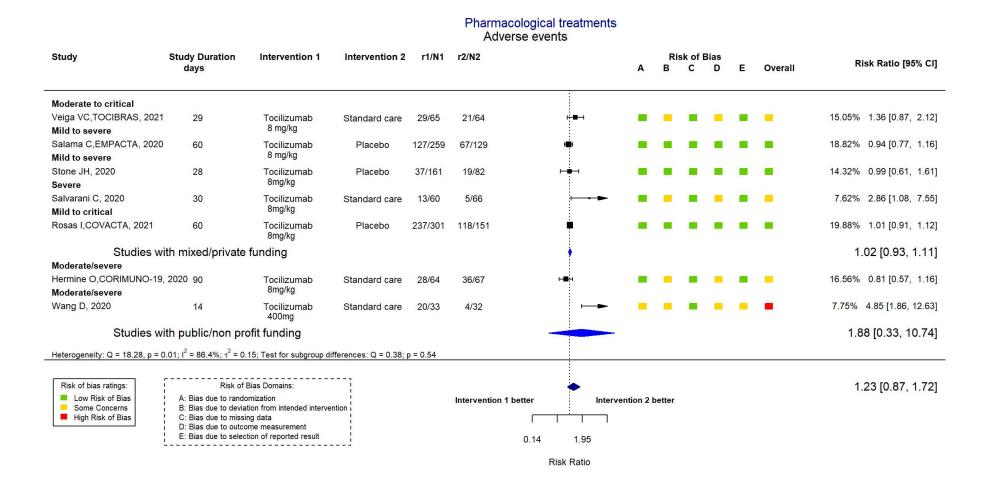
Subgroup analysis.1.3.3 Funding. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



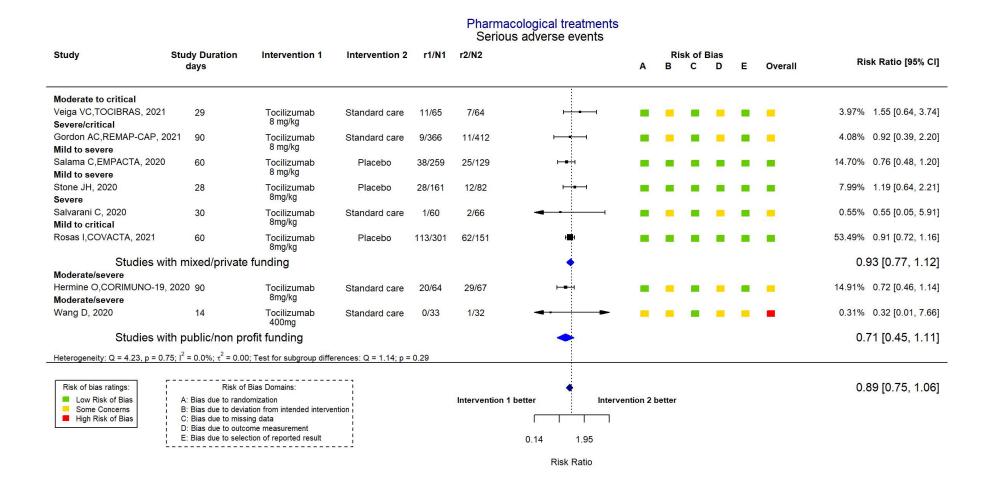
Subgroup analysis. 1.3.4 Funding. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60



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

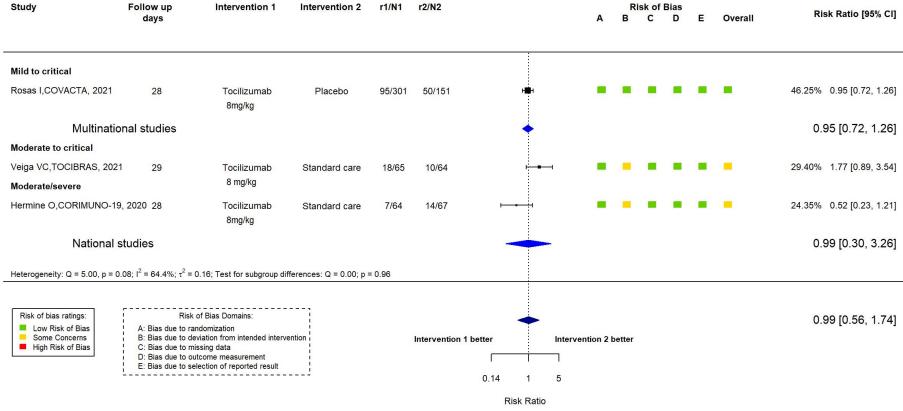


Subgroup analysis. 1.4.1 Location. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28

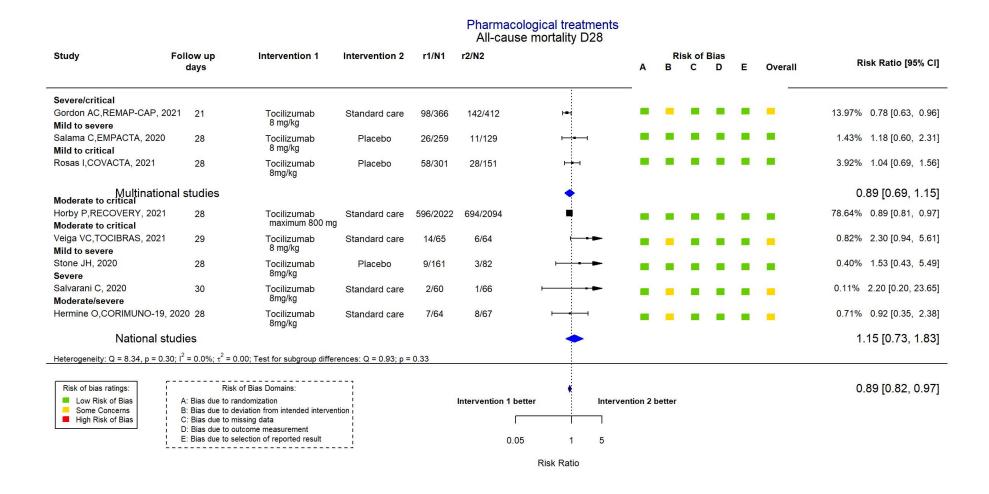
Pharmacological treatments Clinical improvement D28 Study Follow up Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] C D days В E Overall Mild to severe Salama C, EMPACTA, 2020 28 107/128 19.86% 1.05 [0.96, 1.15] Tocilizumab Placebo 218/249 8 mg/kg Mild to critical 3.79% 1.23 [0.91, 1.66] Rosas I, COVACTA, 2021 28 Tocilizumab Placebo 103/294 41/144 8mg/kg Multinational studies 1.06 [0.97, 1.16] Moderate to critical Horby P, RECOVERY, 2021 25.66% 1.14 [1.08, 1.21] 28 **Tocilizumab** 1093/2022 990/2094 Standard care maximum 800 mg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 Tocilizumab Standard care 42/65 48/64 6.09% 0.86 [0.69, 1.08] 8 mg/kg Mild to severe Stone JH, 2020 28 Tocilizumab 147/161 72/81 19.75% 1.03 [0.94, 1.12] Placebo 8mg/kg Severe Salvarani C, 2020 30 16.30% 0.98 [0.87, 1.09] Tocilizumab Standard care 54/60 58/63 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 28 Tocilizumab 52/63 8.56% 1.13 [0.94, 1.36] Standard care 49/67 8mg/kg National studies 1.04 [0.96, 1.14] Heterogeneity: Q = 12.71, p = 0.05; 1^2 = 48.3%; τ^2 = 0.00; Test for subgroup differences: Q = 0.21; p = 0.65 Risk of bias ratings: Risk of Bias Domains: 1.06 [0.99, 1.12] Low Risk of Bias A: Bias due to randomization Intervention 2 better Intervention 1 better Some Concerns B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.14 1.95 Risk Ratio

Subgroup analysis. 1.4.2 Location. 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] Intervention 2 r1/N1 r2/N2 Risk of Bias A B C D E Overall



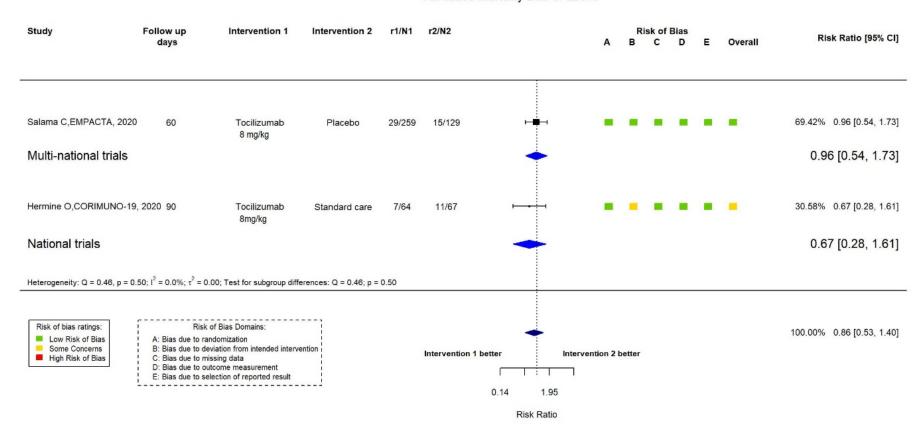
Subgroup analysis.1.4.3 Location. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



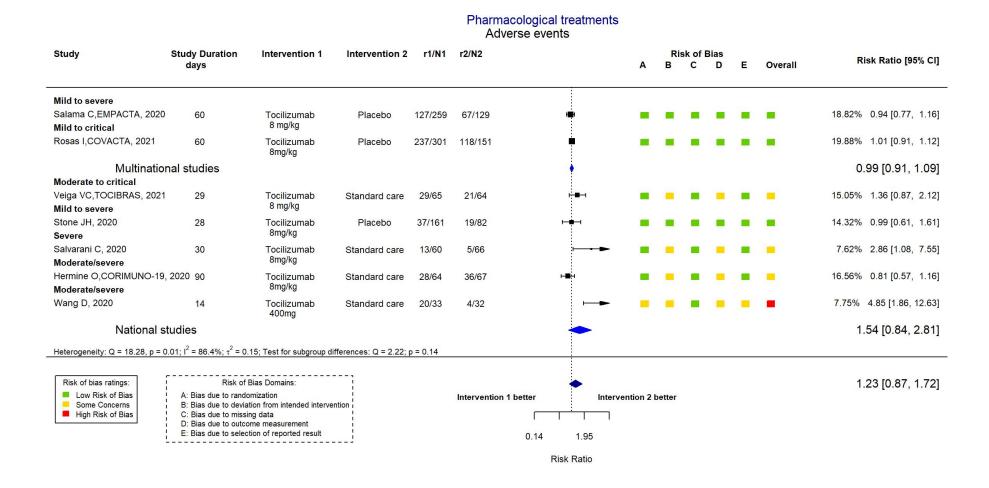
Subgroup analysis. 1.4.4 Location. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

Pharmacological treatments

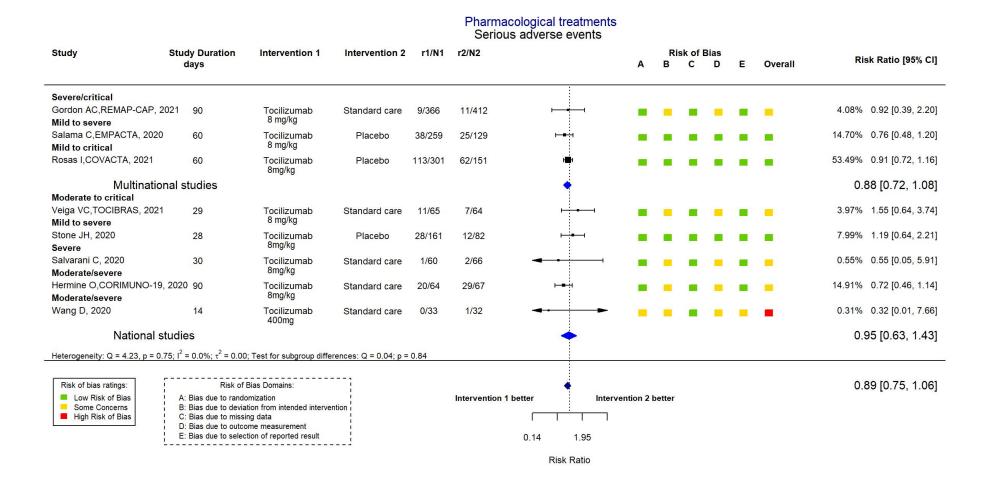
All-cause mortality D60 or above



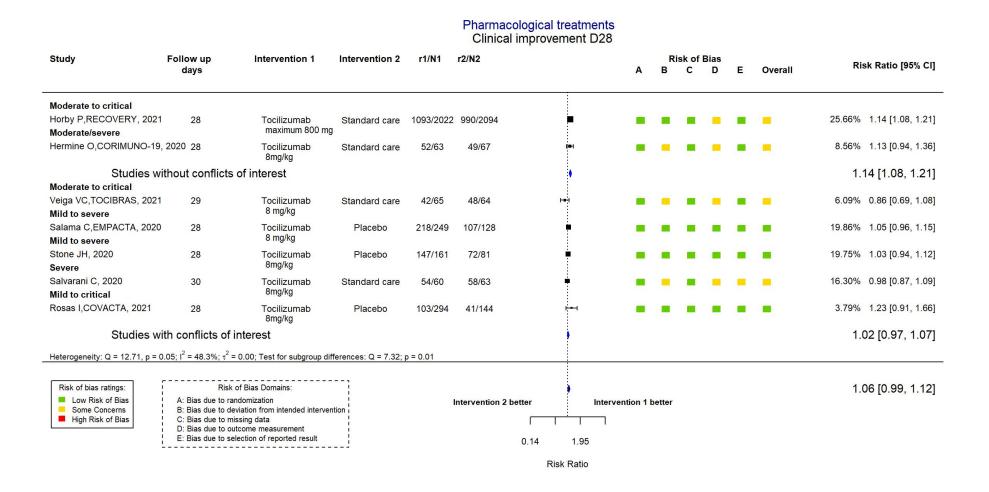
Subgroup analysis. 1.4.5 Location. Tocilizumab versus placebo or standard care. Outcome: Adverse events



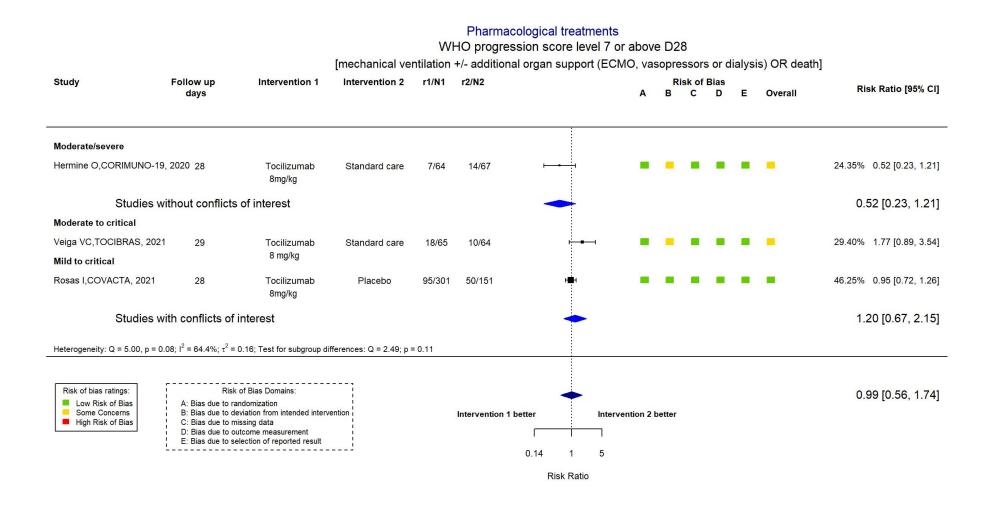
Subgroup analysis. 1.4.6 Location. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events



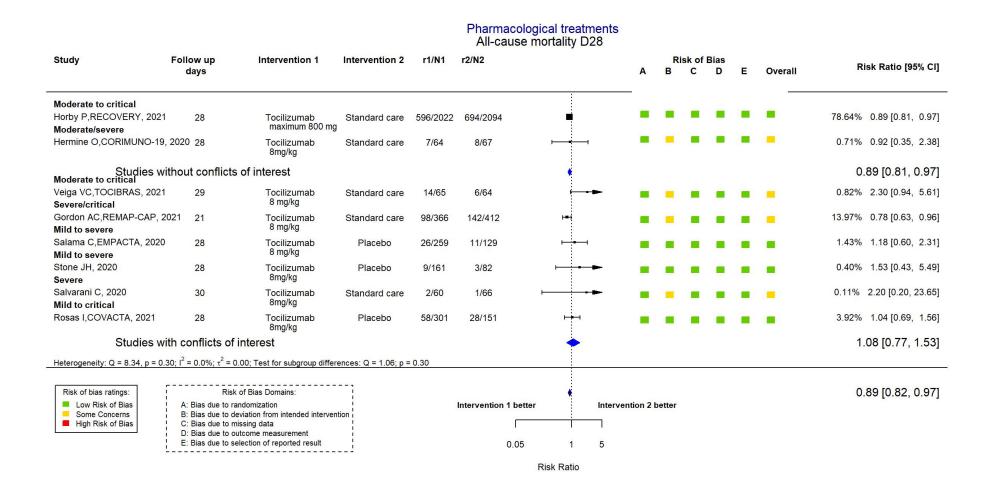
Subgroup analysis. 1.5.1 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28



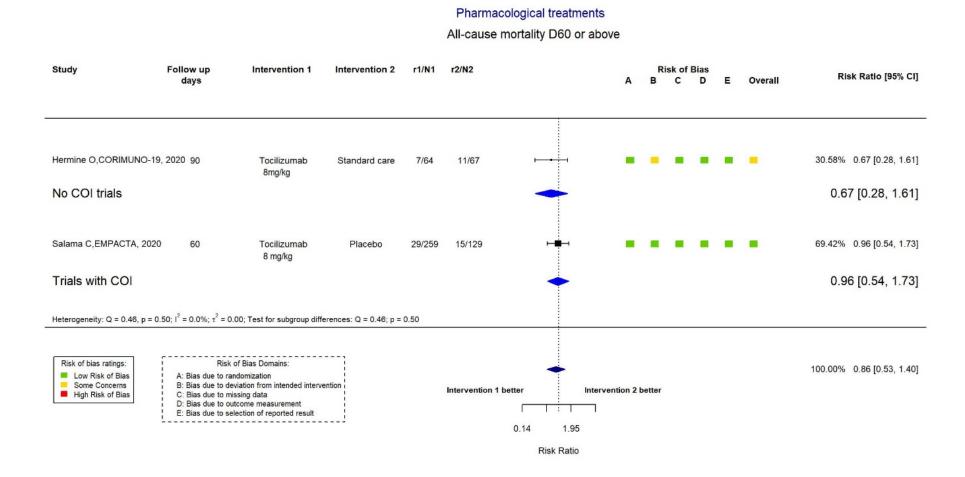
Subgroup analysis. 1.5.2 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



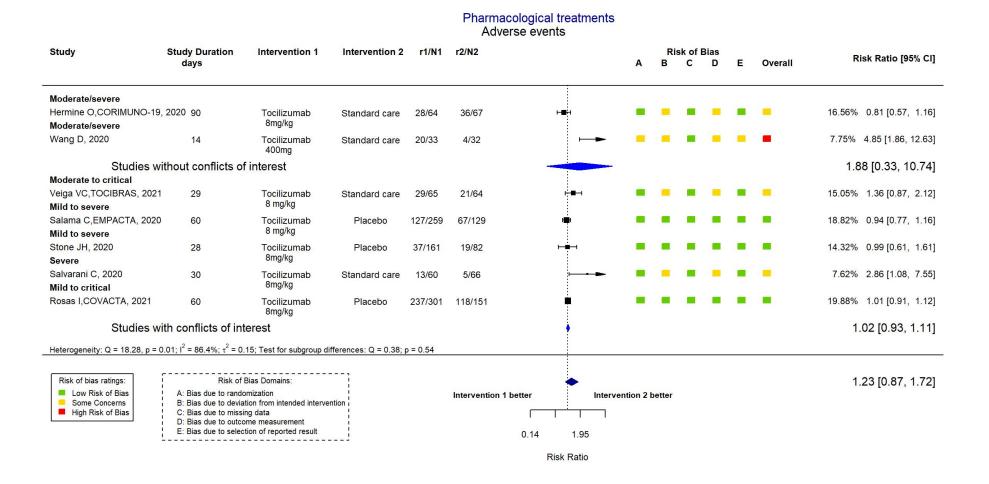
Subgroup analysis. 1.5.3 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



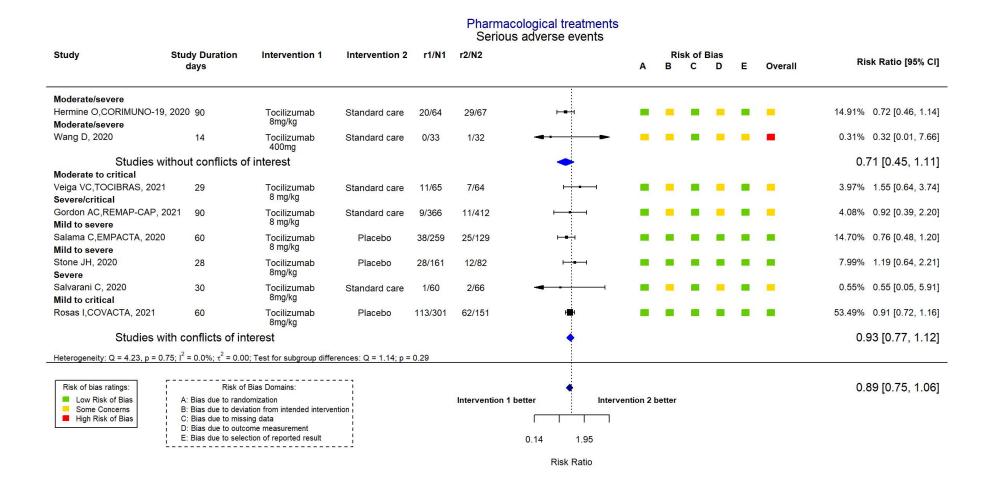
Subgroup analysis. 1.5.4 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60



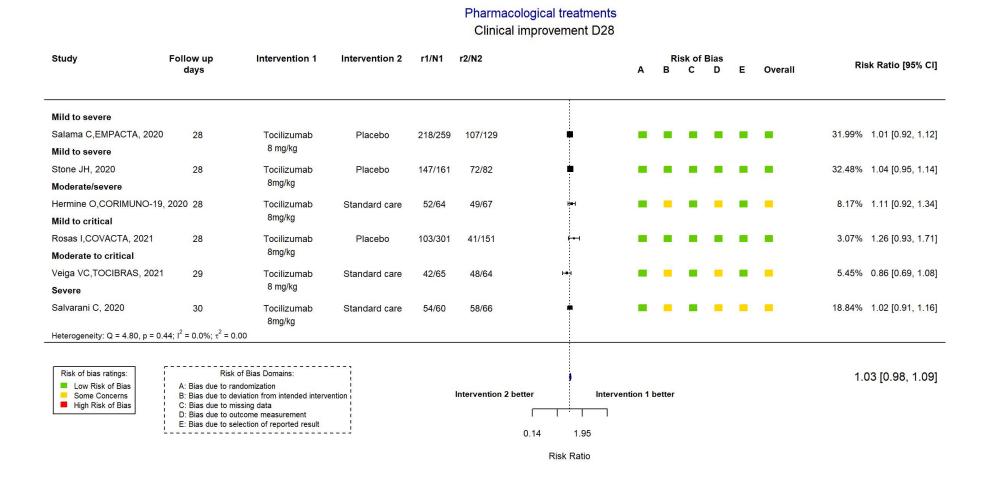
Subgroup analysis. 1.5.5 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Adverse events



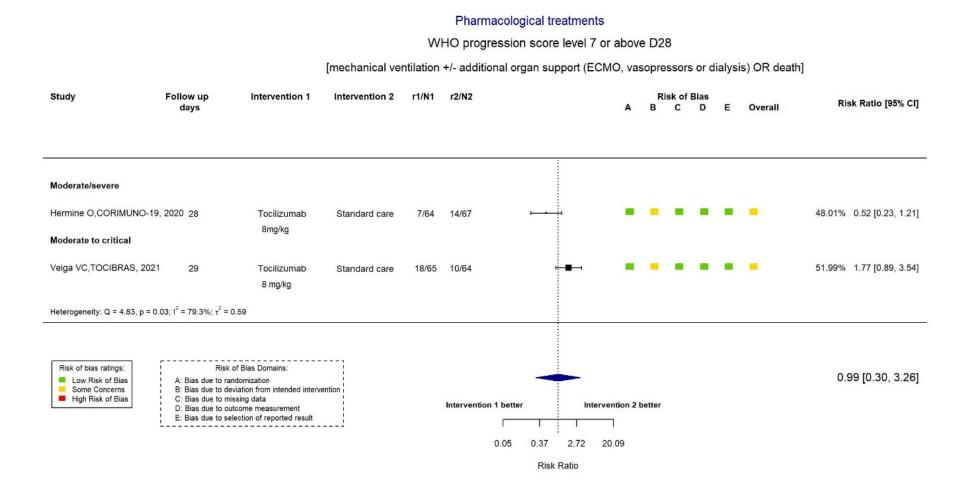
Subgroup analysis. 1.5.6 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Serious Adverse events



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



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.

All-cause mortality D28 Follow up Study Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] days C E Overall Mild to severe Salama C, EMPACTA, 2020 13.97% 1.18 [0.60, 2.31] 28 Tocilizumab Placebo 26/259 11/129 8 mg/kg Mild to severe Stone JH, 2020 4.95% 1.53 [0.43, 5.49] 28 Tocilizumab Placebo 9/161 3/82 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 28 8.18% 0.92 [0.35, 2.38] Tocilizumab Standard care 7/64 8/67 8mg/kg Mild to critical Rosas I, COVACTA, 2021 28 Tocilizumab Placebo 58/301 28/151 25.02% 1.04 [0.69, 1.56] 8mg/kg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 Tocilizumab 14/65 6/64 9.14% 2.30 [0.94, 5.61] Standard care 8 mg/kg Severe Salvarani C, 2020 30 Tocilizumab Standard care 2/60 1/66 1.56% 2.20 [0.20, 23.65] 8mg/kg Severe/critical Gordon AC, REMAP-CAP, 2021 Tocilizumab 98/366 142/412 37.19% 0.78 [0.63, 0.96] Standard care 8 mg/kg Heterogeneity: Q = 8.33, p = 0.22; I^2 = 36.6%; τ^2 = 0.05 Risk of bias ratings: Risk of Bias Domains: 1.04 [0.77, 1.41] Low Risk of Bias A: Bias due to randomization Intervention 1 better Intervention 2 better Some Concerns B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.05 5 Risk Ratio

Pharmacological treatments

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

Low Risk of Bias

Some Concerns

High Risk of Bias

A: Bias due to randomization

C: Bias due to missing data
D: Bias due to outcome measurement
E: Bias due to selection of reported result

B: Bias due to deviation from intended intervention

Adverse events Study **Study Duration** Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] days BCDE Overall Mild to severe Salama C, EMPACTA, 2020 60 **Tocilizumab** Placebo 127/259 67/129 17.10% 0.94 [0.77, 1.16] 8 mg/kg Mild to severe Stone JH, 2020 28 Tocilizumab Placebo 37/161 19/82 3.13% 0.99 [0.61, 1.61] 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 90 Tocilizumab Standard care 28/64 36/67 5.81% 0.81 [0.57, 1.16] 8mg/kg Mild to critical Rosas I, COVACTA, 2021 60 Tocilizumab Placebo 237/301 118/151 69.43% 1.01 [0.91, 1.12] 8mg/kg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 3.75% 1.36 [0.87, 2.12] Tocilizumab Standard care 29/65 21/64 8 mg/kg Severe Salvarani C, 2020 0.78% 2.86 [1.08, 7.55] 30 Tocilizumab Standard care 13/60 5/66 8mg/kg Heterogeneity: Q = 7.95, p = 0.16; I^2 = 0.0%; τ^2 = 0.00 Risk of bias ratings: Risk of Bias Domains: 1.00 [0.92, 1.09]

Intervention 1 better

0.14

1.95 Risk Ratio

Intervention 2 better

Pharmacological treatments

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

Serious adverse events **Study Duration** Study Intervention 1 Intervention 2 r1/N1 Risk of Bias Risk Ratio [95% CI] days C E Overall Mild to severe Salama C, EMPACTA, 2020 14.75% 0.76 [0.48, 1.20] 60 Tocilizumab Placebo 38/259 25/129 -8 mg/kg Mild to severe Stone JH, 2020 8.02% 1.19 [0.64, 2.21] 28 Tocilizumab Placebo 28/161 12/82 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 90 14.96% 0.72 [0.46, 1.14] Tocilizumab Standard care 20/64 29/67 8mg/kg Mild to critical Rosas I, COVACTA, 2021 53.66% 0.91 [0.72, 1.16] 60 Tocilizumab Placebo 113/301 62/151 8mg/kg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 Tocilizumab 11/65 3.98% 1.55 [0.64, 3.74] Standard care 7/64 8 mg/kg Severe Salvarani C, 2020 30 Tocilizumab Standard care 1/60 2/66 0.55% 0.55 [0.05, 5.91] 8mg/kg Severe/critical Gordon AC, REMAP-CAP, 2021 Tocilizumab 4.10% 0.92 [0.39, 2.20] Standard care 9/366 11/412 8 mg/kg Heterogeneity: Q = 3.84, p = 0.70; I^2 = 0.0%; τ^2 = 0.00 Risk of bias ratings: Risk of Bias Domains: 0.89 [0.75, 1.06] Low Risk of Bias A: Bias due to randomization Intervention 1 better Intervention 2 better Some Concerns B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.14 1.95

Pharmacological treatments

Risk Ratio

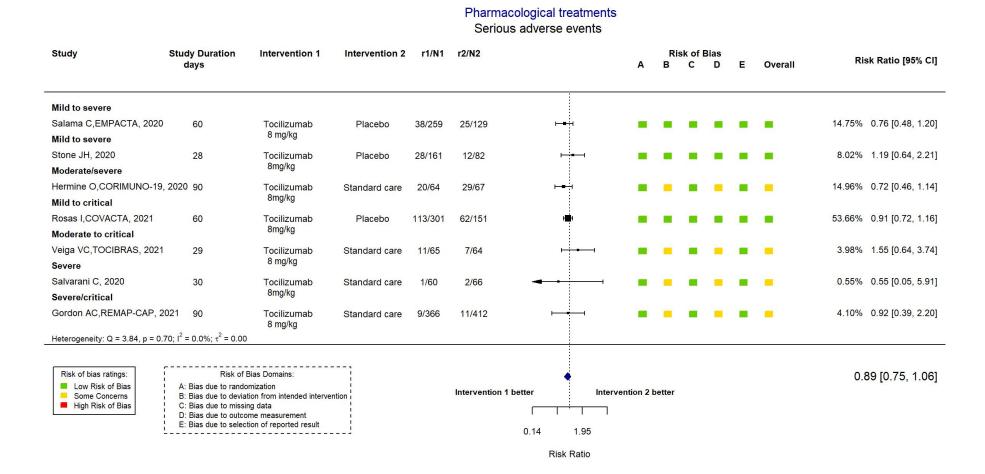
Sensitivity analysis 1.7.1 Without studies at High risk of Bias. Tocilizumab versus placebo or standard care. Outcome: Adverse events.

Pharmacological treatments

Risk Ratio

Adverse events Study **Study Duration** Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] days BCDE Overall Mild to severe Salama C, EMPACTA, 2020 60 Tocilizumab Placebo 127/259 67/129 17.10% 0.94 [0.77, 1.16] 8 mg/kg Mild to severe Stone JH, 2020 28 Tocilizumab Placebo 37/161 19/82 3.13% 0.99 [0.61, 1.61] 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 90 5.81% 0.81 [0.57, 1.16] Tocilizumab Standard care 28/64 36/67 8mg/kg Mild to critical 69.43% 1.01 [0.91, 1.12] Rosas I, COVACTA, 2021 60 Tocilizumab Placebo 237/301 118/151 8mg/kg Moderate to critical Veiga VC, TOCIBRAS, 2021 3.75% 1.36 [0.87, 2.12] 29 Tocilizumab Standard care 29/65 21/64 8 mg/kg Severe Salvarani C, 2020 0.78% 2.86 [1.08, 7.55] 30 Tocilizumab Standard care 13/60 5/66 8mg/kg Heterogeneity: Q = 7.95, p = 0.16; I^2 = 0.0%; τ^2 = 0.00 Risk of bias ratings: Risk of Bias Domains: 1.00 [0.92, 1.09] Low Risk of Bias A: Bias due to randomization Some Concerns Intervention 1 better Intervention 2 better B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.14 1.95

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.

Clinical improvement D28 Study Follow up Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] days B C D E Overall Mild to severe Salama C, EMPACTA, 2020 28 **Tocilizumab** Placebo 218/259 107/129 20.55% 1.01 [0.92, 1.12] 8 mg/kg Mild to severe Stone JH, 2020 28 Tocilizumab Placebo 147/161 72/82 20.69% 1.04 [0.95, 1.14] 8mg/kg Moderate/severe Hermine O, CORIMUNO-19, 2020 28 Tocilizumab Standard care 52/64 49/67 8.62% 1.11 [0.92, 1.34] 8mg/kg Moderate to critical Standard care 1093/2022 990/2094 Horby P, RECOVERY, 2021 28 Tocilizumab 28.52% 1.14 [1.08, 1.21] maximum 800 mg Moderate to critical Veiga VC, TOCIBRAS, 2021 6.20% 0.86 [0.69, 1.08] 29 Tocilizumab Standard care 42/65 48/64 8 mg/kg Severe Salvarani C, 2020 15.43% 1.02 [0.91, 1.16] 30 Tocilizumab Standard care 54/60 58/66 8mg/kg Heterogeneity: Q = 10.21, p = 0.07; I^2 = 46.5%; τ^2 = 0.00 Risk of bias ratings: Risk of Bias Domains: 1.05 [0.99, 1.12] Low Risk of Bias A: Bias due to randomization Some Concerns Intervention 2 better Intervention 1 better B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.14 1.95

Pharmacological treatments

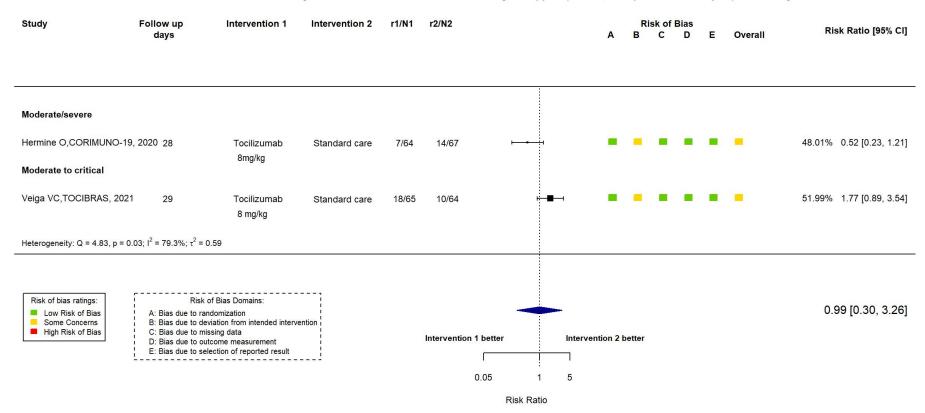
Risk Ratio

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]



Sensitivity analysis 1.8.3 Severity. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28.

All-cause mortality D28 Follow up Study Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] days C E Overall Mild to severe Salama C, EMPACTA, 2020 1.49% 1.18 [0.60, 2.31] 28 Tocilizumab Placebo 26/259 11/129 8 mg/kg Mild to severe Stone JH, 2020 0.41% 1.53 [0.43, 5.49] 28 Tocilizumab Placebo 9/161 3/82 8mg/kg Moderate/severe Hermine O, CORIMUNO-19, 2020 28 0.74% 0.92 [0.35, 2.38] Tocilizumab Standard care 7/64 8/67 8mg/kg Moderate to critical Horby P, RECOVERY, 2021 Standard care 596/2022 81.85% 0.89 [0.81, 0.97] 28 Tocilizumab 694/2094 maximum 800 mg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 Tocilizumab 14/65 6/64 0.85% 2.30 [0.94, 5.61] Standard care 8 mg/kg Severe Salvarani C, 2020 30 Tocilizumab Standard care 2/60 1/66 0.12% 2.20 [0.20, 23.65] 8mg/kg Severe/critical Gordon AC, REMAP-CAP, 2021 Tocilizumab 98/366 142/412 14.54% 0.78 [0.63, 0.96] Standard care 8 mg/kg Heterogeneity: Q = 7.77, p = 0.26; I^2 = 0.0%; τ^2 = 0.00 Risk of bias ratings: Risk of Bias Domains: 0.89 [0.82, 0.96] Low Risk of Bias A: Bias due to randomization Intervention 1 better Intervention 2 better Some Concerns B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.05 5

Pharmacological treatments

Risk Ratio

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

Adverse events Study **Study Duration** Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] days BCDE Overall Mild to severe Salama C, EMPACTA, 2020 60 **Tocilizumab** Placebo 127/259 67/129 21.12% 0.94 [0.77, 1.16] 8 mg/kg Mild to severe Stone JH, 2020 28 Tocilizumab Placebo 37/161 19/82 17.87% 0.99 [0.61, 1.61] 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 90 Tocilizumab Standard care 28/64 36/67 19.57% 0.81 [0.57, 1.16] 8mg/kg Moderate/severe Wang D, 2020 14 Tocilizumab Standard care 20/33 4/32 11.57% 4.85 [1.86, 12.63] 400mg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 18.45% 1.36 [0.87, 2.12] Tocilizumab Standard care 29/65 21/64 8 mg/kg Severe Salvarani C, 2020 11.42% 2.86 [1.08, 7.55] 30 Tocilizumab Standard care 13/60 5/66 8mg/kg Heterogeneity: Q = 18.21, p = 0.00; I^2 = 84.8%; τ^2 = 0.26 Risk of bias ratings: Risk of Bias Domains: 1.36 [0.85, 2.18] Low Risk of Bias A: Bias due to randomization Some Concerns Intervention 1 better Intervention 2 better B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result

0.14

1.95 Risk Ratio

Pharmacological treatments

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

Serious adverse events **Study Duration** Study Intervention 1 Intervention 2 r1/N1 Risk of Bias Risk Ratio [95% CI] days C E Overall Mild to severe Salama C, EMPACTA, 2020 31.61% 0.76 [0.48, 1.20] 60 Tocilizumab Placebo 38/259 25/129 8 mg/kg Mild to severe Stone JH, 2020 28 17.18% 1.19 [0.64, 2.21] Tocilizumab Placebo 28/161 12/82 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 90 32.06% 0.72 [0.46, 1.14] Tocilizumab Standard care 20/64 29/67 8mg/kg Moderate/severe Wang D, 2020 14 Tocilizumab Standard care 0/33 1/32 0.66% 0.32 [0.01, 7.66] 400mg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 8.53% 1.55 [0.64, 3.74] Tocilizumab Standard care 11/65 7/64 8 mg/kg Severe Salvarani C, 2020 30 1.18% 0.55 [0.05, 5.91] Tocilizumab Standard care 1/60 2/66 8mg/kg Severe/critical Gordon AC, REMAP-CAP, 2021 8.78% 0.92 [0.39, 2.20] Tocilizumab Standard care 9/366 11/412 8 mg/kg Heterogeneity: Q = 4.13, p = 0.66; I^2 = 0.0%; τ^2 = 0.00 Risk of bias ratings: Risk of Bias Domains: 0.86 [0.67, 1.12] Low Risk of Bias A: Bias due to randomization Intervention 1 better Intervention 2 better Some Concerns B: Bias due to deviation from intended intervention C: Bias due to missing data High Risk of Bias D: Bias due to outcome measurement E: Bias due to selection of reported result 0.14 1.95

Pharmacological treatments

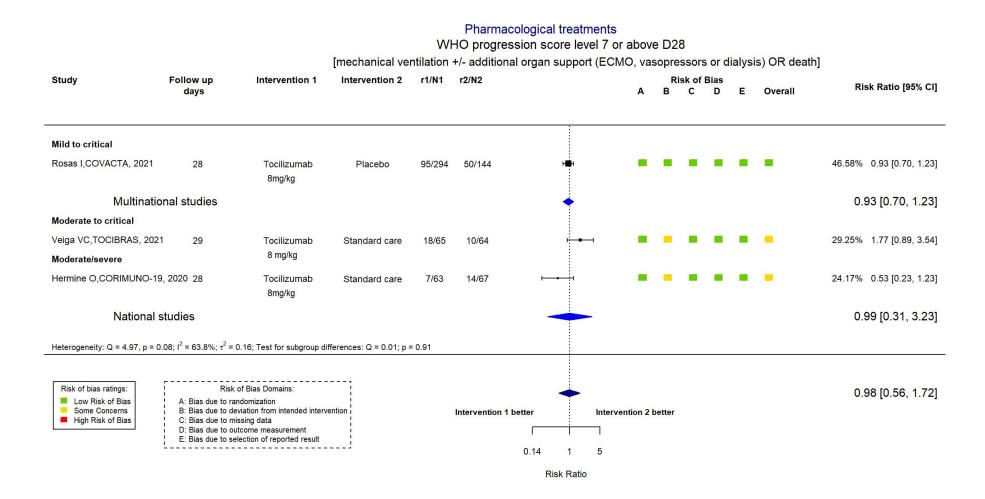
Risk Ratio

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

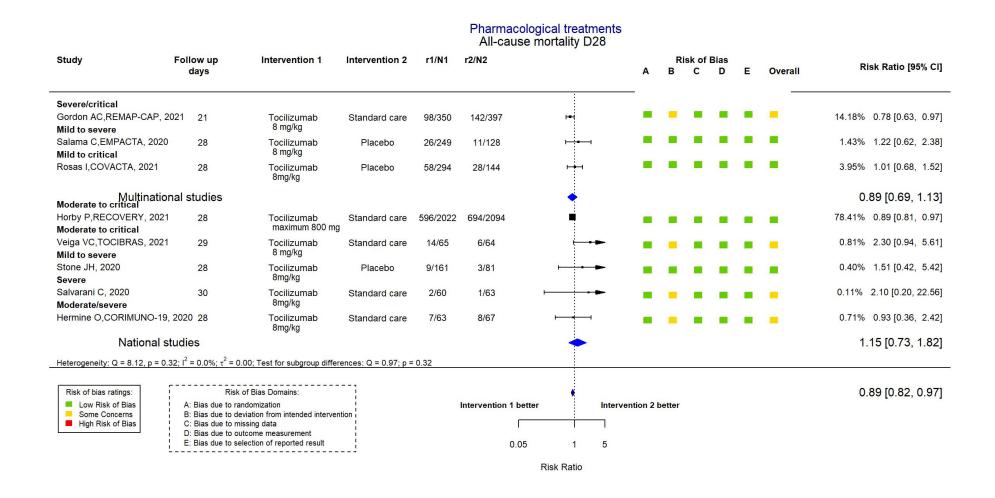
Clinical improvement D28 Follow up Study Intervention 1 Intervention 2 r1/N1 r2/N2 Risk of Bias Risk Ratio [95% CI] days C E Overall Mild to severe Salama C, EMPACTA, 2020 19.86% 1.05 [0.96, 1.15] 28 Tocilizumab Placebo 218/249 107/128 8 mg/kg Mild to severe Stone JH, 2020 19.75% 1.03 [0.94, 1.12] 28 Tocilizumab 72/81 Placebo 147/161 8mg/kg Moderate/severe Hermine O, CORIMUNO-19, 2020 28 8.56% 1.13 [0.94, 1.36] Tocilizumab Standard care 52/63 49/67 8mg/kg Mild to critical Rosas I, COVACTA, 2021 3.79% 1.23 [0.91, 1.66] 28 Tocilizumab Placebo 103/294 41/144 8mg/kg Moderate to critical Horby P, RECOVERY, 2021 28 1093/2022 990/2094 25.66% 1.14 [1.08, 1.21] Tocilizumab Standard care maximum 800 mg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 Tocilizumab Standard care 42/65 48/64 6.09% 0.86 [0.69, 1.08] 8 mg/kg Severe Salvarani C, 2020 30 Tocilizumab 54/60 58/63 _ _ _ _ 16.30% 0.98 [0.87, 1.09] Standard care 8mg/kg Heterogeneity: Q = 12.71, p = 0.05; I^2 = 48.3%; τ^2 = 0.00 Risk of bias ratings: Risk of Bias Domains: 1.06 [0.99, 1.12] Low Risk of Bias A: Bias due to randomization Intervention 2 better Intervention 1 better Some Concerns B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.14 1.95 Risk Ratio

Pharmacological treatments

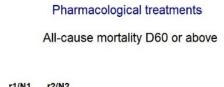
Sensitivity analysis 1.9.2 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28.

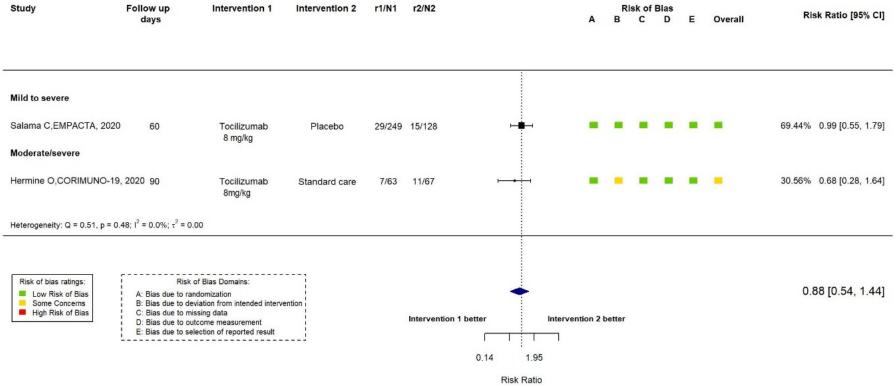


Sensitivity analysis 1.9.3 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28.



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



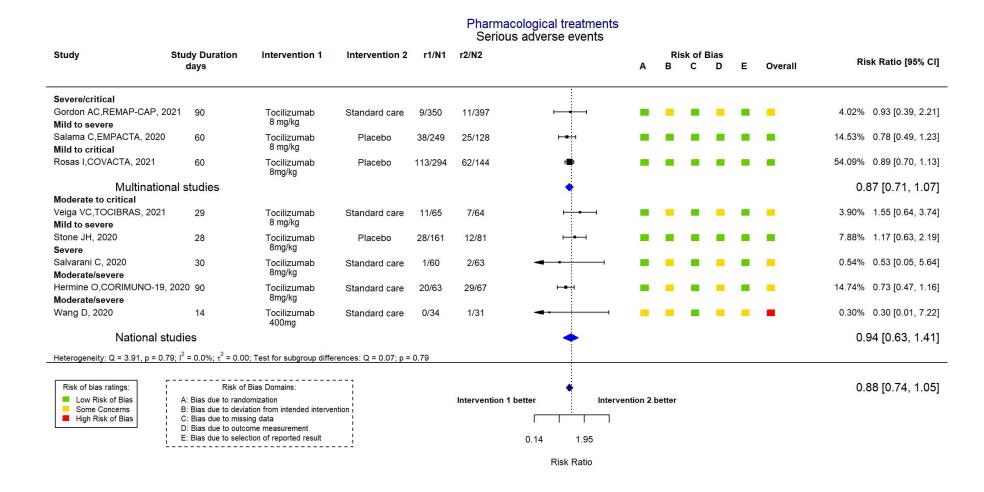


Sensitivity analysis 1.9.5 Participants analyzed. Tocilizumab versus placebo or standard care. Outcome: Adverse events.

Adverse events **Study Duration** Study Intervention 1 Intervention 2 r1/N1 Risk of Bias Risk Ratio [95% CI] days C E Overall Mild to severe Salama C, EMPACTA, 2020 17.51% 0.97 [0.79, 1.20] 60 Tocilizumab Placebo 127/249 67/128 8 mg/kg Mild to severe Stone JH, 2020 14.65% 0.98 [0.60, 1.59] 28 Tocilizumab Placebo 37/161 19/81 8mg/kg Moderate/severe Hermine O,CORIMUNO-19, 2020 90 H**E**H 16.14% 0.83 [0.58, 1.18] Tocilizumab Standard care 28/63 36/67 8mg/kg Moderate/severe Wang D, 2020 9.28% 4.56 [1.75, 11.87] 14 Tocilizumab Standard care 20/34 4/31 400mg Mild to critical Rosas I, COVACTA, 2021 60 Tocilizumab 237/294 118/144 18.11% 0.98 [0.89, 1.08] Placebo 8mg/kg Moderate to critical Veiga VC, TOCIBRAS, 2021 29 Tocilizumab Standard care 29/65 21/64 15.14% 1.36 [0.87, 2.12] 8 mg/kg Severe Salvarani C, 2020 30 Tocilizumab 9.17% 2.73 [1.04, 7.19] Standard care 13/60 5/63 Heterogeneity: Q = 16.91, p = 0.01; I^2 = 91.7%; τ^2 = 0.25 Risk of bias ratings: Risk of Bias Domains: 1.00 [0.92, 1.09] Low Risk of Bias A: Bias due to randomization Intervention 1 better Intervention 2 better Some Concerns B: Bias due to deviation from intended intervention High Risk of Bias C: Bias due to missing data D: Bias due to outcome measurement E: Bias due to selection of reported result 0.14 1.95 Risk Ratio

Pharmacological treatments

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



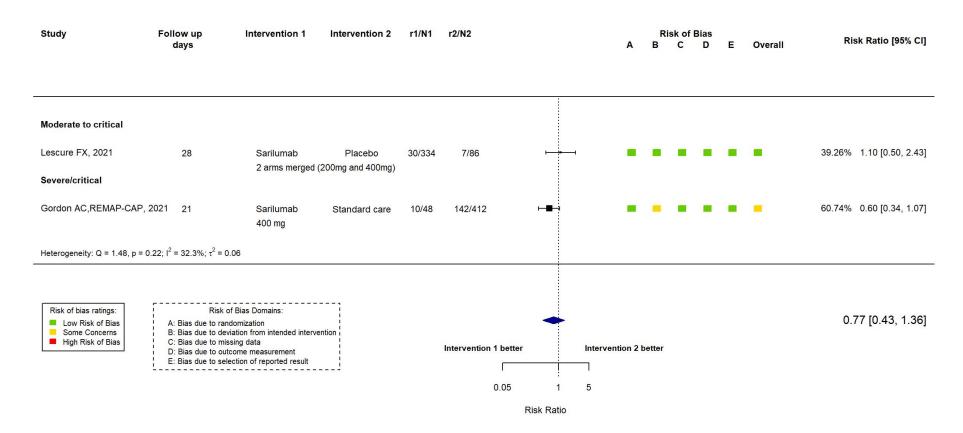
Comparison: Sarilumab versus placebo or standard care

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

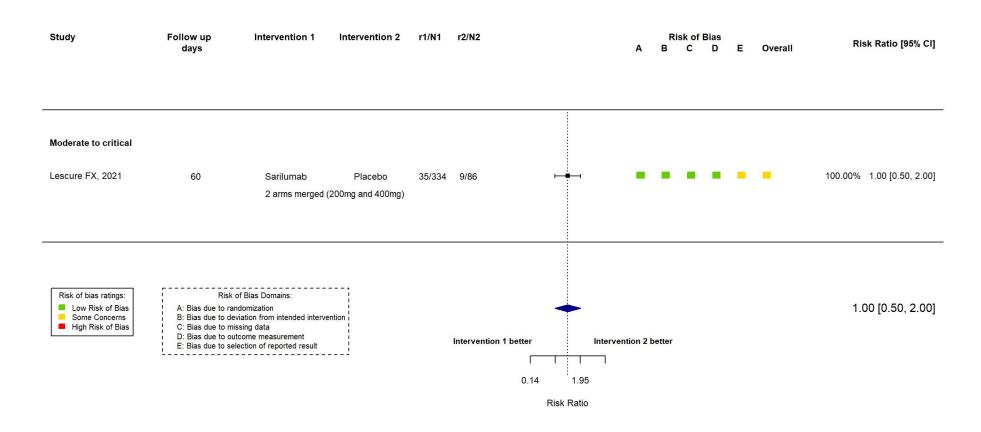
All-cause mortality D28



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

Pharmacological treatments

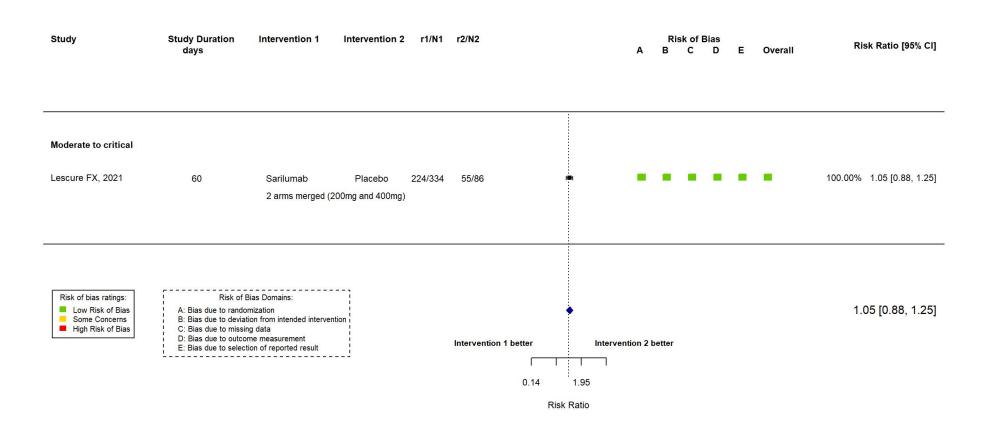
All-cause mortality D60 or above



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

Pharmacological treatments

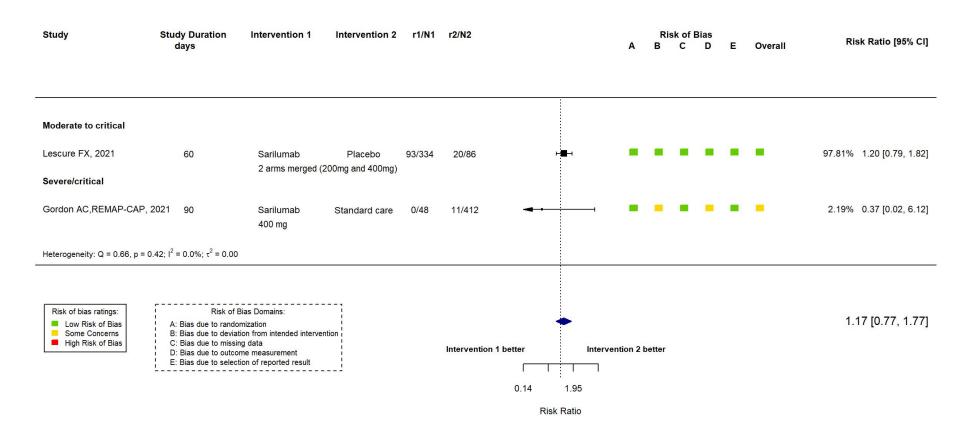
Adverse events



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

Pharmacological treatments

Serious adverse events



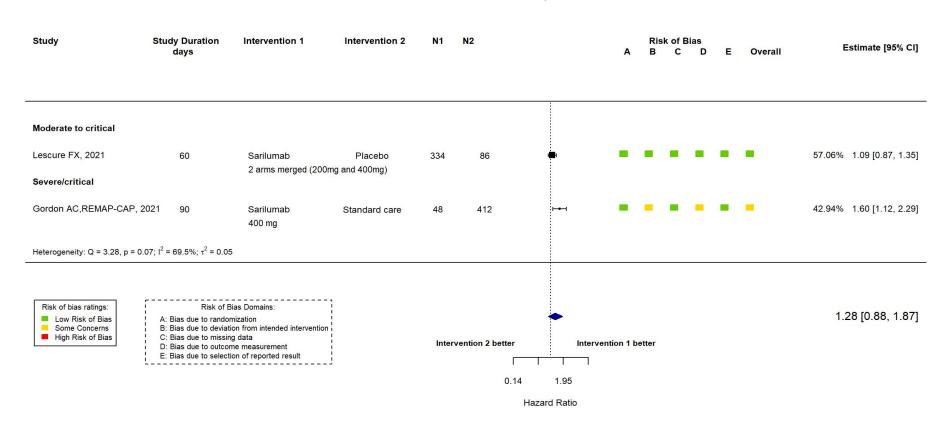
Analysis 2.2.1 Sarilumab versus placebo or standard care. Outcome: Time to clinical improvement

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



Time to death

