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Interleukin-6 blocking agents for treating COVID-19: a living systematic review (Review)

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[Intervention Review]

Interleukin-6 blocking agents for treating COVID-19: a living systematic review

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ABSTRACT

Background

It has been reported that people with COVID-19 and pre-existing autoantibodies against type I interferons are likely to develop an inflammatory cytokine storm responsible for severe respiratory symptoms. Since interleukin 6 (IL-6) is one of the cytokines released during this inflammatory process, IL-6 blocking agents have been used for treating people with severe COVID-19.

Objectives

To update the evidence on the effectiveness and safety of IL-6 blocking agents compared to standard care alone or to a placebo for people with COVID-19.

Search methods

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform, the Living OVerview of Evidence (L·OVE) platform, and the Cochrane COVID-19 Study Register to identify studies on 7 June 2022.

Selection criteria

We included randomized controlled trials (RCTs) evaluating IL-6 blocking agents compared to standard care alone or to placebo for people with COVID-19, regardless of disease severity.

Data collection and analysis

Pairs of researchers independently conducted study selection, extracted data and assessed risk of bias. We assessed the certainty of evidence using the GRADE approach for all critical and important outcomes. In this update we amended our protocol to update the methods used for grading evidence by establishing minimal important differences for the critical outcomes.

Main results

This update includes 22 additional trials, for a total of 32 trials including 12,160 randomized participants all hospitalized for COVID-19 disease. We identified a further 17 registered RCTs evaluating IL-6 blocking agents without results available as of 7 June 2022.

The mean age range varied from 56 to 75 years; 66.2% (8051/12,160) of enrolled participants were men. One-third (11/32) of included trials were placebo-controlled. Twenty-two were published in peer-reviewed journals, three were reported as preprints, two trials had results posted only on registries, and results from five trials were retrieved from another meta-analysis. Eight were funded by pharmaceutical companies.

Twenty-six included studies were multicenter trials; four were multinational and 22 took place in single countries. Recruitment of participants occurred between February 2020 and June 2021, with a mean enrollment duration of 21 weeks (range 1 to 54 weeks). Nineteen trials (60%) had a follow-up of 60 days or more. Disease severity ranged from mild to critical disease. The proportion of participants who were intubated at study inclusion also varied from 5% to 95%. Only six trials reported vaccination status; there were no vaccinated participants included in these trials, and 17 trials were conducted before vaccination was rolled out.

We assessed a total of six treatments, each compared to placebo or standard care. Twenty trials assessed tocilizumab, nine assessed sarilumab, and two assessed clazakizumab. Only one trial was included for each of the other IL-6 blocking agents (siltuximab, olokizumab, and levilimab). Two trials assessed more than one treatment.

Efficacy and safety of tocilizumab and sarilumab compared to standard care or placebo for treating COVID-19

At day (D) 28, tocilizumab and sarilumab probably result in little or no increase in clinical improvement (tocilizumab: risk ratio (RR) 1.05, 95% confidence interval (CI) 1.00 to 1.11; 15 RCTs, 6116 participants; moderate-certainty evidence; sarilumab: RR 0.99, 95% CI 0.94 to 1.05; 7 RCTs, 2425 participants; moderate-certainty evidence). For clinical improvement at ≥ D60, the certainty of evidence is very low for both tocilizumab (RR 1.10, 95% CI 0.81 to 1.48; 1 RCT, 97 participants; very low-certainty evidence) and sarilumab (RR 1.22, 95% CI 0.91 to 1.63; 2 RCTs, 239 participants; very low-certainty evidence).

The effect of tocilizumab on the proportion of participants with a WHO Clinical Progression Score (WHO-CPS) of level 7 or above remains uncertain at D28 (RR 0.90, 95% CI 0.72 to 1.12; 13 RCTs, 2117 participants; low-certainty evidence) and that for sarilumab very uncertain (RR 1.10, 95% CI 0.90 to 1.33; 5 RCTs, 886 participants; very low-certainty evidence).

Tocilizumab reduces all cause-mortality at D28 compared to standard care/placebo (RR 0.88, 95% CI 0.81 to 0.94; 18 RCTs, 7428 participants; high-certainty evidence). The evidence about the effect of sarilumab on this outcome is very uncertain (RR 1.06, 95% CI 0.86 to 1.30; 9 RCTs, 3305 participants; very low-certainty evidence).

The evidence is uncertain for all cause-mortality at ≥ D60 for tocilizumab (RR 0.91, 95% CI 0.80 to 1.04; 9 RCTs, 2775 participants; low-certainty evidence) and very uncertain for sarilumab (RR 0.95, 95% CI 0.84 to 1.07; 6 RCTs, 3379 participants; very low-certainty evidence).

Tocilizumab probably results in little to no difference in the risk of adverse events (RR 1.03, 95% CI 0.95 to 1.12; 9 RCTs, 1811 participants; moderate-certainty evidence). The evidence about adverse events for sarilumab is uncertain (RR 1.12, 95% CI 0.97 to 1.28; 4 RCT, 860 participants; low-certainty evidence).

The evidence about serious adverse events is very uncertain for tocilizumab (RR 0.93, 95% CI 0.81 to 1.07; 16 RCTs; 2974 participants; very low-certainty evidence) and uncertain for sarilumab (RR 1.09, 95% CI 0.97 to 1.21; 6 RCTs; 2936 participants; low-certainty evidence).

Efficacy and safety of clazakizumab, olokizumab, siltuximab and levilimab compared to standard care or placebo for treating COVID-19

The evidence about the effects of clazakizumab, olokizumab, siltuximab, and levilimab comes from only one or two studies for each blocking agent, and is uncertain or very uncertain.

Authors' conclusions

In hospitalized people with COVID-19, results show a beneficial effect of tocilizumab on all-cause mortality in the short term and probably little or no difference in the risk of adverse events compared to standard care alone or placebo. Nevertheless, both tocilizumab and sarilumab probably result in little or no increase in clinical improvement at D28.

Evidence for an effect of sarilumab and the other IL-6 blocking agents on critical outcomes is uncertain or very uncertain. Most of the trials included in our review were done before the waves of different variants of concern and before vaccination was rolled out on a large scale.

An additional 17 RCTs of IL-6 blocking agents are currently registered with no results yet reported. The number of pending studies and the number of participants planned is low. Consequently, we will not publish further updates of this review.

PLAIN LANGUAGE SUMMARY

Are medicines that block interleukin-6 (a protein involved when the body's immune system overreacts) effective treatments for COVID-19 and do they cause unwanted effects?

Key messages

We are very confident that tocilizumab (a medicine that blocks interleukin-6 (IL-6)) reduces the number of hospitalized people who die from COVID-19 within 28 days of treatment. However, it probably results in little or no difference in clinical improvement (defined as leaving the hospital or improvement in COVID-19 symptoms).

Sarilumab probably results in little or no difference in clinical improvement.

We found few studies assessing the other IL-6-blocking medicines. We are, therefore, uncertain about their effects.

A small number of studies have not published any results. These studies treated relatively low numbers of people and their results would not change our current findings.

What is IL-6, and what is its role in COVID-19?

IL-6 is a type of protein called a cytokine, which helps to regulate the body's immune system. In particular, IL-6 triggers inflammation to help the body recognize and fight infection to defend itself against harmful substances, such as viruses.

When a person has COVID-19 it can disrupt their immune system response, causing it to overreact. When the body continually makes IL-6 as part of this response, it can produce high levels of inflammation that damage the body. This can lead to severe breathing difficulties, organ failure and death.

What are IL-6 blocking agents?

IL-6 blocking agents are medicines that stop the IL-6 from working by blocking signals from IL-6 to other parts of the immune system. This reduces inflammation and may help the immune system to fight COVID-19. In turn, this may reduce the need for breathing support with a ventilator (a machine that breathes for a patient) and reduce the number of deaths from COVID-19. These are already known to be safe and effective when they are used to treat conditions that involve an 'overreactive' immune system, such as rheumatoid arthritis.

What did we want to find out?

We wanted to know if IL-6 blocking agents are effective treatments for people with COVID-19, compared with standard care alone or with placebo (a dummy treatment that appears identical to the medicine being tested but without any active medicine). We were particularly interested in the effects of IL-6 blocking agents on:

- whether people's symptoms got better or worse;

- how many people died; and

- any unwanted effects and serious unwanted effects.

What did we do?

We searched for studies that tested if medicines that block interleukin-6 can treat COVID-19 effectively. We looked for randomized controlled studies in which the treatments people received are decided by chance. We compared and summarized the results of the studies. We used a standardized method to rate our confidence in the evidence. The confidence is based on study features such as study design and the number of people included.

What did we find?

We found 32 studies in 12,160 people with COVID-19. The average age of people was 56 to 75 years, and 66% of the participants were men. The studies took place at hospitals in different countries around the world. Eight studies were funded by pharmaceutical companies.

The medicines most tested were tocilizumab and sarilumab.

We found 17 additional registered studies of IL-6-blocking medicines to treat COVID-19; these studies have no published results. Ten of these studies have either been completed or are still in progress. Seven were terminated.

What are the main results of our review?

Compared to placebo or standard treatment, treatment with tocilizumab:

- reduces the number of people with COVID-19 dying, of any cause, around 28 days;

- probably makes little or no difference on clinical improvement around 28 days;

- probably results in little or no difference in unwanted effects.

We are uncertain about the effects of tocilizumab treatment on:

- clinical improvement around 60 days;

- severity of COVID-19; that is, how many patients needed a ventilator or additional organ support or died of COVID-19 around 28 days;

- how many patients die, of any cause, around 60 days.

Compared to placebo or standard treatment, treatment with sarilumab:

- probably makes little or no difference in clinical improvement (defined as leaving the hospital or improvement in COVID-19 symptoms) around 28 days.

We are uncertain about the treatment effects and unwanted events of sarilumab, clazakizumab, olokizumab, siltuximab, and levilimab, compared to placebo or standard treatment.

What are the limitations of the evidence?

Our confidence in the results of clazakizumab, olokizumab, siltuximab, and levilimab is limited because of the low number of studies conducted and the small number of people included in these studies. We were unable to assess the variation in effects due to changes in the standard treatment provided, and we were also unable to see if effects were different in people of different ages or genders.

Further, most of the studies included in the review were conducted before the waves of different variants of concern and before vaccination was rolled out on a large scale.

How up to date is this evidence?

The evidence is up to date to 7 June 2022.

Summary of findings 1. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: hospital inpatients worldwide

Intervention: tocilizumab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with tocilizumab				
Clinical improvement D28[b]	545 per 1000	**573 per 1000** (545 to 605)	**RR 1.05** (1.00 to 1.11)	6116 (15 RCTs)[c]	⊕⊕⊕⊖ Moderate[d,e]	
Clinical improvement D60 or more[f]	609 per 1000	**670 per 1000** (493 to 901)	**RR 1.10** (0.81 to 1.48)	97 (1 RCT)[g]	⊕⊖⊖⊖ Very low[h,i,j]	
WHO progression score (level 7 or above) D28	217 per 1000	**196 per 1000** (157 to 244)	**RR 0.90** (0.72 to 1.12)	2117 (13 RCTs)[k]	⊕⊕⊖⊖ Low[j,l]	
All-cause mortality D28	284 per 1000	**250 per 1000** (230 to 267)	**RR 0.88** (0.81 to 0.94)	7428 (18 RCTs)[m]	⊕⊕⊕⊕ High[d]	One additional study (COVITOZ-01 2021) also reported on the outcome in 26 participants. There were zero events in both groups and the study not contribute to the pooled effect estimate.
All-cause mortality D60 or more	264 per 1000	**240 per 1000** (211 to 274)	**RR 0.91** (0.80 to 1.04)	2775 (9 RCTs)[n]	⊕⊕⊖⊖ Low[j,o]	One additional study (COVITOZ-01 2021) also reported on the outcome in 26 participants. There were zero events in both groups and the study not contribute to the pooled effect estimate.
Adverse events	443 per 1000	**456 per 1000** (421 to 496)	**RR 1.03** (0.95 to 1.12)	1811 (9 RCTs)[p]	⊕⊕⊕⊖ Moderate[q,r]	

(follow-up: range 14 days to 90 days)						
Serious adverse events (follow-up: range 14 days to 90 days)	168 per 1000	**156 per 1000** (136 to 180)	**RR 0.93** (0.81 to 1.07)	2974 (16 RCTs)[s]	⊕⊖⊖⊖ Very low[j,r,t]	One additional study (ARCHITECTS 2021) also reported on the outcome in 21 participants. There were zero events in both groups and the study not contribute to the pooled effect estimate.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; D: day; RCT: randomized controlled trial; RR: risk ratio; WHO: World Health Organization

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 22 July 2022
[b]Defined as a decrease in score by at least 2 points on the 7-category ordinal scale (Salama 2020; Stone 2020; Rosas 2022); an increase of at least 2 points on a 6-category ordinal scale (compared with the worst status at day of randomization) or discharge from the hospital alive (Declercq 2021); discharged at 28-days (ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; Hermine 2021; Hermine 2022; HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Salvarani 2020; Talaschian 2021); not admitted to hospital (discharged alive) (Veiga 2021).
[c]ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; Declercq 2021; Hermine 2021; Hermine 2022; HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Rosas 2022; Salama 2020; Salvarani 2020; Stone 2020; Talaschian 2021; Veiga 2021
[d]Despite some concerns or high risk regarding adequate randomization, deviations from intended interventions, missing data, outcome measurement and selection of reported results, not downgraded for risk of bias because the studies with these concerns contributed only a small proportion of weight to the effect estimate.
[e]Imprecision downgraded by 1 level: wide confidence interval consistent with the possibility for benefit and the possibility for a trivial/no effect
[f]Defined as hospital discharge.
[g]Hermine 2022
[h]Risk of bias downgraded by 1 level: some concerns regarding missing data and outcome measurement.
[i]Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings.
[j]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm.
[k]ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; Hermine 2021; HMO-0224-20 2021; IMMCOVA 2021; Rosas 2022; Rutgers 2021; Salama 2020; Stone 2020; Veiga 2021
[l]Despite some concerns or high risk regarding adequate randomization, deviations from intended interventions, and selection of reported results, not downgraded for risk of bias because the studies with these concerns contributed only a small proportion of weight to the effect estimate.
[m]ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; Declercq 2021; Gordon 2021; Hermine 2021; Hermine 2022; HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Rosas 2022; Rutgers 2021; Salama 2020; Salvarani 2020; Soin 2021; Stone 2020; Talaschian 2021; Veiga 2021
[n]ARCHITECTS 2021; Broman 2022; Declercq 2021; Derde 2021; Hermine 2021; Hermine 2022; HMO-0224-20 2021; Rosas 2022; Salama 2020

[o]Despite some concerns or high risk regarding adequate randomization, deviations from intended interventions, and missing data, not downgraded for risk of bias because the studies with these concerns contributed only a small proportion of weight to the effect estimate.
[p]Hermine 2021; Hermine 2022; Rosas 2022; Salama 2020; Salvarani 2020; Soin 2021; Stone 2020; Veiga 2021; Wang 2021
[q]Imprecision downgraded by 1 level: wide confidence interval consistent with the possibility for a trivial/no effect and the possibility for harm.
[r]One additional study was identified that assessed this outcome (Derde 2021), but no results were reported.
[s]Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; Gordon 2021; Hermine 2021; Hermine 2022; IMMCOVA 2021; Rosas 2022; Salama 2020; Salvarani 2020; Soin 2021; Stone 2020; Talaschian 2021; Veiga 2021; Wang 2021
[t]Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions, missing data, outcome measurement and selection of the reported results.

Summary of findings 2. Sarilumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Sarilumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]						
Patient or population: people with mild/moderate/severe/critical COVID-19						
Setting: hospital inpatients worldwide						
Intervention: sarilumab						
Comparison: standard care/placebo						
Outcomes	**Anticipated absolute effects*** (95% CI)		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with standard care/placebo	**Risk with sarilumab**				
Clinical improvement D28[b]	643 per 1000	**637 per 1000** (604 to 675)	**RR 0.99** (0.94 to 1.05)	2425 (7 RCTs)[c]	⊕⊕⊕⊖ Moderate[d]	
Clinical improvement D60 or more[e]	628 per 1000	**766 per 1000** (572 to 1000)	**RR 1.22** (0.91 to 1.63)	239 (2 RCTs)[f]	⊕⊖⊖⊖ Very low[g,h,i,j]	
WHO progression score (level 7 or above) D28	250 per 1000	**275 per 1000** (225 to 333)	**RR 1.10** (0.90 to 1.33)	886 (5 RCTs)[k]	⊕⊖⊖⊖ Very low[j,l]	
All-cause mortality D28	224 per 1000	**238 per 1000** (193 to 292)	**RR 1.06** (0.86 to 1.30)	3305 (9 RCTs)[m]	⊕⊖⊖⊖ Very low[j,l]	
All-cause mortality D60 or more	294 per 1000	**279 per 1000** (247 to 314)	**RR 0.95** (0.84 to 1.07)	3379 (6 RCTs)[n]	⊕⊖⊖⊖ Very low[j,l]	
Adverse events	408 per 1000	**457 per 1000**	**RR 1.12**	860	⊕⊕⊖⊖	

(follow-up: range 14 days to 90 days)		(396 to 522)	(0.97 to 1.28)	(4 RCTs)[o]	Low[p,q,r]
Serious adverse events (follow-up: range 14 days to 90 days)	243 per 1000	**265 per 1000** (236 to 294)	**RR 1.09** (0.97 to 1.21)	2936 (6 RCTs)[s]	⊕⊕⊖⊖ Low[q,r,t]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; D: day; RCT: randomized controlled trial; RR: risk ratio; WHO: World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 6 September 2022
[b]Defined as discharge at day 28 (Branch-Elliman 2022; Garcia-Vicuna 2022; Hermine 2022; Mariette 2021; Sancho-Lopez 2021); as a 2-point rise in a 7-category ordinal scale or hospital discharge, whichever occurred first (Merchante 2021); as proportion with 1-point improvement in clinical status using a 7-point ordinal scale on day 22 (Sivapalasingam 2022).
[c]Branch-Elliman 2022; Garcia-Vicuna 2022; Hermine 2022; Mariette 2021; Merchante 2021; Sancho-Lopez 2021; Sivapalasingam 2022 (phase 2 and 3)
[d]Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended intervention, missing data, outcome measurement and selection of the reported result.
[e]Defined as hospital discharge.
[f]Hermine 2022; Mariette 2021
[g]Risk of bias downgraded by 1 level: some concerns regarding deviation from intended intervention, missing data, outcome measurement and selection of the reported results
[h]Inconsistency downgraded by 1 level: $I^2 = 50.1\%$
[i]Indirectness downgraded by 1 level: studies from a single country, therefore results in this population might not be generalizable to other settings.
[j]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm
[k]Branch-Elliman 2022; Garcia-Vicuna 2022; Mariette 2021; Sancho-Lopez 2021; Sivapalasingam 2022 (phase 2)
[l]Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions, and missing data
[m]Branch-Elliman 2022; Garcia-Vicuna 2022; Gordon 2021; Hermine 2022; Lescure 2021; Mariette 2021; Merchante 2021; Sancho-Lopez 2021; Sivapalasingam 2022 (phase 2 and 3)
[n]Derde 2021; Garcia-Vicuna 2022; Hermine 2022; Lescure 2021; Mariette 2021; Sivapalasingam 2022 (phase 2)
[o]Hermine 2022; Lescure 2021; Mariette 2021; Sancho-Lopez 2021
[p]Risk of bias downgraded by 1 level: some concerns regarding deviations from intended intervention, missing data, outcome measurement and selection of the reported results.
[q]Imprecision downgraded by 1 level: wide confidence interval consistent with the possibility for no effect/trivial effect and the possibility for harm.
[r]One additional study was identified that assessed this outcome (Derde 2021), but no results were reported.
[s]Garcia-Vicuna 2022; Gordon 2021; Hermine 2022; Lescure 2021; Mariette 2021; Sivapalasingam 2022 (phase 2)
[t]Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended intervention, missing data, and outcome measurement.

Summary of findings 3. Clazakizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Clazakizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: hospital inpatients worldwide

Intervention: clazakizumab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with clazakizumab				
Clinical improvement D28[b]	500 per 1000	**640 per 1000** (485 to 850)	**RR 1.28** (0.97 to 1.70)	152 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e]	
Clinical improvement D60 or more	541 per 1000	**692 per 1000** (535 to 897)	**RR 1.28** (0.99 to 1.66)	152 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e]	
WHO progression score (level 7 or above) D28	446 per 1000	**294 per 1000** (192 to 450)	**RR 0.66** (0.43 to 1.01)	152 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e]	
All-cause mortality D28	253 per 1000	**230 per 1000** (137 to 392)	**RR 0.91** (0.54 to 1.55)	169 (2 RCTs)[f]	⊕⊖⊖⊖ Very low[g,h]	
All-cause mortality D60 or more	361 per 1000	**278 per 1000** (177 to 430)	**RR 0.77** (0.49 to 1.19)	169 (2 RCTs)[f]	⊕⊖⊖⊖ Very low[g,h]	
Adverse events (follow-up: range 14 days to 90 days)	222 per 1000	**251 per 1000** (44 to 1000)	**RR 1.12** (0.20 to 6.24)	17 (1 RCT)[i]	⊕⊕⊖⊖ Low[h,j]	
Serious adverse events (follow-up: range 14 days to 90 days)	434 per 1000	**299 per 1000** (200 to 451)	**RR 0.69** (0.46 to 1.04)	169 (2 RCTs)[f]	⊕⊕⊖⊖ Low[h,j]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; D: day; RCT: randomized controlled trial; RR: risk ratio; WHO: World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 21 July 2022
[b]Defined as change in clinical status, defined by an improvement in status by at least 2 score points on WHO 11-point ordinal scale.
[c]Lonze 2022
[d]Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings.
[e]Imprecision downgraded by 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility of no effect/trivial effect and small sample.
[f]Jordan 2021; Lonze 2022
[g]Indirectness downgraded by 1 level: studies from a single country, therefore results in this population might not be generalizable to other settings.
[h]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm.
[i]Jordan 2021
[j]We presume that the adverse event rates, and the corresponding relative risks, are similar across diverse settings; therefore not downgraded for indirectness.

Summary of findings 4. Olokizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Olokizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: hospital inpatients worldwide

Intervention: olokizumab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with olokizumab				
Clinical improvement D28[b]	758 per 1000	**834 per 1000** (728 to 940)	**RR 1.10** (0.96 to 1.24)	248 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e,f]	

Clinical improvement D60 or more - not reported	-	-	-	-	-
WHO progression score (level 7 or above) D28 - not reported	-	-	-	-	-
All-cause mortality D28	48 per 1000	**73 per 1000** (27 to 198)	**RR 1.50** (0.55 to 4.09)	248 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e,g]
All-cause mortality D60 or more - not reported	-	-	-	-	-
Adverse events - not reported	-	-	-	-	-
Serious adverse events (follow-up: range 14 days to 90 days)	65 per 1000	**81 per 1000** (33 to 197)	**RR 1.25** (0.51 to 3.06)	248 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,g,h]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; D: day; RCT: randomized controlled trial; RR: risk ratio; WHO: World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 29 June 2022
[b]Defined as the proportion of patients with an improvement in clinical status by 2 or more points on the 6-point ordinal scale (where 1 was the most favorable outcome and 6 was the most undesirable outcome) during the study with no use of tocilizumab or sarilumab.
[c]Samsonov 2022
[d]Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and deviations from intended interventions.
[e]Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings.
[f]Imprecision downgraded by 2 levels: wide confidence interval consistent with the possibility for benefit and the possibility for trivial effect/no effect, and small sample size.
[g]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm.
[h]We presume that the adverse event rates and the corresponding relative risks are similar across diverse settings; therefore not downgraded for indirectness.

Summary of findings 5. Siltuximab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Siltuximab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: hospital inpatients worldwide

Intervention: siltuximab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with siltuximab				
Clinical improvement D28[b]	736 per 1000	**714 per 1000** (582 to 869)	**RR 0.97** (0.79 to 1.18)	148 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e]	
Clinical improvement D60 or more - not reported	-	-	-	-	-	
WHO progression score (level 7 or above) D28	167 per 1000	**328 per 1000** (178 to 605)	**RR 1.97** (1.07 to 3.63)	148 (1 RCT)[c]	⊕⊕⊖⊖ Low[d,f]	
All-cause mortality D28	97 per 1000	**131 per 1000** (53 to 327)	**RR 1.35** (0.54 to 3.36)	148 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e]	
All-cause mortality D60 or more	125 per 1000	**198 per 1000** (93 to 423)	**RR 1.58** (0.74 to 3.38)	148 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e]	
Adverse events - not reported	-	-	-	-	-	
Serious adverse events (follow-up: range 14 days to 90 days)	153 per 1000	**197 per 1000** (98 to 400)	**RR 1.29** (0.64 to 2.62)	148 (1 RCT)[c]	⊕⊕⊖⊖ Low[e,g]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; D: day; RCT: randomized controlled trial; RR: risk ratio; WHO: World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 21 July 2022
[b]Defined as an increase of at least 2 points on a 6-category ordinal scale (compared with the worst status at day of randomization) or discharge from the hospital alive.
[c]Declercq 2021
[d]Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings.
[e]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm.
[f]Imprecision downgraded by 1 level: low number of events and/or participants.
[g]We presume that the adverse event rates and the corresponding relative risks are similar across diverse settings; therefore not downgraded for indirectness.

Summary of findings 6. Levilimab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Levilimab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: hospital inpatients worldwide

Intervention: levilimab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with levilimab				
Clinical improvement D28[b]	553 per 1000	**847 per** 1000 (697 to 1000)	**RR 1.53** (1.26 to 1.85)	206 (1 RCT)[c]	⊕⊕⊖⊖ Low[d,e]	
Clinical improvement D60 or more - not reported	-	-	-	-	-	
WHO progression score (level 7 or above) D28 - not reported	-	-	-	-	-	
All-cause mortality D28	39 per 1000	**39 per** 1000 (10 to 151)	**RR 1.00** (0.26 to 3.89)	206 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,f]	
All-cause mortality D60 or more	39 per 1000	**39 per** 1000 (10 to 151)	**RR 1.00** (0.26 to 3.89)	206 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,f]	
Adverse events	233 per 1000	**273 per** 1000 (170 to 436)	**RR 1.17** (0.73 to 1.87)	206 (1 RCT)[c]	⊕⊕⊖⊖ Low[f,g]	

(follow-up: range 14 days to 90 days)					
Serious adverse events (follow-up: range 14 days to 90 days)	19 per 1000	**10 per** 1000 (1 to 105)	**RR 0.50** (0.05 to 5.43)	206 (1 RCT)[c]	⨁⨁⊖⊖ Low[f,g]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Last updated: 29 June 2022
[b]Defined as an improvement of 2 or more point scales of clinical status from baseline on the 7-category ordinal scale or reaching the clinical status of categories 1 or 2 on Day 14.
[c]Lomakin 2021
[d]Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings.
[e]Imprecision downgraded by 1 level: small sample size.
[f]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm.
[g]We presume that the adverse event rates and the corresponding relative risks are similar across diverse settings; therefore not downgraded for indirectness.

BACKGROUND

Description of the condition

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 was first recognized in China in December 2019 and declared as a pandemic on 11 March 2020 by the World Health Organization (WHO). As of July 2022, over 565 million cases have been confirmed worldwide, including more than 6.3 million deaths (Worldometers 2022). The clinical spectrum of SARS-CoV-2 pneumonia ranges from asymptomatic or mild to severe and critical manifestations. Approximately 15% to 30% of patients infected with the wild-type variant of SARS-CoV-2 suffered from acute respiratory distress syndrome (Attaway 2021). Persons with underlying conditions and weakened immune systems are at higher risk of severe illness (Juul 2021).

Enormous efforts have focused on finding treatments to reduce the need for invasive mechanical ventilation and/or the risk of death in these patients. Some treatments have shown to be promising, including interleukin 6 (IL-6) inhibitors (Horby 2021a).

People with severe COVID-19 experience a “cytokine storm syndrome”; a complex milieu of immune misfiring characterized by an early interferonopathy followed by hypercytokinemia with high inflammatory markers and low reparative growth factors (Bastard 2020; Galani 2020; Lucas 2020; Mehta 2020; Pedersen 2020). In this milieu, interleukin 6 (IL-6) stands out as a particularly important biomarker (Chen 2020; Herold 2020; Laguna-Goya 2020; Stukas 2020). IL-6 levels or C-reactive protein (CRP), a marker of IL-6-driven inflammation, are associated with the severity of the disease (Caricchio 2020; Galvan-Roman 2021; Manson 2020; Webb 2020).

Description of the intervention

IL-6 blocking agents are a class of therapeutic agents directed against the IL-6 peptide or receptor that decrease the activity of inflammatory cytokines; thus, they are commonly prescribed in autoimmune diseases and other hyperinflammatory states (Hertanto 2021; Scott 2017; Stone 2017). Available IL-6 blocking agents are classified as anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab, and levilimab) or anti-IL-6 monoclonal antibodies (siltuximab, olokizumab, and clazakizumab).

How the intervention might work

It has been reported that pre-existing autoantibodies neutralizing type I interferons and subsequent high levels of IL-6 are positively associated with outcomes such as the need for intensive care and death in COVID-19 patients (Utrero-Rico 2021; Zhang 2020). The inhibition of IL-6, or its receptors, could curtail the risk of an escalation of the cytokine storm responsible for acute respiratory distress syndrome (ARD), a severe symptom with high mortality (Ghosn 2021; Hojyo 2020; Kimmig 2020; Kyriazopoulou 2021; WHO REACT Working Group 2021).

There are two signaling pathways used by IL-6; one relies on the cell membrane (IL-6 receptor) and the second is a soluble receptor (IL-6 signal transducer). Available IL-6 inhibitors bind specifically to the IL-6 receptor, blocking the signaling cascade (Kang 2020). This immunosuppressive effect of IL-6 blockers might valuably control inflammation and promote disease tolerance in people with COVID-19 characterized by substantial immune system dysfunction (Campochiaro 2020).

Why it is important to do this review

Given the need for an effective treatment for COVID-19 globally, people have been treated with several costly immune-modulating compounds including JAK (janus kinase) inhibitors (Cao 2020; Kalil 2021), and specific cytokine blockers (Guaraldi 2020). The main immunomodulatory therapies that have been explored are JAK inhibition (broad suppression of inflammatory cytokines) and targeted inhibition of IL-1 and IL-6 (CORIMUNO-19 Collaborative group 2021). Policymakers, scientific experts and the public need high--quality, up-to-date evidence evaluating the effectiveness and safety of IL-6 blocking agents for treating COVID-19. This is a high-priority question, for which the existing evidence is inconclusive (Solis-García Del Pozo 2020). A living systematic review is an optimal approach to track and assess the effectiveness of IL-6 blocking agents use in people with COVID-19.

In March 2021, we provided a summary of all the evidence available up to February 2021. It is important to continue to update the results to synthesis the newest evidence about IL-6 blocking agents. A living systematic review is an optimal approach for tracking and assessing the effectiveness of IL-6 blocking agents in people with COVID-19. We provide pairwise analysis of IL-6 blocking agents compared to standard care or placebo.

This is an update of the first publication of this review in March 2021 (Ghosn 2021). This updated review covers the best available evidence up to 7 June 2022; findings have also been updated on the COVID-NMA platform (covid-nma.com) up to 27 September 2022. On this date, the COVID-NMA Initiative has set the last search date for its review on IL-6 blocking agents and other treatment interventions for hospitalized people. We will not publish a new update of this review unless new evidence emerges with the potential to change the certainty of the evidence or our conclusions. The process of the living systematic review is described in Appendix 1.

OBJECTIVES

To update the evidence on the effectiveness and safety of IL-6 blocking agents compared to standard care alone or to placebo in people with COVID-19.

This review is part of a larger project: the COVID-NMA project (Boutron 2020a), which provides decision-makers with a complete, high-quality, and up-to-date mapping and synthesis of evidence on interventions for preventing and treating COVID-19.

METHODS

Criteria for considering studies for this review

Types of studies

The protocol of this review update is available on PROSPERO (CRD42020214700). The methods for the living process of the review are available in Appendix 1.

We included randomized controlled trials (RCTs) of any design (parallel-group, cluster, cross-over and factorial) with no language restrictions. We also included peer-reviewed journal publications, preprints, results posted in trial registries, results provided by

contacting authors and conference abstracts. Early-phase clinical trials, single-arm trials, non-randomized studies, and modeling studies of interventions for COVID-19 were excluded, as were prognostic studies, systematic reviews and meta-analyses, and studies of diagnostic test accuracy.

Types of participants

We included trials evaluating children or adults with suspected, probable or confirmed ambulatory or hospitalized COVID-19 regardless of severity level (see classification in Appendix 2; WHO 2020b).

Types of interventions

We included the following IL-6 blocking agents with no restriction on dose, frequency, or mode of administration.

- Tocilizumab (humanized monoclonal antibody against the IL-6 receptor)
- Sarilumab (human monoclonal antibody against the IL-6 receptor)
- Clazakizumab (humanized rabbit monoclonal antibody against IL-6)
- Olokizumab (humanized monoclonal antibody against IL-6)
- Siltuximab (chimeric monoclonal antibody against IL-6)
- Levilimab (human monoclonal antibody against the IL-6 receptor)

We assumed that participants receiving the intervention may have also received standard care.

Comparators

We considered the following comparators in this review: standard care alone or placebo; standard care as defined by trialists.

Types of outcome measures

Our outcome selection was based on the CORE outcome sets developed by the WHO (WHO Working Group 2020), and advice from content experts.

We predefined the following critical and important outcome measures.

Critical outcomes

We considered the following outcomes with related time points reported as days (D) of follow-up.

- Clinical improvement (D28/ ≥ D60), defined as a hospital discharge or improvement on a scale used by trialists to evaluate clinical progression and recovery. We recorded the scale and the threshold used by authors to define improvement.
- WHO clinical progression score (WHO-CPS) of level 7 or above, i.e. mechanical ventilation +/- additional organ support (extracorporeal membrane oxygenation (ECMO), vasopressors or dialysis) or death (D28/ ≥ D60)
- All-cause mortality (D28/ ≥ D60

All assessments performed at D60 and later were reported as under ≥ D60.

Safety outcomes

- Any adverse events (AE)
- Serious adverse events (SAE)

For each time point, we considered the time of randomization as D0, except if otherwise reported by authors; in that case, we followed their dating.

When outcomes at study level were assessed at time points other than those selected by the review, we chose the closest time point (e.g. D15 for D28).

We presented all critical outcomes in the summary of findings tables.

Important outcomes

- Time to clinical improvement
- Time to WHO clinical progression score of level 7 or above
- Time to death

Search methods for identification of studies

The search relied on the search strategies defined in the protocol of the larger COVID-NMA initiative (covid-nma.com) (Boutron 2020a; Boutron 2020b), and outlined in Appendix 3. The search methods and strategies to identify records for this review were revised approximately yearly to ensure that they reflect any terminology changes in topic areas and the databases.

Electronic searches

- The COVID-19 Living OVerview of Evidence (L·OVE) platform (app.iloveevidence.com/covid19) (last search: 7 June 2022). This platform is a digital repository built by systematic searches in multiple databases, trial registries and preprint servers. Complete data sources and search methods are available at: app.iloveevidence.com/covid19/methods.
- The Cochrane COVID-19 Study Register (covid-19.cochrane.org/) (last search: 7 June 2022). This specialized register is built within the Cochrane Register of Studies (CRS) and maintained by Cochrane information specialists.

Complete data sources and search methods for the register are available at: community.cochrane.org/about-covid-19-study-register.

We also searched the Retraction Watch Database for retracted trials (retractionwatch.com/retracted-coronavirus-covid-19-papers/) (last search 7 June 2022).

If no peer-reviewed publication was available for a given study, we extracted data from the preprint. We recognize that preprints are not peer-reviewed and are living documents that can be updated or published. Therefore, we systematically searched for updates or publications of the preprints using a preprint tracker developed in collaboration with a research team from the French National Centre for Scientific Research (CNRS) (Cabanac 2021; Oikonomidi 2020). As soon as an update was identified, we checked the data for discrepancies against those already extracted, recorded the data not available in the initial report, and updated the analysis if needed.

Searching other resources

Trial registries

We searched the following trial registries for completed trials with posted results, unpublished trials and ongoing trials (last search: 7 June 2022).

- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, www.who.int/ictrp/en/) to identify ongoing and completed clinical trials on COVID-19. We used the List By Health Topic: 2019-nCoV / COVID-19 filter and retrieved all studies identified.
- We also search the EU Clinical Trials Register (www.clinicaltrialsregister.eu/), ClinicalTrials.gov (clinicaltrials.gov/), and the Iranian Registry of Clinical Trials (www.irct.ir/).

Unpublished literature

We searched the European Medicines Agency (EMA) clinical data website (clinicaldata.ema.europa.eu/web/cdp/home) to identify trials submitted to the EMA and searched for the Clinical Study Report of eligible trials.

We also searched the US Food and Drug Administration website to identify FDA approval trials (www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19).

Data collection and analysis

We have provided access to the metaCOVID tool (covid-nma.com), which allows readers to explore the data using the latest iteration of the COVID-NMA database (Evrenoglou 2021).

Selection of studies

We used an Excel spreadsheet to document search dates and the number of citations identified. We used the Rayyan tool to identify duplicates (Ouzzani 2016). Discrepancies on exclusion and screening of full texts were resolved by consensus between each pair of reviewers or by involving a third reviewer. We recorded the reasons for exclusion of all studies after full-text review.

Whenever both preprints and subsequent peer-reviewed publications were available, we updated the results using the latest documents of the trial findings.

Data extraction and management

Pairs of reviewers independently read each preprint, peer-reviewed publication, protocol, and other study reports, extracted needed information, evaluated the completeness of the available data to request what was missing, and assessed the risk of bias. We used a specific structured online data extraction form that allowed for double extraction. The online tool automatically identified the discrepancies between the reviewers, which they then discussed to reach consensus.

The information extracted included study characteristics (such as first author, publication year and journal, funding source, the prevalence of variants of concerns during the study period), the number of participants randomized, participant characteristics (e.g. severity of clinical presentation), comorbidities, co-interventions, intervention details (e.g. dose, schedule), outcome measures, and risk of bias assessment.

Disease severity was classified as described below, according to participants' clinical status or clinical management of participants. This classification relies on an existing classification and clinical expertise (WHO 2020a; WHO 2020b). After considering the description of eligibility criteria as well as the participants' baseline characteristics, we classified severity as follows.

- Ambulatory mild disease — 'outpatients' whose clinical symptoms are mild with no sign of pneumonia on imaging.
- Mild disease — clinical symptoms requiring hospitalization but no need for supplemental oxygen.
- Moderate disease — fever and respiratory symptoms with radiological findings of pneumonia and requiring standard oxygen therapy O_2 (3–5 L/min).
- Severe disease — cases meeting any of the following criteria:
  - respiratory distress (≧ 30 breaths/min);
  - oxygen saturation ≤ 93% at rest in ambient air or oxygen saturation ≤ 97% with O_2≥ 5 L/min;
  - PaO_2/FiO_2 ≦ 300 mmHg (l mmHg = 0.133 kPa). PaO_2/FiO_2 in high-altitude areas (> 1000 m above sea level) is corrected by the following formula: PaO_2/FiO_2 x [atmospheric pressure (mmHg)/760];
  - hospitalized patients receiving non-invasive ventilation (NIV)/high flow nasal oxygen (HFNO).
- Critical disease — cases meeting any of the following criteria:
  - respiratory failure requiring invasive mechanical ventilation;
  - shock;
  - other organ failure requiring admission to an intensive care unit.

Since the classification of severity was heterogeneous among the studies, we reclassified participant disease severity according to the severity criteria above. Consequently, the severity reported by investigators might differ from the severity reported in this review. For example, Gordon 2021 classified the included participants as critical. Yet, according to our definitions, we classified them as severe or critical (patients who receive non-invasive ventilation or high-flow nasal cannula are rated as severely ill in the WHO classification). When no data related to these classifications were available, we requested the information from authors.

To collect information on the prevalence of variants of concern during the trial, we extracted the information if reported in the paper; otherwise, the information was extrapolated from data about the variants' prevalence in the population during the study period. This information was obtained from outbreak.info/ or other sources.

For dichotomous outcomes, we calculated the relative risk (RR) with 95% confidence interval (CI) as a measure of effect. We extracted the number of both events and total participants in each trial arm. For time-to-event outcomes, we extracted the hazard ratio (HR) with 95% CI. When these were not provided, we attempted to obtain them with the tools provided in Tierney 2007. When credible intervals were reported instead of confidence intervals, we extracted the former. In the absence of prior information, these two are not expected to have a substantial

numerical difference. For time to improvement, when available, we extracted the data with death treated as a competing risk. When several analyses were reported, we extracted results from the intention-to-treat (ITT) analysis whenever these were available. If ITT results were not available, we extracted results from any modified ITT analyses.

We systematically contacted the trial authors to ask them for supplementary information unavailable from the trial reports. These data were requested by a personalized email sent by the WHO as a partner in the COVID-NMA project.

Assessment of risk of bias in included studies

We assessed the trials with version 2 of the Cochrane risk of bias tool for randomized trials (RoB 2) (Sterne 2019).

RoB 2 is structured into five domains: 1) risk of bias arising from the randomization process, 2) risk of bias due to deviations from intended interventions, 3) risk of bias due to missing outcome data, 4) risk of bias in the measurement of the outcome, 5) risk of bias in the selection of the reported result. A series of 'signaling questions' elicits information relevant to the risk of bias assessment within each domain. The response options to the signaling questions are: 'yes'; 'probably yes'; 'probably no'; 'no'; and 'no information'. An algorithm generates a judgment of risk of bias for each domain, based on answers to the signaling questions. Judgments can be 'low', 'some concerns' or 'high' risk. Overall risk of bias is considered 'low' if all domains are at 'low risk'; 'some concerns' if at least one domain has 'some concern' and no domain is at 'high' risk of bias; and 'high' if at least one domain is at 'high risk'.

We assessed the risk of bias for all critical and important outcomes as predefined in the protocol of the COVID-NMA living systematic review (Boutron 2020b).

In the context of this review update, we are interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions were received as intended (i.e. ITT effect).

We used an online data extraction tool to record judgments for each domain and time point. All risk of bias assessments were done at the outcome level by two independent review authors. Review authors had epidemiological training or were members of the Cochrane Response team. They were trained using materials developed by the Cochrane Bias Methods Group. These training materials were developed for systematic reviewers participating in data extraction and risk of bias assessment using RoB 2 for the COVID-NMA platform (Nejstgaard 2021). Each review author independently assessed included manuscripts and used signaling questions for each domain of bias, fed into the related algorithm to obtain a judgment. Both review authors recorded their judgment and support for judgment. However, answers to signaling questions were not recorded. To achieve the required consensus, all disagreements in judgment were identified and discussed until consensus was reached. If needed, a third reviewer was involved.

In the context of the COVID-19 pandemic, we also standardized our assessment of some domains.

Domain 2. Bias due to deviations from intended interventions

In trials where participants and carers were not blinded, we specified some deviations that could arise because of the trial context and could affect the trial outcomes:

Cross over from the control group to the intervention group

When the number of participants in the control group receiving the intervention was important, we rated this domain as of 'some concern'.

When the cross-over was planned in the protocol for participants with clinical worsening, we decided to rate this domain as of 'some concern' because the trial context could have influenced the decision to provide the treatment.

Co-interventions

The following co-interventions could affect the trial outcomes.

- Remdesivir and other antivirals
- Corticosteroids
- Biologics

When these co-interventions were reported and balanced, we assessed this domain to be at 'low' risk of bias. When these co-interventions were reported but imbalanced, we rated the domain as of 'some concern' and not at 'high risk' of bias as it is impossible to distinguish deviation due to the trial context from deviation due to the intervention effect.

Domain 2. Analysis to estimate the effect of assignment

We considered ITT analyses to be appropriate.

When the analysis was not done on an ITT basis, we rated this domain on a case-by-case basis depending on the following.

- The number of participants who crossed over and were not analyzed in the group to which they are allocated.
- The number of participants excluded from the analysis for a reason other than missing data, and any imbalance between arms in terms of the number of and reasons for exclusion.

For critical outcomes (binary outcomes) the analysis evaluated was not always based on the analysis reported by authors, but rather on our own analysis, which considered all randomized participants as the denominator.

Domain 4. Bias in the measurement of the outcome

We prespecified the following rules.

- Clinical Improvement (D28/ ≥ D60/time to event): assessment of this outcome requires clinical judgment and can be influenced by knowledge of the intervention assignment, but we judged that this is not likely in the context of the pandemic.
- WHO-CPS level 7 or above (D28/ ≥ D60/time to event): assessment of this outcome is probably not influenced by knowledge of the intervention assignment.
- All-cause mortality (D28/ ≥ D60/time to event): assessment of this outcome is not influenced by knowledge of the intervention assignment.
- Adverse events and serious adverse event:

- when detection of events relies only on measures that cannot be influenced by judgment (e.g. laboratory detected events): assessment of this outcome is probably not influenced by knowledge of the intervention assignment;
- when detection events rely only on measures that can be influenced by judgment (e.g. clinically and laboratory detected events): assessment of this outcome can be influenced by knowledge of the intervention assignment, but such influence is unlikely in the pandemic context.

While we relied on the signaling questions to assess each domain and justify our assessment, we did not record the answers of systematic reviewers or how consensus was obtained for the signaling questions. This was done only at the domain level. The risk of bias assessment was considered part of an evaluation of the certainty of the evidence and as a sensitivity analysis.

For cluster-randomized trials, we planned to rely on the extension of the RoB2 tool for cluster-randomized trials. Particularly, we planned to add the domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial. There were, however, no cluster RCTs reported by the date of the last search.

For the unpublished trials included in this review update, we consulted the results and the risk of bias assessment for the outcomes as reported in a meta-analysis by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group.

For the included studies where results were posted only in trials registers, we used that posted information, as well as its protocol, if available.

Measures of treatment effect

For dichotomous outcomes, we calculated the relative risk (RR) and 95% confidence interval (CI) as the measure of effect, using the number of events and total participants in each arm. For time-to-event outcomes, we extracted the hazard ratios (HR) and 95% CI from the trial reports, and subsequently pooled these in the meta-analysis.

Unit of analysis issues

We extracted data by arm and considered multi-arm studies as independent two-arm studies in the pairwise meta-analyses.

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), for studies with different doses, we combined arms that used different doses of the same drug.

Dealing with missing data

For missing outcome data, we extracted the number of participants who dropped out before completing the trial and noted how trial authors handled missing outcome data. In our primary analysis of the critical outcomes, we followed a conservative approach assuming that participants with missing outcome data did not experience the event of interest. Hence, we calculated all RRs with the number of participants randomized as each group in the denominator. We also conducted sensitivity analyses to assess the potential impact of missing outcome data on the results by using an available case analysis with the number of participants analyzed (e.g. only participants without missing outcome data or only participants who received treatment) in the denominator (see Sensitivity analysis section).

Assessment of heterogeneity

We generated descriptive statistics for both the trial and population characteristics. We examined the distribution of important clinical and methodological variables (e.g. age, disease severity, pre-existing conditions and comorbidities, location). We used visual inspection of forest plots, the I^2 statistic and the magnitude of between-study variance (Tau^2) to estimate the level of heterogeneity. In instances where the level of heterogeneity was estimated to be negligible or close to zero, we refrained from presenting prediction intervals. This is because such intervals would coincide with the confidence intervals of the effect estimate in these cases. Additionally, we avoided reporting prediction intervals for outcomes where only a limited number of studies reported the outcome (Higgins 2021; Riley 2011).

Assessment of reporting biases

We assessed the selective non-reporting or under-reporting of results in the trials identified according to the framework proposed in Chapter 13 of the *Cochrane Handbook* (Higgins 2021).

Assessing the risk of bias due to missing results in the synthesis

We checked whether the results of all our critical and important outcomes were reported as prespecified in the trial register. When registration was not prospective, we also checked the protocol or statistical analysis plan if available. We contacted the corresponding authors of included trials to obtain the missing data.

When trial outcome results were unavailable, we used a matrix indicating the availability of study results as recommended in the *Cochrane Handbook* (Higgins 2021; Kirkham 2018).

We checked whether the results were unavailable because of the result's P value, magnitude, or direction. We considered the risk of bias due to missing results if one specified outcome of the registry was missing in the main report for one of these reasons.

In this update, we explored potential publication bias by generating funnel plots for outcomes with more than 10 studies included (Sterne 2019). We considered $P < 0.5$ as significant for this test.

Data synthesis

We combined trials evaluating the same drug to standard care alone or to placebo comparators together in the same comparison. All eligible RCTs were included in the primary analysis, regardless of the risk of bias assessment.

For binary outcomes, we used the number of events and the number of total participants in each arm to calculate the logRRs and their standard error. Then we pooled the trial-specific effect sizes. For time-to-event outcomes, we directly extracted the HRs and their 95% CIs from the trial reports and subsequently pooled them in the meta-analysis.

For each direct comparison with at least two trials providing data, we present effect estimates with 95% CIs. We used a random-effects model to incorporate the anticipated clinical and methodological heterogeneity across trials. Comparisons from multi-arm or platform trials were treated as independent two-arm

trials since we did not pool comparisons of different drugs in the same meta-analysis.

All analyses were conducted using metaCOVID (Evrenoglou 2021), an R-Shiny application that runs in parallel with the COVID-NMA initiative. The application's aim is to allow all end-users of the COVID-NMA platform to perform their own meta-analyses in a user-friendly environment. All data analyses are based on the latest updated COVID-NMA database regarding treatments and vaccines used against Covid-19. metaCOVID is based on the R-packages metafor (Viechtbauer 2010) and meta (Balduzzi 2019). It is freely available at: covid-nma.com/metacovid/.

Subgroup analysis and investigation of heterogeneity

We conducted prespecified subgroup analyses to explore the impact of trial location (single countries versus multinational), and performed severity subgroup analysis when possible. We also performed post hoc subgroup analyses including funding sources (private versus public/non-profit versus mixed) and conflict of interests (conflict of interests declared versus no conflict of interests).

Sensitivity analysis

We performed sensitivity analyses by excluding trials with high overall risk of bias and RCTs reported only as preprint. We also undertook a sensitivity analysis to assess the potential impact of missing outcome data on the results by using an available case analysis with the number of participants analyzed instead of those randomized (Chaimani 2018; Mavridis 2015; Mavridis 2018; White 2008).

Summary of findings and assessment of the certainty of the evidence

To evaluate the confidence to be placed in the results of the pairwise comparisons for critical and important outcomes, we used the GRADE approach (Schünemann 2022b). We created summary of findings tables to present the estimated relative and absolute risks for all comparisons and prioritized the presentation of the following seven critical outcomes: clinical improvement (D28 and ≥D60), WHO-CPS level 7 or above (D28), all-cause mortality (D28 and ≥D60), adverse events and serious adverse events.
We did not include studies with no events in GRADE since they do not contribute to the pooled effect estimate. Absolute effects were calculated with GRADEpro GDT using the baseline risks in the control groups of the included studies for each outcome. We calculated the baseline risk for time-to-event outcomes using the baseline risk in the control groups of the included studies in the corresponding dichotomous outcome. One review author assessed overall certainty of the evidence, and another review author cross-checked this.

We used the five GRADE considerations (limitations in design, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence related to studies that contributed data to pairwise meta-analyses for prespecified outcomes. We used the new approach proposed by GRADE for assessing imprecision (Schünemann 2022).

We considered the size of the absolute risk and its confidence intervals and set minimal important difference thresholds at 5% (50 per 1000) for the outcomes of clinical improvement, time to clinical improvement, and adverse events. For mortality outcomes, time to death, WHO score 7 and above, time to WHO score 7 and above, and serious adverse events, we set the threshold at 1% (10 per 1000). Absolute differences smaller than 5% (or 1% respectively) are considered to indicate trivial/no effect, and differences of more than 5% (or 1% respectively) are considered clinically important benefit/harm.

The evidence profiles provide the effect estimate and the associated certainty of evidence for each outcome of interest (Appendix 4).

RESULTS

Description of studies

For a full description of studies, please see Characteristics of included studies, In addition, a summary table of baseline characteristics for all trials is available in Appendix 5. Characteristics of excluded studies and unpublished registered studies are summarized in Characteristics of excluded studies and Appendix 6.

Results of the search

The results of the weekly search updates are detailed in Figure 1. On 7 June 2022, we retrieved a total of 49,770 published references after excluding duplicates; 35 records were eligible for full-text screening and 30 reports of 32 RCTs evaluating IL-6 blocking agents were included. The search of clinical trial registries retrieved additional 17 registered trials that had neither published nor posted results and two canceled registered trials. No reports were identified from the EMA or FDA. We did not identify any retracted articles concerning IL-6 blocking agents.

Figure 1. Flowchart of included randomized controlled trials (RCTs) of interleukin 6 (IL-6) blocking agents (last search date: 7 June 2022) ICTRP: World Health Organization (WHO) International Clinical Trials Registry Platform

[a] Multiple arm RCTs evaluated both tocilizumab and sarilumab (one published and one unpublished result), [b] One factorial RCT evaluated tocilizumab and siltuximab, and consequently, they appear twice.

–**Figure 1.** Flowchart of included randomized controlled trials (RCTs) of interleukin 6 (IL-6) blocking agents (last search date 7 June 2022)
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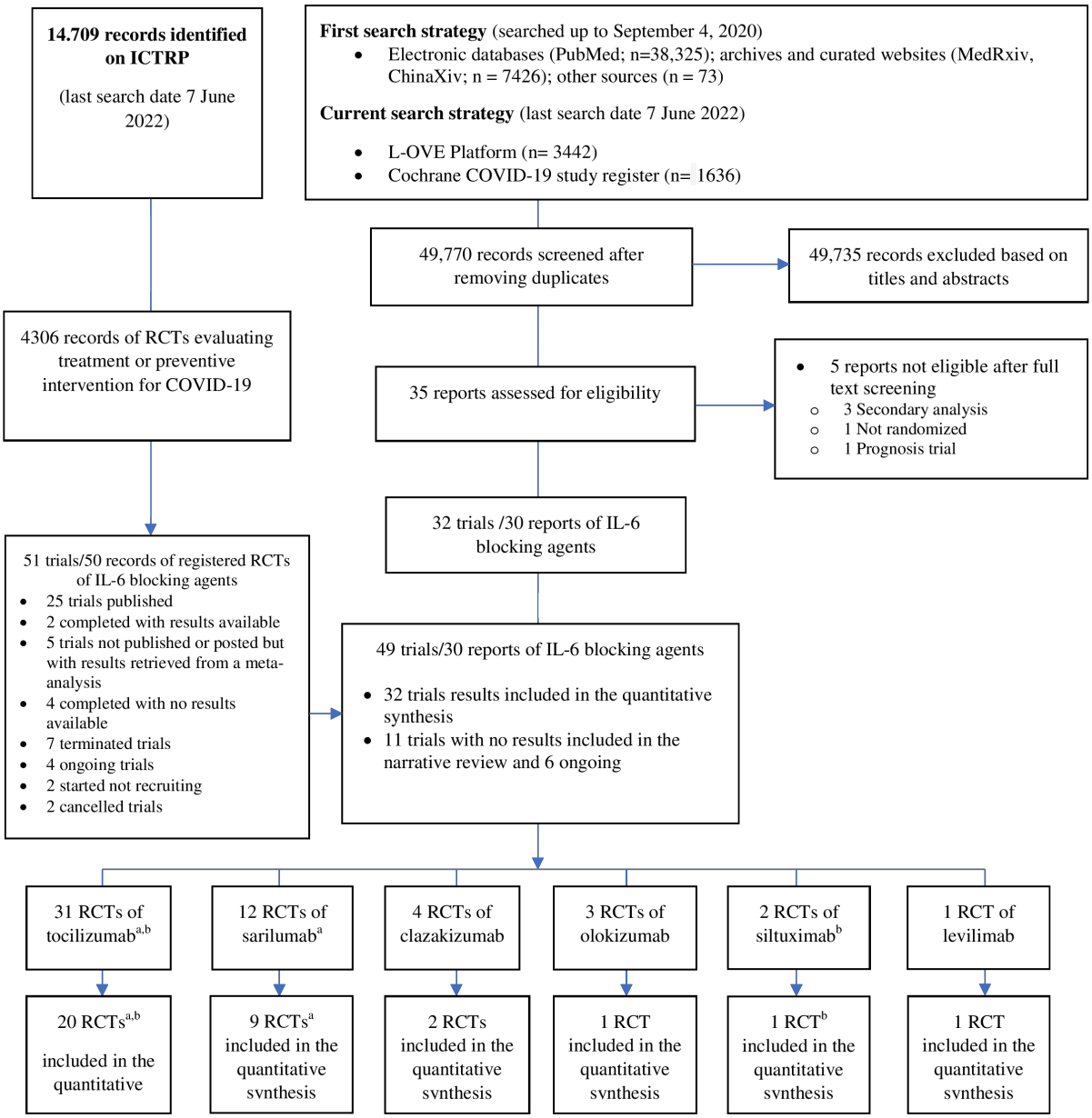


Figure 1. (Continued)

This review update identified 22 new trials with results that are included in the meta-analysis. The previous review included 10 RCTs (Ghosn 2021). Of the 32 trials included in this current update version, 20 trials evaluated tocilizumab, nine evaluated sarilumab, two evaluated clazakizumab, and there was one each for olokizumab, siltuximab, and levilimab. Of note, one platform multi-arm trial, REMAP-CAP, evaluated two IL-6 blocking agents (tocilizumab and sarilumab) (Derde 2021; Gordon 2021), and one factorial design trial evaluated two IL-6 blocking agents (tocilizumab and siltuximab) (Declercq 2021).

Included studies

Source of the data

Reports of 22 RCTs with results were published in peer-reviewed journals (Branch-Elliman 2022; Broman 2022; Declercq 2021; Garcia-Vicuna 2022; Hermine 2021 (reporting results of CORIMUNO-TOCI-1 of the CORIMUNO-19 Cohort); Hermine 2022 (reporting results of two trials of the CORIMUNO-19 cohort: CORIMUNO-TOCI-2 and CORIMUNO-SARI-2); Horby 2021b; Lescure 2021; Lomakin 2021; Lonze 2022; Mariette 2021; Merchante 2021; Rosas 2022; Salama 2020; Salvarani 2020; Sancho-Lopez 2021; Sivapalasingam 2022 (reporting results of phase 2 and 3 analysis populations); Soin 2021; Stone 2020; Veiga 2021; Wang 2021). Three trials were available as preprints (Derde 2021; Rutgers 2021; Talaschian 2021); for REMAP-CAP, findings were initially published in a peer-reviewed journal (Gordon 2021), and updated findings were released in a second report (Derde 2021), which at the time of writing remains available only as a preprint. Two trials were not published at the time of writing but posted their results on ClinicalTrials.gov (Jordan 2021; Samsonov 2022). We also included results of five unpublished trials (ARCHITECTS 2021; COVIDOSE-2 2021; COVITOZ-01 2021; HMO-0224-20 2021; IMMCOVA 2021), obtained from a meta-analysis by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group (WHO REACT Working Group 2021). We contacted authors of 31 included trials for additional information and received replies from eight authors, three of whom shared additional information. Because of the unavailability of contact information, we could not contact the authors of COVITOZ-01 2021 (Appendix 7).

Study design

Twenty-five trials used a two-arm parallel-group randomized design (ARCHITECTS 2021; Branch-Elliman 2022; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Garcia-Vicuna 2022; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Jordan 2021; Lomakin 2021; Mariette 2021; Rosas 2022; Rutgers 2021; Salama 2020; Salvarani 2020; Sancho-Lopez 2021; Soin 2021; Stone 2020; Talaschian 2021; Veiga 2021; Wang 2021); five had three arms (Lescure 2021; Lonze 2022; Merchante 2021; Samsonov 2022; Sivapalasingam 2022(reporting results of phase 2 and 3)), and one had four (REMAP-CAP (Derde 2021; Gordon 2021)). Finally, there was one factorial-design study (Declercq 2021). Six studies were platform trials (Derde 2021; Gordon 2021; Hermine 2022 (CORIMUNO-TOCI-2, CORIMUNO-SARI-2); Horby 2021b; Lescure 2021; Mariette 2021) and 11 were placebo-controlled (ARCHITECTS 2021; HMO-0224-20 2021; Jordan 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Rosas 2022; Salama 2020; Samsonov 2022; Sivapalasingam 2022; Stone 2020).

The total sample comprised 12,160 randomized participants, and the median sample size was 131 (interquartile range (IQR): 54 to 248; range: 17 to 4116). Eight trials did not reach their target sample size. Salvarani 2020 included 32% (126/398) of the target population when its Scientific Committee decided to interrupt the trial for futility, and COVITOZ-01 2021 was terminated for futility with an actual enrollment of 33% (26/78) of the planned sample size. Wang 2021 achieved only 35% of its planned sample size (65 randomized/188 planned) because of the rapid decline in the number of people with COVID-19 in China. REMAP-CAP (Derde 2021; Gordon 2021) was stopped at a scheduled interim analysis on the decision of the data safety monitoring board. Veiga 2021 was terminated after the first interim analysis on the recommendation of the data monitoring committee due to an excessive number of deaths at 15 days in the tocilizumab group. Recruitment to Branch-Elliman 2022 was terminated due to concerns about the high probability that intubation or death rates were higher in the sarilumab arm than the standard-care arm; it thus did not reach its target sample size. Jordan 2021 did not provide any information about why it recruited only 28% of its target sample. Stone 2020 amended the trial protocol in June 2020 to reduce the target sample size in the protocol from 278 participants (85% power) to 243 (80% power) as the enrollment rate slowed significantly with the waning of the pandemic in the Boston area.

The last known status of ARCHITECTS 2021, COVIDOSE-2 2021 and IMMCOVA 2021 is "ongoing". HMO-0224-20 2021's recruitment status was “recruiting” and was changed by clinicaltrials.gov to “unknown” as the completion date has passed, and the status has not been updated within the last two years. Rutgers 2021 reported 30-day outcomes only; the three-month endpoints have not yet been reported.

Study registration

All trial registration records were available; nine were registered retrospectively (Broman 2022; COVITOZ-01 2021; Garcia-Vicuna 2022; HMO-0224-20 2021; Lomakin 2021; Lonze 2022; Salvarani 2020; Samsonov 2022; Veiga 2021). The interval between registration and the study start was 54 days in Broman 2022, 43 days in COVITOZ-01 2021, 27 days in HMO-0224-20 2021, 21 days in Lomakin 2021, 16 days in Veiga 2021, 14 days in Salvarani 2020, 13 days in Samsonov 2022, 8 days in Lonze 2022, and 7 days in Garcia-Vicuna 2022.

Settings

All participants were hospital inpatients when recruited.

Multicenter trials comprised 26 of these studies. Of them, four were multinational (REMAP-CAP (Derde 2021; Gordon 2021; Lescure 2021; Rosas 2022; Salama 2020), and 22 were conducted in single countries: Belgium (Declercq 2021), Brazil (Veiga 2021), China

(Wang 2021), France (Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2, CORIMUNO-SARI-2); Mariette 2021), India (Soin 2021), Israel (HMO-0224-20 2021), Italy (Salvarani 2020), Russia (Lomakin 2021; Samsonov 2022), Spain (Merchante 2021; Sancho-Lopez 2021), Sweden (IMMCOVA 2021), the Netherlands (Rutgers 2021), the UK (Horby 2021b), and the USA (Branch-Elliman 2022; COVIDOSE-2 2021; Lonze 2022; Sivapalasingam 2022; Stone 2020).

Of the six single-center trials, one took place in Iran (Talaschian 2021), one in Finland (Broman 2022), and two each in the USA (ARCHITECTS 2021 Jordan 2021) and in Spain (COVITOZ-01 2021; Garcia-Vicuna 2022).

The trials were performed between February 2020 and June 2021, with a mean duration of study enrollment of 21 weeks (range: 1 to 54). Twenty-eight trials were conducted during exposure to the wild-type SARS-CoV-2 strains in 2020, and four during exposure to the wild-type and the alpha variant (COVITOZ-01 2021; HMO-0224-20 2021; Merchante 2021; Sancho-Lopez 2021) (Appendix 8).

Eleven studies had a follow-up of 90 days (ARCHITECTS 2021; Broman 2022; COVITOZ-01 2021; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2022 (CORIMUNO-TOCI-2, CORIMUNO-SARI-2); HMO-0224-20 2021; Mariette 2021; Rutgers 2021), eight reported a follow-up of 60 days (Hermine 2021; Jordan 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Rosas 2022; Salama 2020; Sivapalasingam 2022), 12 reported a follow-up of one month (28 to 30 days) (Branch-Elliman 2022; COVIDOSE-2 2021; Horby 2021b; IMMCOVA 2021; Merchante 2021; Salvarani 2020; Samsonov 2022; Sancho-Lopez 2021; Soin 2021; Stone 2020; Talaschian 2021; Veiga 2021), and one study had a follow-up of only 14 days (Branch-Elliman 2022).

Characteristics of participants

A total of 12,160 participants (32 RCTs) were included in the analysis of this review. Overall, 8131 participants (20 RCTs) were included in the analysis comparing tocilizumab to standard care or placebo; 3748 participants (nine RCTs) in the analysis comparing sarilumab to standard care or placebo; 169 participants (two RCTs) in the analysis comparing clazakizumab to placebo; and 248 participants (one RCT) in the analysis comparing olokizumab to placebo. The platform trial comparing siltuximab to standard care included 148 participants, and the RCT analyzing levilimab compared to placebo included 206 participants. The mean age range varied from 56 to 75 years and the percentage of men ranged from 5% to 90%.

All participants were hospitalized for COVID-19. Participants had mild to critical disease in one RCT (n = 452) (Rosas 2022), mild to severe diseases in five RCTs (n = 737) (Branch-Elliman 2022; COVITOZ-01 2021; Garcia-Vicuna 2022; Salama 2020; Stone 2020), moderate to severe disease in 10 RCTs (n = 890) (Broman 2022; COVIDOSE-2 2021; Hermine 2021; IMMCOVA 2021; Jordan 2021; Lomakin 2021; Mariette 2021; Merchante 2021; Talaschian 2021; Wang 2021), moderate to critical disease in eight (n = 7368) (Declercq 2021; Horby 2021b; Lescure 2021; Lonze 2022; Rutgers 2021; Sivapalasingam 2022 (reporting results of phase 2 and 3); Soin 2021; Veiga 2021), moderate disease in one (n = 201) (Sancho-Lopez 2021), severe disease in one RCT (n = 126) (Salvarani 2020), severe to critical disease in five (n = 2365) (REMAP-CAP (Derde 2021; Gordon 2021); Hermine 2022 (CORIMUNO-TOCI-2, CORIMUNO-SARI-2); HMO-0224-20 2021; Samsonov 2022), and critical disease in one trial (n = 21) (ARCHITECTS 2021).

C-reactive protein level varied but was high in most trials with a median between 40 and 200 mg/L, except for Wang 2021, where it was only slightly elevated at 7.58 mg/L. Similarly, IL-6 level was high in most of the trials with a median between 24 and 255 pg/mL, except for five trials (Declercq 2021; Garcia-Vicuna 2022; Lescure 2021; Lomakin 2021; Sancho-Lopez 2021), where it was normal to slightly elevated (median, between 9 and 19.20 pg/ml).

Only six trials reported the vaccination status of participants (Broman 2022; Hermine 2022 (CORIMUNO-TOCI-2, CORIMUNO-SARI-2); Rosas 2022; Salama 2020; Stone 2020); there were no fully vaccinated participants included in these trials. Seventeen trials were conducted before vaccination was rolled out.

The percentage of participants who were on oxygen at baseline but not intubated varied at study inclusion from 5% to 100%, specifically: 5% (ARCHITECTS 2021), 26% (Hermine 2022), 39% (HMO-0224-20 2021), 52% (Branch-Elliman 2022), 56% (Rosas 2022), 61% (COVIDOSE-2 2021; Lomakin 2021), 65% (COVITOZ-01 2021), 67% (Derde 2021), 74% (Wang 2021), 84% (Stone 2020; Veiga 2021), 86% (Declercq 2021), 87% (Garcia-Vicuna 2022; Lescure 2021), 88% (Merchante 2021; Salama 2020), 89% (Soin 2021), 90% (Broman 2022; Talaschian 2021), 96% (Rutgers 2021), 97% (Mariette 2021), 99% (Hermine 2021), and 100% (IMMCOVA 2021; Sancho-Lopez 2021; Sivapalasingam 2022).

Horby 2021b reported that 41% received noninvasive high-flow oxygen but provided no data on the number of participants receiving low-flow oxygen. Three trials did not provide this information (Lonze 2022; Salvarani 2020; Samsonov 2022).

The following 12 trials reported the percentage of patients who were intubated at baseline: 5% (Soin 2021), 6% (Declercq 2021), 12% (Lescure 2021), 14% (Horby 2021b), 16% (Veiga 2021), 22% (Sivapalasingam 2022), 24% (Lonze 2022), 31% (Derde 2021), 37% (Rosas 2022), 61% (HMO-0224-20 2021; Hermine 2022 (CORIMUNO-TOCI-2)), 62% (Hermine 2022 (CORIMUNO-SARI-2)), and 95% (ARCHITECTS 2021). Other trials had no participants intubated at baseline (Branch-Elliman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Garcia-Vicuna 2022; Hermine 2021; IMMCOVA 2021; Jordan 2021; Lomakin 2021; Mariette 2021; Merchante 2021; Salama 2020; Salvarani 2020; Sancho-Lopez 2021; Talaschian 2021; Wang 2021), while two (Broman 2022; Stone 2020) each had a single participant in the control group intubated at baseline. Two trials did not provide this information (Rutgers 2021; Samsonov 2022).

Details of the interventions

Fifteen trials evaluated tocilizumab 8 mg/kg by infusion for one day with a maximum of an 800 mg single dose (ARCHITECTS 2021; COVITOZ-01 2021; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); HMO-0224-20 2021; IMMCOVA 2021; Rosas 2022; Rutgers 2021; Salama 2020; Salvarani 2020; Stone 2020; Talaschian 2021; Veiga 2021), while Soin 2021 evaluated tocilizumab at a dose of 6 mg/kg. In Broman 2022 and Horby 2021b, the dose was adapted to participant's weight according to a prespecified algorithm. One trial evaluated a lower dose of 400 mg by infusion for one day (Wang 2021), and another trial evaluated a one-off low dose of 40 mg or 120 mg (COVIDOSE-2 2021). A second infusion was allowed in

13 trials (ARCHITECTS 2021; COVITOZ-01 2021; REMAP-CAP (Derde 2021; Gordon 2021); Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); Horby 2021a; Rosas 2022; Rutgers 2021; Salama 2020; Salvarani 2020; Soin 2021; Talaschian 2021; Wang 2021).

In three trials, participants received sarilumab at 400 mg in a single-dose infusion (Derde 2021 Hermine 2022 (CORIMUNO-SARI-2); Mariette 2021). Three trials compared two doses of sarilumab 200 mg and 400 mg; participants received sarilumab at 200 mg or 400 mg either by infusion in Sivapalasingam 2022 and Lescure 2021, or subcutaneously in Merchante 2021. In Garcia-Vicuna 2022 and Branch-Elliman 2022, participants received 400 mg per day subcutaneously. Sancho-Lopez 2021 used an algorithm to adapt the dose between 200 mg and 400 mg according to the participant's weight.

Hermine 2022 (CORIMUNO-SARI-2) and Mariette 2021 provided sarilumab as a 400 mg IV infusion once, with a second infusion at day three in the absence of a clinical response. Lescure 2021 allowed the possibility of a second dose within 24 to 48 hours. In Sivapalasingam 2022, re-dosing was possible for clinical worsening at 24 hours with up to four doses weekly.

Clazakizumab was administered as one dose of 25 mg. A second dose was allowed within three days of the first, depending on the CRP level in Lonze 2022 Jordan 2021 allowed a second dose 24 hours after the first dose up to day 14.

Olokizumab was provided as a 64 mg subcutaneous dose once only in Samsonov 2022 siltuximab as a single dose of 11 mg/kg by IV infusion (Declercq 2021), and levilimab was administered subcutaneously twice on day one at a dose of 162 mg; a 324 mg rescue dose was allowed if clinical status worsened (Lomakin 2021).

The comparator was standard care with placebo in 11 trials (ARCHITECTS 2021; HMO-0224-20 2021; Jordan 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Rosas 2022; Salama 2020; Samsonov 2022; Sivapalasingam 2022; Stone 2020) and standard care in the other 21 trials (Branch-Elliman 2022; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); Horby 2021b; IMMCOVA 2021; Mariette 2021; Merchante 2021; Rutgers 2021; Salvarani 2020; Sancho-Lopez 2021; Soin 2021; Talaschian 2021; Veiga 2021; Wang 2021).

The use of steroids at baseline or during the study was reported in 31 trials (ARCHITECTS 2021; Branch-Elliman 2022; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Mariette 2021; Merchante 2021; Rosas 2022; Rutgers 2021; Salama 2020; Salvarani 2020; Samsonov 2022; Sancho-Lopez 2021; Sivapalasingam 2022; Soin 2021; Stone 2020; Talaschian 2021; Veiga 2021; Wang 2021). Six trials reported that more participants received steroids in the control group (ARCHITECTS 2021; Broman 2022; COVITOZ-01 2021; Rosas 2022; Salama 2020; Talaschian 2021). In ARCHITECTS 2021 and Broman 2022, 100% of controls received steroids. In Sancho-Lopez 2021; all participants received steroids. Jordan 2021 did not report this information.

The protocol of one trial planned for some cross-over (Salvarani 2020), and 22% of participants in the control arm received the experimental treatment.

Funding and conflict of interest

Fourteen trials were funded by public/non-profit sources (ARCHITECTS 2021; Branch-Elliman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Mariette 2021; Talaschian 2021; Wang 2021), nine received mixed funding (REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Lonze 2022; Merchante 2021; Rosas 2022; Rutgers 2021; Salvarani 2020; Soin 2021; Veiga 2021), and eight were funded by pharmaceutical companies (Jordan 2021; Lescure 2021; Lomakin 2021; Salama 2020; Samsonov 2022; Sancho-Lopez 2021; Sivapalasingam 2022; Stone 2020). Broman 2022 reported that they received no external funds.

The authors of 12 trials declared potential conflict of interest (Branch-Elliman 2022; Broman 2022; Lescure 2021; Lomakin 2021; Lonze 2022; Rosas 2022; Salama 2020; Salvarani 2020; Sivapalasingam 2022; Soin 2021; Stone 2020; Veiga 2021), and those of 13 did not (Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); Horby 2021b; Mariette 2021; Merchante 2021; Rutgers 2021; Sancho-Lopez 2021; Talaschian 2021; Wang 2021). We could not retrieve information about conflict of interest for seven trials (ARCHITECTS 2021; COVIDOSE-2 2021; COVITOZ-01 2021; HMO-0224-20 2021; IMMCOVA 2021; Jordan 2021; Samsonov 2022).

Excluded studies

We excluded five reports after full-text screening; the reasons for exclusion were secondary analysis (three reports), not randomized (one report) and prognosis trial (one report). Details of these reports can be found in Characteristics of excluded studies.

Registered studies with no published results

From the trial registries, we identified an additional 17 trials for which no results have been published or posted in the registries (as of 7 June 2022); in addition, we identified two canceled registered trials, one assessing tocilizumab (NCT04361552) and one assessing olokizumab (NCT04452474). See Appendix 6; Studies awaiting classification; Ongoing studies.

Tocilizumab

Eleven trials assessed tocilizumab versus standard care or placebo with unpublished results (EUCTR2020-001275-32-DK; EUCTR2020-001408-41-DE; EUCTR2020-001770-30-BE; NCT04335071; NCT04690920; ACTRN12620000580976; CTRI/2020/12/029793; EUCTR2020-001767-86-IE; IRCT20200510047383N1; IRCT20200525047570N1; IRCT20201024049134N2). Of these, one trial has been completed but results were unavailable (NCT04690920; 200 participants enrolled), and three other RCTs (220 participants) were marked on the registry as “recruitment completed based on the expected completion date” (IRCT20200510047383N1; IRCT20200525047570N1; IRCT20201024049134N2); we cannot be sure that these studies were completed (the registry has never been updated since registration). Three were terminated without results available (EUCTR2020-001275-32-

DK; EUCTR2020-001770-30-BE; NCT04335071), and one terminated with results posted for three participants out of 200 planned (EUCTR2020-001408-41-DE). One trial was ongoing (EUCTR2020-001767-86-IE; 90 participants) and two are not yet recruiting (ACTRN12620000580976; CTRI/2020/12/029793; total 204 participants planned).

Sarilumab

We identified three unpublished trials: two terminated without results (EUCTR2020-001275-32-DK; EUCTR2020-001290-74-ES) and one trial is ongoing (171 participants planned) (EUCTR2020-001390-76-IT). One terminated multi-arm trial evaluated sarilumab compared to tocilizumab and standard care (EUCTR2020-001275-32-DK).

Clazakizumab

We identified two unpublished trials assessing clazakizumab compared to standard care or placebo: one terminated without results available (NCT04381052), and one is ongoing (results posted for one participant out of 60 planned) (NCT04494724).

Olokizumab

We identified one ongoing trial (204 participants planned) (NCT05187793).

Siltuximab

We identified one terminated trial (555 participants planned) (NCT04616586).

Levilimab

No unpublished results have been found for levilimab compared to standard care or placebo.

Risk of bias in included studies

Risk of bias assessments summarize the risk of bias assessment by comparison and by outcome. For 'tocilizumab vs standard care/placebo' see Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, and Table 10. For 'sarilumab vs standard care/placebo', see Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, Table 17, Table 18, Table 19, and Table 20. For 'clazakizumab vs standard care/placebo', see Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, and Table 27. For 'olokizumab vs standard care/placebo', see Table 28, Table 29, and Table 30. For 'siltuximab vs standard care/placebo', see Table 31, Table 32, Table 33, Table 34, Table 35, Table 36, Table 37, and Table 38. For 'levilimab vs standard care/placebo', see Table 39, Table 40, Table 41, Table 42, and Table 43.

Overall, we judged three trials to be at high risk of bias (HMO-0224-20 2021; Talaschian 2021; Wang 2021).

Risk of bias arising from the randomization process

Randomization was described adequately and was appropriate in 25 trials (ARCHITECTS 2021; Branch-Elliman 2022; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); Horby 2021b; IMMCOVA 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Mariette 2021; Merchante 2021; Rosas 2022; Salama 2020; Salvarani 2020; Sancho-Lopez 2021; Soin 2021; Stone 2020; Veiga 2021). There were some concerns in six trials because the method used to conceal treatment allocation was unclear (Jordan 2021; Rutgers 2021; Samsonov 2022; Sivapalasingam 2022; Talaschian 2021; Wang 2021). There was no imbalance in baseline data indicative of a problem with the randomization process. We could not assess one trial due to the absence of a publication (HMO-0224-20 2021), but considered it to be at high risk of bias based on its assessment in the meta-analysis published by the WHO REACT Working Group.

Risk of bias due to deviations from intended interventions

We judged the risk of bias due to deviation from intended interventions to be low for all outcomes reported in 17 trials (ARCHITECTS 2021; Branch-Elliman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Jordan 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Rutgers 2021; Sivapalasingam 2022; Stone 2020). Of the 17 trials, 10 were not blinded.

However, we rated this domain as of some concern for at least one of the outcomes reported in 11 unblinded trials (Broman 2022; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; Mariette 2021; Merchante 2021; Salvarani 2020; Sancho-Lopez 2021; Soin 2021; Veiga 2021; Wang 2021) and four blinded trials (Rosas 2022; Salama 2020; Samsonov 2022; Talaschian 2021).

At least some of the reported co-interventions were not balanced in six studies (Garcia-Vicuna 2022; Hermine 2021; Mariette 2021; Salvarani 2020; Samsonov 2022; Talaschian 2021); and this could have affected the outcomes.

In Salvarani 2020, 23% of participants allocated to the standard care arm received tocilizumab, mainly because of clinical worsening. This decision was planned in the protocol. Nevertheless, its administration could have been influenced by the trial context, and this domain was consequently rated as presenting some concerns. These deviations could be responsible for underestimating the treatment effect. Other trials raised some concerns because the co-interventions were not completely reported (Broman 2022; REMAP-CAP (Derde 2021; Gordon 2021); Merchante 2021; Samsonov 2022; Sancho-Lopez 2021; Soin 2021; Veiga 2021; Wang 2021).

Finally, we rated Salama 2020 as raising some concerns for important outcomes because participants who did not receive the drug (10 vs 1) were excluded from the analysis post-randomization.

It should be noted that in Horby 2021b, 18% of participants allocated to tocilizumab did not receive the treatment allocated. We considered this deviation probably did not arise because of the trial context and assessed the domain to be low risk.

Risk of bias due to missing outcome data

We judged the risk of bias due to incomplete outcome data as low for 28 trials and all outcomes since there was no or a low amount of missing data in the included trials (ARCHITECTS 2021; Branch-Elliman 2022; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Jordan 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Mariette 2021; Merchante 2021; Rosas 2022; Rutgers 2021; Salama 2020; Salvarani 2020; Samsonov 2022;

Sancho-Lopez 2021; Soin 2021; Stone 2020; Veiga 2021; Wang 2021). Reports of preliminary analyses with missing information because follow-up was not completed were rated at low risk of bias. In four studies, data were unavailable for all or nearly all the participants randomized; however, the reasons for missing data could but were not likely to depend on the true value of the outcomes, and thus we judged the risk of bias to be of some concerns (Hermine 2022 (CORIMUNO-TOCI-2, CORIMUNO-SARI-2); Sivapalasingam 2022; Talaschian 2021).

Risk of bias in the measurement of the outcome

We judged the risk of bias to be low for all outcomes in the 11 blinded trials (ARCHITECTS 2021; Jordan 2021; Lescure 2021; Lomakin 2021; Lonze 2022; Rosas 2022; Salama 2020; Samsonov 2022; Sivapalasingam 2022; Stone 2020; Talaschian 2021) and the five open-label trials (COVIDOSE-2 2021; COVITOZ-01 2021; HMO-0224-20 2021; IMMCOVA 2021; Rutgers 2021).

In the other 16 open trials, we considered the risk of bias to be low for observer-reported outcomes not involving clinical judgment (i.e. mortality, WHO score seven and above, time to death and time to WHO score seven and above). We judged there to be some concerns for the outcomes that could potentially be influenced by knowledge of the intervention assignment (i.e. clinical improvement, time to clinical improvement, adverse events and serious adverse events) (Branch-Elliman 2022; Broman 2022; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2, CORIMUNO-SARI-2); Horby 2021b; Mariette 2021; Merchante 2021; Salvarani 2020; Sancho-Lopez 2021; Veiga 2021; Soin 2021; Wang 2021).

Risk of bias in the selection of the reported results

The protocol was available for 21 trials (Branch-Elliman 2022; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); Horby 2021b; Jordan 2021; Lonze 2022; Mariette 2021; Merchante 2021; Rosas 2022; Salama 2020; Salvarani 2020; Samsonov 2022; Sancho-Lopez 2021; Soin 2021; Stone 2020; Veiga 2021; Wang 2021). Neither the protocol nor the statistical analysis plan was available for the other 11 trials (ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; HMO-0224-20 2021; IMMCOVA 2021; Lescure 2021; Lomakin 2021; Rutgers 2021; Sivapalasingam 2022; Talaschian 2021).

Overall, we judged 21 trials to be at low risk of bias in this domain for all outcomes (ARCHITECTS 2021; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; REMAP-CAP (Derde 2021; Gordon 2021); Garcia-Vicuna 2022; Hermine 2021; HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Jordan 2021; Merchante 2021; Rosas 2022; Rutgers 2021; Salama 2020; Samsonov 2022; Sancho-Lopez 2021; Soin 2021; Stone 2020; Veiga 2021; Wang 2021).

This domain was, however, considered to present some concern for 11 trials (Branch-Elliman 2022; Broman 2022; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); Lescure 2021; Lomakin 2021; Lonze 2022; Mariette 2021; Salvarani 2020; Sivapalasingam 2022; Talaschian 2021).

Branch-Elliman 2022; Hermine 2022 (CORIMUNO-TOCI-2; CORIMUNO-SARI-2); Lescure 2021; Lonze 2022; Mariette 2021; Rosas 2022; Rutgers 2021; Salvarani 2020; and Sivapalasingam 2022 reported some outcomes that had not been prespecified in the registry.

The protocol and statistical analysis plan were not available, and the registry was retrospective for Broman 2022 and Lomakin 2021. Finally, the outcomes extracted from Talaschian 2021 for this meta-analysis were not prespecified.

Bias due to missing results in the synthesis

In Appendix 9, we present a matrix indicating the availability of trial results for the critical and important outcomes of each comparison included in the review. Most trials (29/32, 90.6%) reported or provided results for all the review outcomes, as prespecified in the trial registry. Evaluating tocilizumab, Wang 2021 prespecified all-cause mortality on D28 as an outcome but did not report it. Similarly, Samsonov 2022, evaluating olokizumab, prespecified the outcome of time to clinical improvement, but did not report it.

We explored the presence of small-study effects through funnel plots for outcomes with results from more than 10 trials. For tocilizumab compared to standard care or placebo, funnel plots generally appeared symmetrical with no clear evidence of any small-study effect (Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7).

Figure 2. Funnel plot Tocilizumab vs standard care or placebo. All cause mortality D28

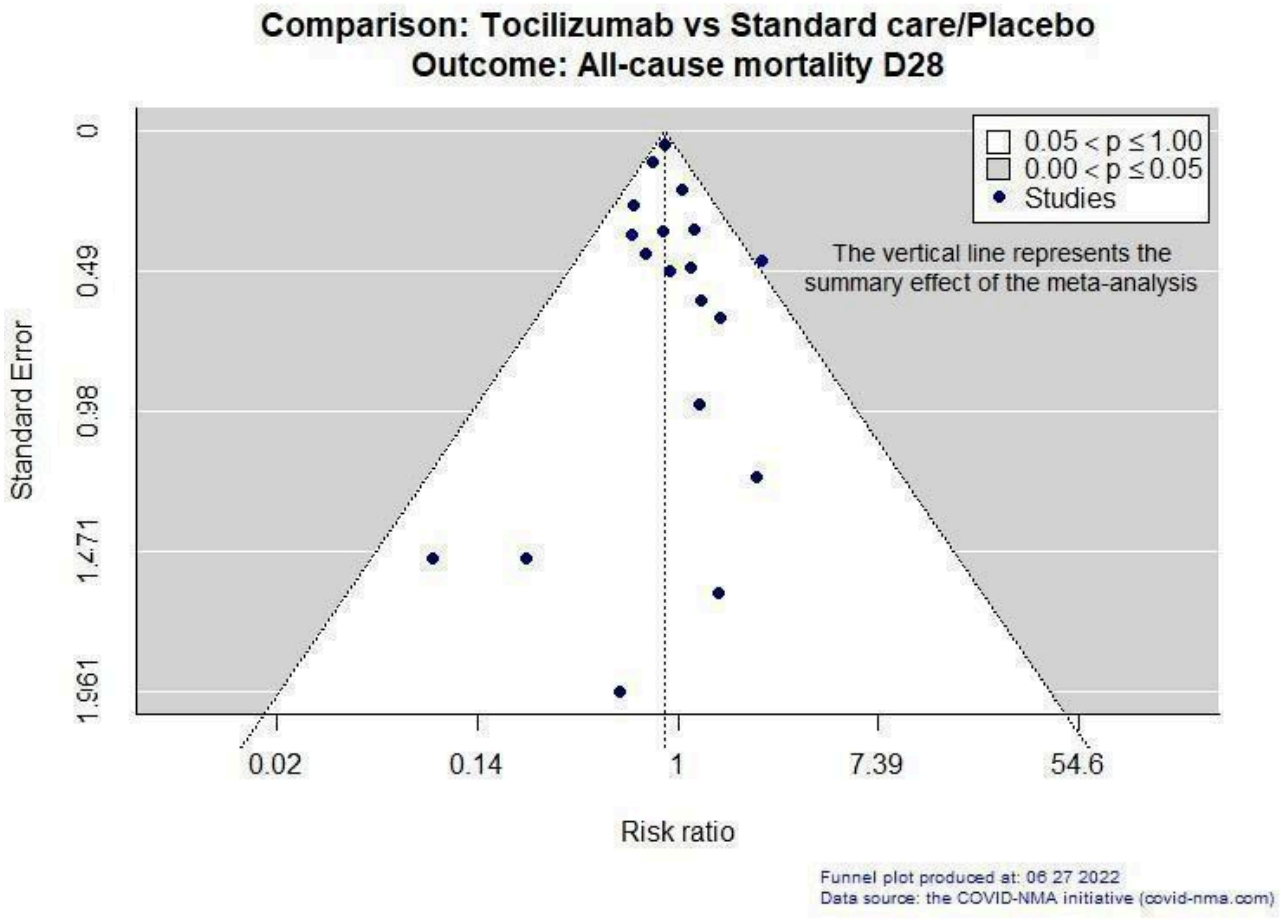


Figure 3. 8.1.2 Funnel plot Tocilizumab compared to standard care or placebo

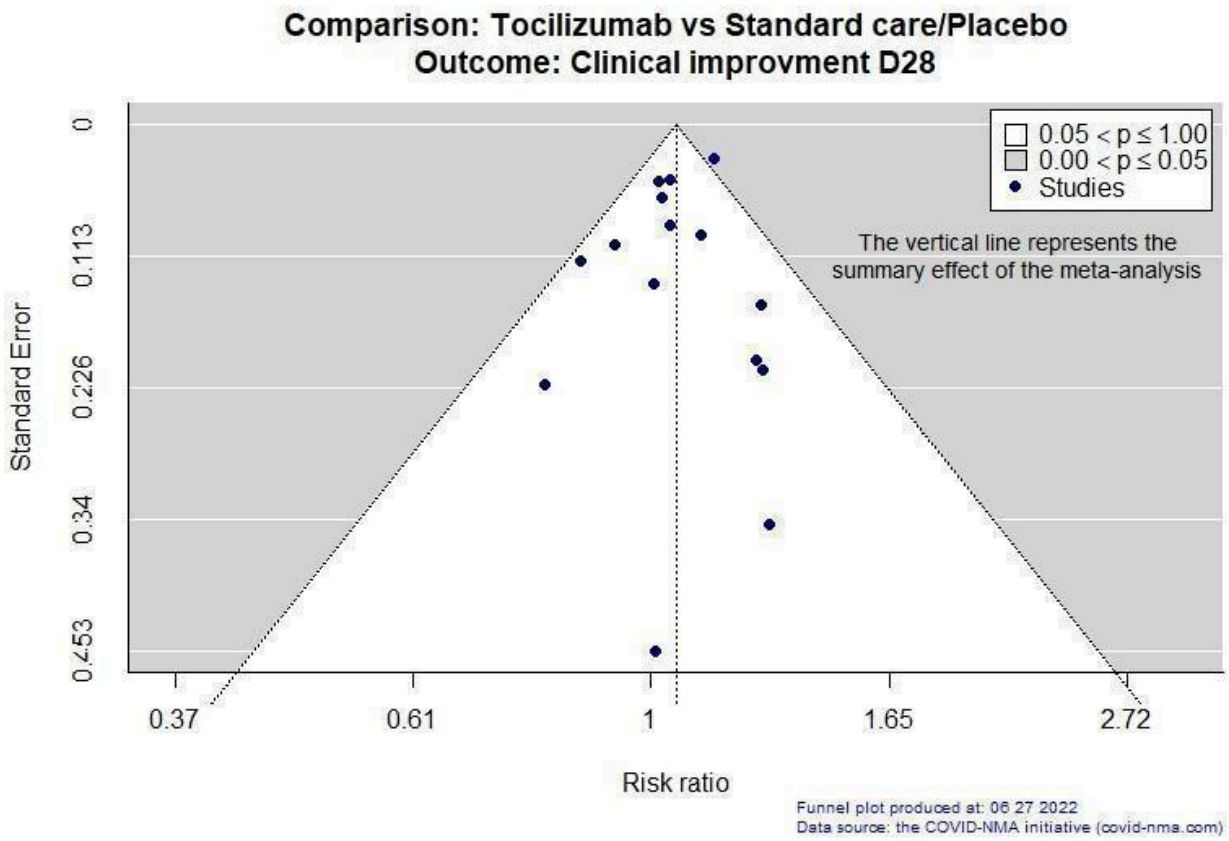


Figure 4. 8.1.2 Funnel plot Tocilizumab compared to standard care or placebo. Clinical improvement D28

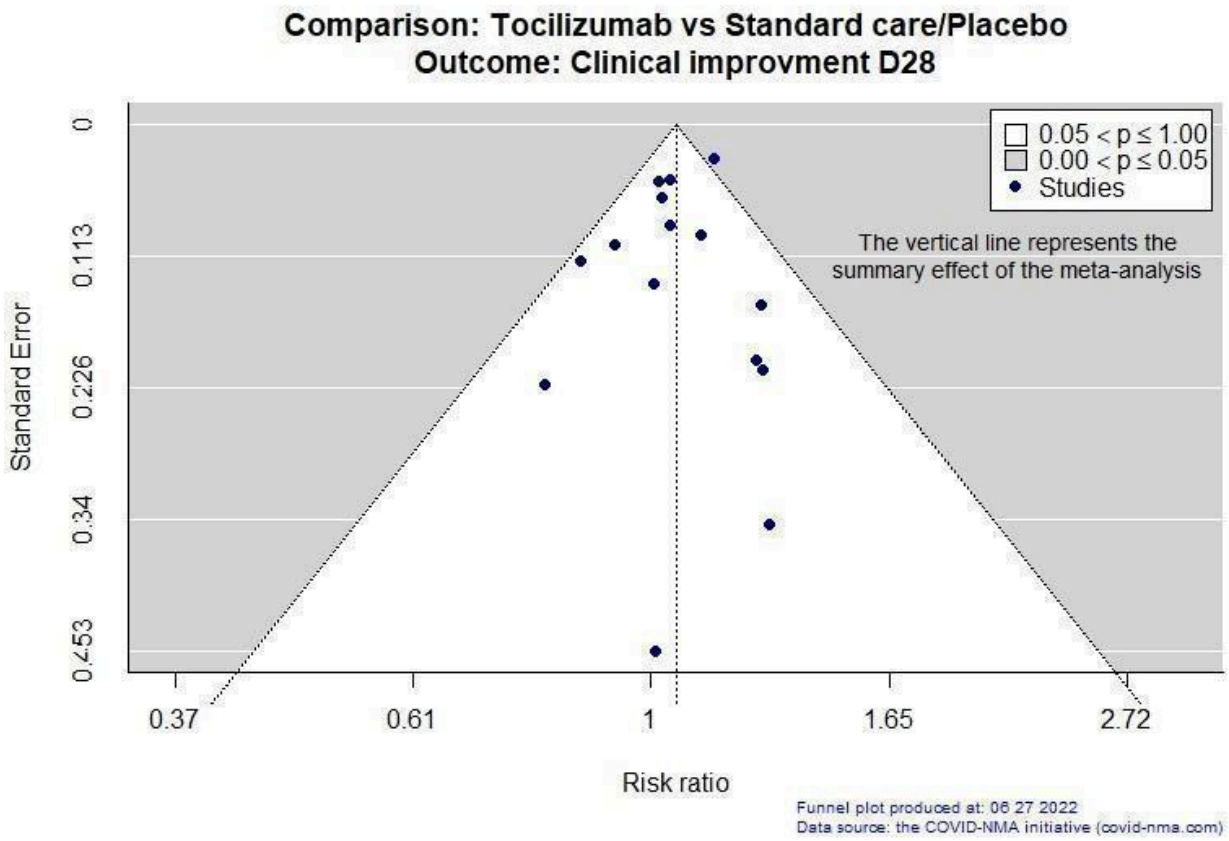


Figure 5. 8.1.2 Funnel plot Tocilizumab compared to standard care or placebo. WHO score 7 D28

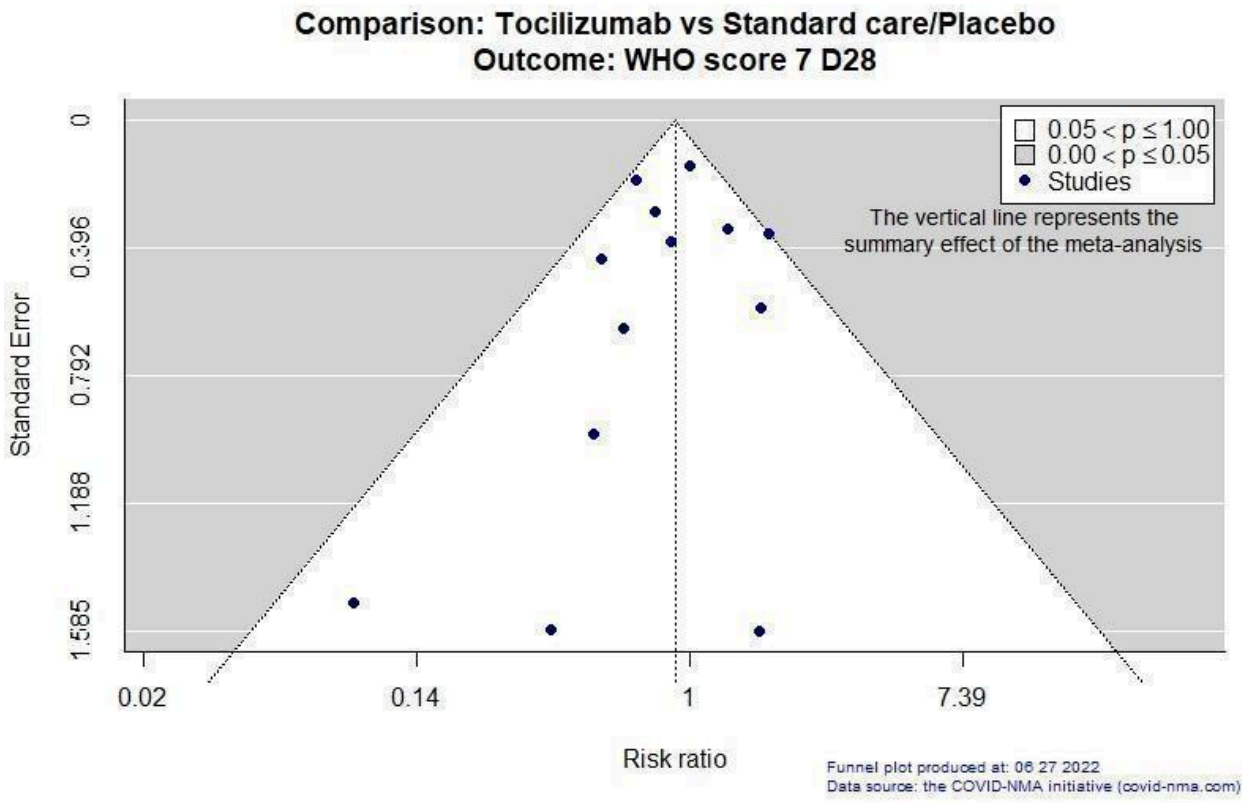


Figure 6. 8.1.2 Funnel plot Tocilizumab compared to standard care or placebo. Adverse events

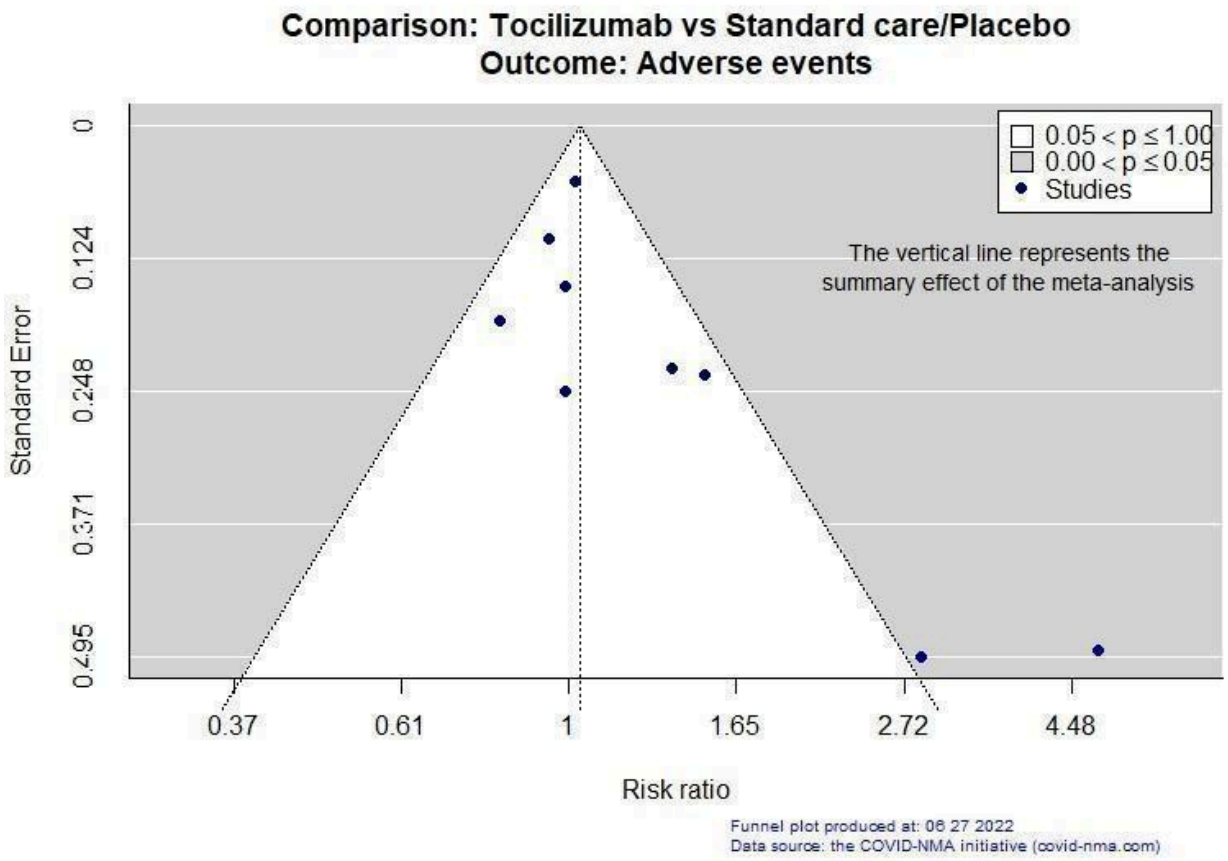
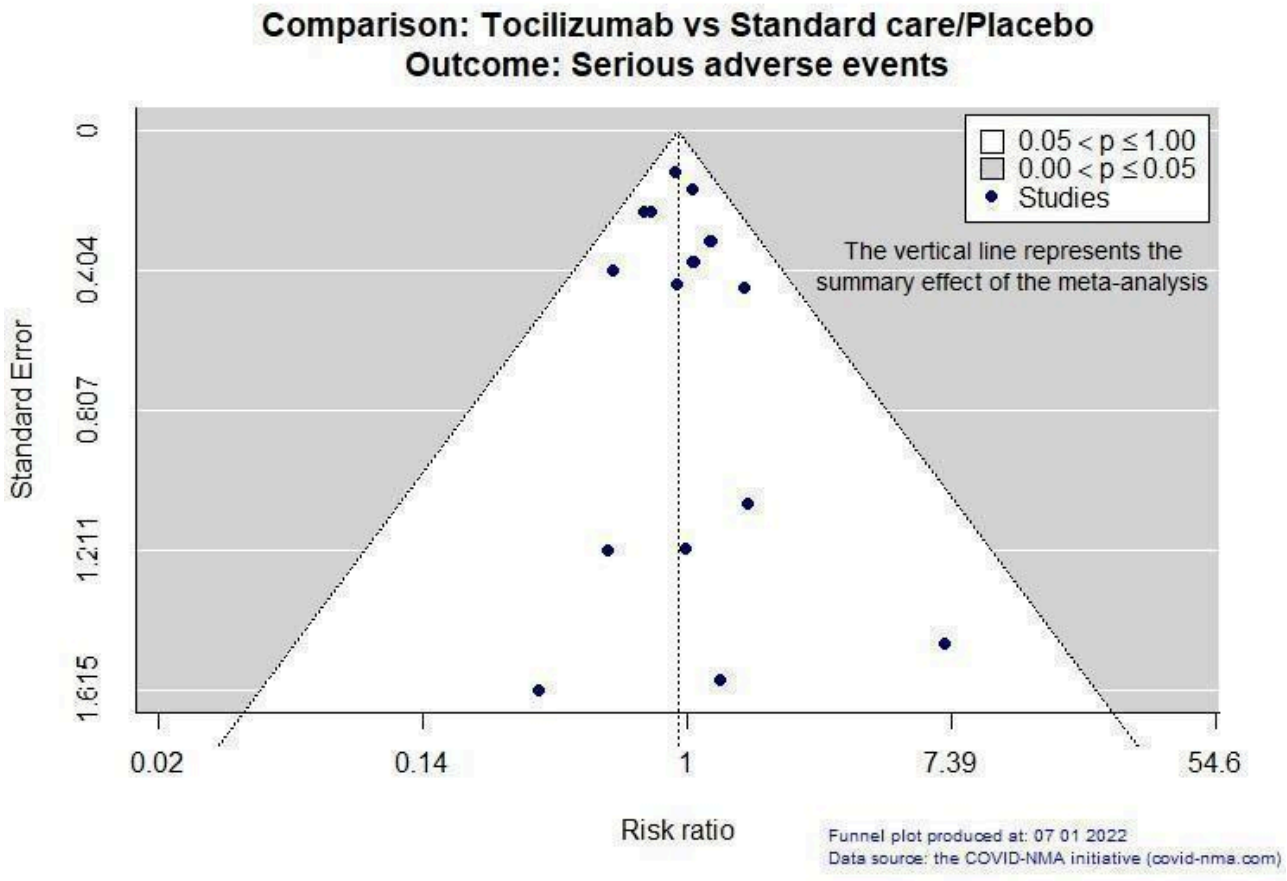


Figure 7. 8.1.2 Funnel plot Tocilizumab compared to standard care or placebo. Serious adverse events



Effects of interventions

See: **Summary of findings 1** Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19; **Summary of findings 2** Sarilumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19; **Summary of findings 3** Clazakizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19; **Summary of findings 4** Olokizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19; **Summary of findings 5** Siltuximab compared to standard care/placebo for mild/moderate/severe/critical COVID-19; **Summary of findings 6** Levilimab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Tocilizumab versus standard care/placebo

We report the certainty of the evidence for critical outcomes in Summary of findings 1 and for important outcomes in Appendix 10 'Summary of Findings - important outcomes'. The outcome 'WHO progression score (level 7 or above) D60 or more' was not reported in all trials.

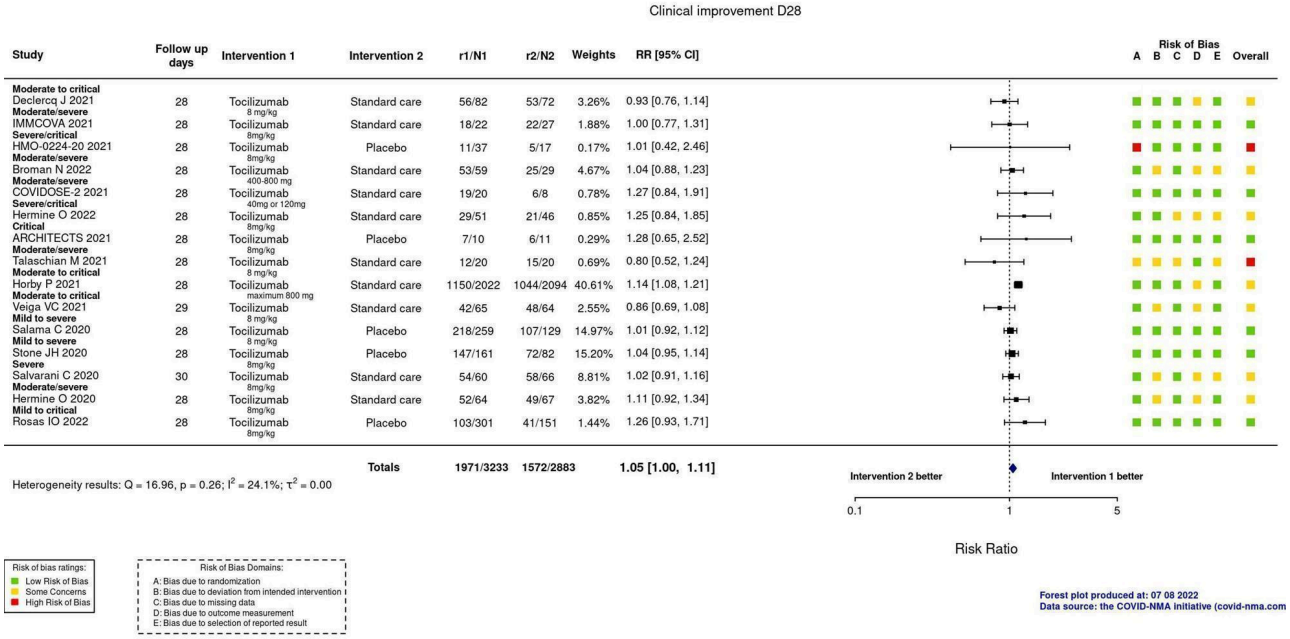
Critical outcomes

Clinical improvement

Clinical improvement was defined by a score decrease of at least two points on a 7-category ordinal scale (Rosas 2022; Salama 2020; Stone 2020), an increase of at least two points on a 6-category ordinal scale (compared with the worst status the day of randomization) or discharge from the hospital alive (Declercq 2021; Veiga 2021), or discharge at D28 (ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); HMO-0224-20 2021; HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Salvarani 2020; Talaschian 2021).

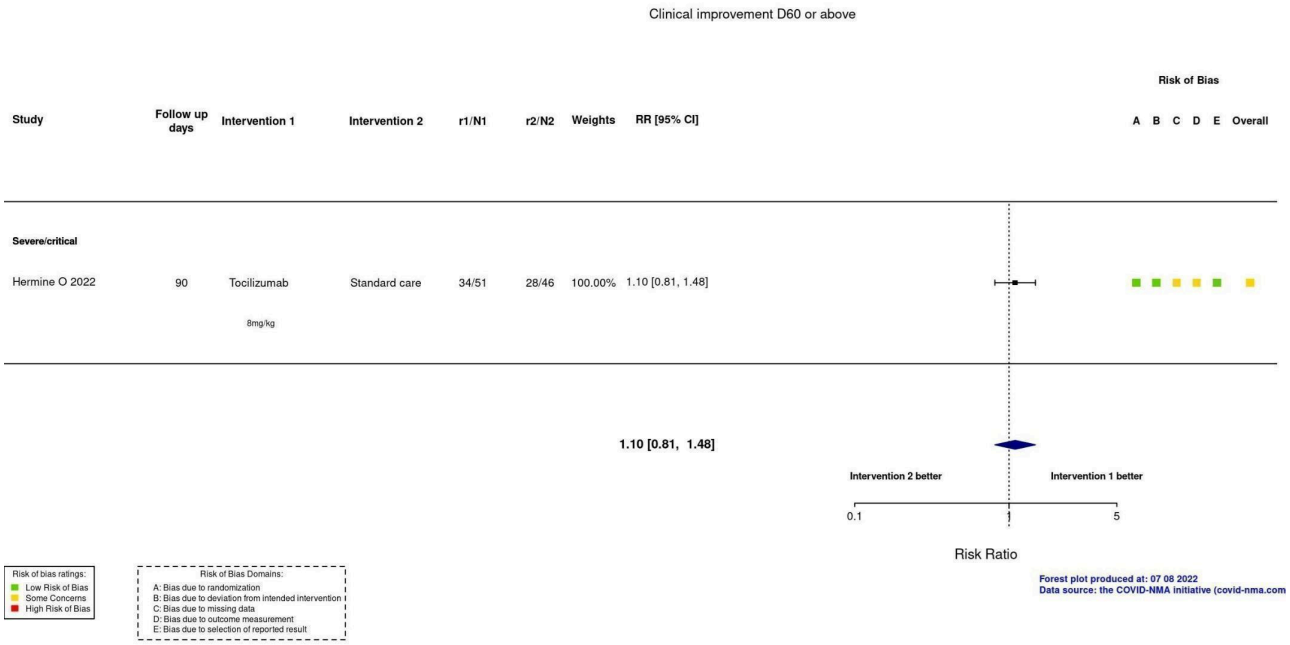
In all, 15 RCTs (6116 participants) reported the proportion of participants meeting these criteria for improvement at D28 (ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; Declercq 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Rosas 2022; Salama 2020; Salvarani 2020; Stone 2020; Talaschian 2021; Veiga 2021). Tocilizumab probably produces little or no increase in clinical improvement at D28 (RR 1.05, 95% CI 1.00 to 1.11; I^2 = 24.1%; 15 RCTs; 6116 participants; absolute effect: 27 more per 1000 (from 0 fewer to 60 more); moderate-certainty evidence; Figure 8).

Figure 8. Analysis 1.1.1 Tocilizumab versus placebo or standard care. Outcome: Clinical improvement 28



One study reported a longer follow-up of clinical improvement at ≥ D60 (Hermine 2022 (CORIMUNO-TOCI-2)). The evidence for an effect of tocilizumab compared to standard care on clinical improvement at ≥ D60 is very uncertain (RR 1.10, 95% CI 0.81 to 1.48; 1 RCT; 97 participants; absolute effect: 61 more per 1000 (from 116 fewer to 292 more); very low-certainty evidence; Figure 9).

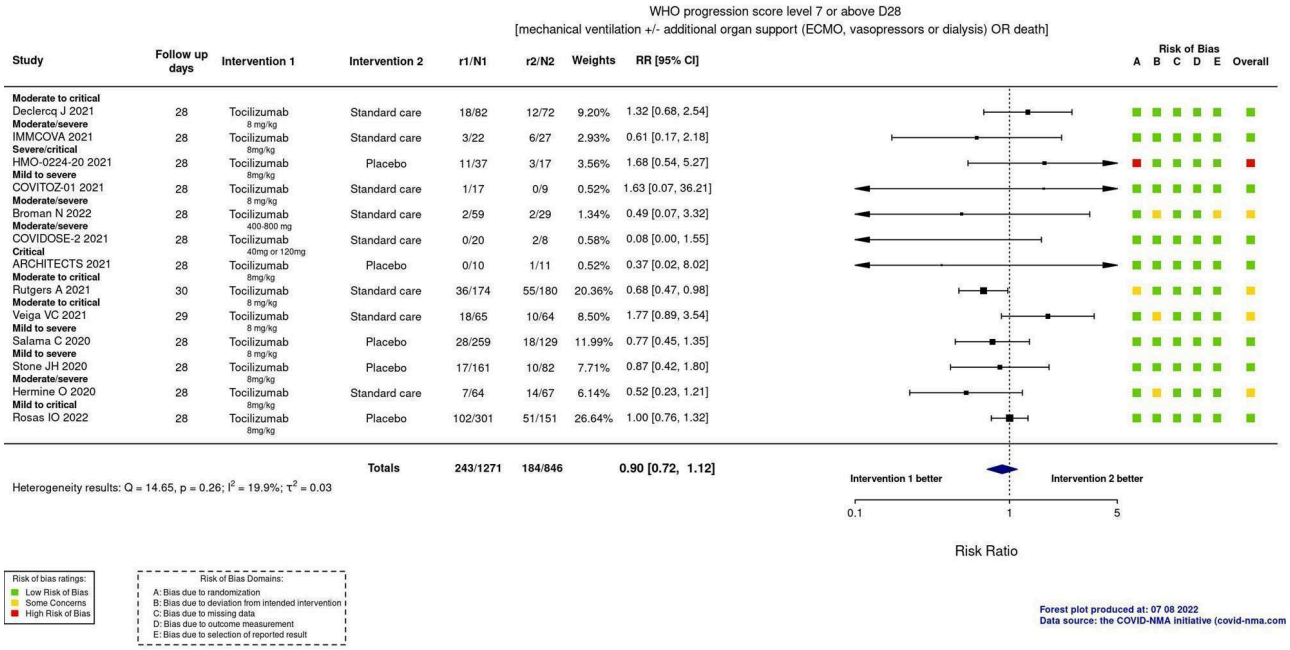
Figure 9. Analysis 1.1.2 Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D60



WHO Clinical Progression Score of level 7 or above (i.e. the proportion of participants with mechanical ventilation +/- additional organ support or death)

Thirteen RCTs (2117 participants) reported the proportion of participants with mechanical ventilation or death at D28 (ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; Hermine 2021; HMO-0224-20 2021; IMMCOVA 2021; Rosas 2022; Rutgers 2021; Salama 2020; Stone 2020; Veiga 2021). Overall, the evidence is uncertain for the effect of tocilizumab on the proportion of participants with a WHO-CPS of level 7 or above at D28 (RR 0.90, 95% CI 0.72 to 1.12; I^2 = 19.9 %; 13 RCTs, 2117 participants; absolute effect: 22 fewer per 1000 (from 61 fewer to 26 more); low-certainty evidence; Figure 10).

Figure 10. Analysis 1.1.3 Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



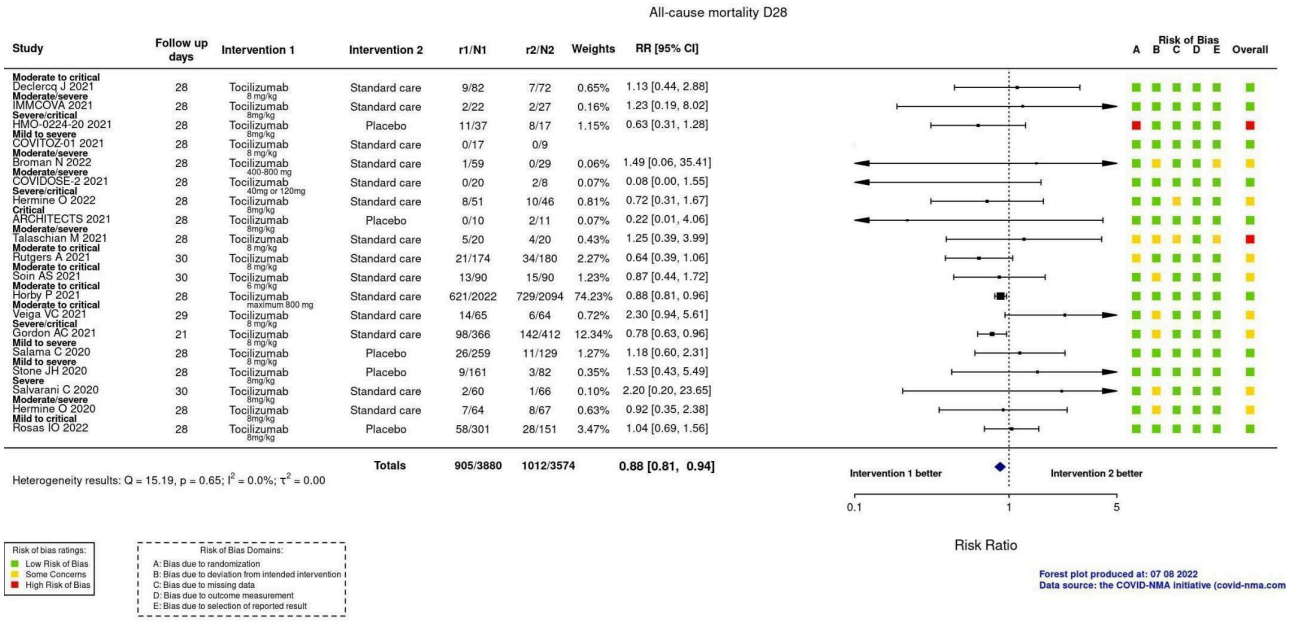
We did not obtain data for longer-term follow-up (≥ D60).

All-cause mortality

Eighteen RCTs (7428 participants) reported all-cause mortality at D28 (ARCHITECTS 2021; Broman 2022; COVIDOSE-2 2021; Declercq 2021; Gordon 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); HMO-0224-20 2021; Horby 2021b; IMMCOVA 2021; Rosas 2022; Rutgers 2021; Salama 2020; Salvarani 2020; Soin 2021; Stone 2020; Talaschian 2021; Veiga 2021), and nine RCTs (2775 participants) at ≥ D60 (ARCHITECTS 2021; Broman 2022; Declercq 2021; Derde 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); HMO-0224-20 2021; Rosas 2022; Salama 2020). One additional study (COVITOZ-01 2021), which did not contribute to the pooled effect estimate, also reported on the outcome in 26 participants with zero events in both groups.

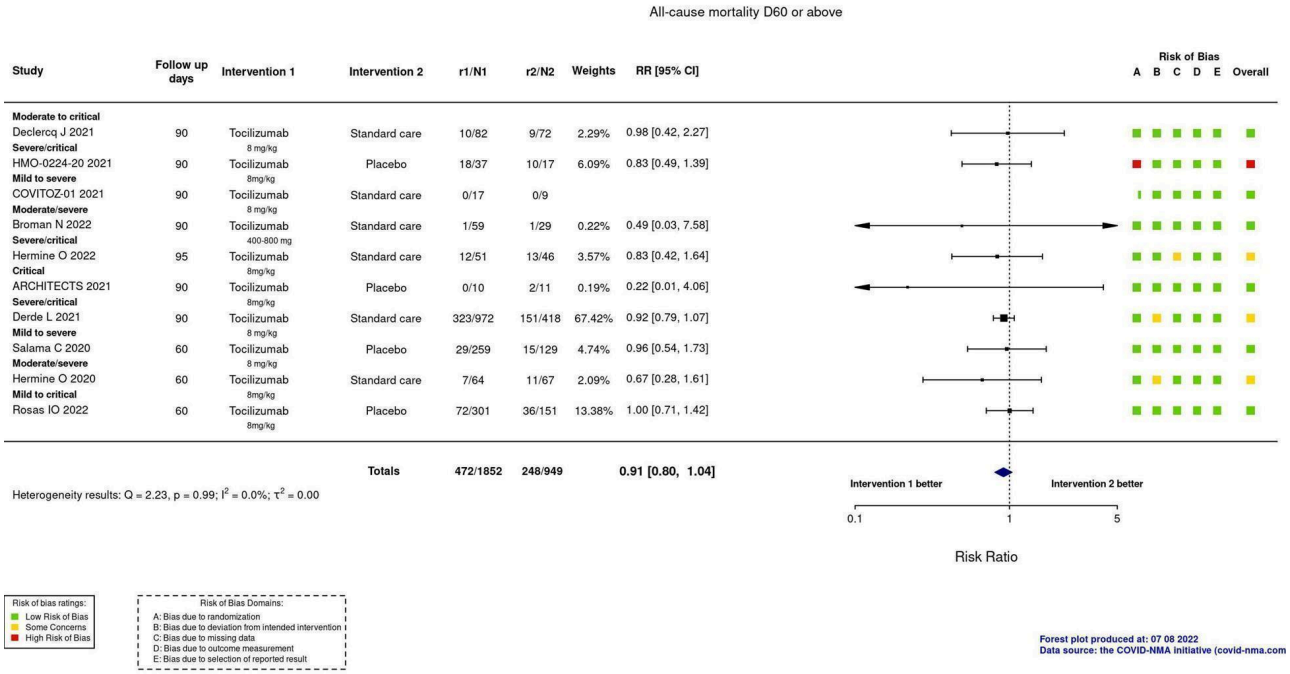
Tocilizumab reduces all-cause mortality at D28 compared to standard care alone or to placebo (RR 0.88, 95% CI 0.81 to 0.94; I^2 = 0.0%; 18 RCTs, 7428 participants; absolute effect 34 fewer per 1000 (from 54 fewer to 17 fewer); high-certainty evidence; Figure 11).

Figure 11. Analysis 1.1.4 Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28



The evidence of an effect of tocilizumab on all-cause mortality is uncertain at ≥ D60 (RR 0.91, 95% CI 0.80 to 1.04; I^2 = 0.0%; 9 RCTs; 2775 participants; absolute effect: 24 fewer per 1000 (from 53 fewer to 11 more); low-certainty evidence; Figure 12).

Figure 12. Analysis 1.1.5 Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

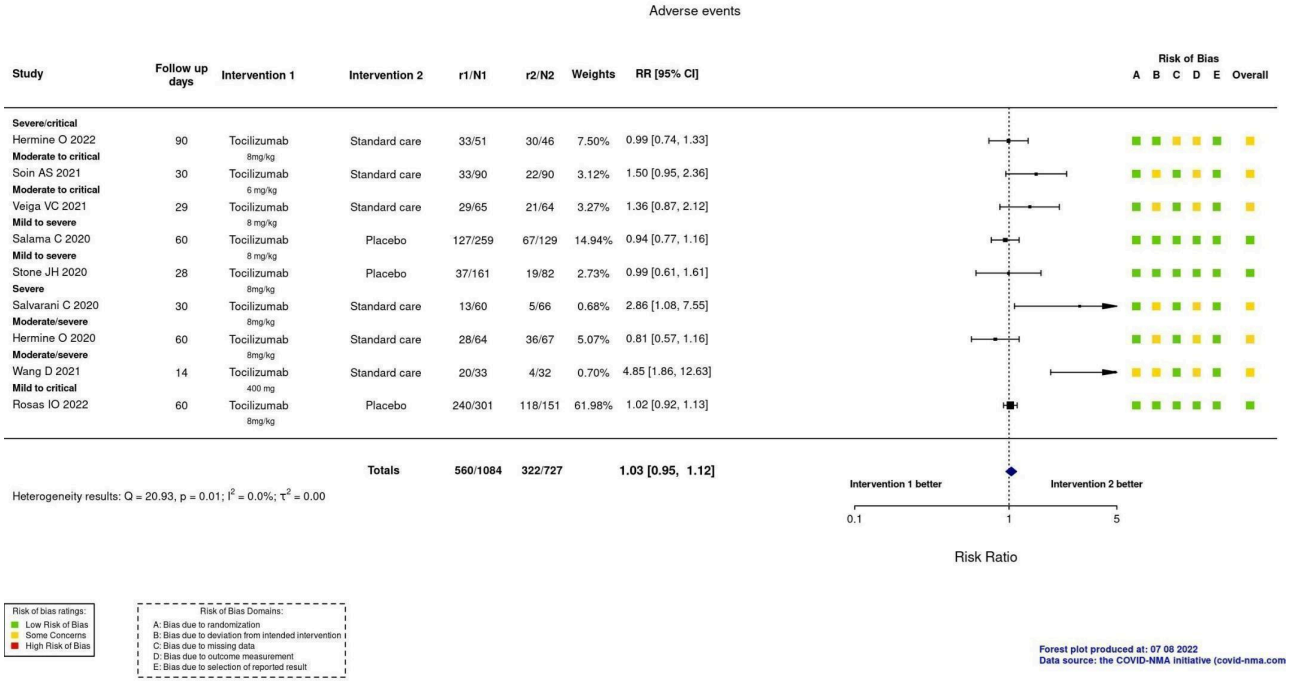


Adverse events (AEs)

AEs were assessed by spontaneous reporting (Rosas 2022; Wang 2021), active monitoring (Salvarani 2020; Stone 2020), both methods (Hermine 2022 (CORIMUNO-TOCI-2); Soin 2021) and by unknown methods in three RCTs (Hermine 2021; Salama 2020; Veiga 2021).

AEs were reported in nine RCTs (1811 participants) (Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); Rosas 2022; Salama 2020; Salvarani 2020; Soin 2021; Stone 2020; Veiga 2021; Wang 2021). Tocilizumab probably results in little to no difference in the risk of adverse events (RR 1.03, 95% CI 0.95 to 1.12; I^2 = 0.0%; 9 RCTs, 1811 participants; absolute effect: 13 more per 1000 (from 22 fewer to 53 more); moderate-certainty evidence; Figure 13).

Figure 13. Analysis 1.1.6 Tocilizumab versus placebo or standard care. Outcome: Adverse events

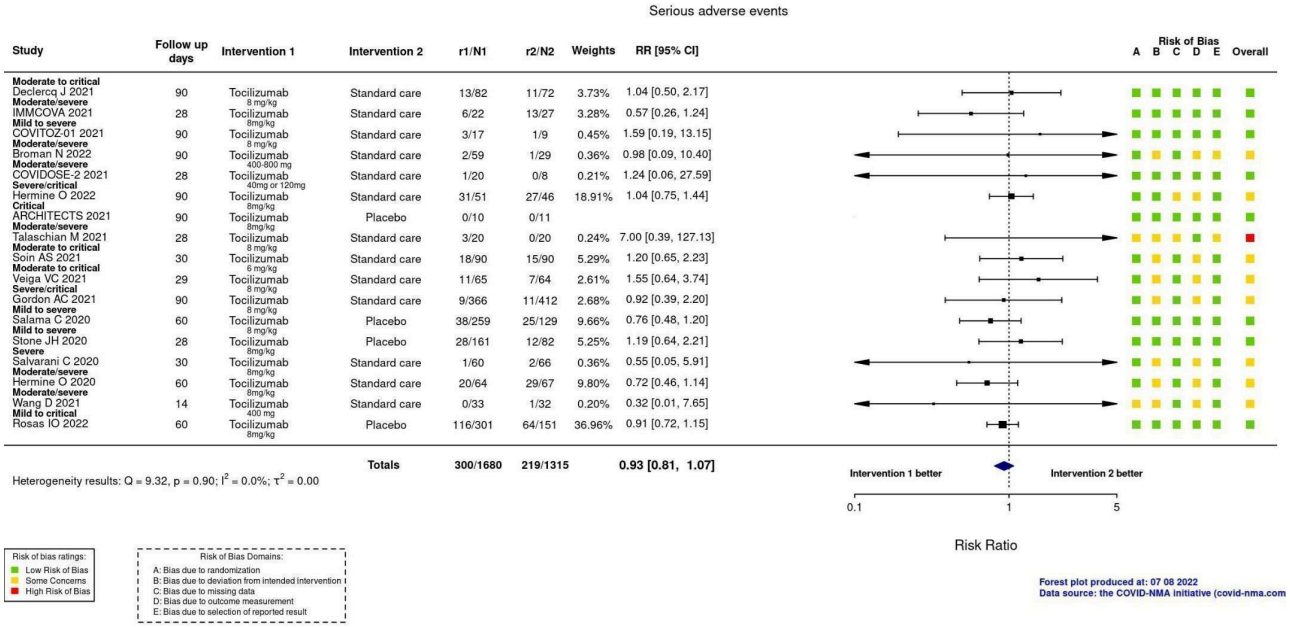


Serious adverse events (SAEs)

SAEs were reported in 16 RCTs (2974 participants) (Broman 2022; COVIDOSE-2 2021; COVITOZ-01 2021; Declercq 2021; Gordon 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); IMMCOVA 2021; Rosas 2022; Salama 2020; Salvarani 2020; Soin 2021; Stone 2020; Talaschian 2021; Veiga 2021; Wang 2021). Another study (ARCHITECTS 2021), which did not contribute to the pooled effect estimate, also reported on the outcome in 21 participants with zero events in both groups.

The evidence comparing tocilizumab to standard care alone or to placebo on serious adverse events is very uncertain (RR 0.93, 95% CI 0.81 to 1.07; I^2 = 0.0%; 16 RCTs, 2974 participants; absolute effect: 12 fewer per 1000 (from 32 fewer to 12 more); very low-certainty evidence; Figure 14).

Figure 14. Analysis 1.1.7 Tocilizumab versus placebo or standard care. Outcome: Serious adverse events



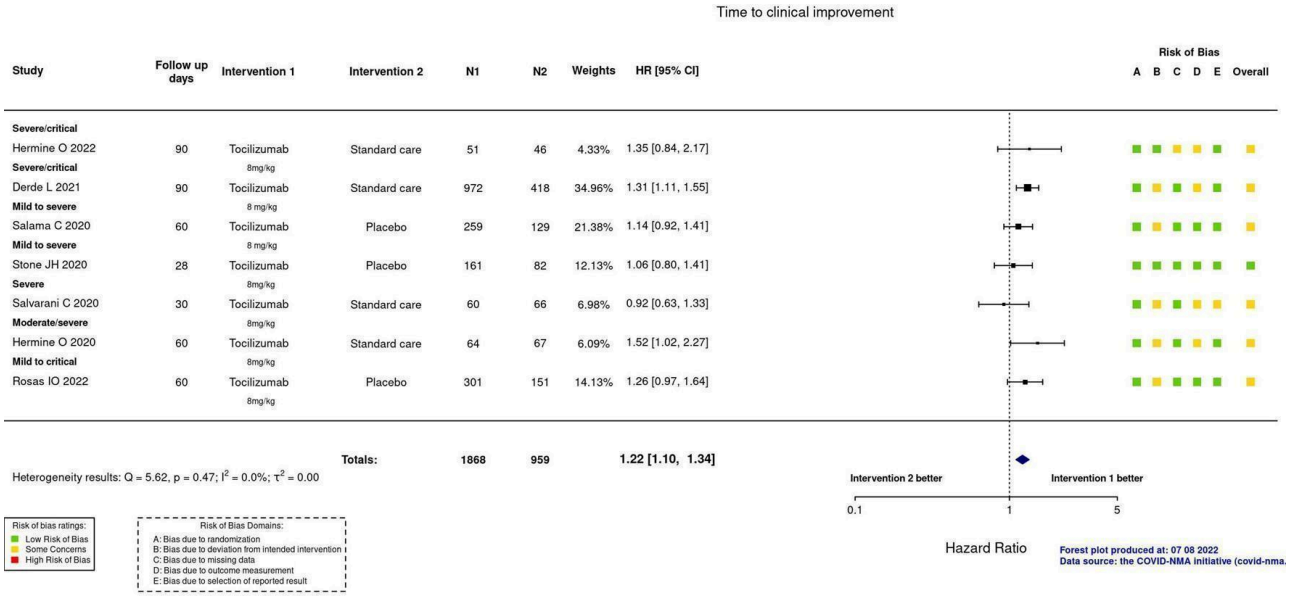
Important outcomes

We report the certainty of evidence for the important outcomes in Appendix 10.

Time to clinical improvement

This outcome was reported in seven RCTs (2827 participants) (Derde 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); Rosas 2022; Salama 2020; Salvarani 2020; Stone 2020). The time of follow-up ranged between 28 days and 90 days. The evidence of the effect of tocilizumab on time to clinical improvement compared to standard care alone or to placebo is uncertain (HR 1.22, 95% CI 1.10 to 1.34; I^2 = 0.0%; 7 RCTs, 2827 participants; absolute effect: 72 more per 1000 (from 35 more to 105 more); low-certainty evidence; Figure 15).

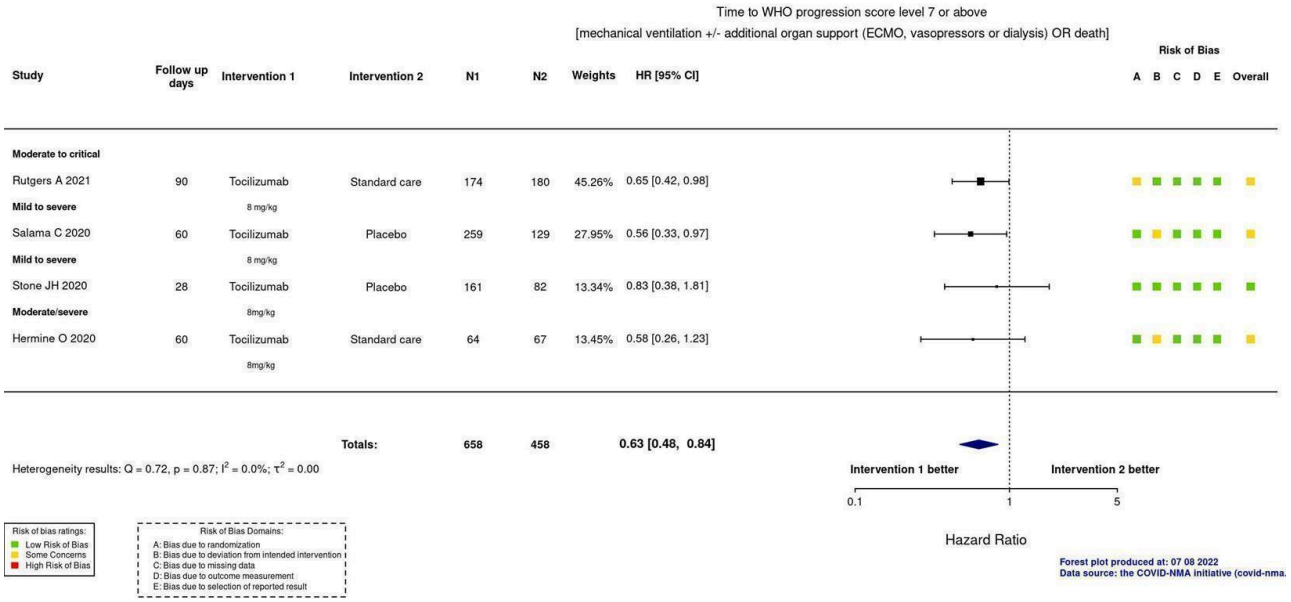
Figure 15. Analysis 1.2.1 Tocilizumab versus placebo or standard care. Outcome: Time to clinical improvement



Time to WHO Clinical Progression Score of level 7 or above

This outcome was reported in four RCTs (1116 participants) (Hermine 2021; Rutgers 2021; Salama 2020; Stone 2020). Tocilizumab reduces the probability that an individual would reach the WHO-CPS of level 7 or above compared to standard care alone or to placebo at a specific time point (D28 up to D90) (HR 0.63, 95% CI 0.48 to 0.84; I^2 = 0.0%; 4 RCTs, 1116 participants; absolute effect: 73 fewer per 1000 (from 104 fewer to 31 fewer); high-certainty evidence; Figure 16).

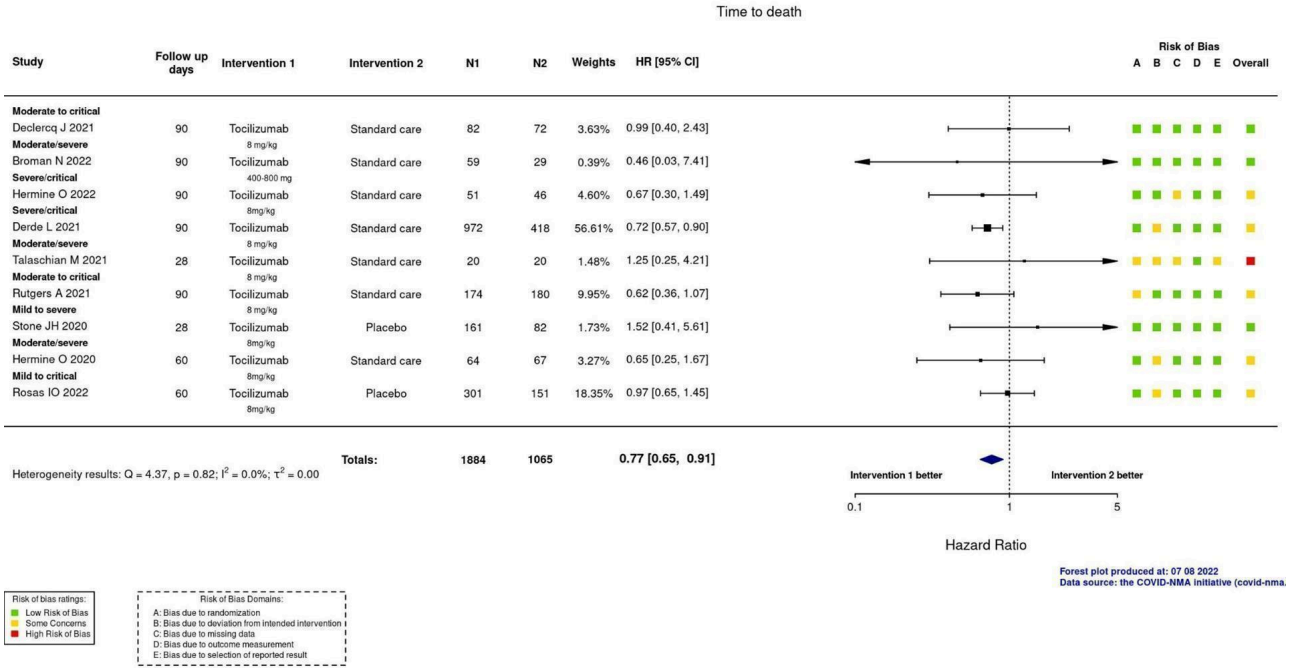
Figure 16. Analysis 1.2.2 Tocilizumab versus placebo or standard care. Outcome: Time to WHO progression score (level 7 and above)



Time to death

This outcome was reported in nine RCTs (2949 participants) (Broman 2022; Declercq 2021; Derde 2021; Hermine 2021; Hermine 2022 (CORIMUNO-TOCI-2); Rosas 2022; Rutgers 2021; Stone 2020; Talaschian 2021). Tocilizumab probably reduces the probability that an individual would die compared to standard care alone at a specific time point (D28 up to D90) (HR 0.77, 95% CI 0.65 to 0.91; I^2 = 0.0%; 9 RCTs; 2949 participants; absolute effect: 50 fewer per 1000 (from 78 fewer to 19 fewer); moderate-certainty evidence; Figure 17).

Figure 17. Analysis 1.2.3 Tocilizumab versus placebo or standard care. Outcome: Time to death



Sarilumab versus standard care/placebo

We have included results from nine trials and merged the results reporting on different doses of sarilumab in our analysis (Lescure 2021; Merchante 2021; Sivapalasingam 2022 (reporting results of phase 2 and 3 analysis populations)). We report the certainty of the evidence for critical outcomes in Summary of findings 2 and for important outcomes in Appendix 11 'Summary of Findings 8 - important outcomes'. The outcome WHO progression score (level 7 or above) at D60 or more was not reported.

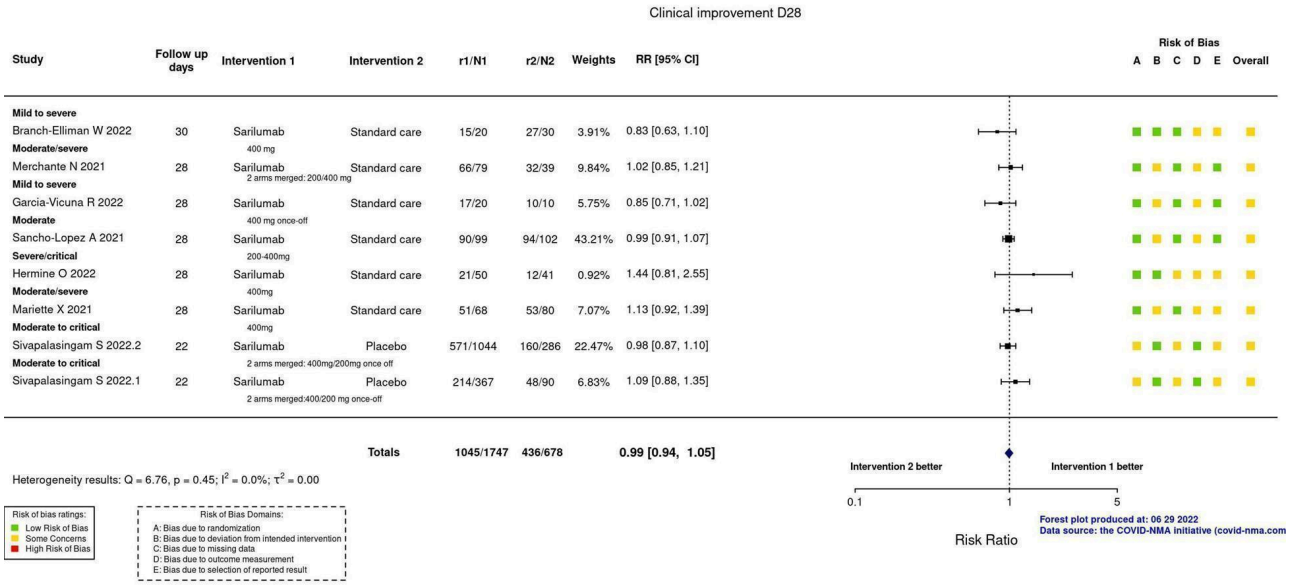
Critical outcomes

Clinical improvement

Clinical improvement was defined as discharge at day 28 (Branch-Elliman 2022; Garcia-Vicuna 2022; Hermine 2022 (CORIMUNO-SARI-2); Mariette 2021; Sancho-Lopez 2021); as a 2-point rise in a 7-category ordinal scale or hospital discharge, whichever occurred first (Merchante 2021), or as the proportion with a 1-point improvement in clinical status using a 7-point ordinal scale on day 22 (Sivapalasingam 2022). Sivapalasingam 2022 reported results from phase 2 and phase 3 datasets.

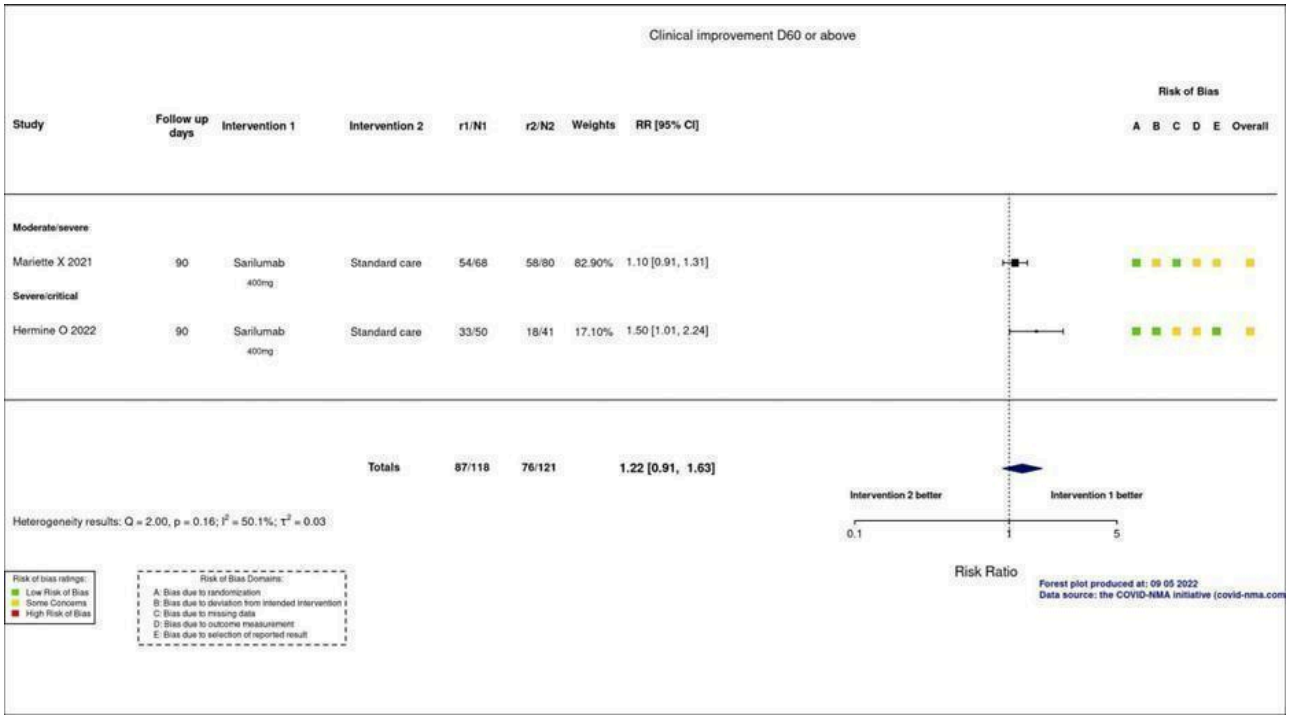
Seven RCTS (2425 participants) reported the proportion of participants achieving clinical improvement at D28 (Branch-Elliman 2022; Garcia-Vicuna 2022; Hermine 2022 (CORIMUNO-SARI-2); Mariette 2021; Merchante 2021; Sancho-Lopez 2021; Sivapalasingam 2022 (Sivapalasingam 2022.1 results from phase 2; Sivapalasingam 2022.2 results from phase 3)). Sarilumab probably results in little or no increase in clinical improvement at D28 compared to standard care alone or placebo (RR 0.99, 95% CI 0.94 to 1.05; I^2 = 0.0%; 7 RCTs; 2425 participants; absolute effect: 6 fewer per 1000 (from 39 fewer to 32 more); moderate-certainty evidence; Figure 18).

Figure 18. Analysis 2.1.1 Sarilumab versus placebo or standard care. Outcome: Clinical improvement D28
Sivapalasingam 2022: Sivapalasingam 2022.1 refers to the phase 2 results; Sivapalasingam 2022.2 refers to the phase 3 results.



Two studies (239 participants) reported a longer follow-up of clinical improvement, defined as hospital discharge at ≥ D60 (Hermine 2022 (CORIMUNO-SARI-2); Mariette 2021). The evidence of an effect of sarilumab on clinical improvement, compared to standard care alone, at ≥ D60 is very uncertain (RR 1.22, 95% CI 0.91 to 1.63; 2 RCTs; 239 participants; absolute effect: 138 more per 1000 (from 57 fewer to 396 more); very low-certainty evidence; Figure 19).

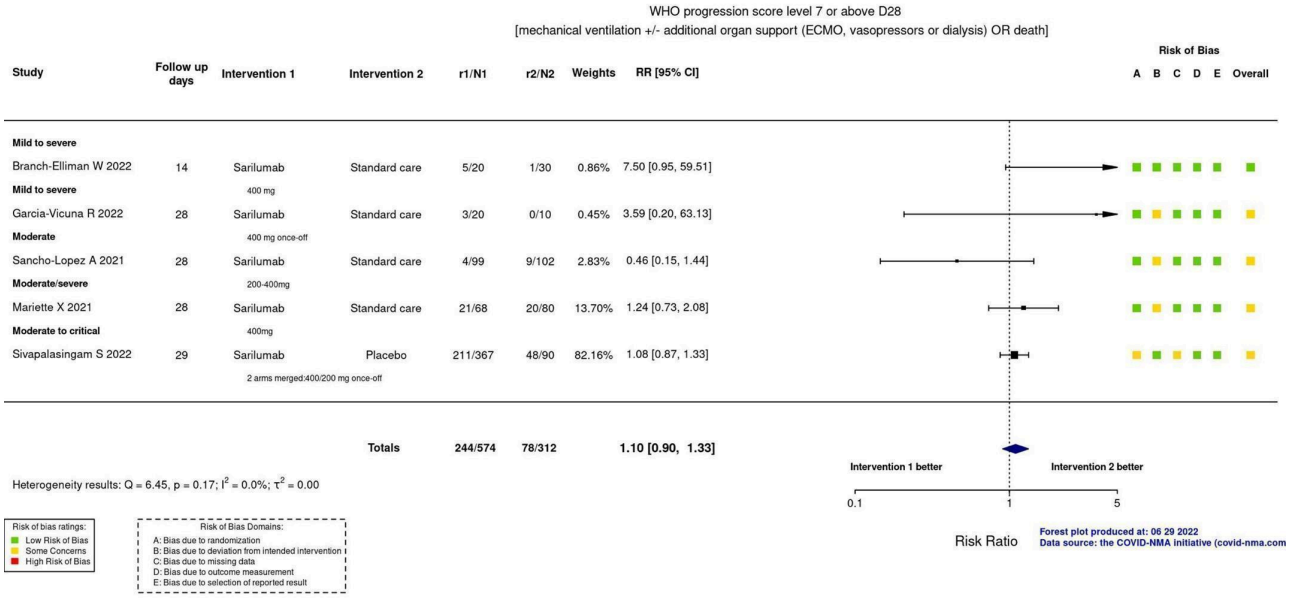
Figure 19. Analysis 2.1.2 Sarilumab versus placebo or standard care. Outcome: Clinical improvement D60



WHO Clinical Progression Score of level 7 or above (i.e. the proportion of participants with mechanical ventilation +/- additional organ support or death)

Five RCTs (886 participants) reported the proportion of participants with mechanical ventilation or death at D28 (Branch-Elliman 2022; Garcia-Vicuna 2022; Mariette 2021; Sancho-Lopez 2021; Sivapalasingam 2022 (phase 2)). The evidence of the effect of sarilumab on the proportion of participants with a WHO-CPS of level 7 or above at D28 is very uncertain (RR 1.10, 95% CI 0.90 to 1.33; I^2 = 0.0 %; 5 RCTs, 886 participants; absolute effect: 25 more per 1000 (from 25 fewer to 83 more); very low-certainty evidence; Figure 20). We did not obtain data for longer-term follow-up (≥ D60).

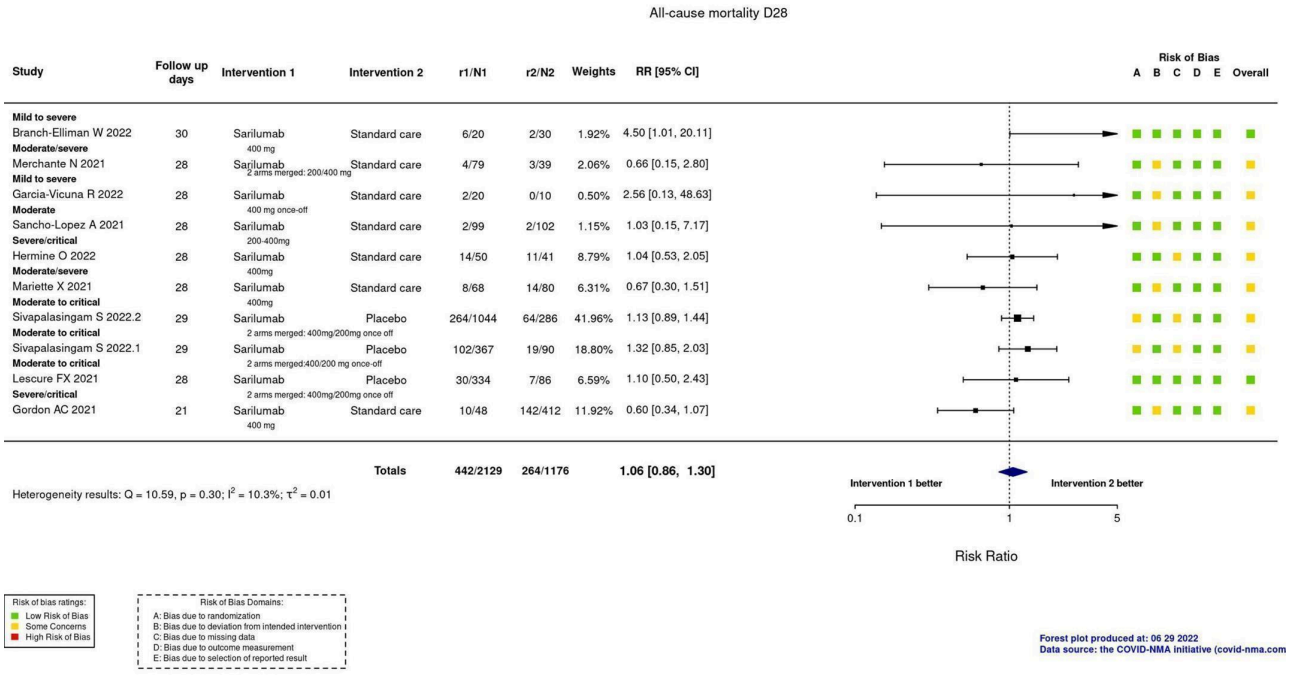
Figure 20. Analysis 2.1.3 Sarilumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



All-cause mortality

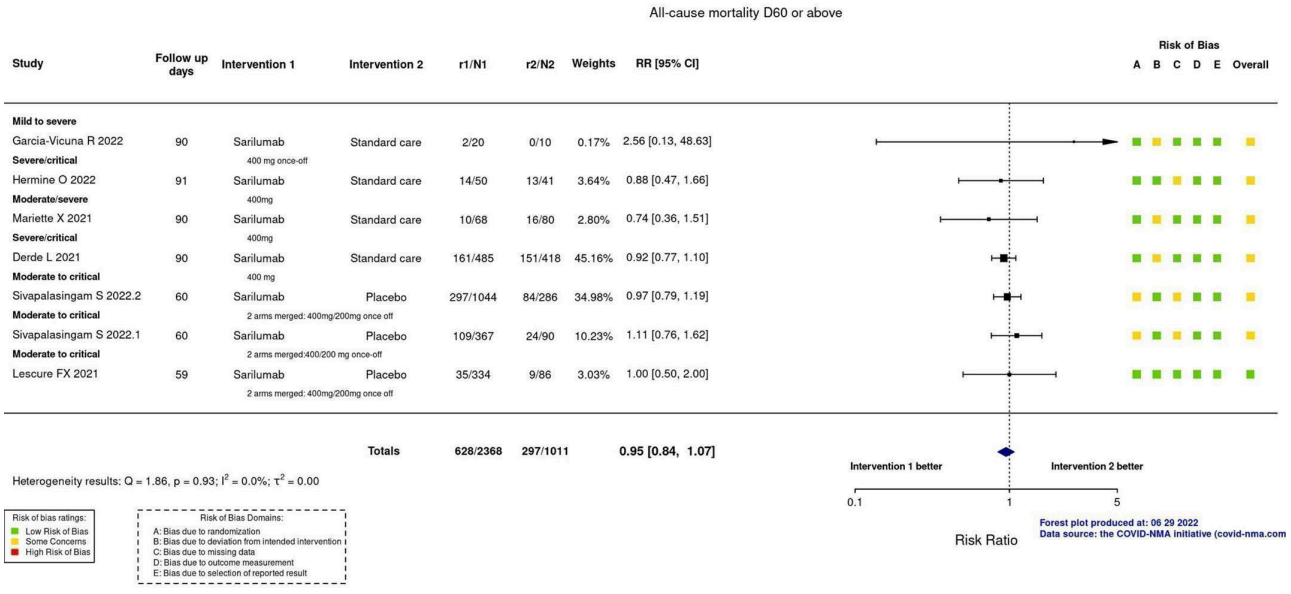
Nine RCTs (3305 participants) reported all-cause mortality at D28 (Branch-Elliman 2022; Garcia-Vicuna 2022; Gordon 2021; Hermine 2022 (CORIMUNO-SARI-2); Lescure 2021; Mariette 2021; Merchante 2021; Sancho-Lopez 2021; Sivapalasingam 2022 (Sivapalasingam 2022.1 results from phase 2; Sivapalasingam 2022.2 results from phase 3)). The evidence for an effect of sarilumab compared to standard care alone or placebo on all-cause mortality at D28 is very uncertain (RR 1.06, 95% CI 0.86 to 1.30; I^2 = 10.3%; 9 RCTs, 3305 participants; absolute effect: 13 more per 1000 (from 31 fewer to 67 more); very low-certainty evidence; Figure 21).

Figure 21. Analysis 2.1.4 Sarilumab versus placebo or standard care. Outcome: All-cause mortality D28



Six RCTs (3379 participants) reported all-cause mortality at ≥ D60 (Derde 2021; Garcia-Vicuna 2022; Hermine 2022 (CORIMUNO-SARI-2); Lescure 2021; Mariette 2021; Sivapalasingam 2022 (Sivapalasingam 2022.1 results from phase 2; Sivapalasingam 2022.2 results from phase 3)). The evidence for an effect of sarilumab compared to standard care alone or placebo on all-cause mortality at ≥ D60 is very uncertain (RR 0.95, 95% CI 0.84 to 1.07; I^2 = 0.0%; 6 RCTs, 3379 participants; absolute effect: 15 fewer per 1000 (from 47 fewer to 21 more); very low-certainty evidence; Figure 22).

Figure 22. Analysis 2.1.5 Sarilumab versus placebo or standard care. Outcome: All-cause mortality D60

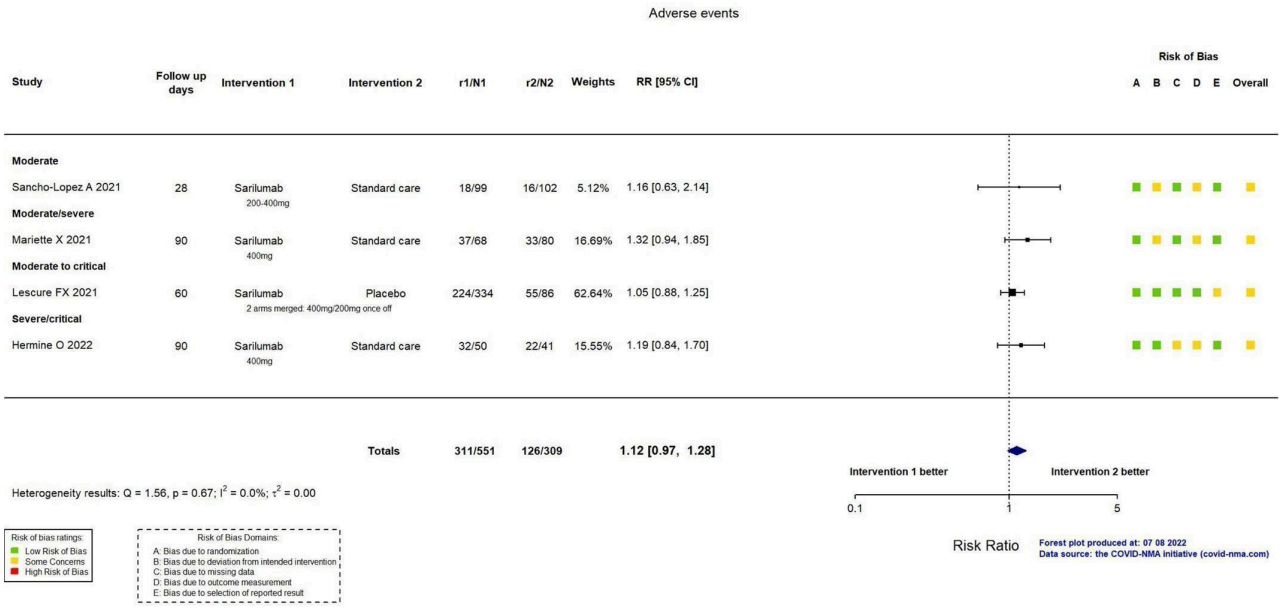


Adverse events

Two trials assessed AEs with active monitoring (Lescure 2021; Mariette 2021), and two trials used active monitoring and spontaneous reporting (Hermine 2022 (CORIMUNO-SARI-2); Sancho-Lopez 2021).

Four trials (860 participants) reported adverse events (Hermine 2022 (CORIMUNO-SARI-2); Lescure 2021; Mariette 2021; Sancho-Lopez 2021). The evidence for an effect of sarilumab compared to standard care alone or placebo on adverse events is uncertain (RR 1.12, 95% CI 0.97 to 1.28; I^2 = 0.0%; 4 RCTs, 860 participants; absolute effect 49 more per 1000 (from 12 fewer to 51 more); low-certainty evidence; Figure 23).

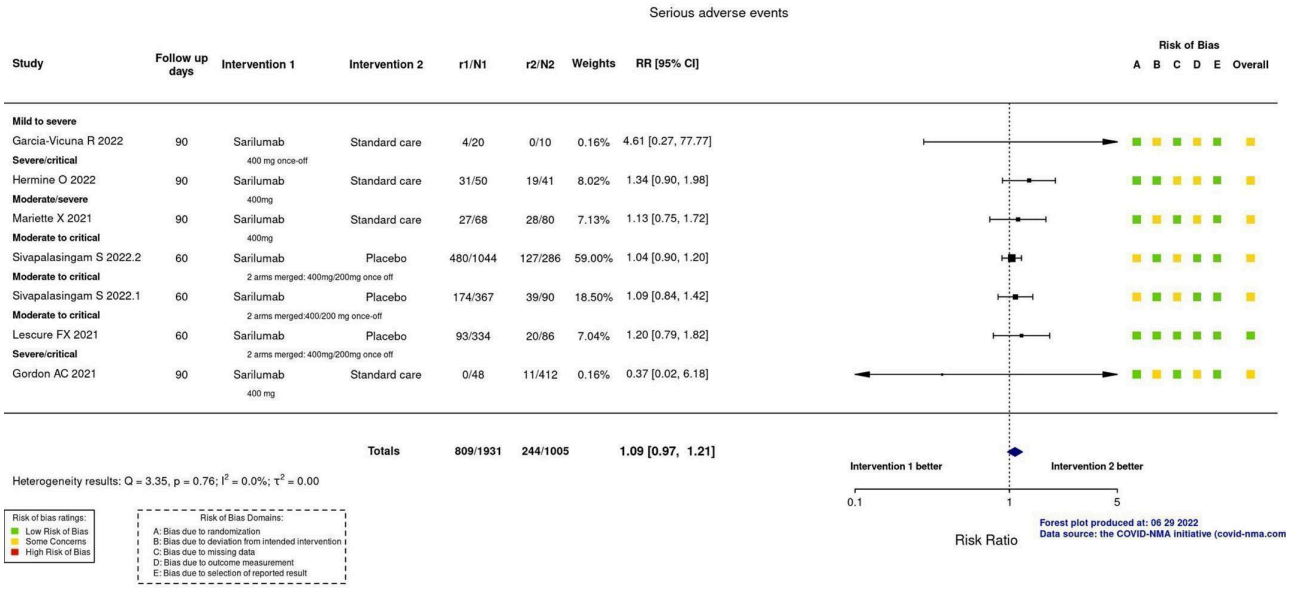
Figure 23. Analysis 2.1.6 Sarilumab versus placebo or standard care. Outcome: Adverse events



Serious adverse events

Six trials (2936 participants) reported serious adverse events (Garcia-Vicuna 2022; Gordon 2021; Hermine 2022 (CORIMUNO-SARI-2); Lescure 2021; Mariette 2021; Sivapalasingam 2022 (Sivapalasingam 2022.1 results from phase 2; Sivapalasingam 2022.2 results from phase 3)). The evidence for an effect of sarilumab compared to standard care alone or placebo on serious adverse events is uncertain (RR 1.09, 95% CI 0.97 to 1.21; I^2 = 0.0%; 6 RCTs, 2936 participants; absolute effect 22 more per 1000 (from 7 fewer to 51 more); low-certainty evidence; Figure 24).

Figure 24. Analysis 2.1.7 Sarilumab versus placebo or standard care. Outcome: Serious adverse events

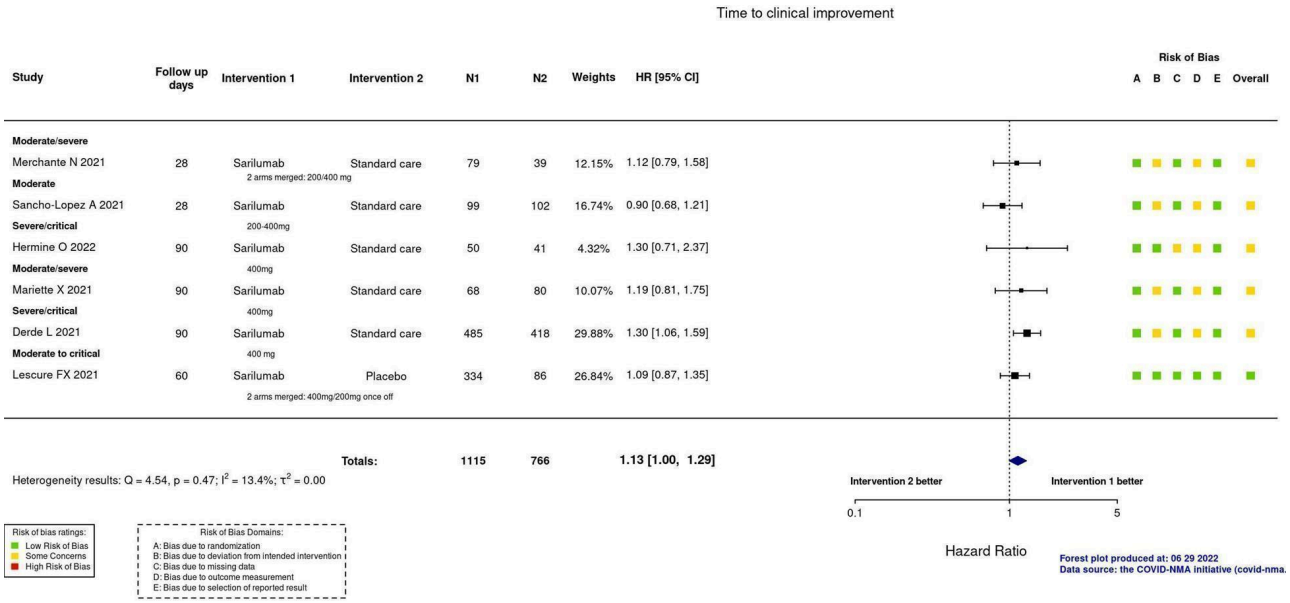


Important outcomes

Time to clinical improvement

Six trials (1881 participants) reported on time to clinical improvement (Derde 2021; Hermine 2022 (CORIMUNO-SARI-2); Lescure 2021; Mariette 2021; Merchante 2021; Sancho-Lopez 2021). The evidence for an effect of sarilumab compared to standard care alone or placebo on time to clinical improvement is uncertain (HR 1.13, 95% CI 1.00 to 1.29; I^2 = 13.4%; 6 RCTs, 1881 participants; absolute effect 41 more per 1000 (from 0 to 82 more); low-certainty evidence; Figure 25).

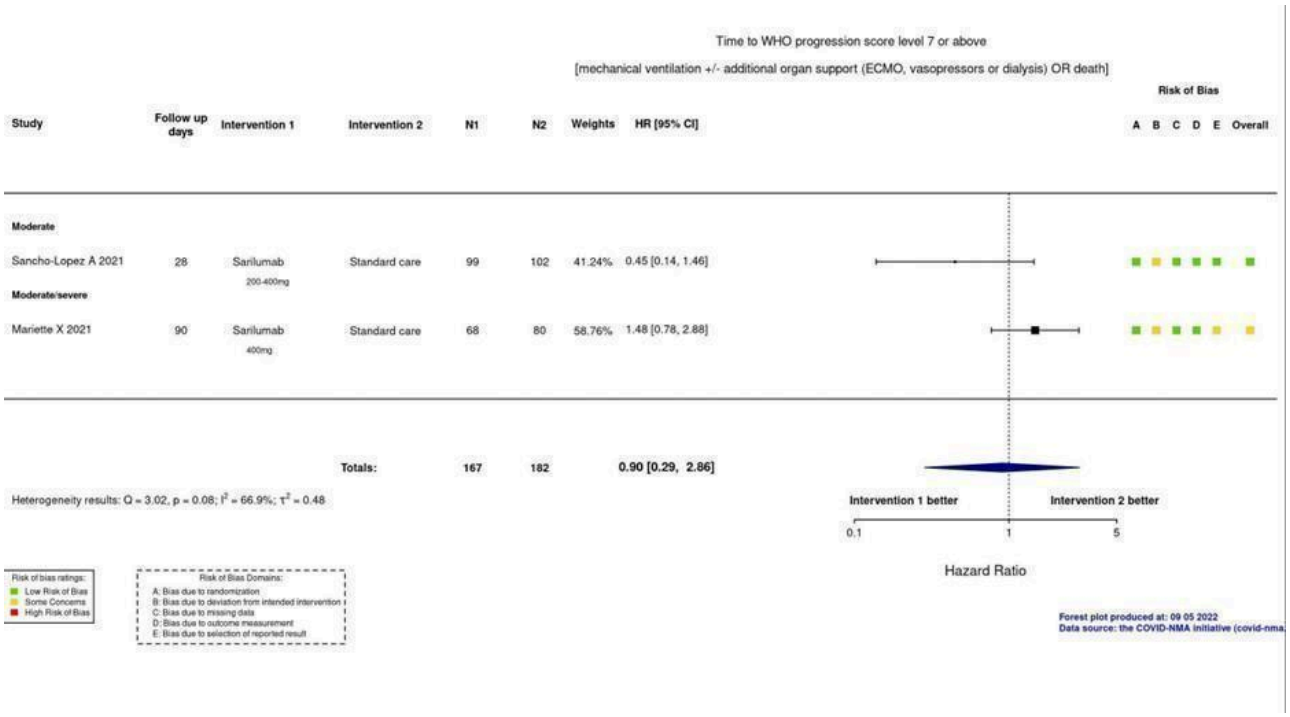
Figure 25. Analysis 2.2.1 Sarilumab versus placebo or standard care. Outcome: Time to clinical improvement



Time to WHO Clinical Progression Score of level 7 or above

Two trials (349 participants) reported on time to WHO-CPS of level 7 or above with 28 days follow-up (Mariette 2021; Sancho-Lopez 2021). The evidence for an effect of sarilumab compared to standard care alone on time to WHO-CPS of level 7 is very uncertain (HR 0.90, 95% CI 0.29 to 2.86; 2 RCTs, 349 participants; absolute effect 15 fewer per 1000 (from 110 fewer to 232 more); very low-certainty evidence; Figure 26).

Figure 26. Analysis 2.2.2 Sarilumab versus placebo or standard care. Time to WHO Clinical Progression Score of level 7 or above

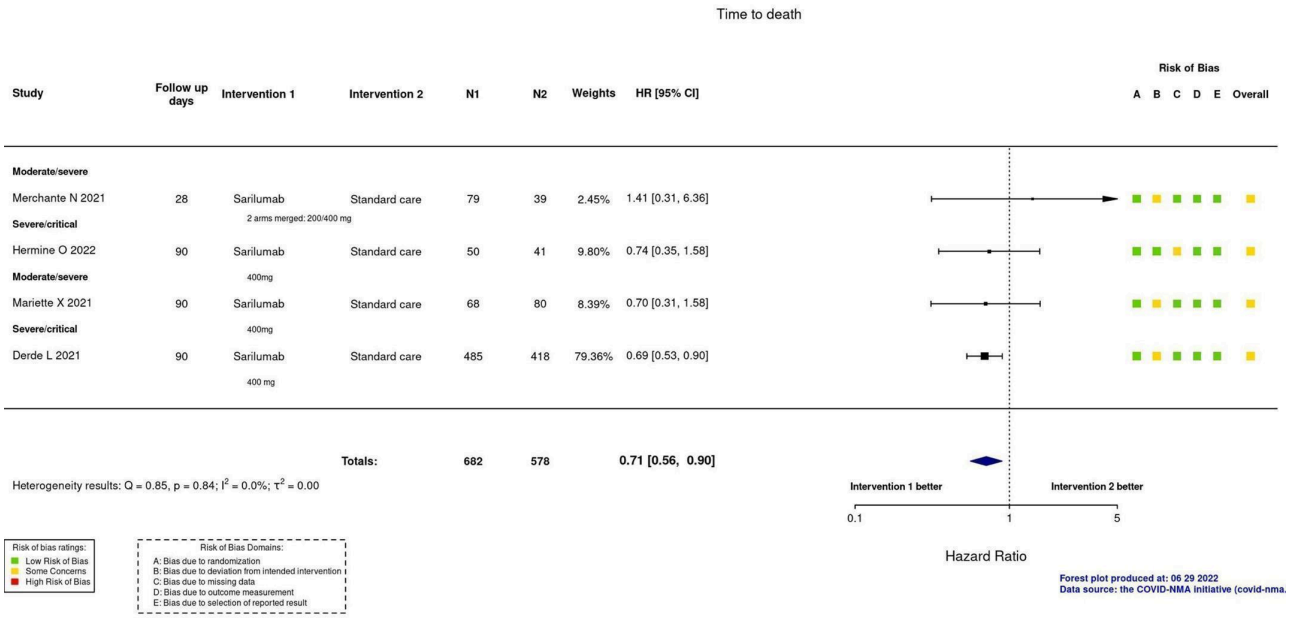


Time to death

Four trials (1260) reported time to death with a follow-up ranging from 28 to 90 days (Derde 2021; Hermine 2022 (CORIMUNO-SARI-2); Mariette 2021; Merchante 2021).

Sarilumab reduces the probability that an individual would die compared to standard care alone at a specific time point D28 up to 90 (HR 0.71, 95% CI 0.56 to 0.90; I^2 = 0.0%; 4 RCTs, 1260 participants; absolute effect 80 fewer per 1000 (from 124 fewer to 26 fewer); high-certainty evidence; Figure 27).

Figure 27. Analysis 2.2.3 Sarilumab versus placebo or standard care. Outcome: Time to death



Clazakizumab versus placebo

We identified two trials evaluating the effect of clazakizumab versus placebo: one has been published (Lonze 2022), while the other posted results concerning only 28% of its target sample size (17 recruited/60 planned) (Jordan 2021).

We report the certainty of the evidence for critical outcomes in Summary of findings 3. The important outcomes were not reported.

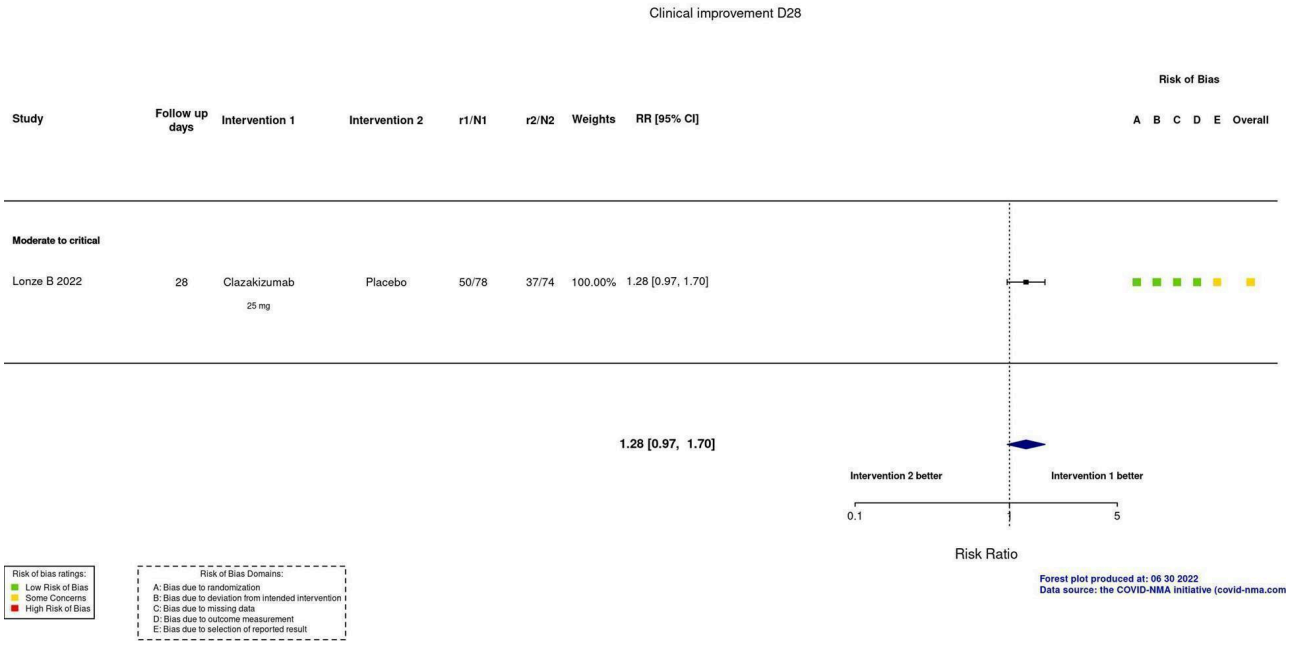
Critical outcomes

Clinical improvement

Lonze 2022 reported clinical improvement on D28, defined as an improvement from baseline by at least two points on the WHO 11-point ordinal scale.

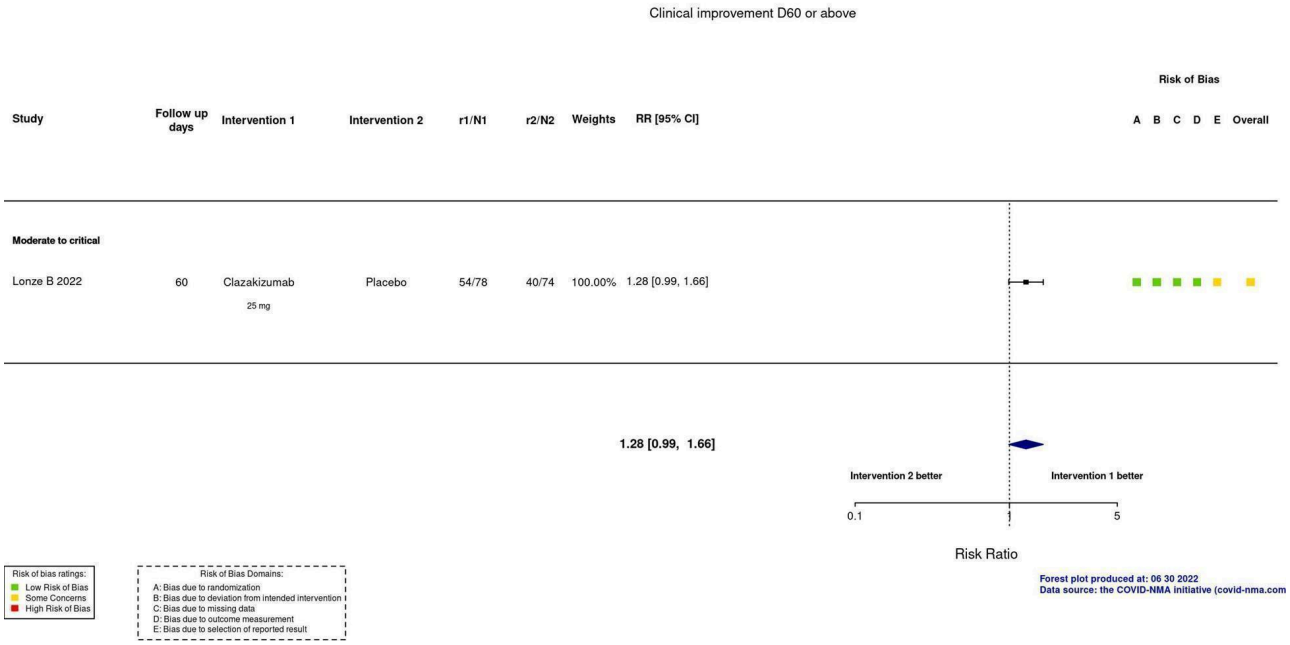
The evidence of an effect of clazakizumab on clinical improvement at D28, compared to placebo, is very uncertain (RR 1.28, 95% CI 0.97 to 1.70; 1 RCT; 152 participants; absolute effect: 140 more per 1000 (from 15 fewer to 350 more); very low-certainty evidence; Figure 28).

Figure 28. Analysis 3.1.1 Clazakizumab versus placebo or standard care. Outcome: Clinical improvement 28



Lonze 2022 also reported on a longer-term follow-up for clinical improvement (≥ D60). The evidence of clazakizumab effect on clinical improvement at D ≥ 60, compared to placebo, is very uncertain (RR 1.28, 95% CI 0.99 to 1.66; 1 RCT; 152 participants; absolute effect: 151 more per 1000 (from 5 fewer to 357 more); very low-certainty evidence; Figure 29).

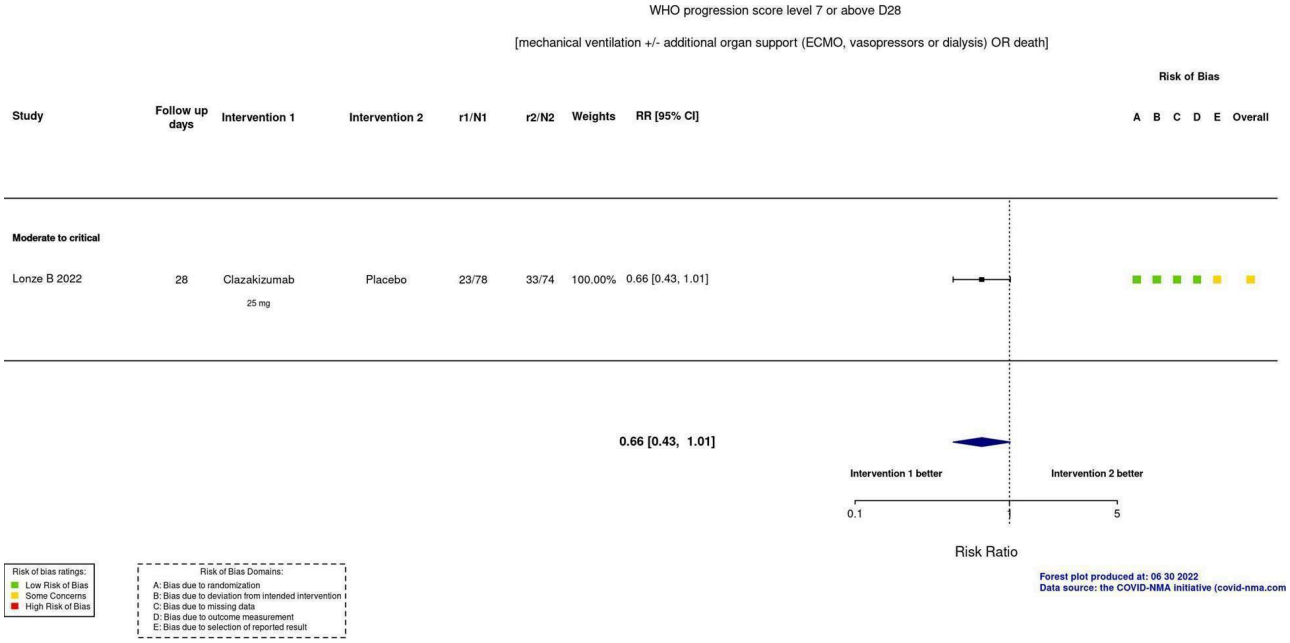
Figure 29. Analysis 3.1.2 Clazakizumab versus placebo or standard care. Outcome: Clinical improvement D60



WHO Clinical Progression Score of level 7 or above (i.e. the proportion of participants with mechanical ventilation +/- additional organ support or death)

Lonze 2022 reported on the proportion of participants with mechanical ventilation or death. The evidence of the effect of clazakizumab on the proportion of participants with a WHO-CPS of level 7 or above at D28 is very uncertain (RR 0.66, 95% CI 0.43 to 1.01; 1 RCT, 152 participants; absolute effect: 152 more per 1000 (from 254 fewer to 4 more); very low-certainty evidence; Figure 30). We did not obtain data for longer-term follow-up (≥ D60).

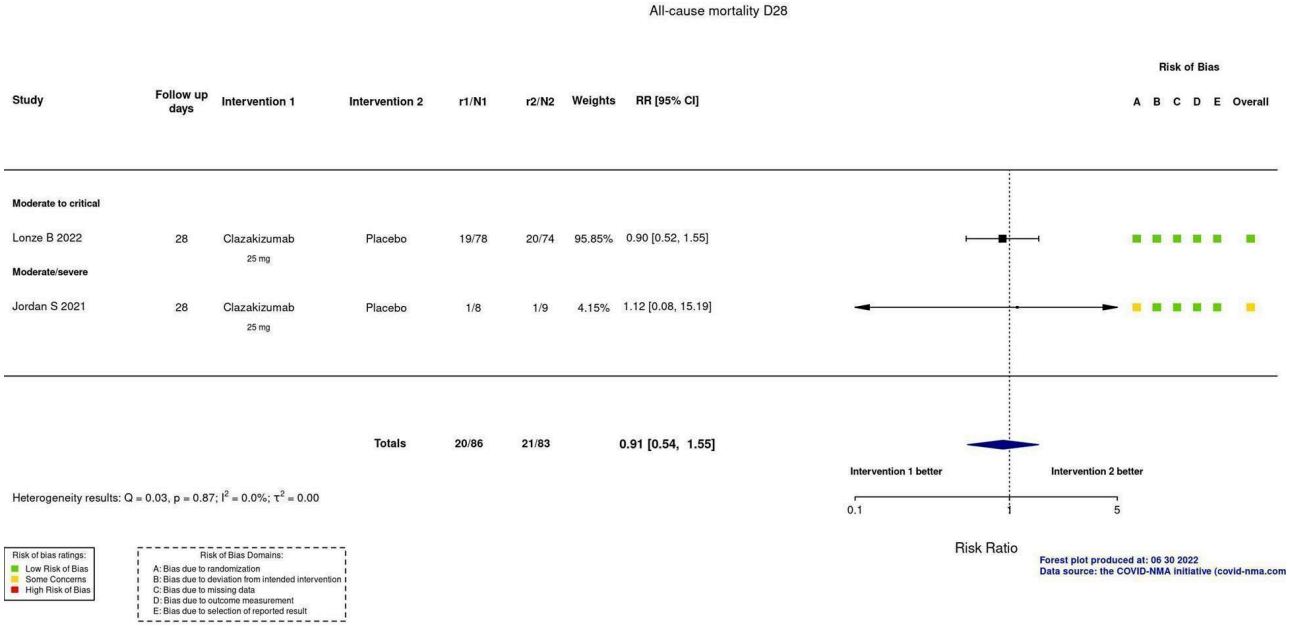
Figure 30. Analysis 3.1.3 Clazakizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



All-cause mortality

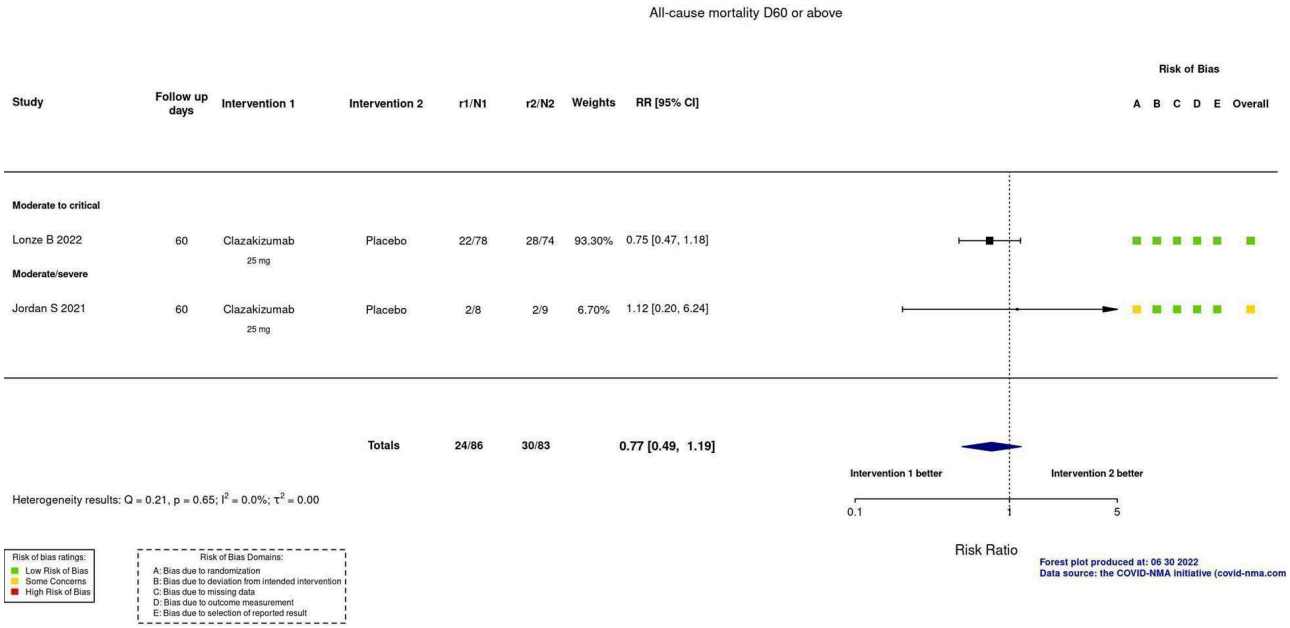
Two RCTs (169 participants) reported all-cause mortality at D28 and ≥ D60 (Jordan 2021; Lonze 2022). The evidence for an effect of clazakizumab compared to placebo on all-cause mortality at D28 is very uncertain (RR 0.91, 95% CI 0.54 to 1.55; I^2 = 0.0 %; 2 RCTs, 169 participants; absolute effect: 23 fewer per 1000 (from 116 fewer to 139 more); very low-certainty evidence; Figure 31).

Figure 31. Analysis 3.1.4 Clazakizumab versus placebo or standard care. Outcome: All-cause mortality D28



The evidence for an effect of clazakizumab compared to placebo on all-cause mortality at ≥ D60 is also very uncertain (RR 0.77, 95% CI 0.49 to 1.19; I^2 = 0.0%; 2 RCTs, 169 participants; absolute effect: 83 fewer per 1000 (from 184 fewer to 69 more); very low-certainty evidence; Figure 32).

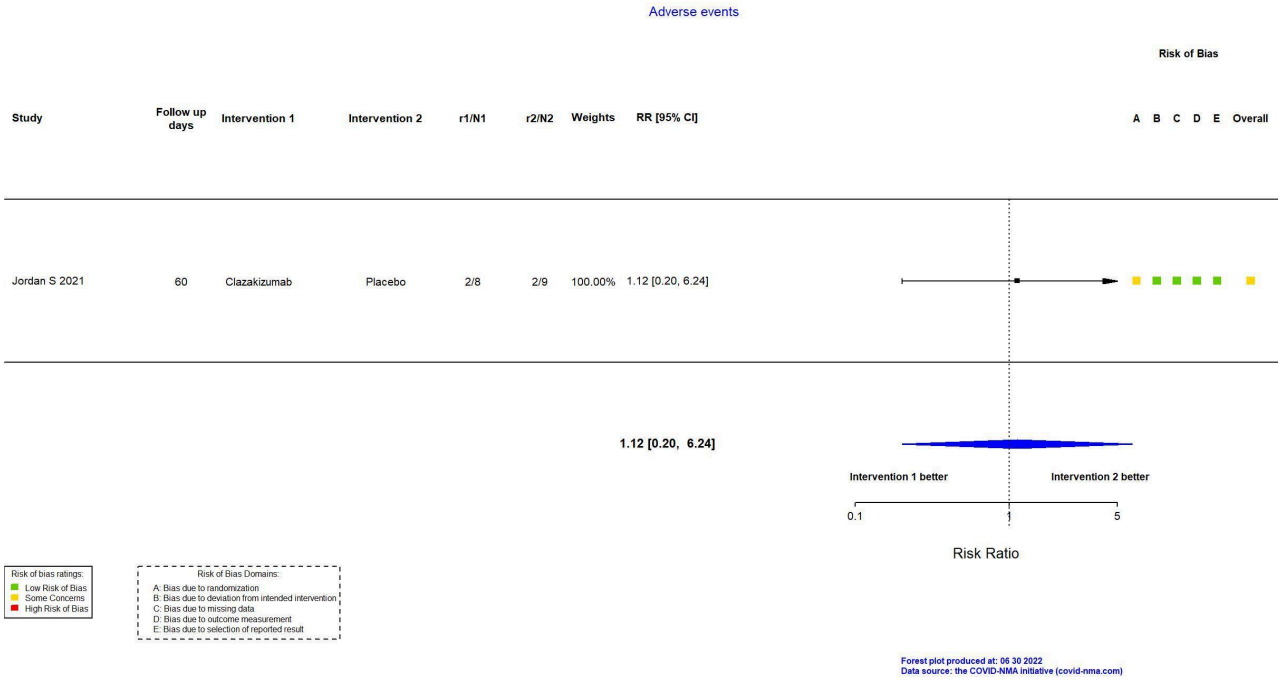
Figure 32. Analysis 3.1.5 Clazakizumab versus placebo or standard care. Outcome: All-cause mortality D60



Adverse events

Jordan 2021 reported adverse events assessed by active monitoring for 17 included participants. The evidence of clazakizumab effect on adverse events, compared to standard care alone, is uncertain (RR 1.12, 95% CI 0.20 to 6.24; 1 RCT, 17 participants; absolute effect 29 more per 1000 (from 178 fewer to 1000 more); low-certainty evidence; Figure 33).

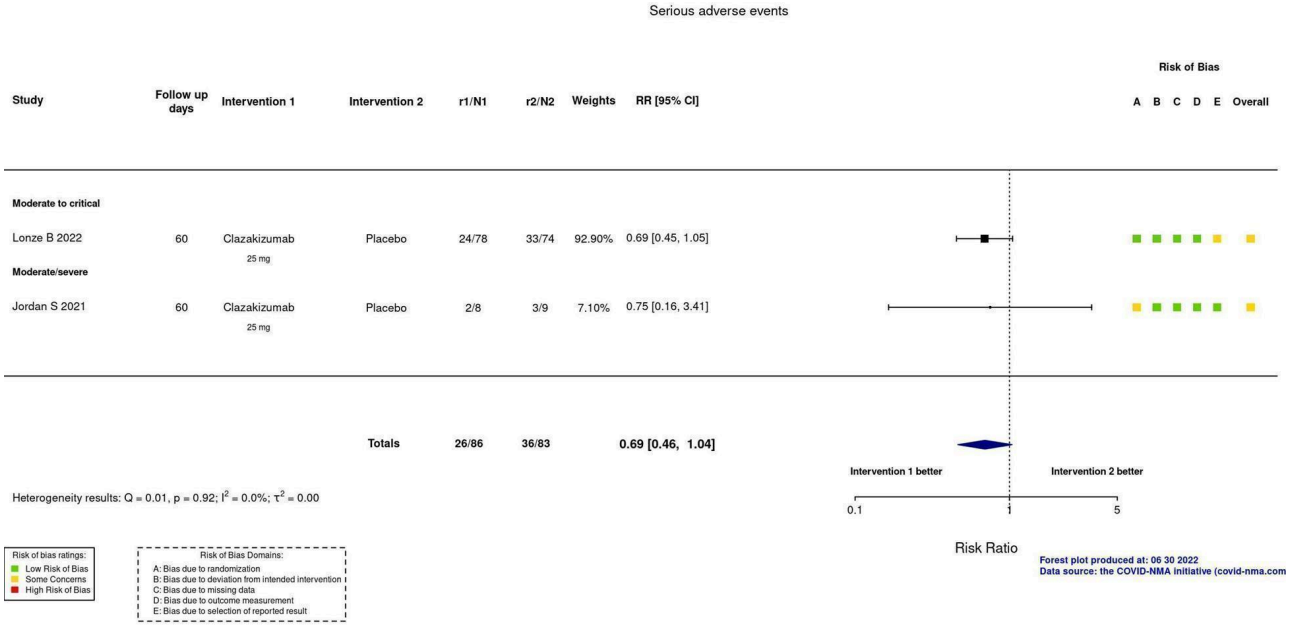
Figure 33. Analysis 3.1.6 Clazakizumab versus placebo or standard care. Outcome: Adverse events



Serious adverse events

Lonze 2022 and Jordan 2021 (169 participants) reported serious adverse events. The evidence of clazakizumab's effect on serious adverse events, compared to placebo alone, is uncertain (RR 0.69, 95% CI 0.46 to 1.04; I^2= 0.0%; 2 RCTs, 169 participants; absolute effect 134 fewer per 1000 (from 234 fewer to 17 more); low-certainty evidence; Figure 34).

Figure 34. Analysis 3.1.7 Clazakizumab versus placebo or standard care. Outcome: Serious adverse events



Important outcomes

None of the studies included reported results for any of the important outcomes, namely, time to clinical improvement, time to WHO score seven, and above and time to death.

Olokizumab versus placebo

We have identified and included results from a three-arm trial evaluating the effect of olokizumab (n = 124) versus placebo (n = 124) (Samsonov 2022). As the trial is not yet published, we considered the results posted on clinicaltrials.gov under registration number NCT04380519. We report the evidence of certainty for critical outcomes in Summary of findings 4. The WHO progression score (level 7 or above) at D60 or more and important outcomes were not reported.

Critical outcomes

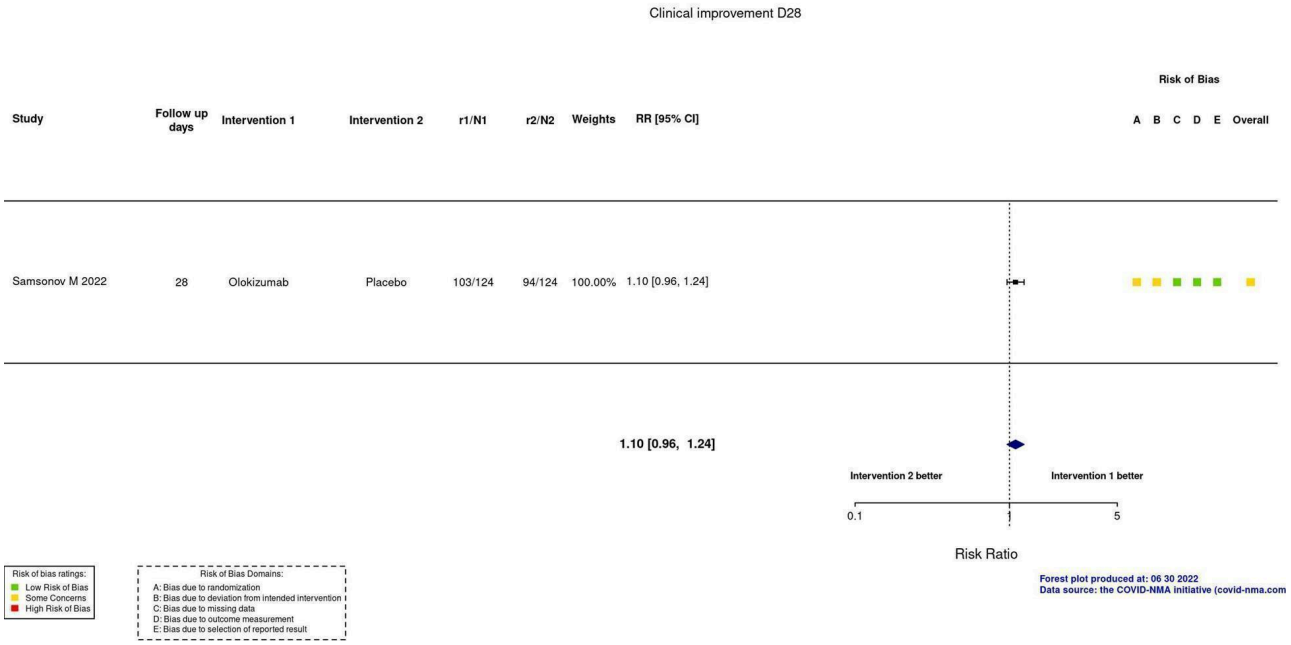
No data are available for clinical improvement (≥ D60), WHO-CPS of level 7 or above (D28, ≥ D60), all-cause mortality (≥ D60) and adverse events.

Clinical improvement

Samsonov 2022 reported on clinical improvement at D28, defined as an improvement from baseline by at least two points on a 6-point ordinal scale.

The evidence for an effect of olokizumab on clinical improvement, compared to placebo at D28 is very uncertain (RR 1.10, 95% CI 0.96 to 1.24; 1 RCT, 248 participants; absolute effect: 76 more per 1000 (from 30 fewer to 182 more); very low-certainty evidence; Figure 35).

Figure 35. Analysis 4.1.1 Olokizumab versus placebo or standard care. Outcome: Clinical improvement 28

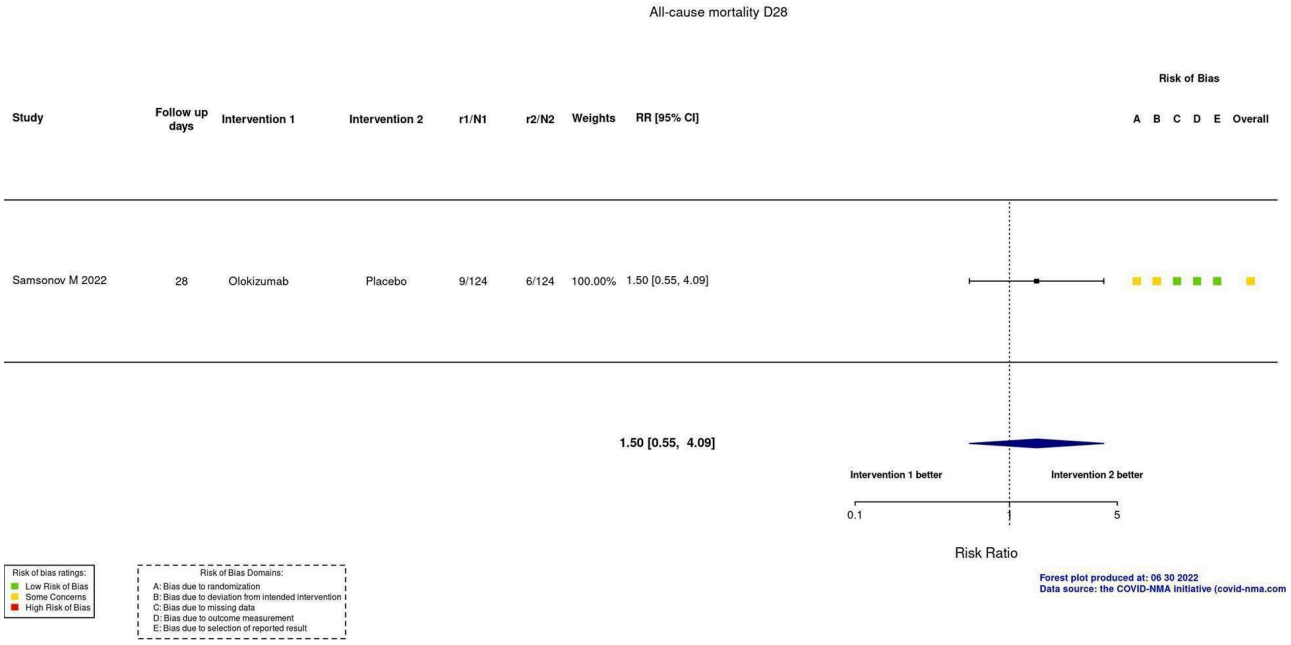


All-cause mortality

Samsonov 2022 reported all-cause mortality at D28.

The evidence for an effect of olokizumab compared with all-cause mortality at D28 is very uncertain (RR 1.50, 95% CI 0.55 to 4.09; 1 RCT, 248 participants; absolute effect: 24 more per 1000 (from 22 fewer to 150 more); very low-certainty evidence; Figure 36).

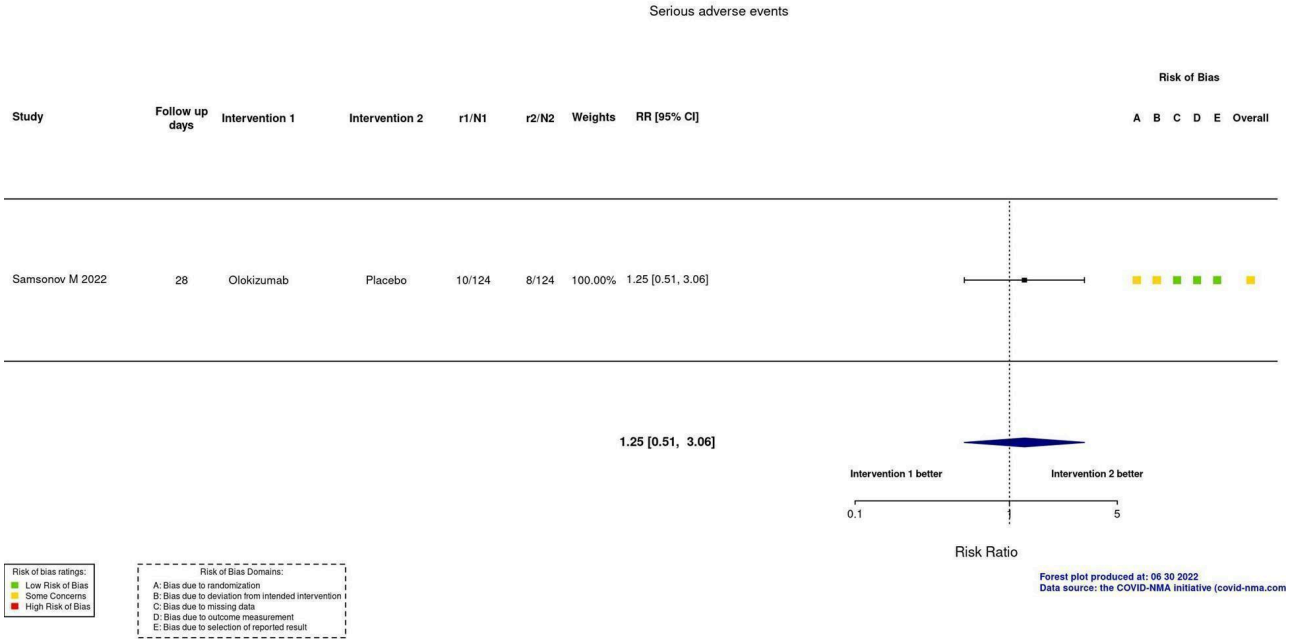
Figure 36. Analysis 4.1.2 Olokizumab versus placebo or standard care. Outcome: All-cause mortality D28



Serious adverse events

Samsonov 2022 (248 participants) reported serious adverse events. The evidence for an effect of olokizumab compared to placebo on serious adverse events is very uncertain (RR 1.25, 95% CI 0.51 to 3.06; 1 RCT, 248 participants; absolute effect: 16 more per 1000 (from 32 fewer to 133 more); very low-certainty evidence; Figure 37).

Figure 37. Analysis 4.1.3 Olokizumab versus placebo or standard care. Outcome: Serious adverse events



Important outcomes

No data are available for any important outcomes; time to clinical improvement, time to WHO-CPS of level 7 or above, and time to death.

Siltuximab versus standard care

We have identified and included results from one 2 × 2 factorial design trial evaluating the effect of siltuximab versus standard care (Declercq 2021). We report the certainty of the evidence for critical outcomes in Summary of findings 5. Also see Appendix 12 'Summary of Findings 9 - important outcomes'. WHO progression score (level 7 or above) at D60 or more was not reported.

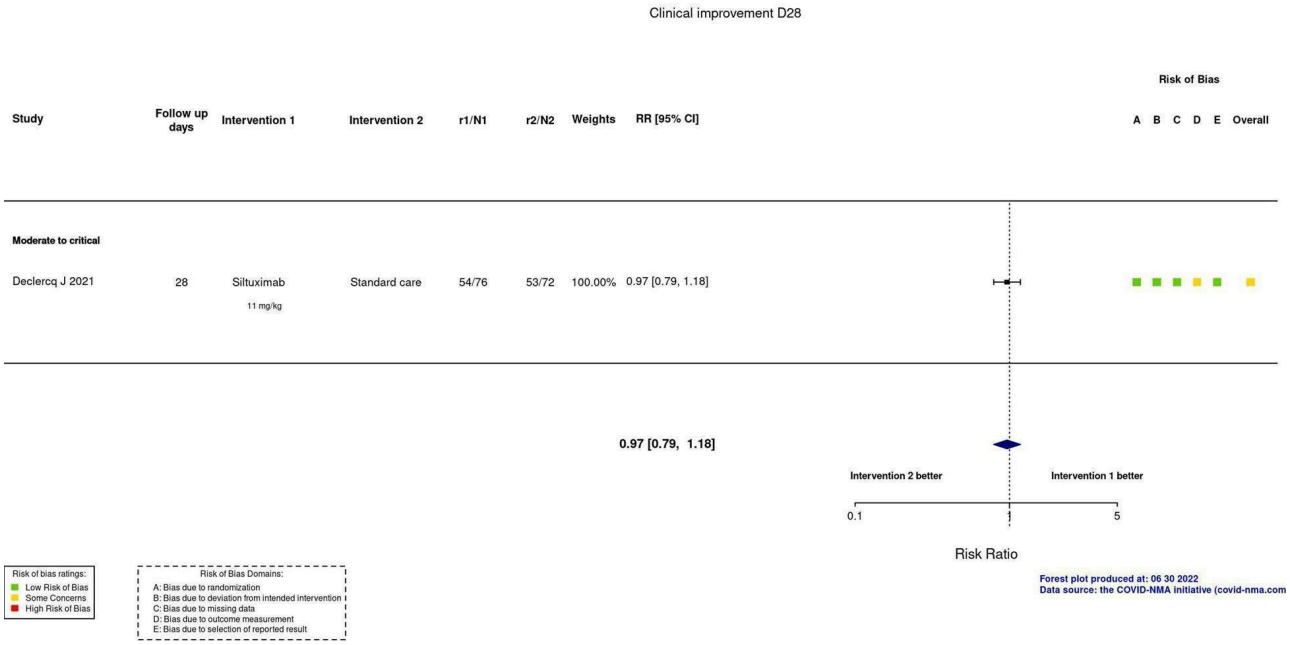
Critical outcomes

Clinical improvement

The definition of clinical improvement extracted is "an increase of at least two points on a 6-category ordinal scale (compared with the worst status at the day of randomization) or discharge from the hospital alive" (Declercq 2021).

The evidence for an effect of siltuximab compared to standard care alone or placebo on clinical improvement at D28 is very uncertain (RR 0.97, 95% CI 0.79 to 1.18; 1 RCT, 148 participants; absolute effect: 22 fewer per 1000 (from 155 fewer to 132 more); very low-certainty evidence; Figure 38).

Figure 38. Analysis 5.1.1 Siltuximab versus placebo or standard care. Outcome: Clinical improvement 28

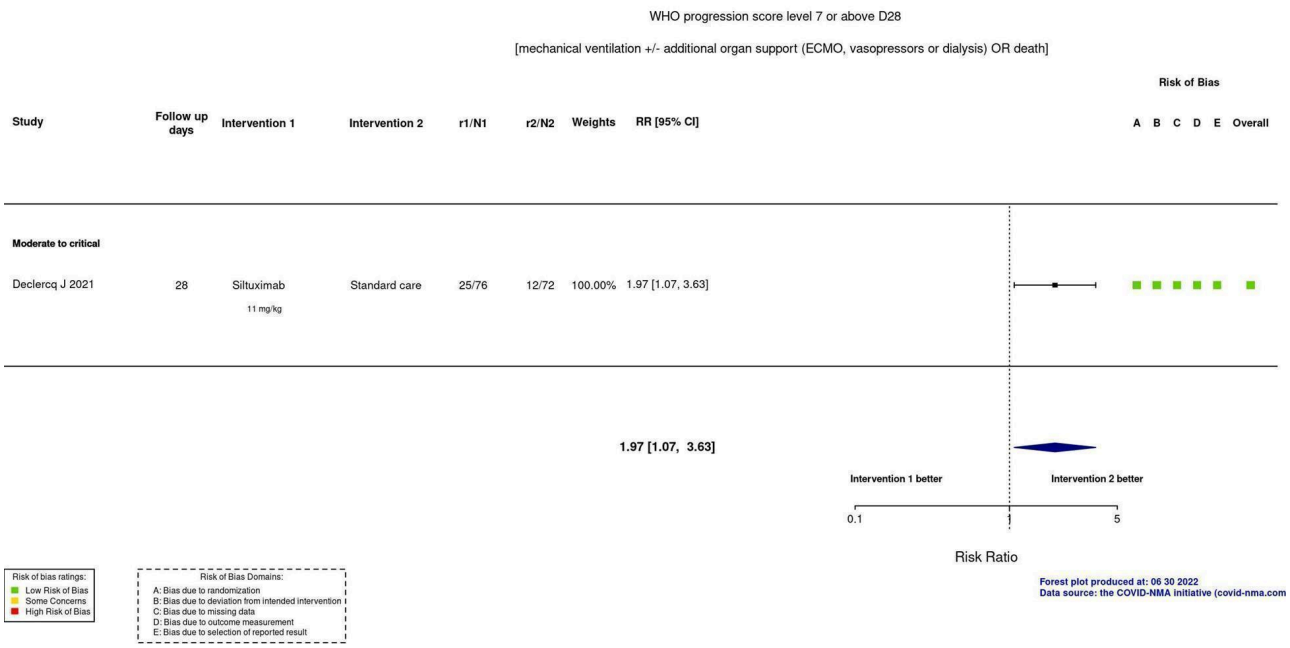


No data are available for longer-term clinical improvement (≥ D60).

WHO Clinical Progression Score of level 7 or above (i.e. the proportion of participants with mechanical ventilation +/- additional organ support or death)

The evidence is uncertain for the effect of siltuximabon on the proportion of participants with a WHO-CPS of level 7 or above at D28 (RR 1.97, 95% CI 1.07 to 3.36; 1 RCT, 148 participants; absolute effect: 162 more per 1000 (from 12 more to 438 more); low-certainty evidence; Figure 39). We did not obtain data for longer-term follow-up (≥ D60).

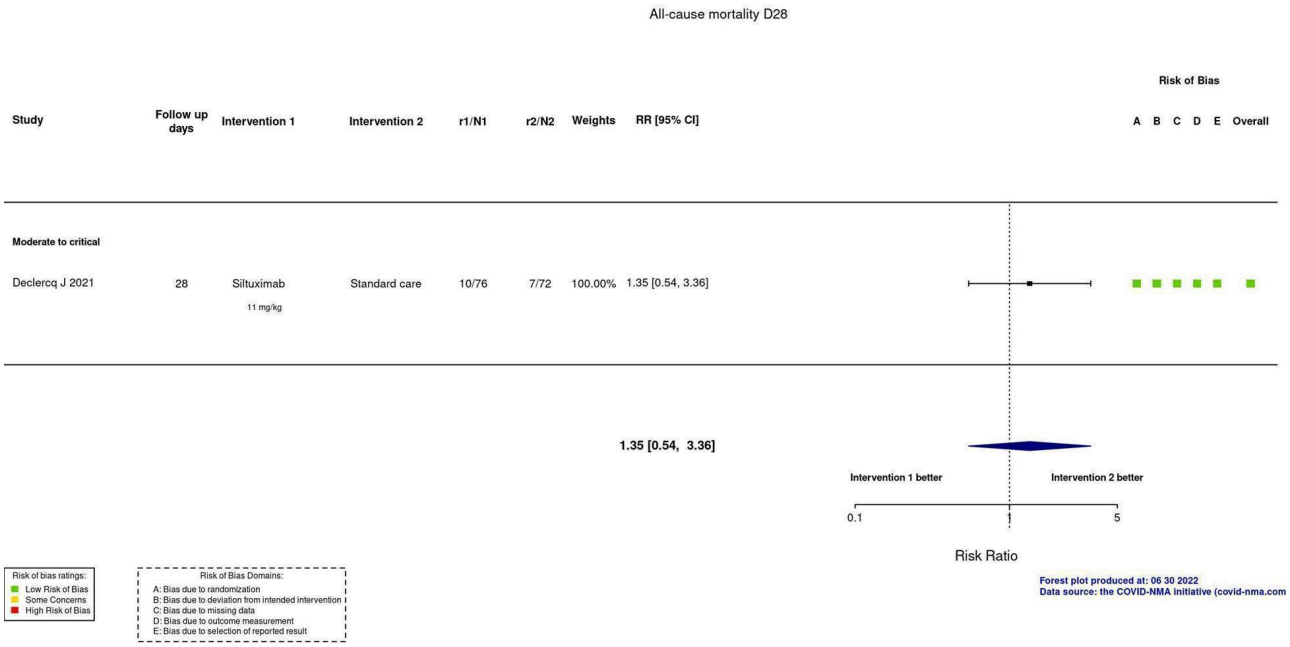
Figure 39. Analysis 5.1.2 Siltuximab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28



All-cause mortality

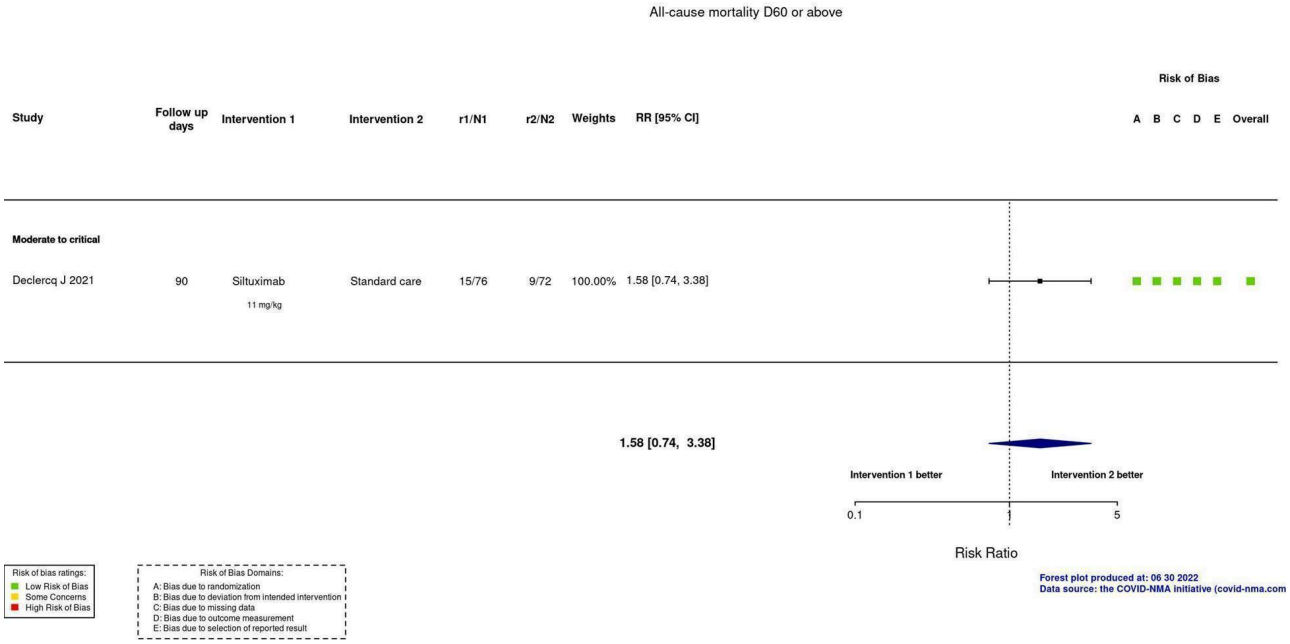
The evidence for an effect of siltuximab compared to standard care on all-cause mortality at D28 is very uncertain (RR 1.35, 95% CI 0.54 to 3.36; 1 RCT, 148 participants; absolute effect: 34 fewer per 1000 (from 45 fewer to 229 more); very low-certainty evidence; Figure 40).

Figure 40. Analysis 5.1.3 Siltuximab versus placebo or standard care. Outcome: All-cause mortality D28



Similarly, the evidence of its effect on all-cause mortality at ≥ D60, compared to placebo alone, is very uncertain (RR 1.58, 95% CI 0.74 to 3.38; 1 RCT, 148 participants; absolute effect 73 more per 1000 (from 33 fewer to 298 more); very low-certainty evidence; Figure 41).

Figure 41. Analysis 5.1.4 Siltuximab versus placebo or standard care. Outcome: All-cause mortality D60



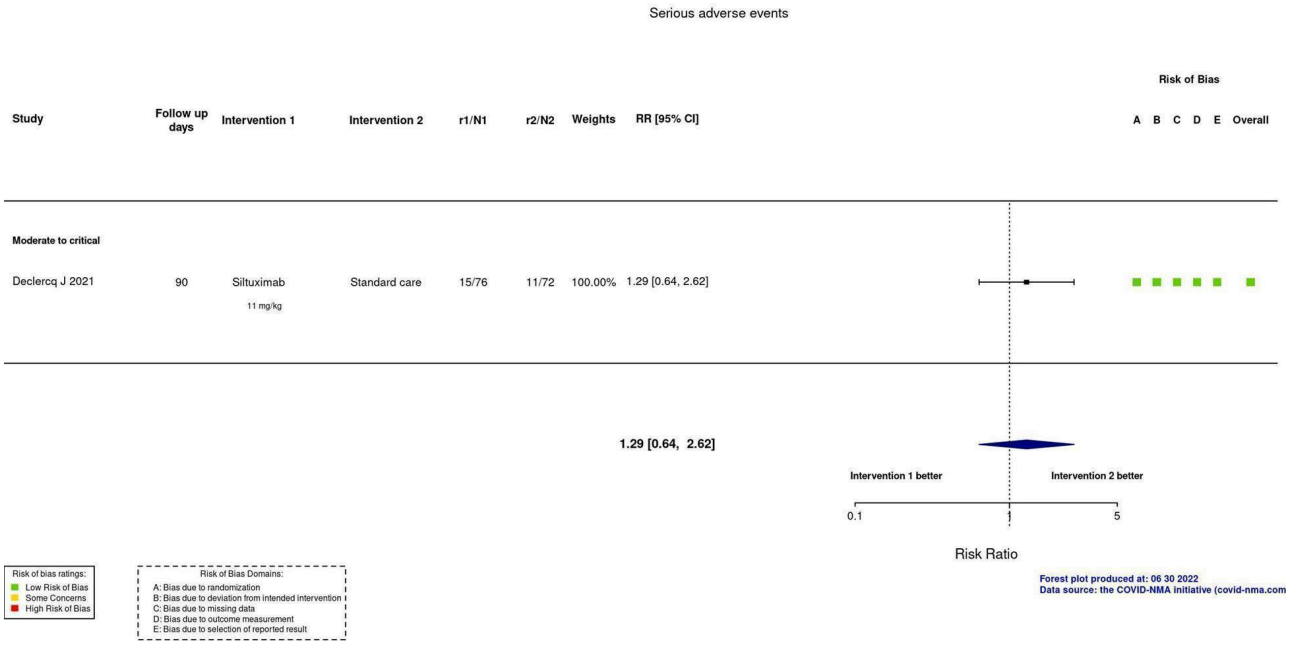
Adverse events

We did not obtain results on adverse events.

Serious adverse events

The evidence for an effect of siltuximab compared to placebo alone at ≥ D60 is uncertain (RR 1.29, 95% CI 0.64 to 2.62; 1 RCT, 148 participants; absolute effect 44 more per 1000 (from 55 fewer to 248 more); low-certainty evidence; Figure 42).

Figure 42. Analysis 5.1.5 Siltuximab versus placebo or standard care. Outcome: Serious adverse events



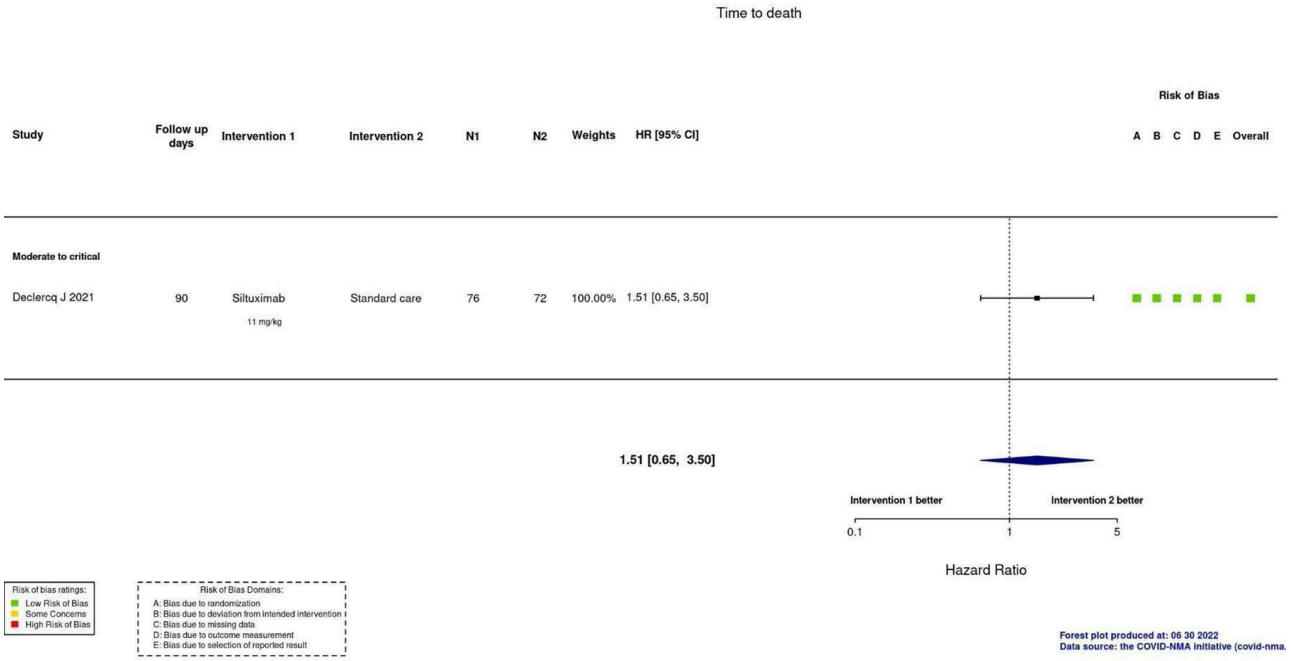
Important outcomes

No data are available for any important outcomes; time to clinical improvement, time to WHO-CPS level 7 or above.

Time to death

The evidence for an effect of siltuximab compared to standard care alone or placebo on time to death is very uncertain (HR 1.51, 95% CI 0.65 to 3.50; 1 RCT, 148 participants; absolute effect: 58 more per 1000 (from 42 fewer to 248 more; very low-certainty evidence; Figure 43).

Figure 43. Analysis 5.2.1 Siltuximab versus placebo or standard care. Outcome: Time to death



Levilimab versus placebo

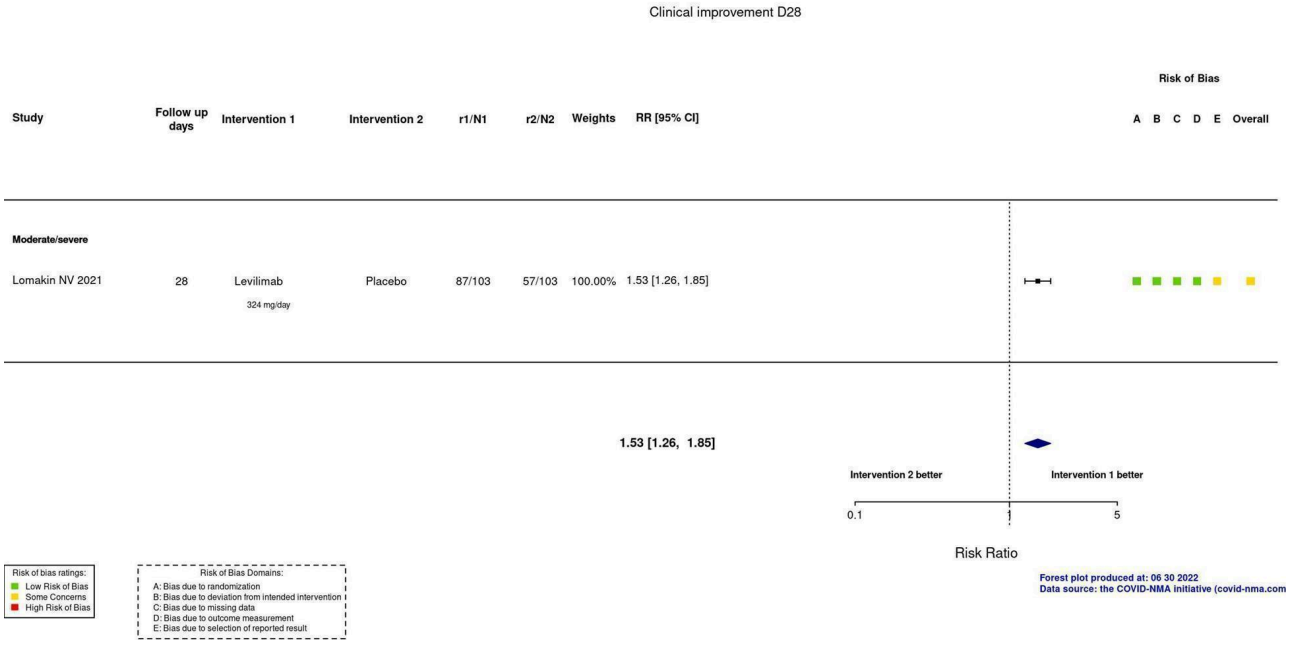
We have identified and included results from one trial evaluating the effect of levilimab versus placebo (Lomakin 2021). We report the certainty of the evidence for critical outcomes in Summary of findings 6. The WHO progression score (level 7 or above) at D60 or more and the important outcomes were not reported.

Critical outcomes

Clinical improvement

The evidence of levilimab's effect, compared to placebo, on clinical improvement at D28 is uncertain (RR 1.53, 95% CI 1.26 to 1.85; 1 RCT, 206 participants; absolute effect: 293 more per 1000 (from 144 more to 470 more); low-certainty evidence; Figure 44). Clinical improvement was defined as an improvement of two or more points from baseline on the 7-category ordinal scale of clinical status, or reaching categories 1 or 2 on Day 14.

Figure 44. Analysis 6.1.1 Levilimab versus placebo or standard care. Outcome: Clinical improvement 28



No available information was obtained about clinical improvement at D60 or more.

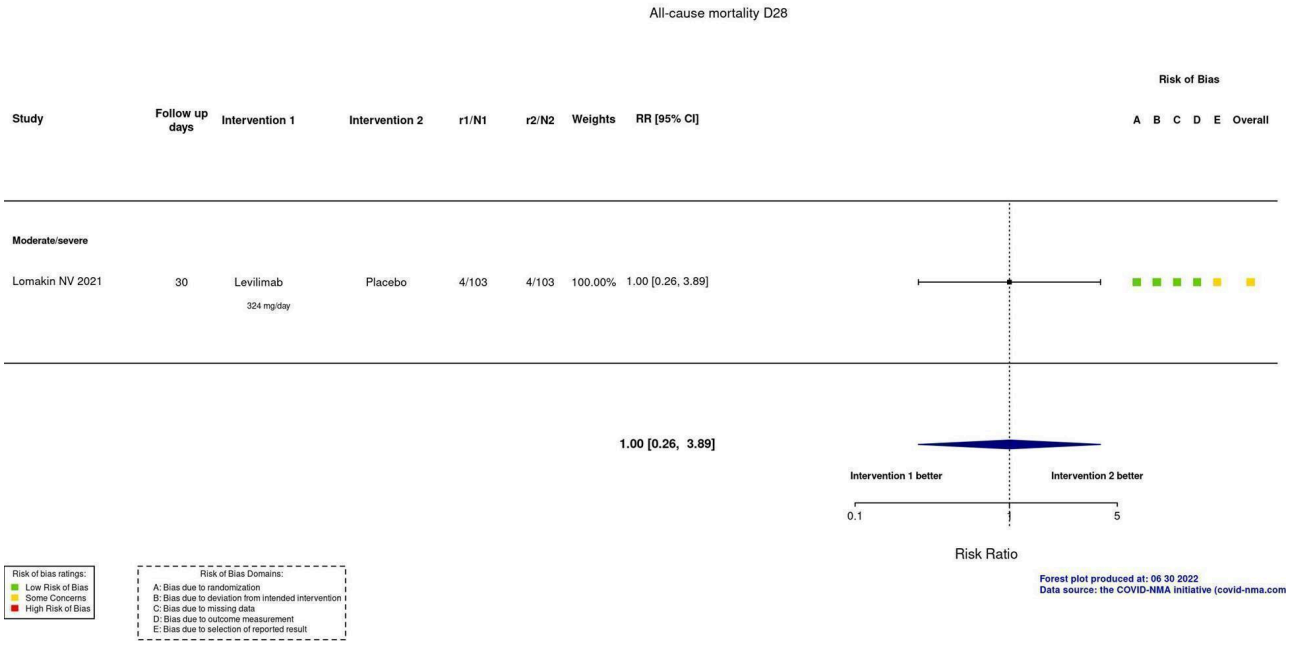
WHO Clinical Progression Score of level 7 or above (i.e. the proportion of participants with mechanical ventilation +/- additional organ support or death)

We did not obtain data on WHO-CPS of level 7 or above around D28, or for longer-term follow-up (≥ D60).

All-cause mortality

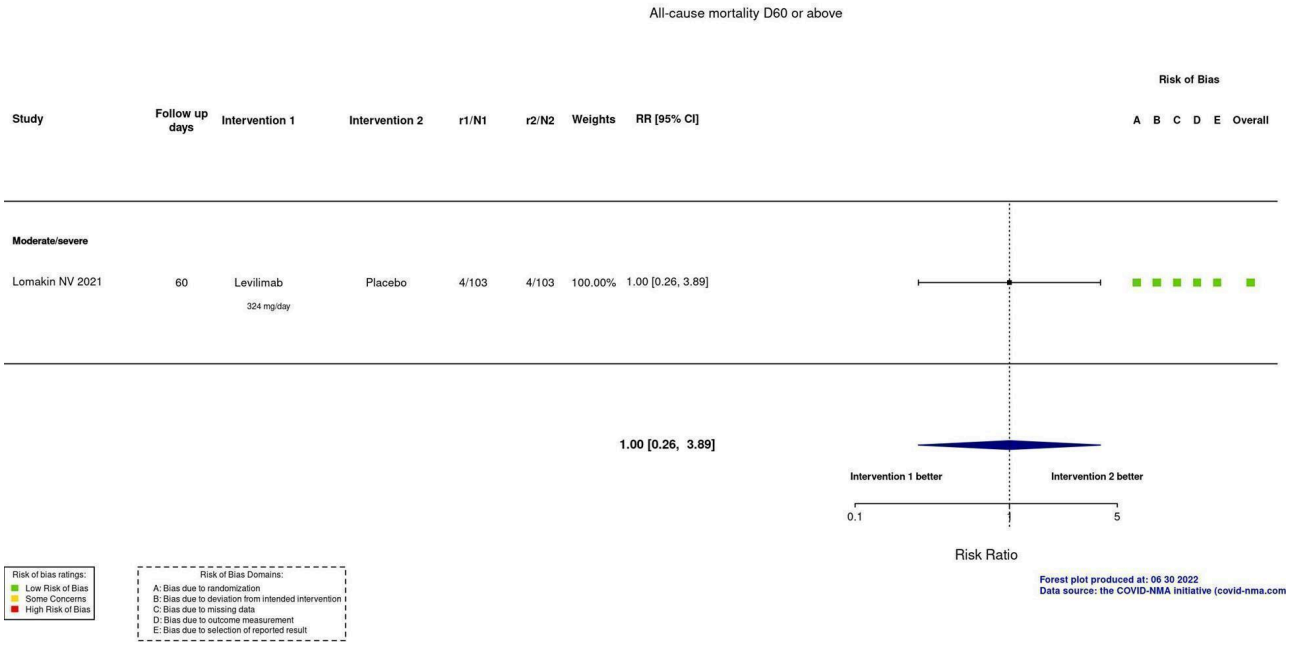
The evidence for an effect of levilimab compared to placebo on all-cause mortality at D28 is very uncertain (RR 1.00, 95% CI 0.26 to 3.89; 1 RCT, 206 participants; absolute effect: 0 fewer per 1000 (from 29 fewer to 112 more); very low-certainty evidence; Figure 45).

Figure 45. Analysis 6.1.2 Levilimab versus placebo or standard care. Outcome: All-cause mortality D28



The evidence of levilimab's effect, compared to placebo, on all-cause mortality at ≥ D60 is also very uncertain (RR 1.00, 95% CI 0.26 to 3.89; 1 RCT, 206 participants; absolute effect: 0 fewer per 1000 (from 29 fewer to 112 more); very low-certainty evidence; Figure 46).

Figure 46. Analysis 6.1.3 Levilimab versus placebo or standard care. Outcome: All-cause mortality D60

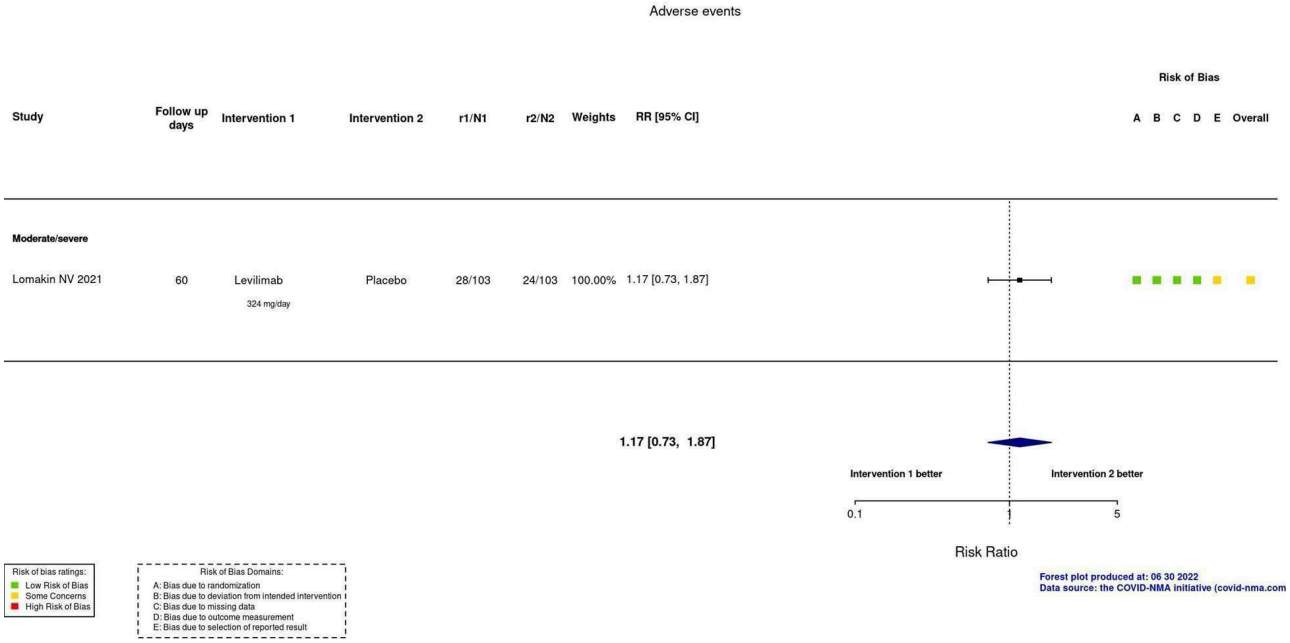


Adverse events

Adverse events were assessed by spontaneous reporting and active monitoring.

The evidence for an effect of levilimab compared to placebo on adverse events is uncertain (RR 1.17, 95% CI 0.73 to 1.87; 1 RCT, 206 participants; absolute effect 40 more per 1000 (from 63 fewer to 203 more); low-certainty evidence; Figure 47).

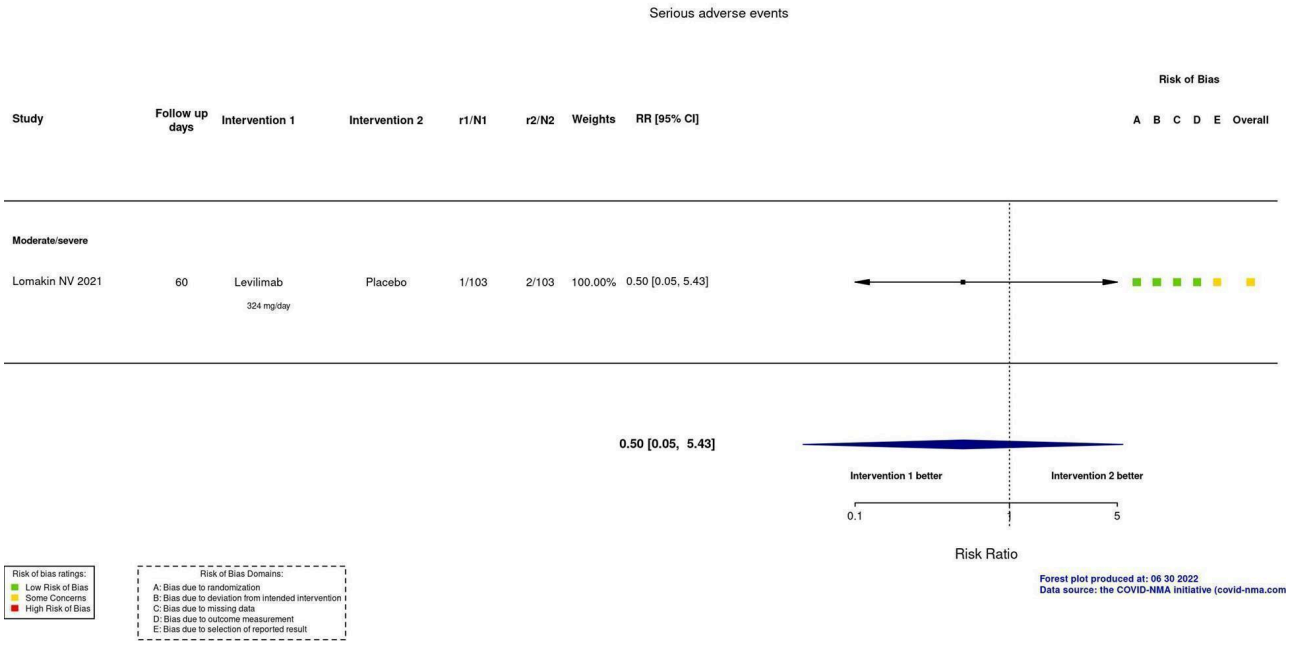
Figure 47. Analysis 6.1.4 Levilimab versus placebo or standard care. Outcome: Adverse events



Serious adverse events

The evidence for an effect of levilimab compared to placebo on serious adverse events is uncertain (RR 0.50, 95% CI 0.05 to 5.43; 1 RCT, 206 participants; absolute effect 10 fewer per 1000 (from 18 fewer to 86 more); low-certainty evidence; Figure 48).

Figure 48. Analysis 6.1.5 Levilimab versus placebo or standard care. Outcome: Serious adverse events



Important outcomes

None of the included studies reported any of the important outcomes, namely time to clinical improvement, time to WHO score level 7 and above and time to death.

Investigation of heterogeneity

The limited number of RCTs that provided results and the absence of variation across trials in some variables such as age and gender prevented us from performing all the preplanned subgroup analyses (see Differences between protocol and review). We also considered two post hoc subgroup analyses based on the type of funding and the presence of conflicts of interest.

Overall, subgroup analyses were possible only for the following comparisons.

- Tocilizumab
  - Analysis by type of funding: see Figure 49, Figure 50, Figure 51, Figure 52, Figure 53, and Figure 54.
  - Analysis by type of location: see Figure 55, Figure 56, Figure 57,Figure 58, Figure 59, and Figure 60.
  - Analysis by conflict of interests see: Figure 61, Figure 62, Figure 63, Figure 64, Figure 65, and Figure 66.
  - Analysis by patient severity see: Figure 67, Figure 68, Figure 69, Figure 70, and Figure 71.
- Sarilumab
  - Analysis by type of funding see: Figure 72, Figure 73, Figure 74, Figure 75, Figure 76, and Figure 77.
  - Analysis by type of location see: Figure 78, Figure 79, Figure 80, and Figure 81.
  - Analysis by conflict of interests see: Figure 82, Figure 83, Figure 84, Figure 85, Figure 86, and Figure 87.
- Clazakizumab
  - Analysis by conflict of interests: see Figure 88, Figure 89, and Figure 90.

Figure 49. Subgroup analysis. 1.3.1 Funding. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28

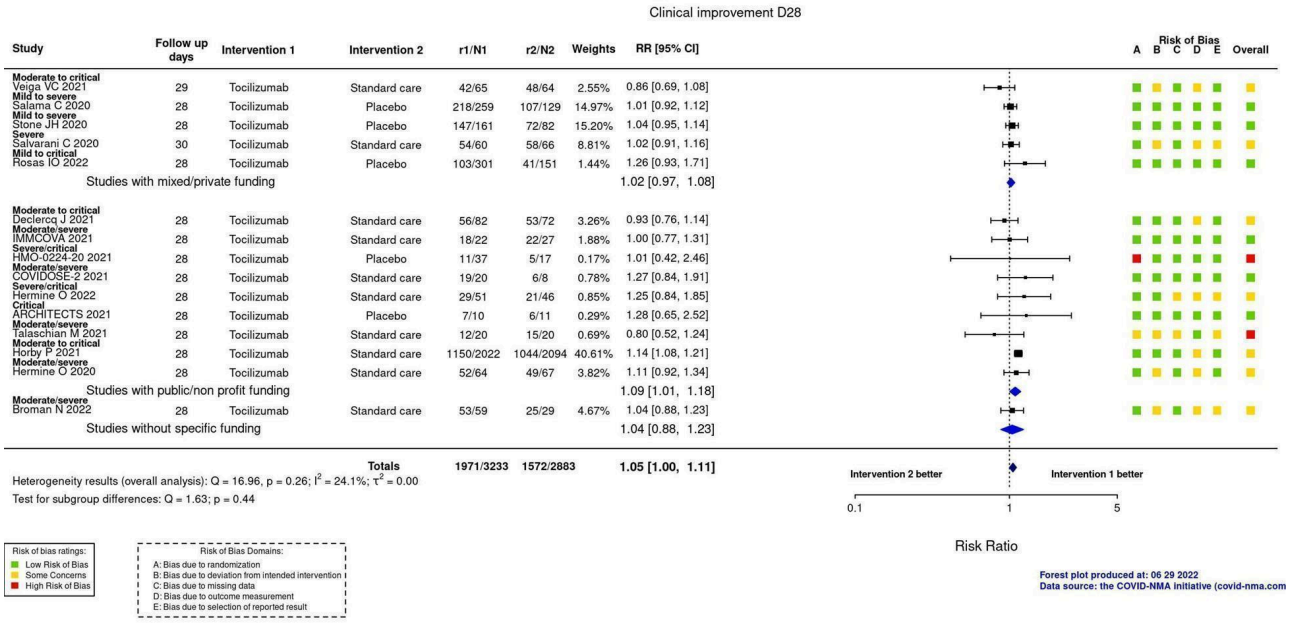


Figure 50. Subgroup analysis.1.3.2 Funding. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

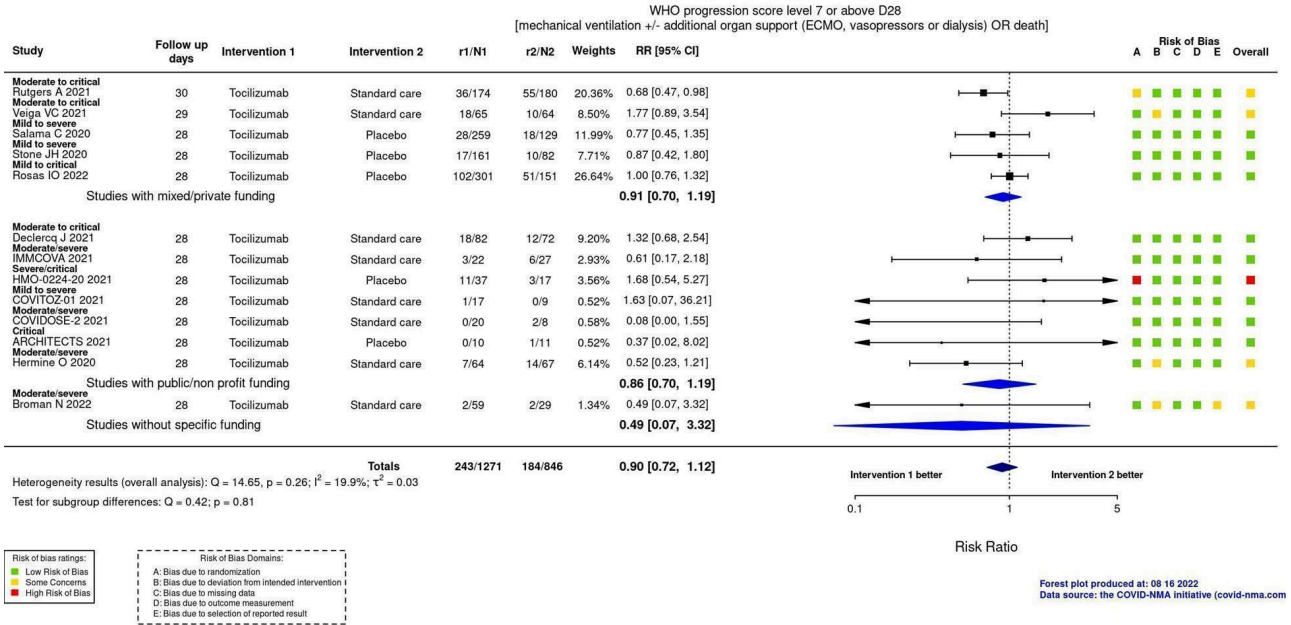


Figure 51. Subgroup analysis.1.3.3 Funding. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28

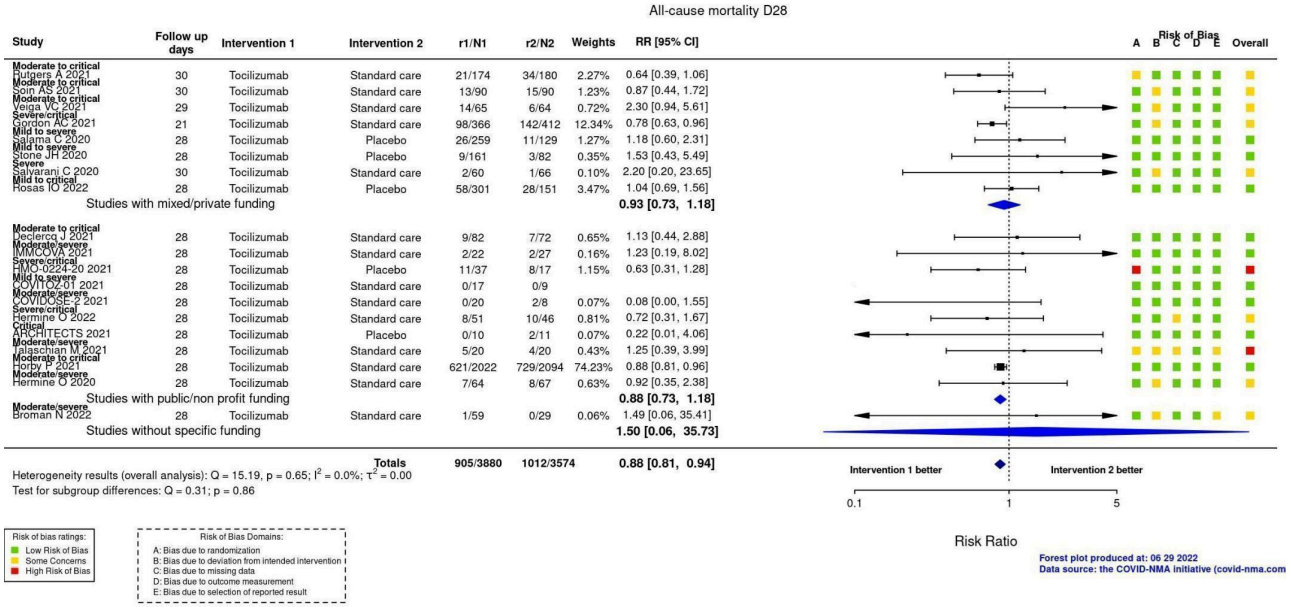


Figure 52. Subgroup analysis. 1.3.4 Funding. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

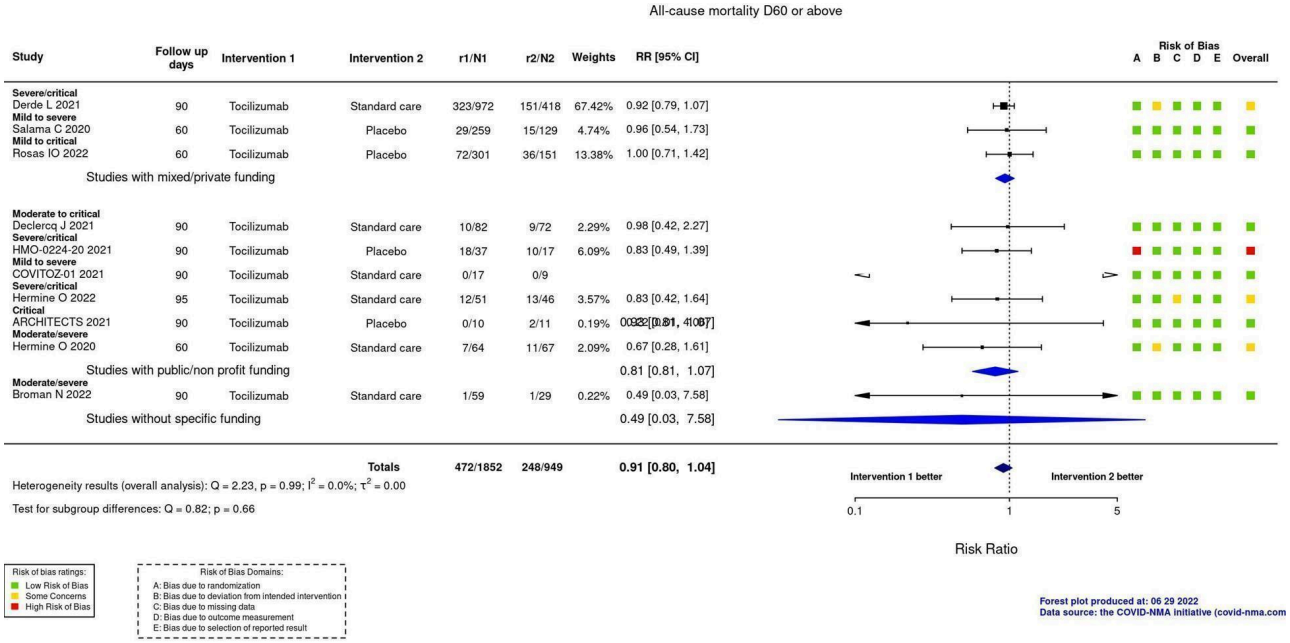


Figure 53. Subgroup analysis. 1.3.5 Funding. Tocilizumab versus placebo or standard care. Outcome: Adverse events

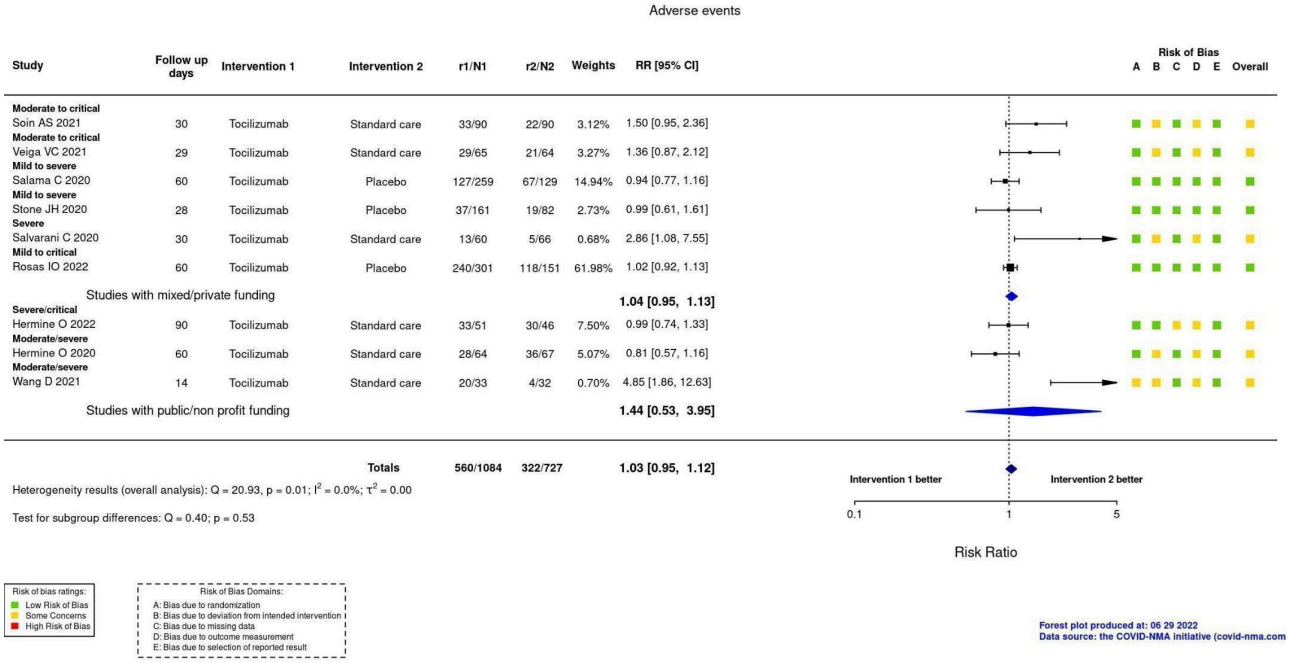


Figure 54. Subgroup analysis. 1.3.6 Funding. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events

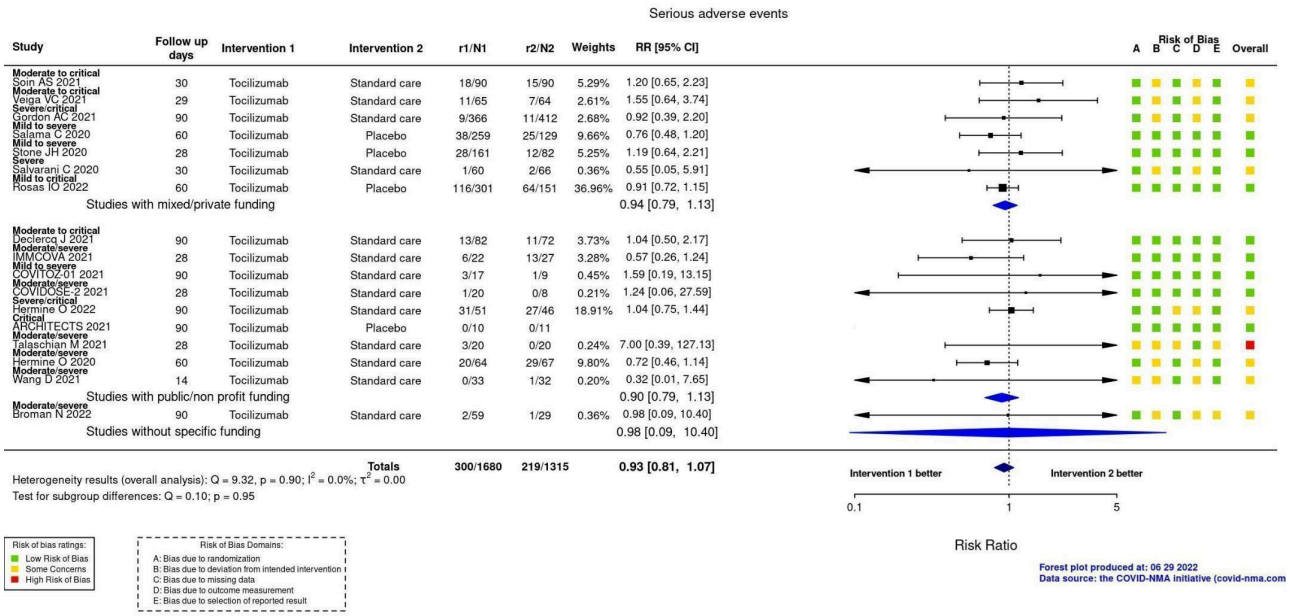


Figure 55. Subgroup analysis. 1.4.1 Location. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28

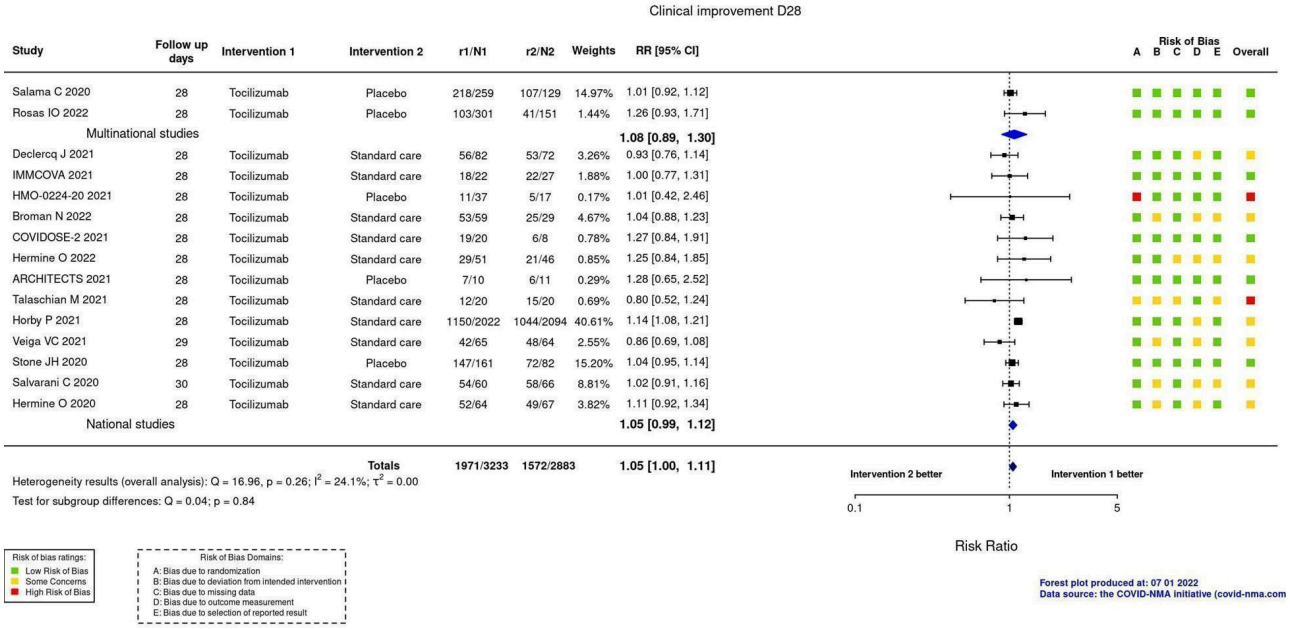


Figure 56. Subgroup analysis. 1.4.2 Location. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

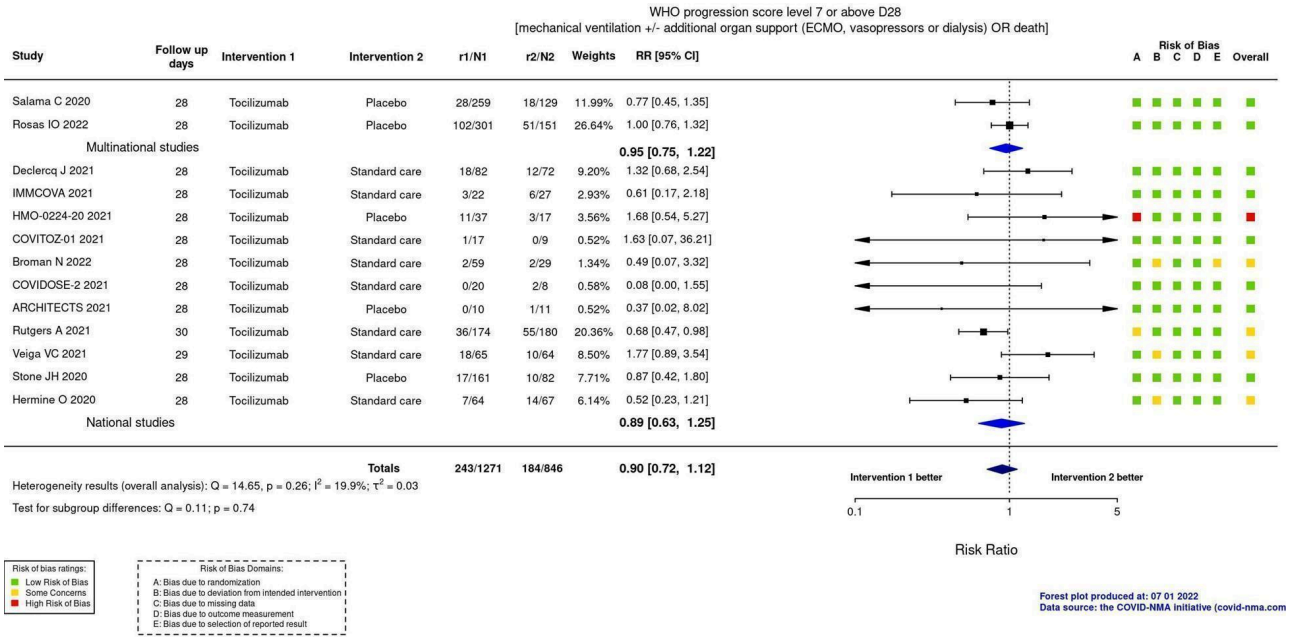


Figure 57. Subgroup analysis.1.4.3 Location. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28

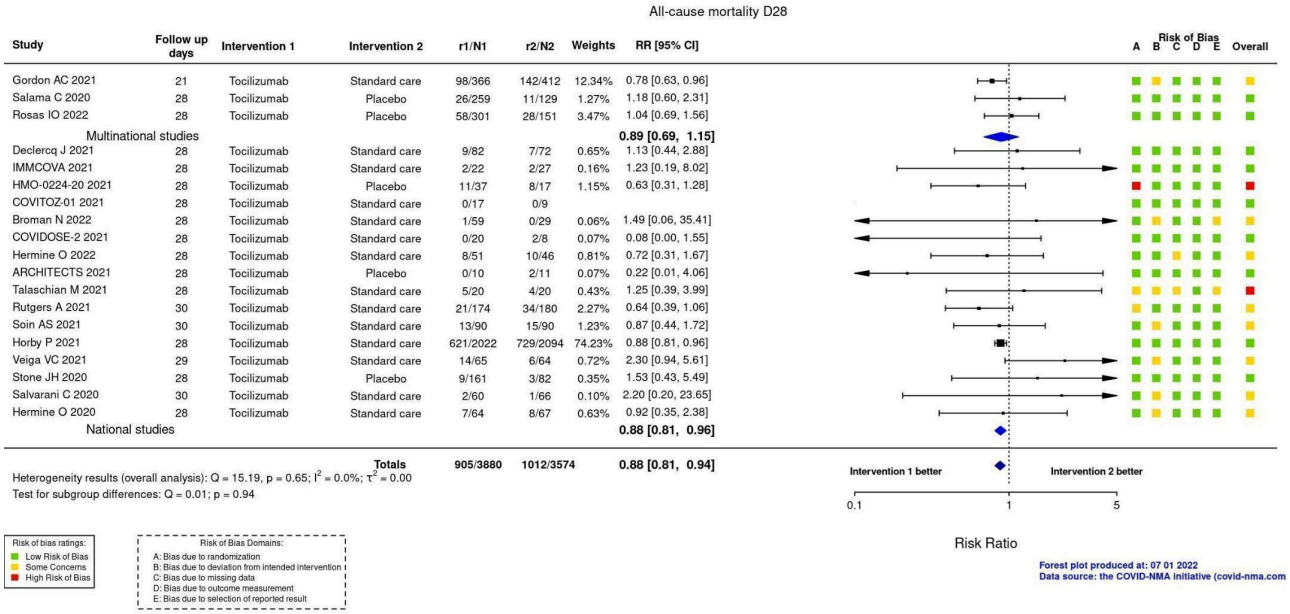


Figure 58. Subgroup analysis. 1.4.4 Location. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

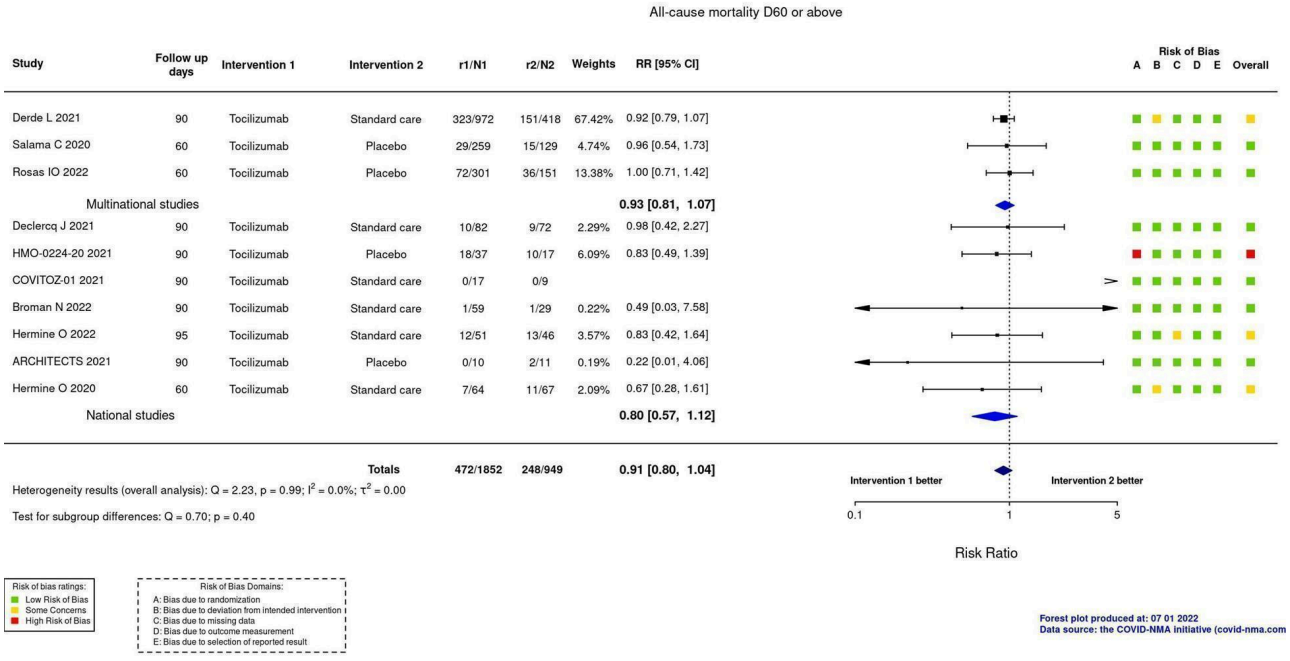


Figure 59. Subgroup analysis. 1.4.5 Location. Tocilizumab versus placebo or standard care. Outcome: Adverse events

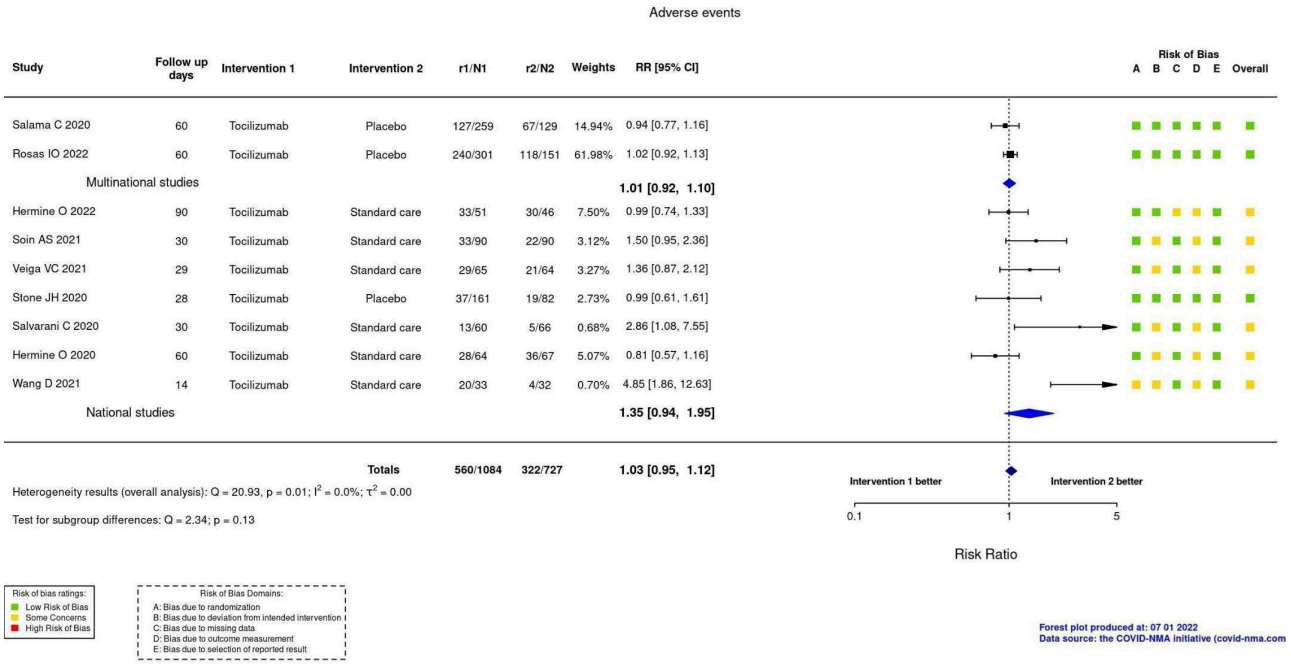


Figure 60. Subgroup analysis. 1.4.6 Location. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events

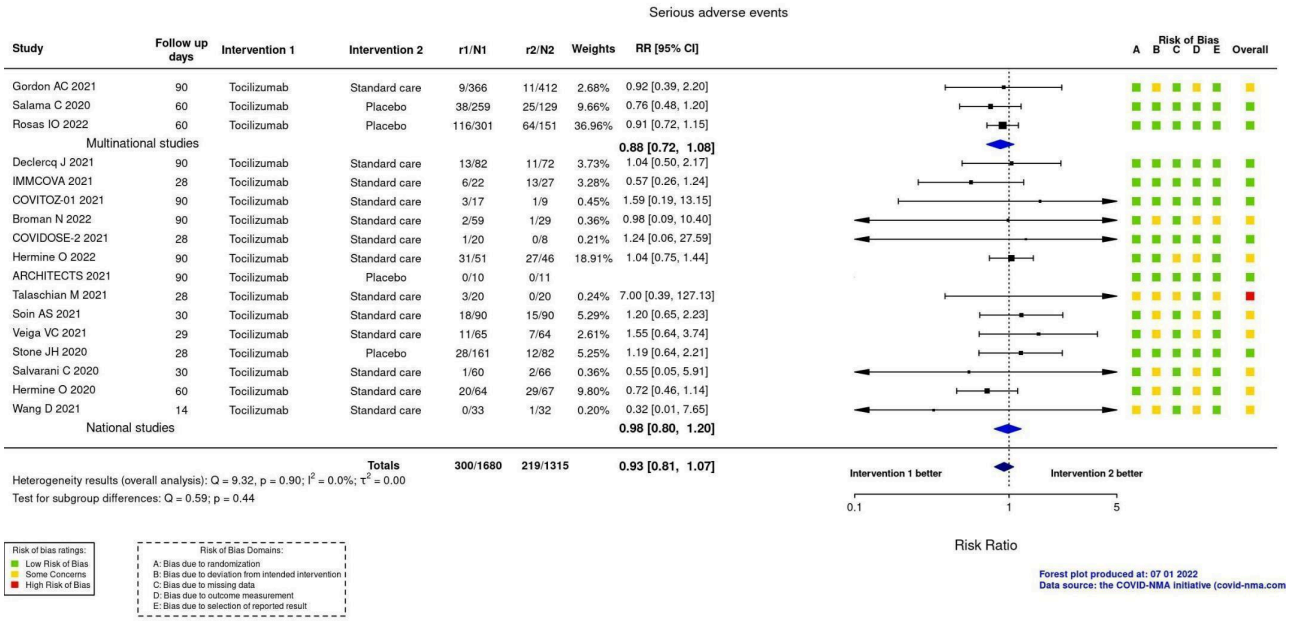


Figure 61. Subgroup analysis. 1.5.1 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28

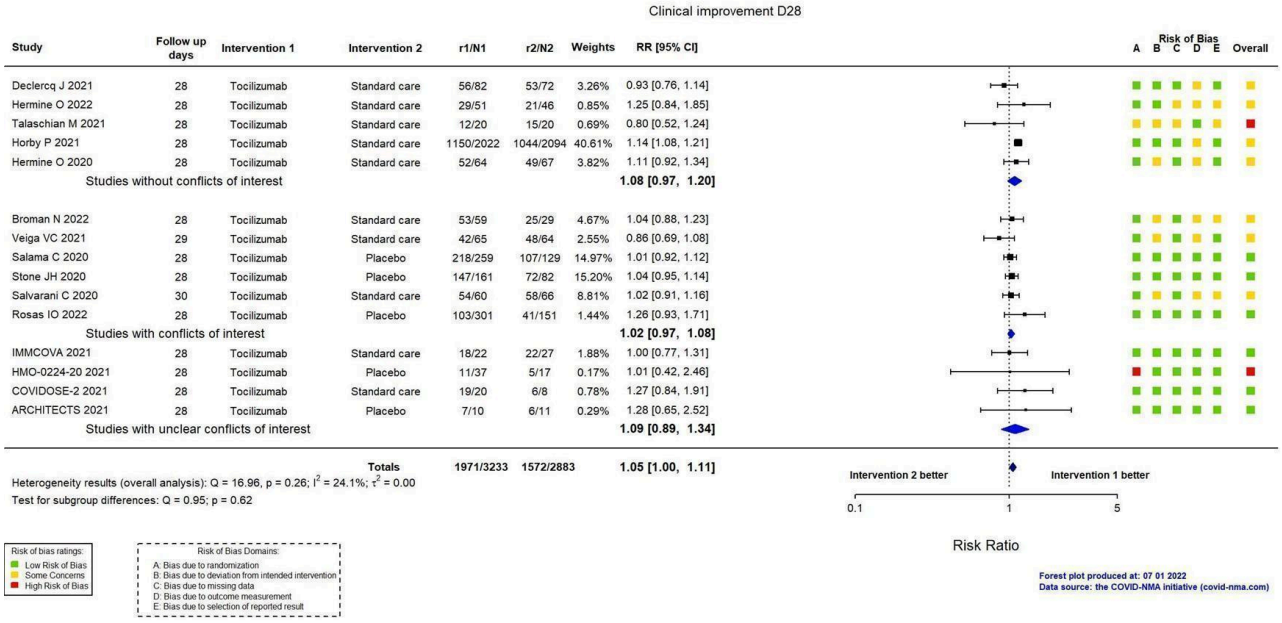


Figure 62. Subgroup analysis. 1.5.2 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

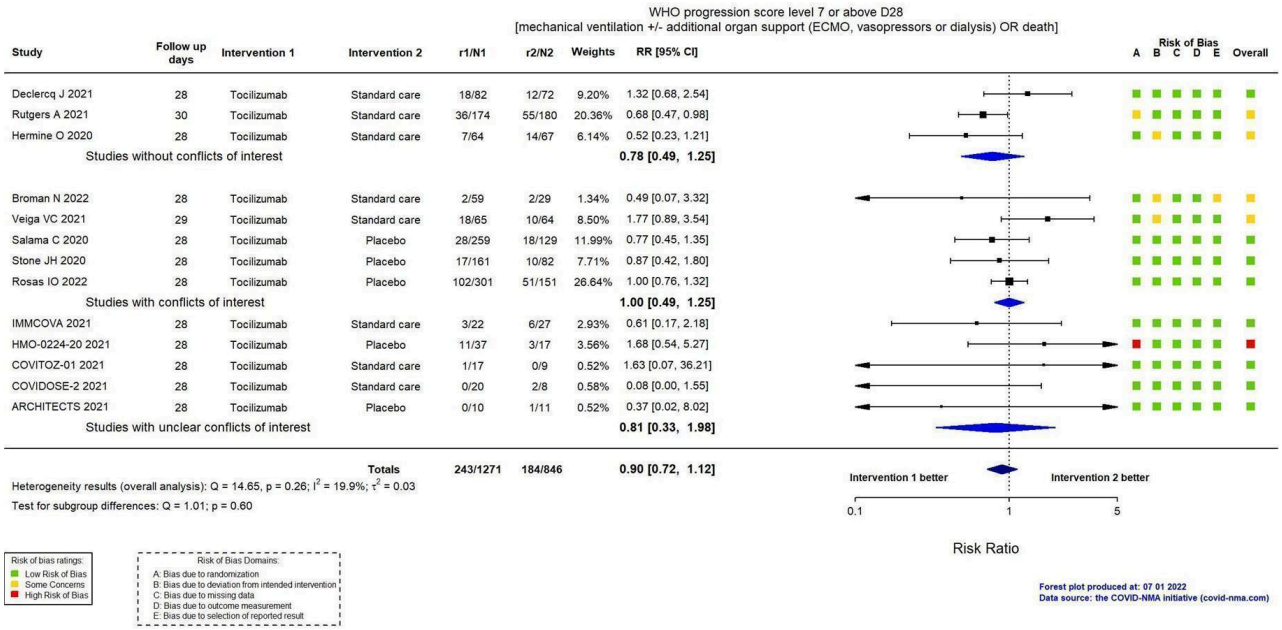


Figure 63. Subgroup analysis. 1.5.3 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28

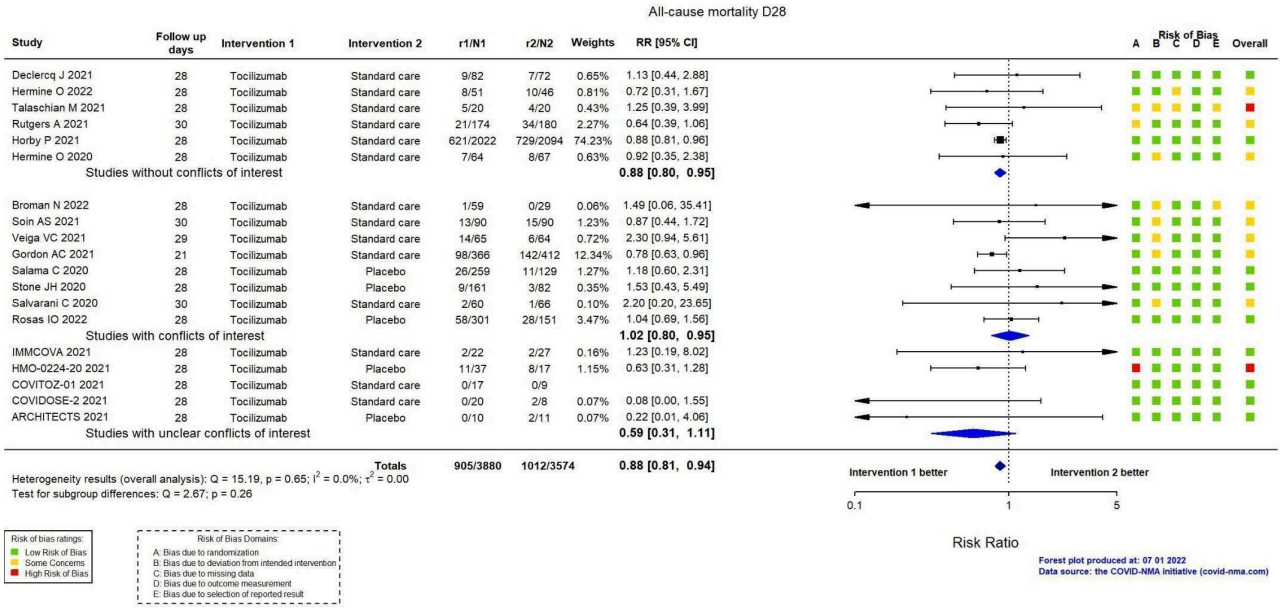


Figure 64. Subgroup analysis. 1.5.4 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

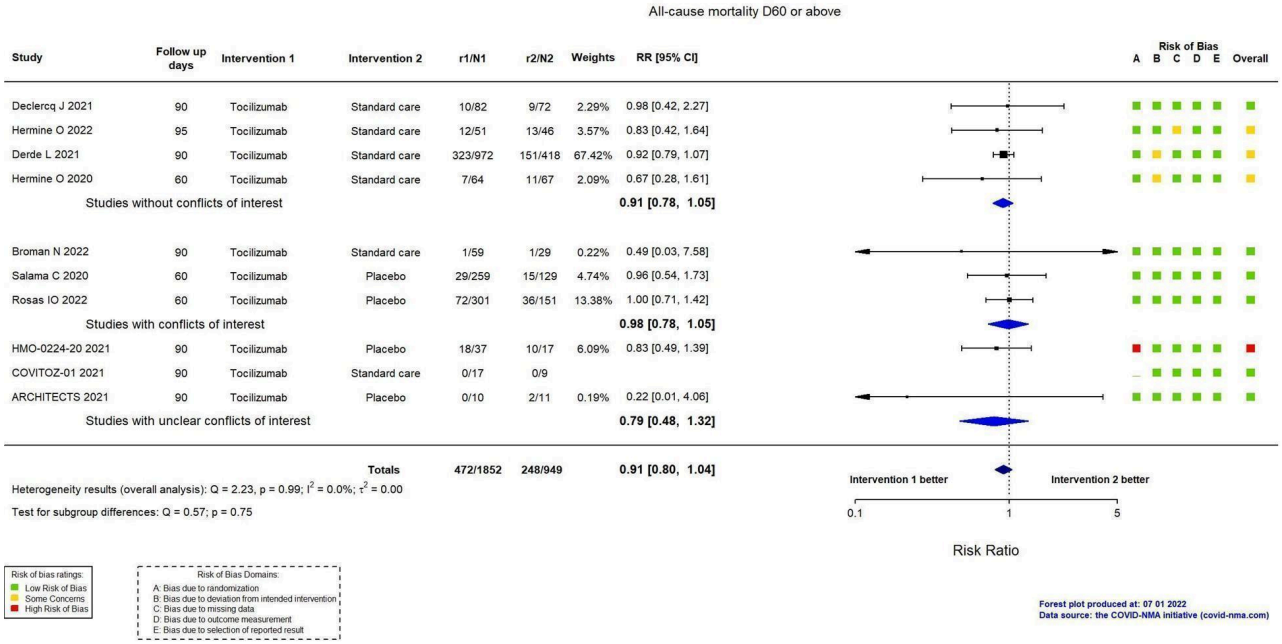


Figure 65. Subgroup analysis. 1.5.5 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Adverse events

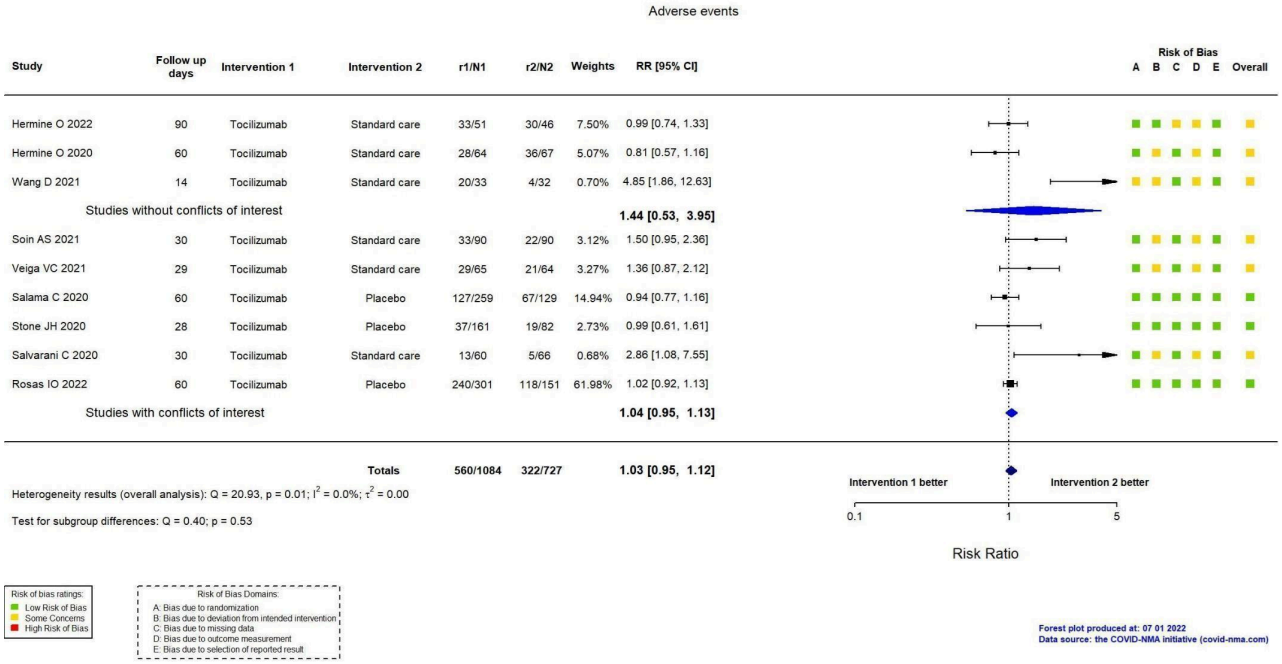


Figure 66. Subgroup analysis. 1.5.6 Conflict of Interests. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events

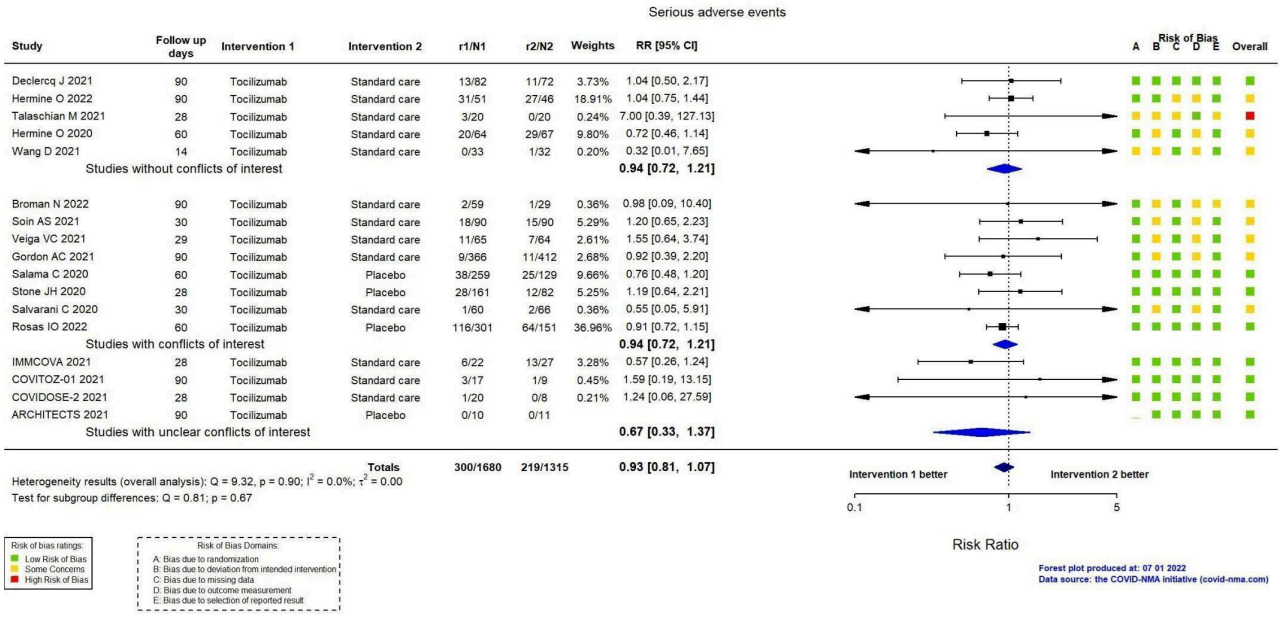


Figure 67. Subgroup analysis. 1.6.1 Severity. Tocilizumab versus placebo or standard care. Outcome: Clinical improvement D28

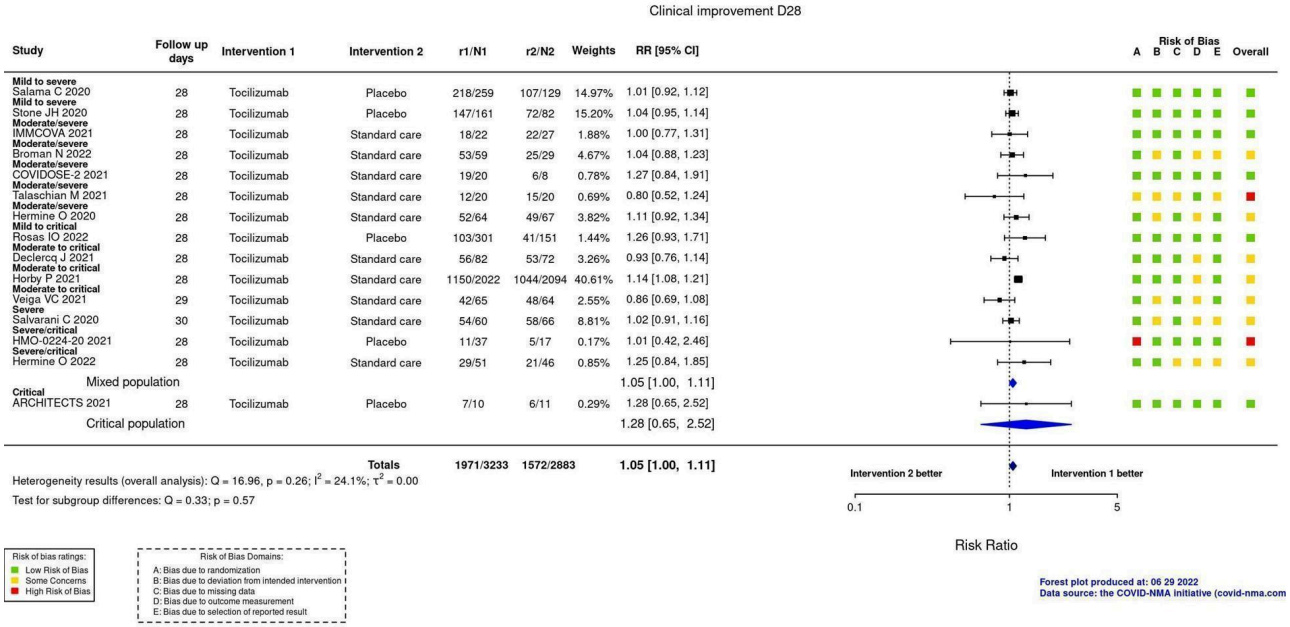


Figure 68. Subgroup analysis. 1.6.2 Severity. Tocilizumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

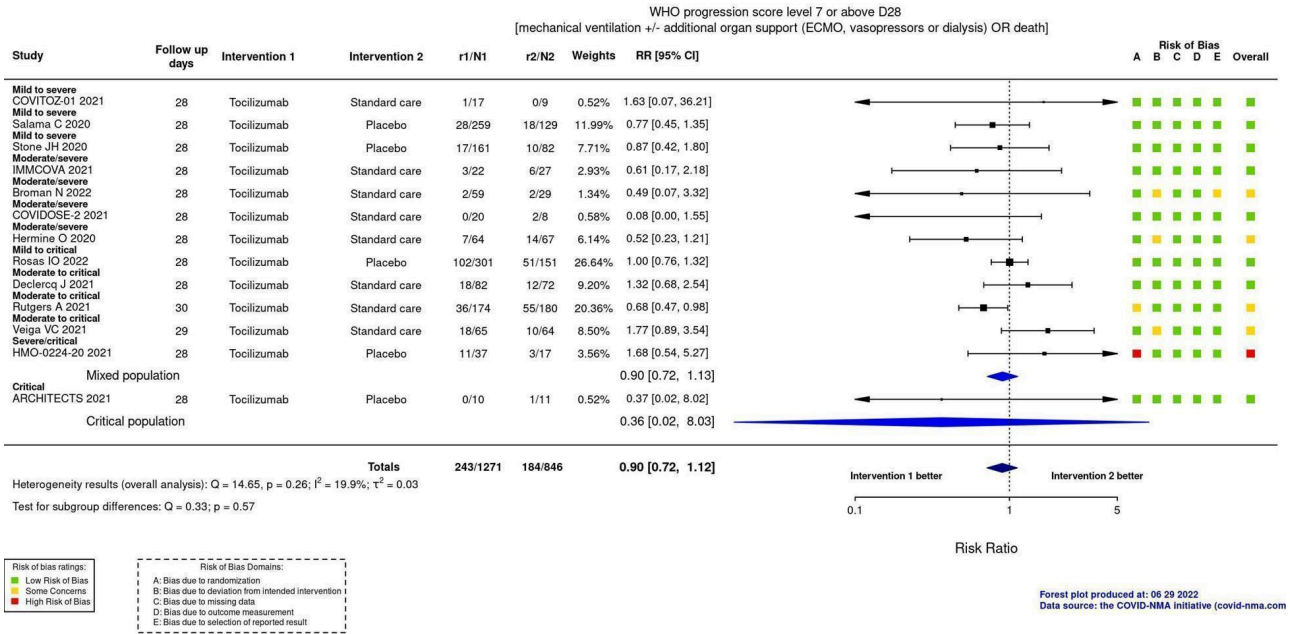


Figure 69. Subgroup analysis. 1.6.3 Severity. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D28

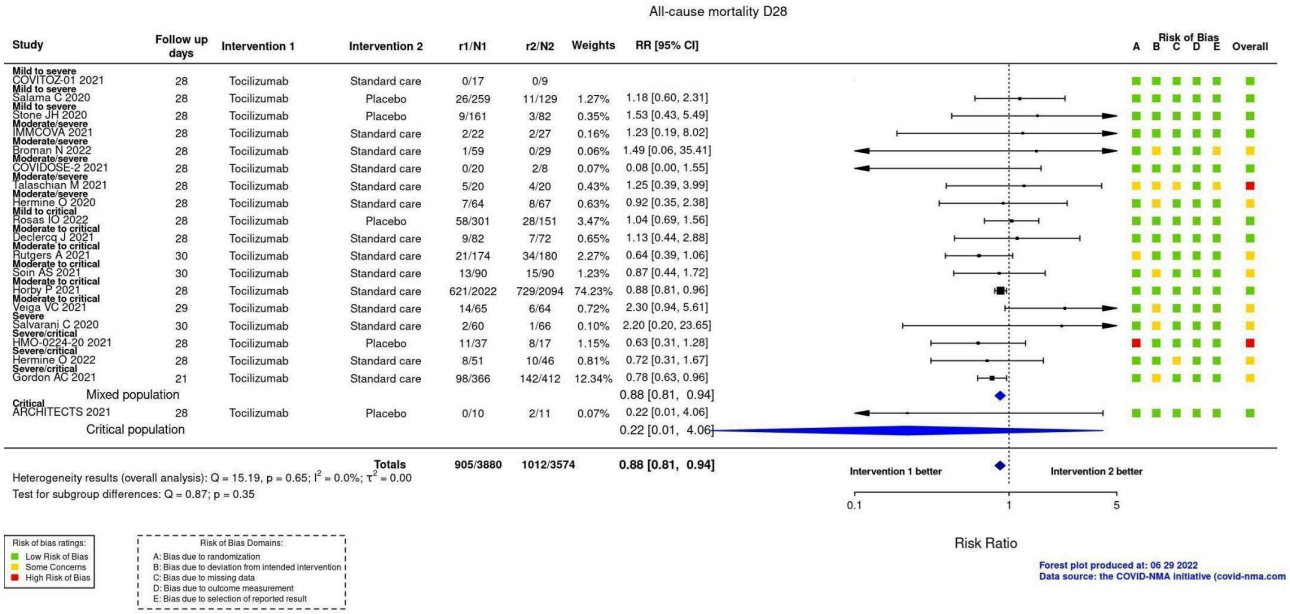


Figure 70. Subgroup analysis. 1.6.4 Severity. Tocilizumab versus placebo or standard care. Outcome: All-cause mortality D60

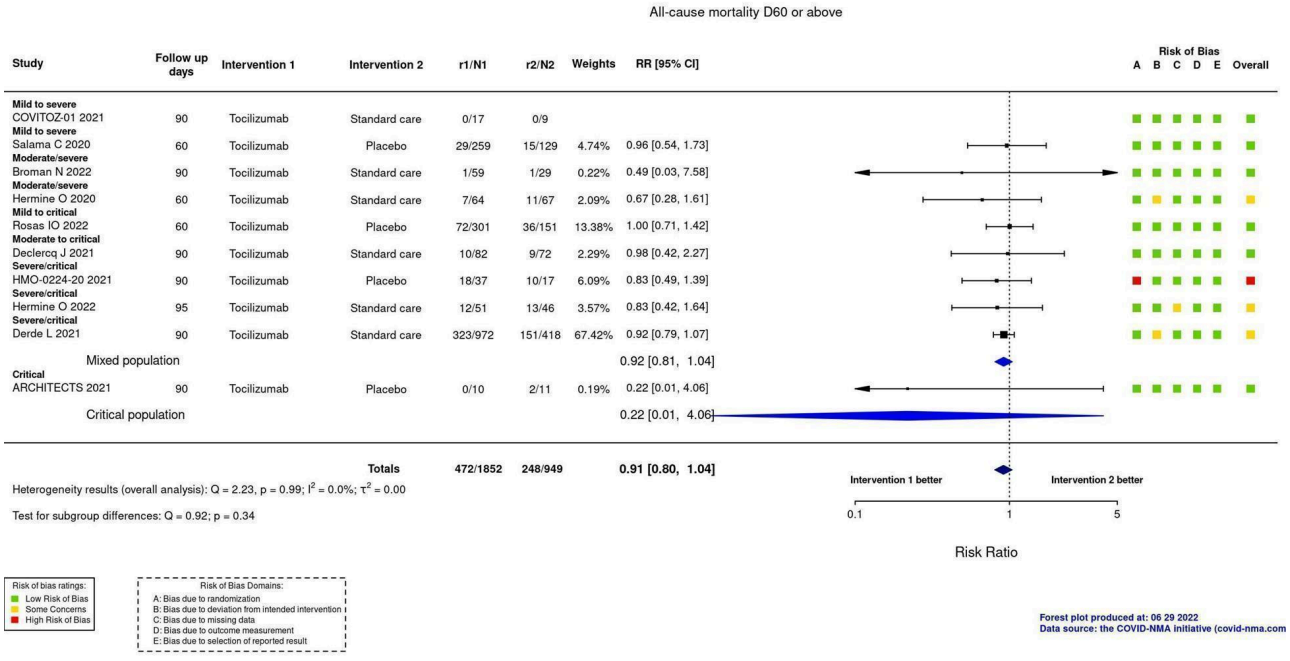


Figure 71. Subgroup analysis. 1.6.5 Severity. Tocilizumab versus placebo or standard care. Outcome: Serious adverse events

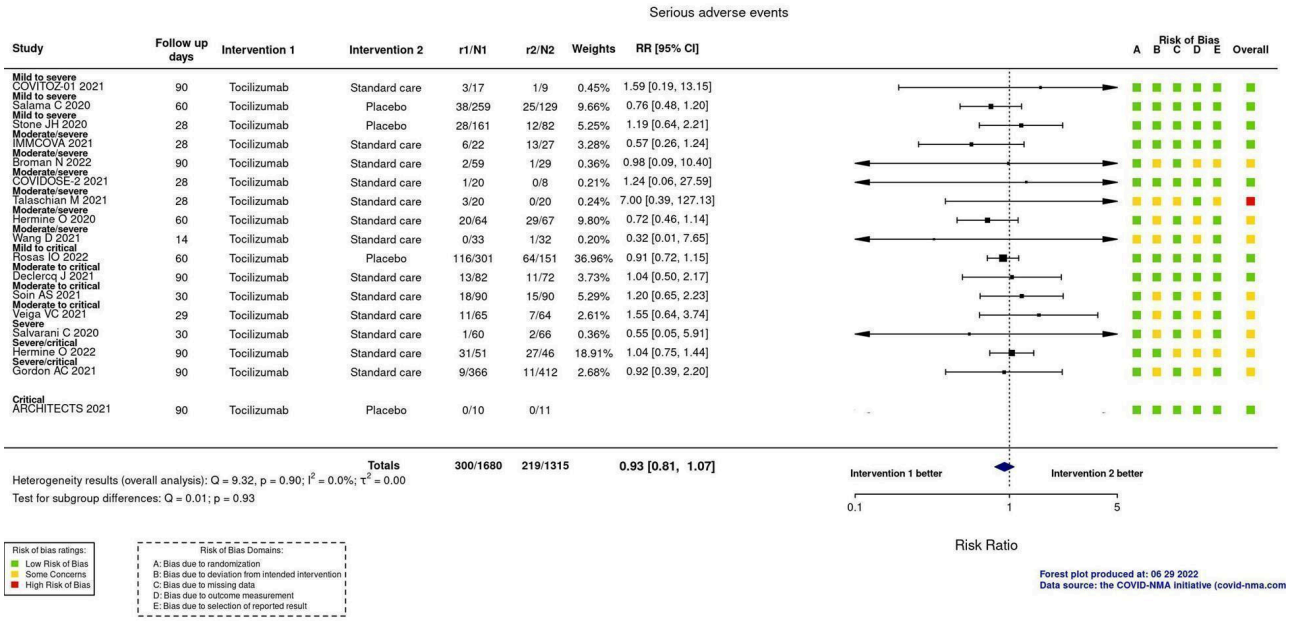


Figure 72. Subgroup analysis. 2.3.1 Funding. Sarilumab versus placebo or standard care. Outcome: Clinical improvement D28

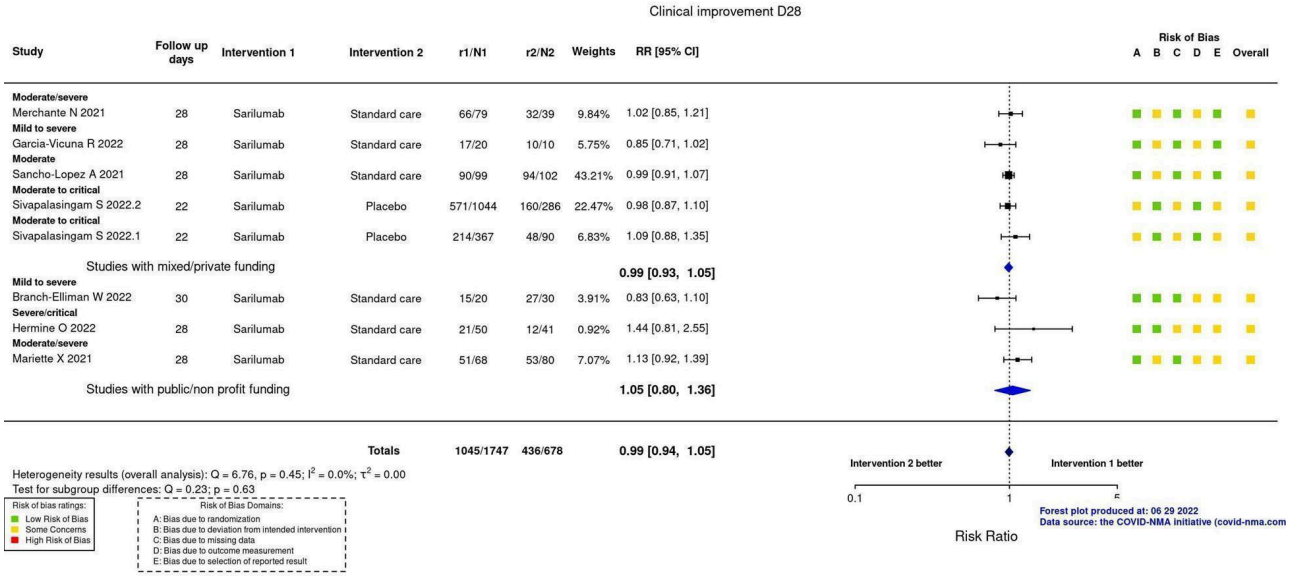


Figure 73. Subgroup analysis.2.3.3 Funding. Sarilumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

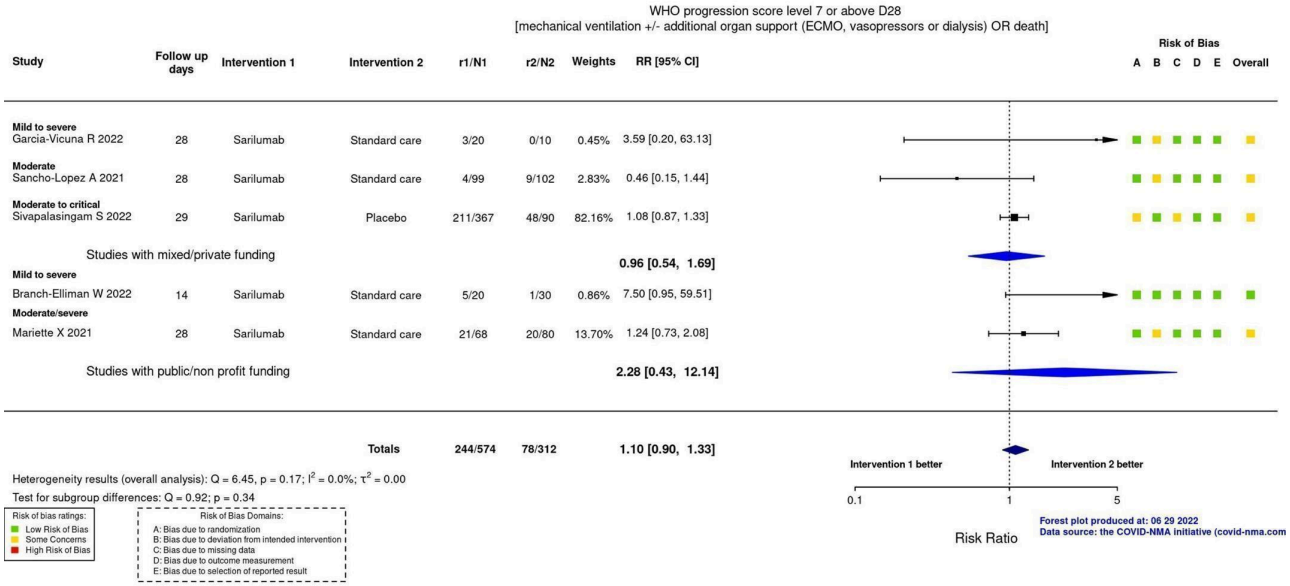


Figure 74. Subgroup analysis.2.3.4 Funding. Sarilumab versus placebo or standard care. Outcome: All-cause mortality D28

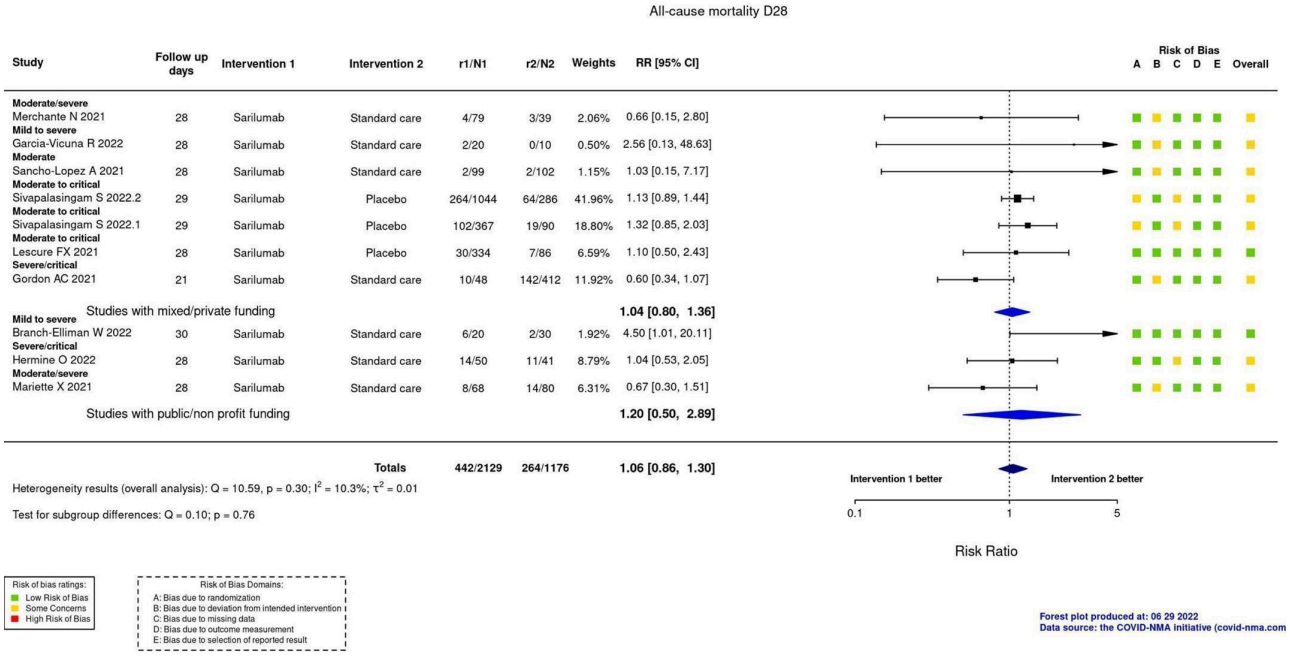


Figure 75. Subgroup analysis. 2.3.5 Funding. Sarilumab versus placebo or standard care. Outcome: All-cause mortality D60

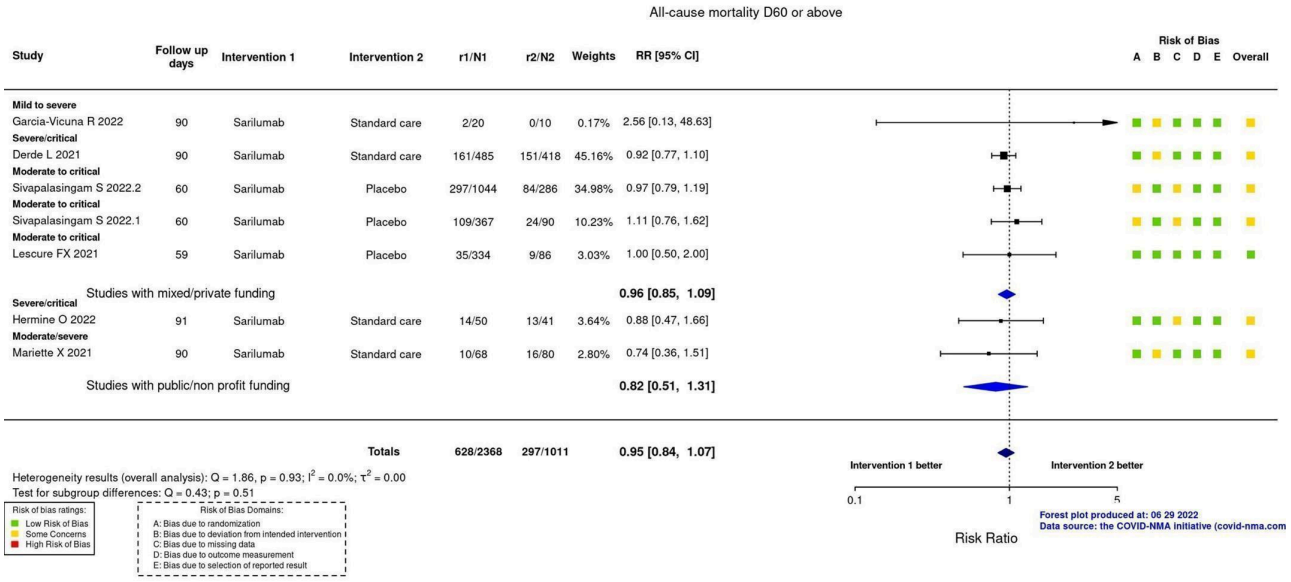


Figure 76. Subgroup analysis. 2.3.6 Funding. Sarilumab versus placebo or standard care. Outcome: Adverse events

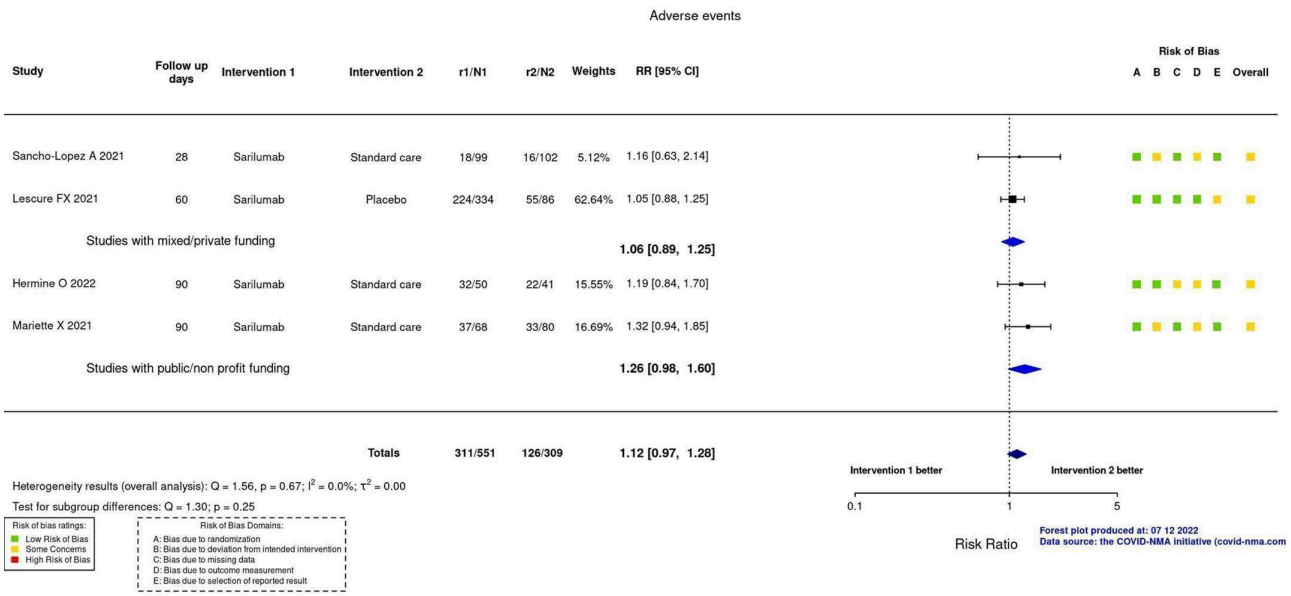


Figure 77. Subgroup analysis. 2.3.7 Funding. Sarilumab versus placebo or standard care. Outcome: Serious adverse events

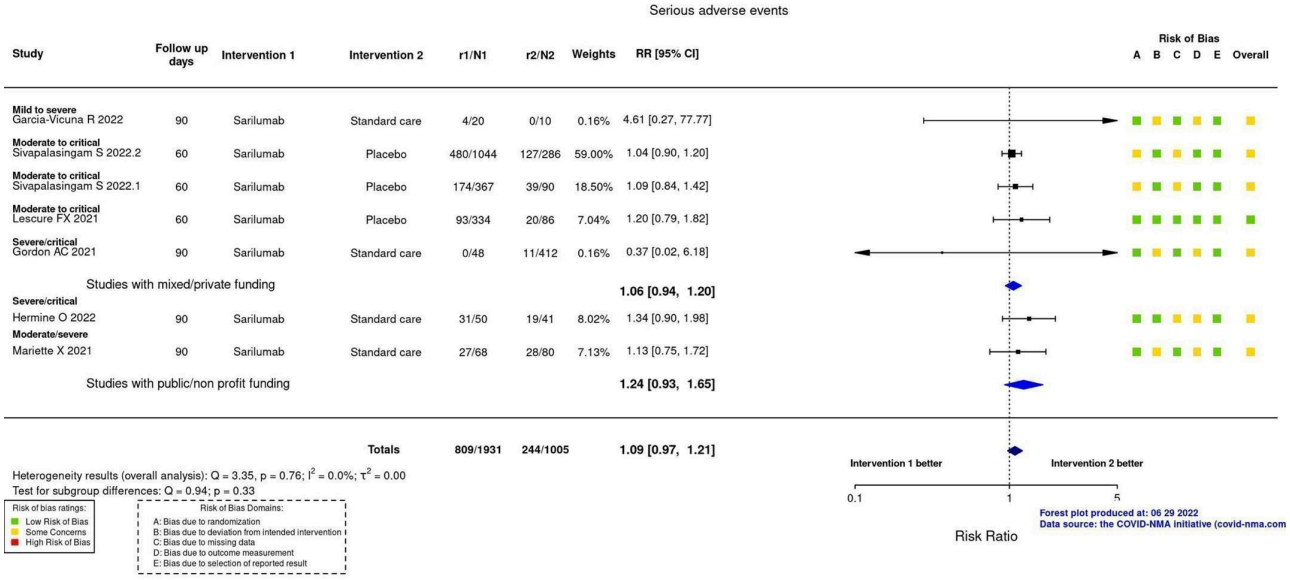


Figure 78. Subgroup analysis.2.4.1 Location. Sarilumab versus placebo or standard care. Outcome: All-cause mortality D28

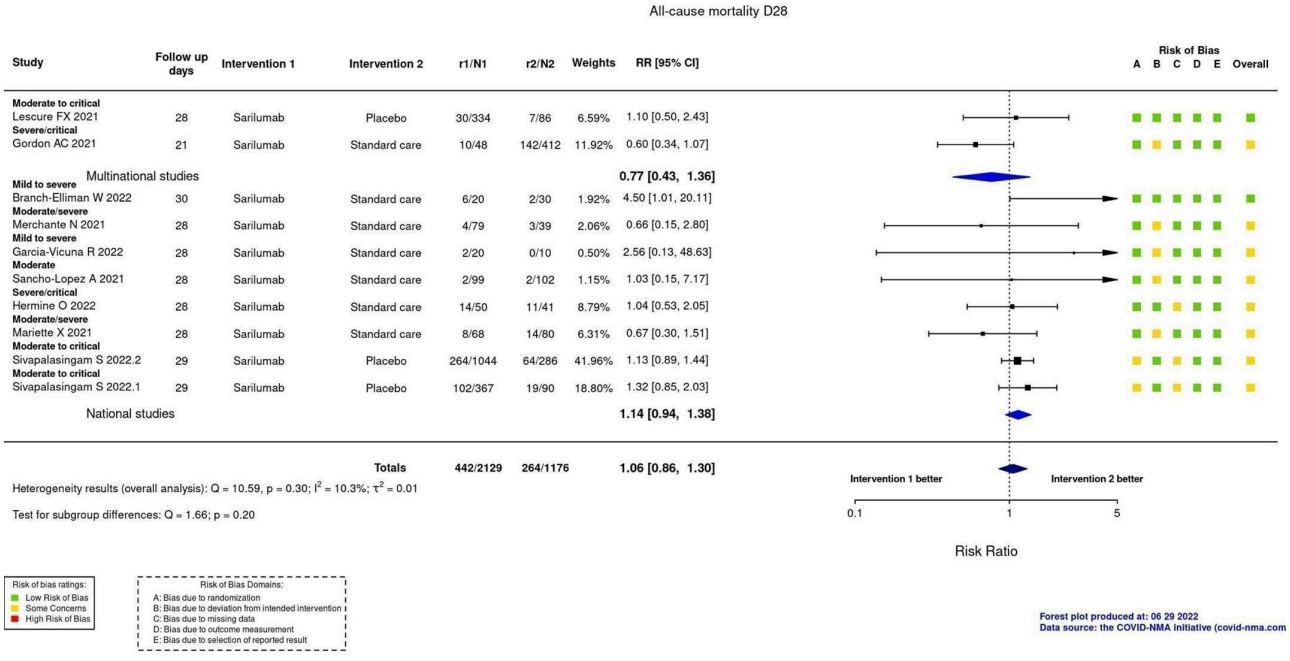


Figure 79. Subgroup analysis. 2.4.2 Location. Sarilumab versus placebo or standard care. Outcome: All-cause mortality D60

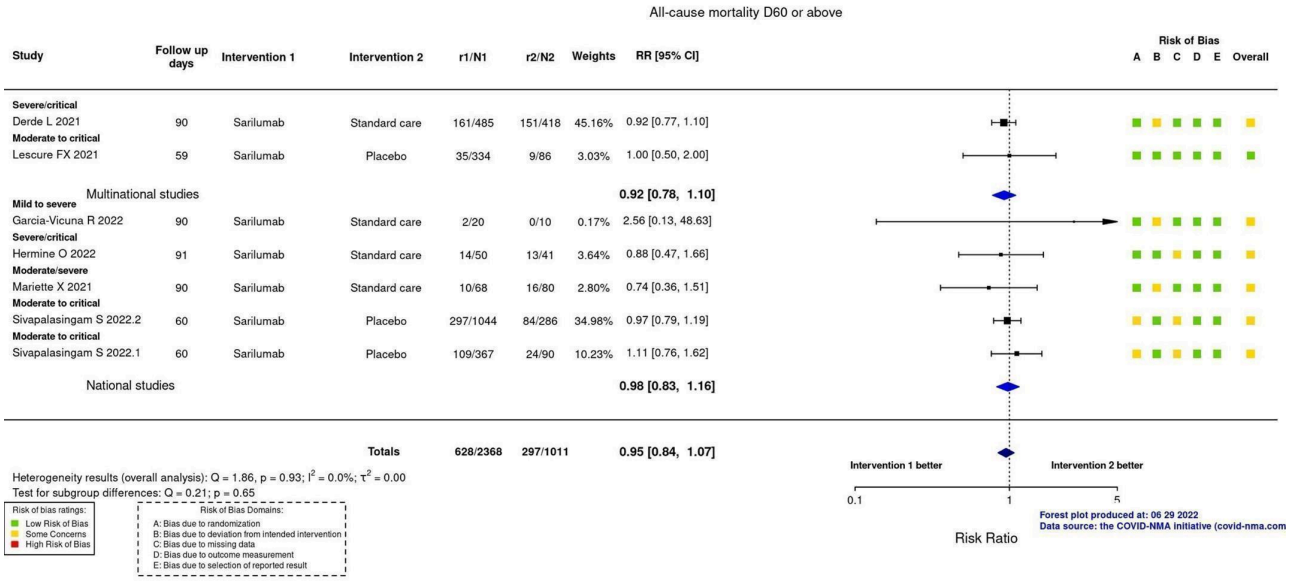


Figure 80. Subgroup analysis. 2.4.3 Location. Sarilumab versus placebo or standard care. Outcome: Adverse events

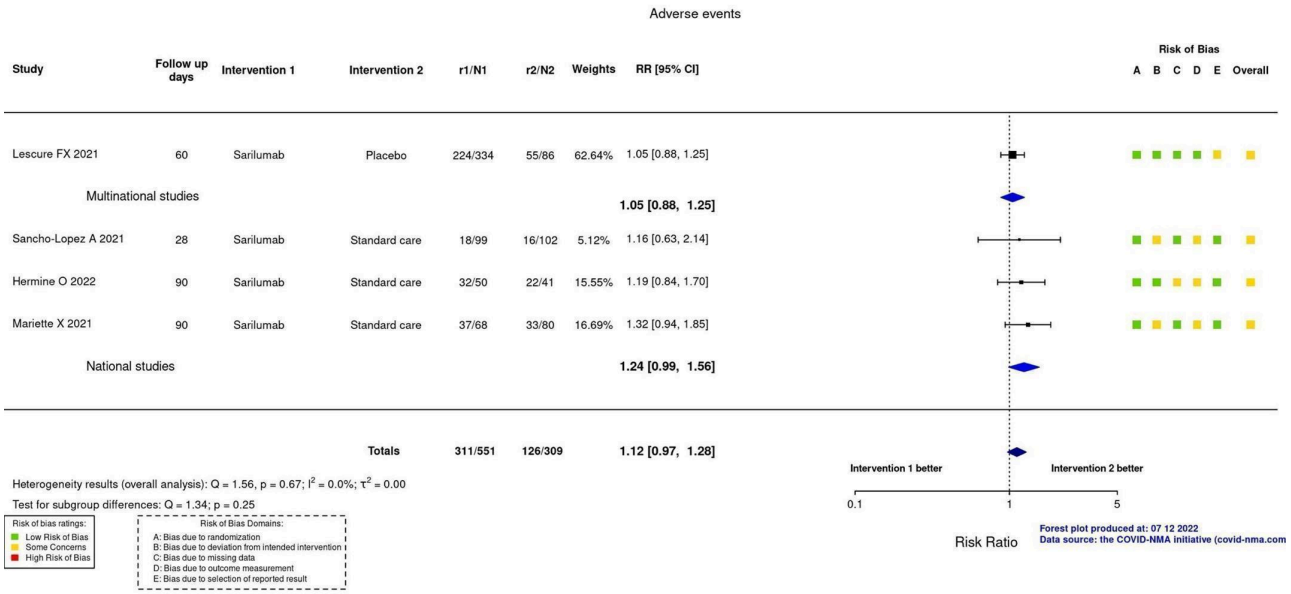


Figure 81. Subgroup analysis. 2.4.4 Location. Sarilumab versus placebo or standard care. Outcome: Serious adverse events

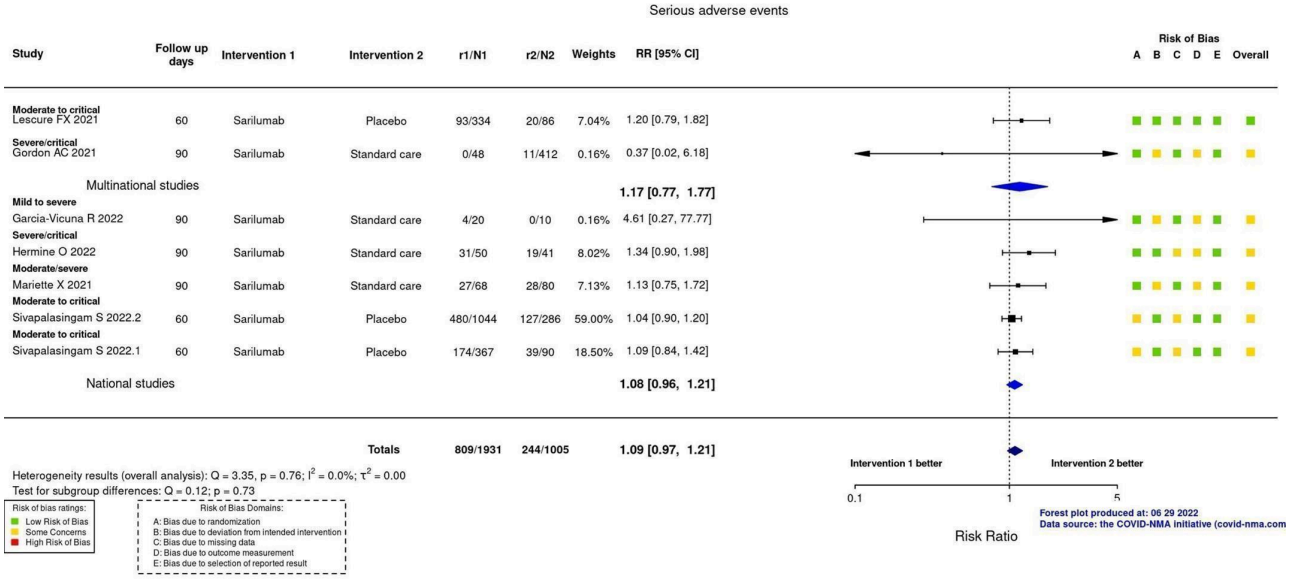


Figure 82. Subgroup analysis. 2.5.1 Conflict of Interests. Sarilumab versus placebo or standard care. Outcome: Clinical improvement D28

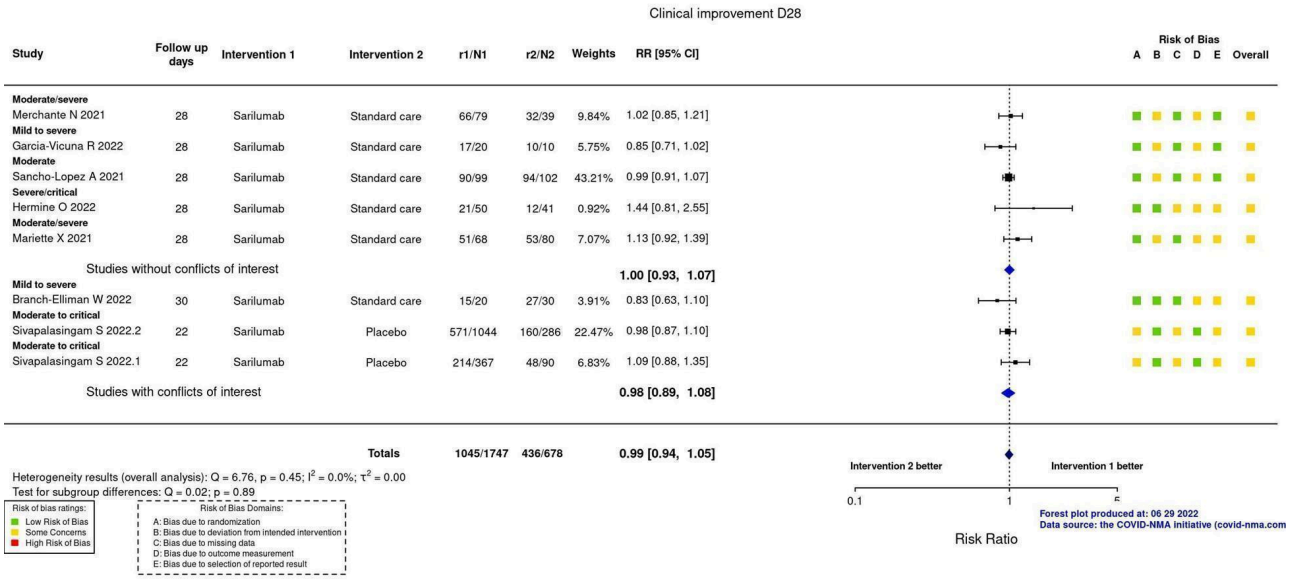


Figure 83. Subgroup analysis. 2.5.2 Conflict of Interests. Sarilumab versus placebo or standard care. Outcome: WHO progression score (level 7 or above) D28

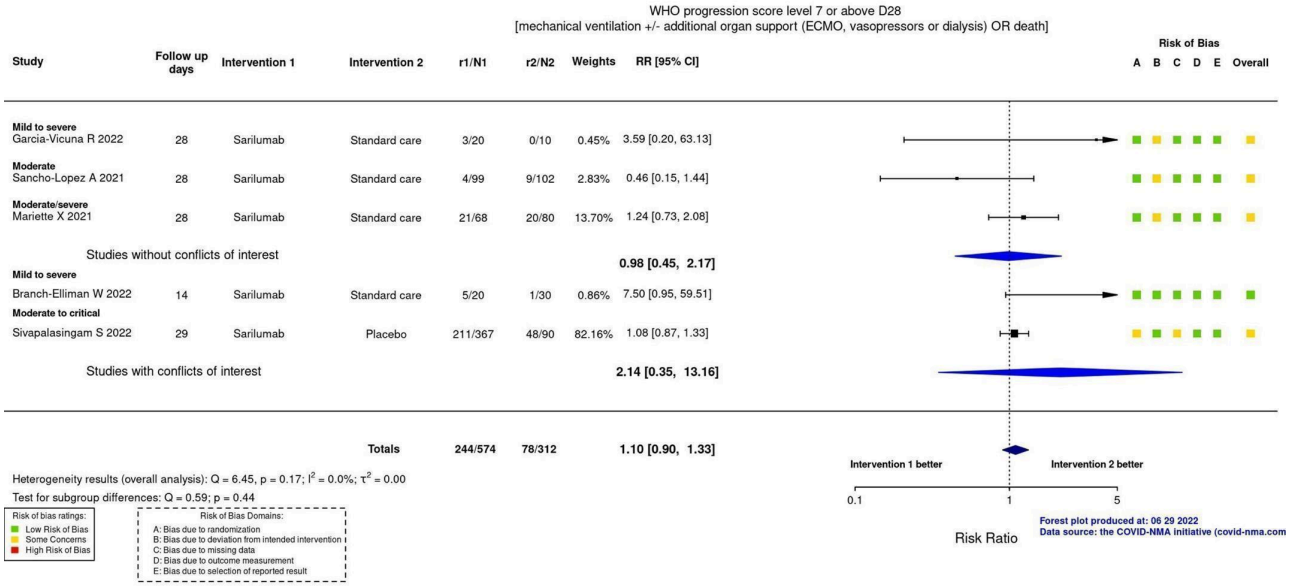


Figure 84. Subgroup analysis. 2.5.3 Conflict of Interests. Sarilumab versus placebo or standard care. Outcome: All-cause mortality D28

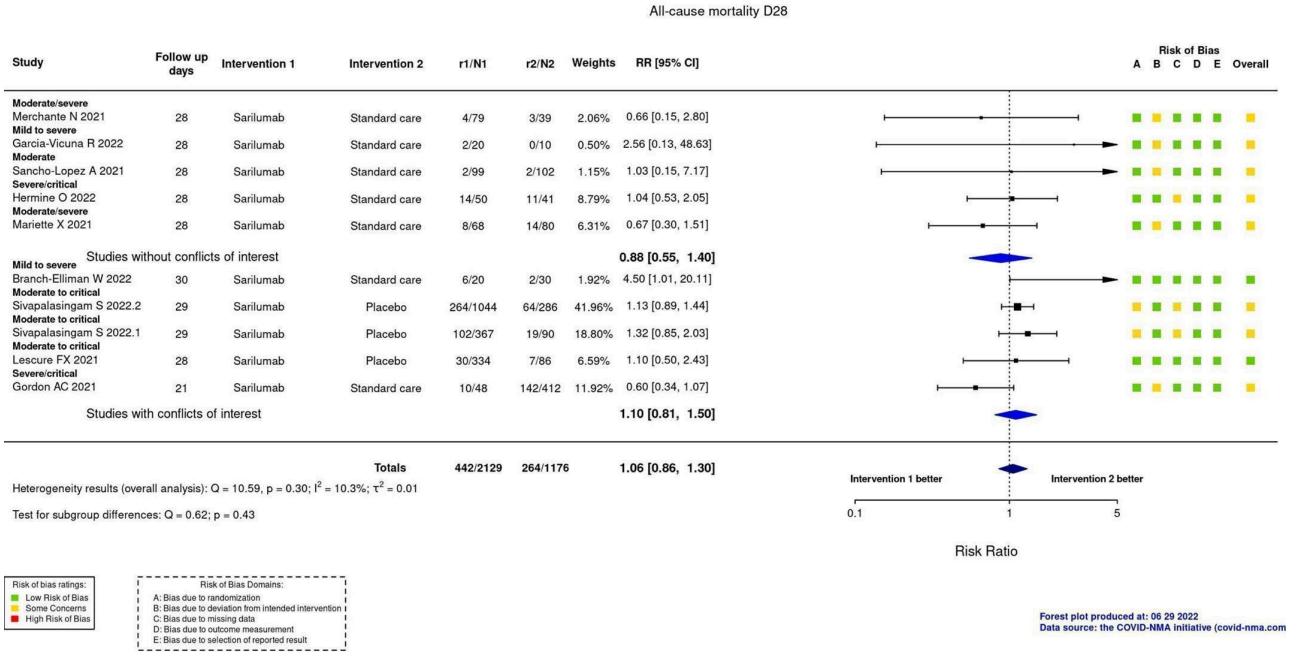


Figure 85. Subgroup analysis. 2.5.4 Conflict of Interests. Sarilumab versus placebo or standard care. Outcome: All-cause mortality D60

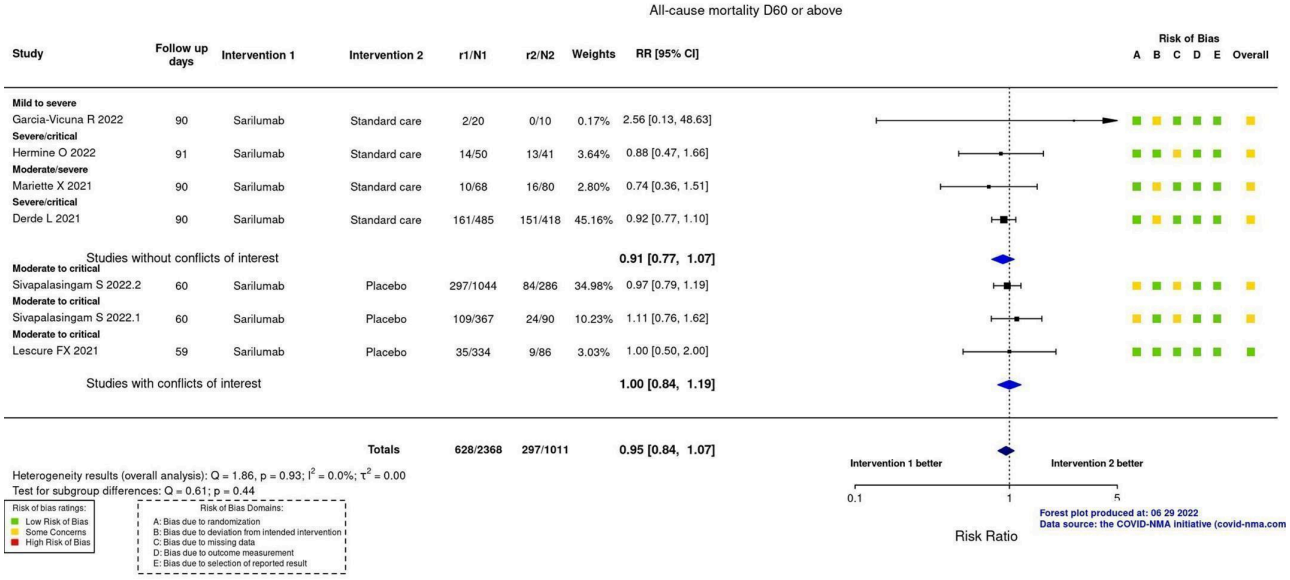


Figure 86. Subgroup analysis. 2.5.5 Conflict of Interests. Sarilumab versus placebo or standard care. Outcome: Adverse events

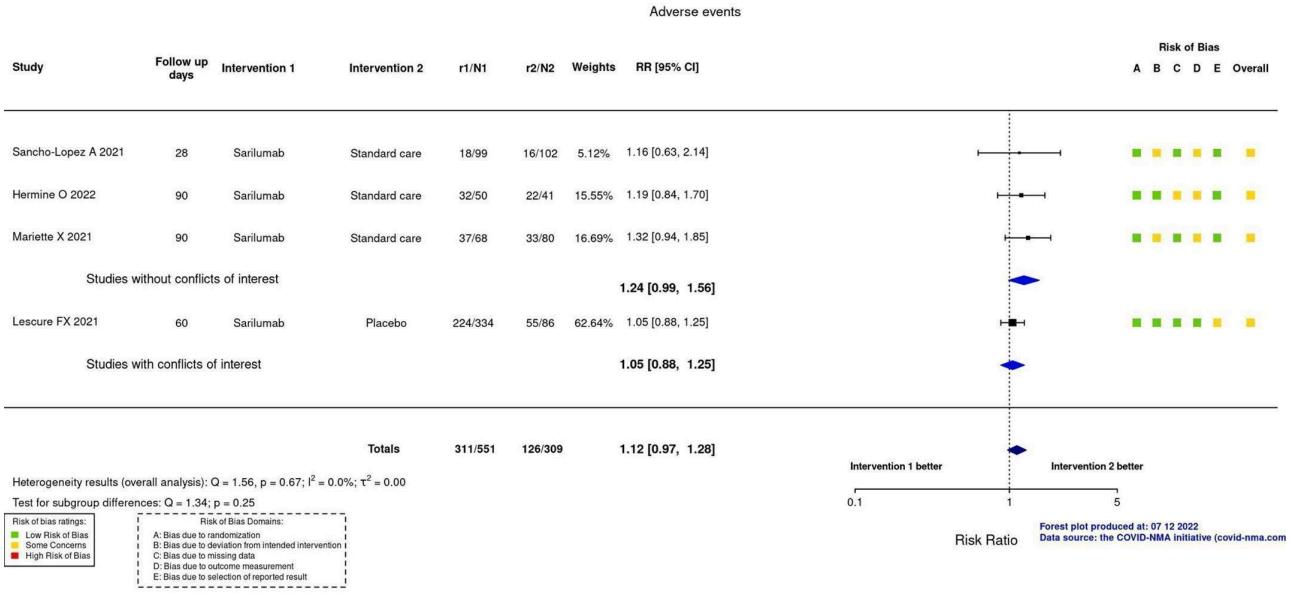


Figure 87. Subgroup analysis. 2.5.6 Conflict of Interests. Sarilumab versus placebo or standard care. Outcome: Serious adverse events

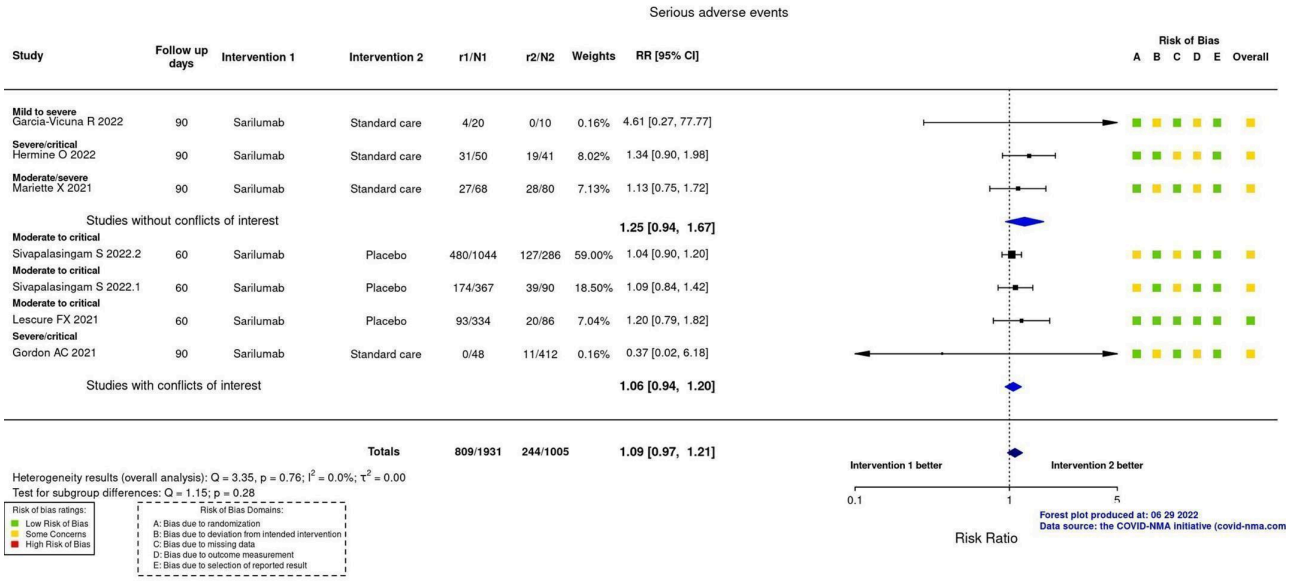


Figure 88. Subgroup analysis. 3.3.1 Conflict of interest. Clazakizumab versus placebo. Outcome: All-cause mortality D28

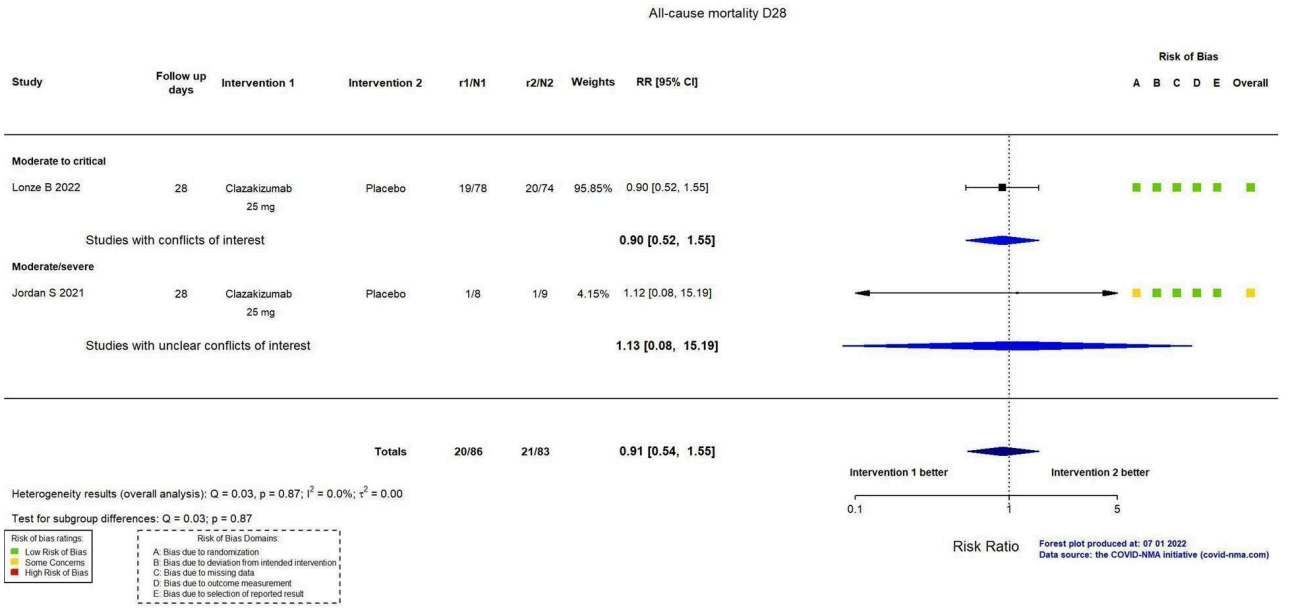


Figure 89. Subgroup analysis. 3.3.2 Conflict of interest. Clazakizumab versus placebo or standard care. Outcome: All-cause mortality D60

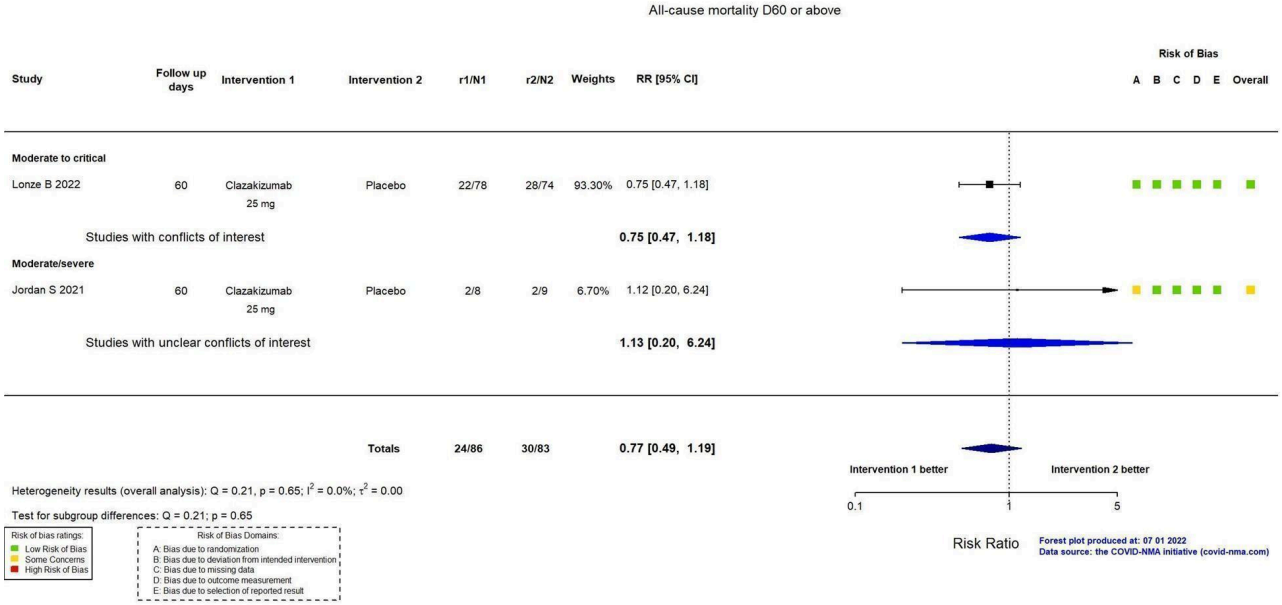
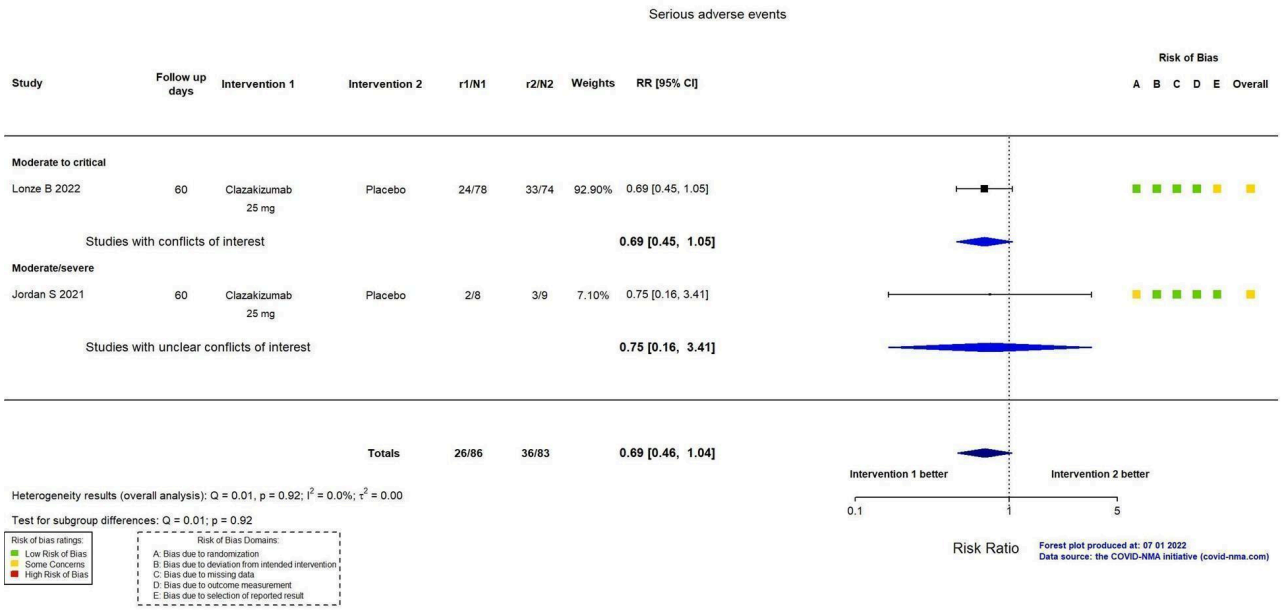


Figure 90. Subgroup analysis. 3.3.3 Conflict of interest. Clazakizumab versus placebo or standard care. Outcome: Serious adverse events



None of the characteristics explored explained any heterogeneity.

Sensitivity analysis

Details of the sensitivity analyses are available in Appendix 13.

We performed sensitivity analyses for all comparisons versus controls for available case analysis. No important discrepancies in the summary results were observed when we used the number analyzed in the RCTs instead of the number randomized as the denominator.

Sensitivity analyses excluding high-risk studies were possible only for tocilizumab, with two high-risk of bias studies included; the exclusion of these high-risk of bias trials (HMO-0224-20 2021; Talaschian 2021) did not change the results.

Sensitivity analyses excluding preprint and unpublished results were possible for some outcomes for tocilizumab, sarilumab and clazakizumab. Results were consistent when considering only trials reported as peer-reviewed articles.

DISCUSSION

Summary of main results

This review provides an updated assessment of the efficacy and safety of IL-6 blocking agents for people with COVID-19 disease. We now include 32 RCTs (involving 12,160 participants) with reported results; 22 of them are newly identified for this update. The majority of the trial participants had moderate to critical disease with a mean age ranging from 56 to 65 years. When compared to placebo or standard care, tocilizumab reduces all-cause mortality at D28 (high-certainty evidence). The evidence is very uncertain about the effect of sarilumab on all-cause mortality at D28. The evidence is uncertain for all cause-mortality at ≥ D60 for tocilizumab and very uncertain for sarilumab. Nevertheless, tocilizumab and sarilumab probably result in little or no increase in clinical improvement at D28 (moderate-certainty evidence). The effect on the proportion of participants with a WHO-CPS level of 7 or above remains uncertain at D28 for tocilizumab and the evidence is very uncertain about the effect of sarilumab. Tocilizumab probably results in little or no difference in the risk of adverse events (moderate-certainty evidence). The evidence on serious adverse events is very uncertain for tocilizumab and uncertain for sarilumab.

With respect to important outcomes, we conclude that tocilizumab reduces the probability that an individual would reach the WHO-CPS of level 7 or above compared to standard care alone or to placebo at a specific time point D28 up to D90. It probably reduces the probability that an individual would die compared to standard care alone at a specific time point D28 up to D90. Finally, sarilumab reduces the probability that an individual would die compared to standard care alone at a specific time point of D28 up to D90.

For the other IL-6 blocking agents evaluated in this meta-analysis, the evidence of their effects was uncertain or very uncertain, mainly due to the very small number of studies evaluating them.

Due to insufficient data, we could not provide information on immunocompromised people and the most clinically vulnerable people, and could not present the results disaggregated by gender.

Finally, most of the studies included in this review took place during infection with the wild-type strain, before the emergence of variants of concern. Only four studies were conducted during a period that included infections by both the wild type and the alpha variant. Most of the trials included in this review update were conducted before COVID-19 vaccines against SARS-CoV-2 infections were rolled out on a large scale.

Overall completeness and applicability of evidence

We identified 49 registered RCTs evaluating IL-6 blocking agents; two-thirds of these registered trials reported results included in this meta-analysis. This quantity of evidence was adequate to judge the effectiveness and safety of IL-6 blocking agents — mainly tocilizumab and sarilumab. Of the 17 registered trials with no published results, only one trial evaluating tocilizumab, with 200 participants, was completed by December 2020 and its results have not been published. Three other trials of tocilizumab, conducted in Iran, were stated in the registry to have completed recruitment based on the expected completion date. We cannot, however, be sure that the study was actually completed since the investigators did not update the information on the registry (Iranian registry) since registration. No further completed studies of IL-6 blocking agents are expected. Unpublished results of registered trials could produce evidence from six trials with only around 730 participants planned, 294 of them for tocilizumab and 171 for sarilumab.

Accordingly, the information for tocilizumab collected in this review covers most of the critical and important outcomes, thus allowing a clear judgment of its efficacy and safety. This calls into question the need to continue updating this review unless we find evidence justifying a major change in our conclusions.

All ongoing and not recruiting studies were registered between April and December 2020, except for one registered in January 2022 evaluating olokizumab. For the other drugs, one ongoing trial with a small sample size has not reported results for olokizumab or clazakizumab, and there are no other ongoing registered trials for levilimab and siltuximab.

Most of the trials included (26/32, 81.25%) were multicenter trials; and four were multinational.

Moreover, the studies defined the outcome of clinical improvement differently. Definitions included at least one or two points on the WHO severity score or hospital discharge. We considered all the definitions of clinical improvement.

It is worth mentioning that many jurisdictions outside the USA have suffered from ongoing shortages of tocilizumab (Cancer Discov 2021; Verma 2021). As a result, some centers resorted to using lower doses of tocilizumab due to shortages (Stukas 2022), and at least one small RCT has shown comparable biochemical and clinical outcomes between lower dose and standard dose tocilizumab (Kumar 2022).

Quality of the evidence

Overall for tocilizumab, the certainty of the evidence was very low for clinical improvement at D60 or later and for serious adverse events due to imprecision, indirectness and risk of bias. The level of certainty was low for the WHO-CPS score (level 7 or higher) at D28 and all-cause mortality at D60 or later because of very serious imprecision; it was moderate for clinical improvement at D28 and for adverse events, due to serious imprecision. Finally, the certainty of the evidence for all-cause mortality at D28 was high.

For sarilumab, the certainty of evidence was very low for four critical outcomes (clinical improvement on D60 or later, the WHO-CPS score (7 or higher) at D28, all-cause mortality at D28, all-cause mortality at D60 or later), mainly because of serious risk of bias and very serious imprecision, and low for adverse events

and serious adverse events because of serious risk of bias and imprecision. Despite the serious risk of bias, which we downgraded by one level for the clinical improvement outcome around D28, we assessed the certainty to be moderate, as we had no other concerns regarding imprecision, inconsistency, or indirectness for this particular outcome.

For clazakizumab, olokizumab, siltuximab, and levilimab, the certainty of evidence was low or very low for all reported outcomes.

Reasons for downgrading the certainty were mainly because of serious indirectness, and very serious imprecision. More details are given in the summary of finding tables.

Potential biases in the review process

To minimize potential bias in the review, we complied with the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), and assessed the effects of potential biases in sensitivity analyses. First, we continue to use the L-OVE platform and the Cochrane clinical trial registry to search for new trials and inclusions. The search strategy has been peer-reviewed and provided 100% sensitivity on the identification of COVID-19 RCTs, thus considerably reducing the workload (Pierre 2022). The platform also retrieved results posted on the clinicaltrials.gov registry and included in the analysis of this review, either as an update for an already published article or as the only available results for an unpublished study. Second, to increase our review's informative value, we continue to search and track all registered trials in a living mapping of registered trials. Third, two reviewers both screen studies, extract information, and perform risk of bias assessments. They then reach a consensus, conduct quality control after analysis, and grade the evidence. The project life cycle has a duration of two weeks and now runs on a daily basis for extraction and risk of bias assessment, weekly for screening, and every two weeks for updating analyses, grades, and quality control. The process is continuous and all updates of this review using the latest COVID-NMA database are publicly available on the COVID-NMA platform (covid-nma.com). Furthermore, analyses can be performed with the metaCOVID tool (covid-nma.com/metacovid/).

Moreover, we included data from preprints, posted results, and other meta-analyses to ensure inclusion of the best available evidence. These publications have potentially differing quality, and results may change once peer-reviewed journal publications are available (Oikonomidi 2020). To overcome this issue, we have developed a preprint tracker to be informed of updates so that we can update data collection and data analysis when a preprint is modified or published. We also explored the effect later through a sensitivity analysis that showed consistent results when we considered only trials reported as peer-reviewed articles (thus excluding preprints).

Finally, we decided not to pool different IL-6 blocking agents because we have no evidence that their effects are sufficiently similar. We have also been unable to assess the variation in effects due to changes in the standard care provided.

Agreements and disagreements with other studies or reviews

We identified 19 systematic reviews focusing on IL-6 blocking agents for COVID-19 published in 2022; three were updated after June 2021 (Boppana 2022; Peng 2022; Yu 2022). Among them, two assessed tocilizumab (Boppana 2022; Peng 2022) and the third assessed tocilizumab and sarilumab (Yu 2022). All included RCTs only. In most outcomes in those reviews that overlapped with ours, the results were consistent.

Among the living systematic reviews that we are aware of (Cruciani 2021; Juul 2021; Khan 2021; PAHO 2022; Siemieniuk 2020; Tleyjeh 2021), only the one by the Pan American Health Organization has been updated since June 2021 (PAHO 2022); it has in fact been publishing monthly updates since September 2020. Their results are consistent with ours regarding the effects of tocilizumab, sarilumab, clazakizumab, siltuximab, and levilimab on mortality, clinical improvement, and serious adverse events, with only a few discrepancies regarding the GRADE assessment (likely due to the use of different criteria to downgrade for imprecision).

AUTHORS' CONCLUSIONS

Implications for practice

In people hospitalized with COVID-19, tocilizumab reduces all-cause mortality at day 28 (D28) and probably results in little or no difference in the risk of adverse events. Nevertheless, evidence suggests that treatment with either tocilizumab or sarilumab probably results in little or no increase in clinical improvement at D28, and the evidence for their efficacy on other outcomes is uncertain.

Evidence for an effect of each of the other interleukin-6 (IL-6) blocking agents, namely, clazakizumab, olokizumab, siltuximab, and levilimab, is uncertain or very uncertain, mainly due to the low number of events and participants. Moreover, most evidence comes from the wild-type form of the SARS-CoV2 virus in unvaccinated patients.

Implications for research

For this update of a living systematic review investigating the efficacy and safety of Il-6 blocking agents for people hospitalized with COVID-19, we have included data from 32 randomized trials involving 12,160 randomized participants.

Little evidence is expected from further trials for IL-6 blocking agents. Tocilizumab has been provided in clinical practice for treating people with COVID-19; this will allow for additional information that may show up from real-world data. With the data available, we were not able to explore heterogeneity related to age and gender. Additionally, we could not provide information on immunocompromised people or the most clinically vulnerable people. Individual participant data meta-analyses are needed to be able to identify the subgroups of people who are more likely to benefit from this treatment.

The findings of this review have been updated on the COVID-NMA platform (covid-nma.com) up to 27 September 2022. On this date, the COVID-NMA initiative set the last search date for this review on IL-6 blocking agents and other treatment interventions for hospitalized patients. We are unlikely to publish a new update of this review unless there are future trials that show major effects that are likely to alter the conclusions of this review and change treatment decisions. It is worth noting that further analysis can be performed through the metaCOVID tool within the COVID-NMA platform (covid-nma.com/metacovid/). This web application allows the end-users of the COVID-NMA platform to directly use the

latest COVID-NMA database and perform meta-analyses tailored to their needs in a user-friendly environment. The results of all analyses are summarized in the form of downloadable forest plots. A key feature of the application is that the numerical results are presented alongside study characteristics and risk of bias assessments (Evrenoglou 2021).

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Editorial and peer-review contributions

Cochrane Public Health supported the authors in the development of this review update. The following people conducted the editorial process for this update.

- Sign-off Editor (final editorial decision): Harald Herkner, Medical University of Vienna, Austria; Co-ordinating Editor of Cochrane Emergency and Critical Care
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial comments/guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy-editing and production): Andrea Takeda, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Luke YC Chen, Division of Hematology, University of British Columbia (clinical/content review); Corrado Campochiaro, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy (clinical/content review); Stella O'Brien (consumer review); Robert Walton, Cochrane UK (summary versions review); Nuala Livingstone, Cochrane Evidence Production & Methods Directorate (methods review). One additional peer reviewer provided search peer review but chose not to be publicly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ARCHITECTS 2021

Study characteristics	
Methods	RCT **Blinding:** double-blind **Date of study:** 12 June 2020 to 28 August 2020 **Location:** single center; USA **Follow-up duration (days):** 90
Participants	**Population:** patients with confirmed COVID-19 (critical) admitted to a single center in the USA. **Randomized:** 21 participants n1 = 10; n2= 11 **Analyzed:** 21 **Characteristics of participants** Mean age: 61.5 years 12 males (57%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = 0; severe: n = 1; critical: n = 20 Patients on oxygen without intubation: n = 1; intubated: n = 20 C-reactive protein: median: 62 to 101.9 mg/L Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • Hospitalized with COVID-19 pneumonia, based on chest X-ray or CT scan • Evidence of hyperinflammation: IL-6 > 40 pg/mL OR ferritin > 2000 ng/mL. One or more of the following: impending need for requiring invasive or non-invasive mechanical ventilation OR shock requiring vasopressor (without evidence of bacterial / fungal infection) OR need for extracorporeal membrane oxygenation (ECMO) OR severe, refractory ARDS (PaO2/FiO2 < 200 mmHg) **Exclusion criteria** • Known severe allergic reactions to tocilizumab or other monoclonal antibodies • Active tuberculosis infection based on history • Suspected active bacterial, fungal, viral, or other infection (besides COVID-19) • In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments • Having received oral anti-rejection or immunomodulatory drugs (including tocilizumab) with the past 6 months • Participating in other drug clinical trials (participation in COVID-19 trials allowed) • Self-reported pregnant or breastfeeding • Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 10 x upper limit of normal (ULN) detected within 24 hours at baseline • Absolute neutrophil count (ANC) < 1000/mL at baseline • Platelet count < 50,000/mL at baseline
Interventions	**Intervention:** tocilizumab (8 mg/kg (max 800 mg) IV single dose, may be repeated once) **Control:** placebo **Definition of standard care:** NR **Co-interventions:** steroid use at baseline Tocilizumab: 9 (90%) Placebo: 11 (100%)
Outcomes	**Primary outcome of the trial** NR (study unpublished)

ARCHITECTS 2021 *(Continued)*

Note: The definition of clinical improvement extracted is "hospital discharge".

Notes	**Funding:** public/nonprofit (Queen's Medical Centre) **Conflict of interest:** NR **Protocol:** NR **Statistical plan:** NR **Overall comment** The study is not published yet. Data presented were extracted from study registry and WHO REACT Working Group 2021. The authors have been contacted in order to obtain the results.

Branch-Elliman 2022

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** From 10 April 2020 to 3 February 2021 **Location:** multicenter: USA **Follow-up duration (days):** 30
Participants	**Population:** patients with confirmed COVID-19 (mild-severe) admitted to 5 centers in USA **Randomized:** 50 participants n1 = 20; n2 = 30 **Analyzed:** 50 **Characteristics of participants** Mean/median age: sarilumab: 75 years; standard care: 71 years 46 males (92%) Admitted to ICU: n=NR Severity: mild: n = 24; moderate: n = NR; severe: n = NR; critical: n = 0 Patients on oxygen without intubation: n = 26; intubated: n = 0 C-reactive protein: median 73 to 96 mg/L Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • Positive SARS-CoV-2 diagnostic test (either PCR or antigen testing) no more than 4 weeks prior to enrollment • Presence of symptoms of < 14 days duration prior to enrollment • Hospitalization with moderate COVID-19 disease, defined using the Brescia COVID-19 respiratory severity score **Exclusion criteria** • Critical COVID-19, defined by mechanical ventilation and/or expected death within 24 hours • Pregnancy • Enrollment in another interventional clinical trial • Chronic administration of certain immunosuppressive drugs (e.g. chronic prednisone > 10 mg/day, JAK inhibitors, or immunosuppressive biologics)
Interventions	**Intervention:** sarilumab (400 mg subcutaneously single dose (first 9 participants received 200 mg)) **Control:** standard care **Definition of standard care:** determined by the treating physicians and local treatment guidance and not predetermined by study investigators **Steroid use at baseline or any time during the study**

Branch-Elliman 2022 *(Continued)*

	During the study Sarilumab: 17 (85%) Standard care: 26 (87%)
Outcomes	**Primary outcome of the trial** A composite of intubation or death within 14 days following randomization Note: The definition of clinical improvement extracted is "Discharge".
Notes	**Funding:** public/nonprofit (NIH NHLBI; The VISN-1 Clinical Trials Network and the VA Boston Healthcare System) **Conflict of interest:** yes, declared. WBE, PM, and JMS were site investigators for a study funded by Gilead Sciences (funds to institution). WBE was supported by NIH grant. All other authors report no conflicts of interest to report. **Protocol:** yes **Statistical plan:** yes In addition to the published article, the registry, protocol, statistical analysis plan and supplementary appendices were used in data extraction and assessment of risk of bias. The primary outcome in the article reflects that in the registry. Recruitment to the trial was terminated out of concern for the high probability that rates of intubation or death were higher in the sarilumab arm than the standard care arm, and therefore the study did not achieve its target sample size.

Broman 2022

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 12 August 2020 to 16 June 2021 **Location:** single center; Finland **Follow-up duration (days):** 90

Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) admitted to a single center in Finland.
	Randomized: 88 participants n1 = 29; n2 = 59
	Analyzed: 86
	Characteristics of participants
	Mean/median age: standard care: 59 years; tocilizumab: 58 years
	48 males (56%)
	Admitted to ICU: n = 11
	Severity: mild: n = 0; moderate: n = 59; severe: n = 20; critical: n = 1
	Patients on oxygen without intubation: n = 79; intubated: n = 1
	C-reactive protein: mean: 87 to 91 mg/L
	
	Interleukin-6: median: 34 to 44 pg/mL
	
	Number of vaccinated participants: 0
	Inclusion criteria
	
	• Written informed consent obtained
	• Hospitalized with COVID-19 disease
	• Age ≥ 18 years
	• SARS CoV-2 NhO posit
	• Peripheral oxygen saturation </93% on ambient air or respiratory rate >30 /min
	• Any 2 of the 4:
	  ○ Interleukin-6 > 11.8 ng/L (2 x upper limit of normal (ULN))
	  ○ Ferritin >300 µg/L in women or >800 µg/L in men (2 × ULN)

Broman 2022 *(Continued)*

- D-dimer >1.5 mg/L
- C-reactve protein >40 mg/l without obvious presence of bacterial infection.

Exclusion criteria

- Known severe allergic reactions to monoclonal antibodies
- Active confirmed tuberculosis with ongoing treatment or obvious tuberculosis or obvious other bacterial, fungal or viral infection (besides COVID-19)
- In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Long-term oral anti-rejection or immunomodulatory drugs (including corticosteroids equivalent to methylprednison 15 mg/day)
- Pregnant or lactating women. If needed, exclusion of pregnancy should be performed by laboratory test (U-hCG-O)
- Participating in other drug clinical trials
- Absolute neutrophil count < 1 x 10 E9/l
- Platelet count <50 x 10 E9/l
- ALAT > 10 x ULN

Interventions	**Intervention:** tocilizumab (400 mg for < 60 kg, 600 mg for 60 to 90 kg, and 800 mg for > 90 kg; IV single dose) **Control:** standard care **Definition of standard care:** did not include antivirals (e.g. remdesivir) or hydroxychloroquine or other experimental treatments, but could include subcutaneous low-molecular weight heparin and glucocorticoids. **Steroid use at baseline or any time during the study** At baseline Standard care: 29 (100%) Tocilizumab: 52 (91%)
Outcomes	**Primary outcome of the trial** The primary endpoint was clinical status at day 28 assessed using a 7-category ordinal scale, where 1 is at home, normal daily activities; 2 is at home, assistance needed; 3 is hospitalized, no supplemental oxygen; 4 is hospitalized (non-ICU), receiving supplemental oxygen; 5 is in ICU, no invasive mechanical ventilation (IMV); 6 is in ICU receiving IMV and/or extracorporeal membrane oxygenation; and 7 is dead. Note: The definition of clinical improvement extracted is "hospital discharge"
Notes	**Funding:** no specific funding (No external funding was received for this study or article) **Conflict of interest:** yes, declared. N. Broman reports receiving funding from University of Turku. T. Feuth reports receiving compensation for a lecture outside the submitted work from GlaxoSmithKline. U. Hohenthal reports receiving compensation for serving on the advisory board outside the submitted work from GlaxoSmithKline and congress travel from Grifols Nordic, MSD-Finland, and Pfizer. P. Jalava-Karvinen reports receiving compensation for serving on the advisory board outside the submitted from GlaxoSmithKline and MSD-Finland; travel grants from Gilead, MSD, and Pfizer; and stock ownership of Orion. H. Marttila reports receiving compensations for lectures, travel grants, or advisory boards outside the submitted work from MSD Finland, Pfizer, Immunodiagnostic, and Roche Diagnostics. J. Oksi reports receiving compensations for lectures or advisory boards outside the submitted work from Biocodex, Gilead, GlaxoSmithKline, MSD-Finland, Orion, and Roche. All other authors declare no conflicts of interest. **Protocol:** NR **Statistical plan:** NR Data presented were originally extracted from study registry and WHO REACT Working Group 2021. On 14 April 2022, the extraction and risk of bias assessments were updated with information from the published article. There is no change from the trial registration in the intervention and control treatments. The registry primary outcome reflects the reported primary outcome. Of note: the outcomes Mortality (D60 or more) and Time to death were not reported in the 2022 publication and thus are the

Broman 2022 *(Continued)*

original extractions from WHO REACT Working Group 2021. Furthermore, we extracted data reported as severe adverse events in the published report under our serious adverse events outcome.

COVIDOSE-2 2021

Study characteristics

Methods	RCT **Blinding:** unblinded **Date of study:** September 2020 to 31 January 2021 **Location:** multicenter: USA **Follow-up duration (days):** 28
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) admitted to multiple centers in the USA **Randomized:** 28 participants n1 = 20; n2 = 8 **Analyzed:** 27 **Characteristics of participants** Mean/median age: tocilizumab: 65 years; standard care: 65 years 19 males (70%) Admitted to ICU: n = NR Severity; mild: n = 0; moderate: n = NR; severe: n=NR; critical: n = 0 Patients on oxygen without intubation: n = 17; intubated: n = 0 C-reactive protein: median: 101.0 to 102.0 mg/L Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • Adults ≥ 18 years of age • Approval from the patient's primary inpatient service • Hospitalized • Fever, documented in electronic medical record and defined as: T ≥ 38 degrees C by any conventional clinical method (forehead, tympanic, oral, axillary, rectal) • Positive test for active SARS-CoV-2 infection • Radiographic evidence of infiltrates on chest radiograph (CXR) or computed tomography (CT) • Ability to provide written informed consent on the part of the subject or, in the absence of decisional capacity of the subject, an appropriate surrogate (e.g. a legally authorized representative) **Exclusion criteria** • Concurrent use of invasive mechanical ventilation • Concurrent use of vasopressor or inotropic medications • Previous receipt of tocilizumab or another anti-IL6R or IL-6 inhibitor in the year prior • Known history of hypersensitivity to tocilizumab • Diagnosis of end-stage liver disease or listed for liver transplant • Elevation of AST or ALT in excess of 10 times the upper limit of normal • Neutropenia (absolute neutrophil count < 500/uL) • Thrombocytopenia (platelets < 50,000/uL) • On active therapy with a Bruton's tyrosine kinase-targeted agent, which include the following: acalabrutinib, ibrutinib, zanubrutinib • On active therapy with a JAK2-targeted agent, which include the following: tofacitinib, baricitinib, upadacitinib, ruxolitinib • Any of the following biologic immunosuppressive agent (and any biosimilar versions thereof) administered in the past 6 months or less: abatacept, adalimumab, alemtuzumab, atezolizumab, belimum-

COVIDOSE-2 2021 *(Continued)*

	ab, blinatumomab, brentuximab, certolizumab, daratumumab, durvalumab, eculizumab, elotuzumab, etanercept, gemtuzumab, golimumab, ibritumomab, infliximab, inotuzumab, ipilimumab, ixekizumab, moxetumomab, nivolumab, obinutuzumab,ocrelizumab, ofatumumab, pembrolizumab, polatuzumab, rituximab, rituximab, sarilumab, secukinumab, tocilizumab, tositumumab, tremelimumab, urelumab, ustekinumab • History of bone marrow transplantation (including chimeric antigen receptor T-cell) or solid organ transplant • Known history of Hepatitis B or Hepatitis C (patients who have completed curative-intent anti-HCV treatments are not excluded from trial) • Positive result on hepatitis B or C screening • Known history of mycobacterium tuberculosis infection at risk for reactivation • Known history of gastrointestinal perforation • Active diverticulitis • Multi-organ failure as determined by primary treating physicians • Any other documented serious, active infection besides COVID-19 - including but not limited to: lobar pneumonia consistent with bacterial infection, bacteremia, culture-negative endocarditis, or current mycobacterial infection - at the discretion of primary treating physicians • Pregnant patients or nursing mothers • Patients who are unable to discontinue scheduled antipyretic medications, either as monotherapy (e.g. acetaminophen or ibuprofen [aspirin is acceptable]) or as part of combination therapy (e.g., hydrocodone/acetaminophen, aspirin/acetaminophen/caffeine [Excedrin®]). • CRP < 40 mg/L
Interventions	**Intervention:** tocilizumab (40 mg or 120 mg single dose) **Control:** standard care **Definition of standard care:** NR **Steroid use at baseline or any time during the study** At baseline Tocilizumab: 6 (32%) Standard care: 2 (25%)
Outcomes	**Primary outcome of the trial** NR (unpublished study) Note: The definition of clinical improvement extracted is "discharged at 28-days".
Notes	**Funding:** public/nonprofit (University of Chicago) **Conflict of interest:** yes, declared. **Protocol:** NR **Statistical plan:** NR The study is not published yet. Data presented were extracted from study registry and WHO REACT Working Group 2021. The authors have been contacted in order to obtain the results.

COVITOZ-01 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 4 May 2020 to 21 October 2020 **Location:** single center; Spain **Follow-up duration (days):** 90
Participants	**Population:** patients with suspected or confirmed COVID-19 (mild-moderate-severe) admitted to a single center in Spain.

COVITOZ-01 2021 *(Continued)*

	Randomized: 26 participants n1 = 9; n2 = 17 **Analyzed:** 26 **Characteristics of participants** Mean/median age: standard care: 58 years; tocilizumab: 58 years 17 males (65%) Admitted to ICU: n = 0 Severity: mild: n = 9; moderate: n = NR; severe: n=NR; critical: n = 0 Patients on oxygen without intubation: n = 17; intubated: n = 0 C-reactive protein: median: 73.6 to 195.2 mg/L Interleukin-6: median: 8.8 to 51 pg/mL Number of vaccinated participants: NR **Inclusion criteria** • Patients over 18 years of age who have given their informed consent • The patient is diagnosed with mild-moderate SARS-CoV-2 pneumonia confirmed microbiologically ≤ 7 days before randomization, and presents: basal oxygen saturation > 90%; CURB-65 ≤ 1; PaO2 / FiO2 ≥ 300 or SatO2/FiO2 ≥ 315 • The patient is hospitalized or meets hospital admission criteria • The patient is not expected to enter the ICU or die in the next 24 hours **Exclusion criteria** • Participants in another simultaneous clinical trial • Use of other immunomodulators • Coinfection with the hepatitis B virus • Pregnancy (or planning to become pregnant during the course of the study), or lactation period • Presence of laboratory abnormalities of grade ≥ 4.
Interventions	**Intervention:** tocilizumab (8 mg/kg (max 800 mg) IV single dose OR two doses) **Control:** standard care **Definition of standard care:** NR **Steroid use at baseline or any time during the study** At baseline Standard care: 7 (78%) Tocilizumab: 10 (59%)
Outcomes	**Primary outcome of the trial** NR (unpublished study) Note: The definition of clinical improvement extracted is "hospital discharge".
Notes	**Funding:** public/nonprofit (Hospital Universitario Ramon y Cajal) **Conflict of interest:** NR **Protocol:** NR **Statistical plan:** NR The study is not yet published. Data presented were extracted from study registry and WHO REACT Working Group 2021. The authors have been contacted in order to obtain the results. COVITOZ-01 study was terminated for futility reasons with actual enrollment (26/78) being 33% of the planned sample size.

Declercq 2021

Study characteristics	
Methods	RCT

Declercq 2021 *(Continued)*

Blinding: unblinded
Date of study: 4 April 2020 to 6 December 2020
Location: multicenter: Belgium
Follow-up duration (days): 90

Participants

Population: patients with confirmed COVID-19 (moderate-critical) admitted to 16 centers in Belgium.
Randomized: 342 participants n1 = 43; n2 = 32; n3 = 37; n4 = 82; n5 = 76; n6 = 72
Analyzed: 342
Characteristics of participants
Mean/median age
Anakinra: 65 years
Anakinra + tocilizumab: NR
Anakinra + siltuximab: NR
Tocilizumab: NR
Siltuximab: NR
Standard care: 63 years
90 males (26%)
Admitted to ICU: n = NR
Severity: mild: n = NR; moderate: n = NR; severe: n = NR; critical: n = NR
Patients on oxygen without intubation: n = 167; intubated: n = 22
C-reactive protein: median: 120 to 150 mg/L

Interleukin-6: median: 9 to 8 pg/mL

Number of vaccinated participants: NR
Inclusion criteria

- Older than 18 years
- Had a laboratory proven diagnosis of COVID-19 with symptoms between 6 and 16 days
- A ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2; P:F ratio) of less than 350 mm Hg on room air or less than 280 mm Hg on supplemental oxygen and bilateral pulmonary infiltrates.
- Either a single ferritin concentration measurement of more than 2000 µg/L at inclusion when they immediately required high flow oxygen or mechanical ventilation, or a ferritin concentration of more than 1000 µg/L, which had been increasing over the previous 24 h, or lymphopenia below 800/mL with two of the following criteria: an increasing ferritin concentration of more than 700 µg/L, an increasing lactate dehydrogenase concentration of more than 300 international units (IU)/L, an increasing CRP concentration of more than 70 mg/L, or an increasing D-dimers concentration of more than 1000 ng/mL. If the patient had three of the previous criteria at hospital admission with lymphopenia of less than 800/µL, there was no need to document an increase over 24 h.

Exclusion criteria

- Mechanical ventilation for more than 24 h at randomization
- A clinical frailty scores greater than 3 before SARS-CoV-2 infection
- Unlikelihood to survive beyond 48 h based on clinical assessment
- An active co-infection defined on clinical grounds (positive blood or sputum cultures)
- Thrombocytopenia of less than 50 000/µL
- Neutropenia of less than 1500/µL
- History of bowel perforation or diverticulitis
- High dose systemic steroid or immunosuppressive drug use for a COVID-19-unrelated disorder

Interventions

Intervention

- Anakinra (100 mg once daily subcutaneously for 28 days or until hospital discharge)
- Anakinra + tocilizumab (anakinra 100 mg once daily subcutaneously for 28 days or until hospital discharge + tocilizumab 8 mg/kg IV single dose (not exceeding 800 mg))
- Anakinra + siltuximab (anakinra 100 mg once daily subcutaneously for 28 days or until hospital discharge + siltuximab 11 mg/kg IV single dose)

Declercq 2021 *(Continued)*

- Tocilizumab (8 mg/kg IV single dose (not exceeding 800 mg))
- Siltuximab (11 mg/kg IV single dose)

Control: standard care
Definition of standard care: most patients (42%) randomly assigned before August 2020 received hydroxychloroquine as per standard care and most patients (84%) randomly assigned from August 2020, onwards received dexamethasone as per standard care. From Table 1, almost half received antibiotics.

Steroid use at baseline or any time during the study
At baseline
Anakinra: 29 (67%)
Anakinra + tocilizumab: NR
Anakinra + siltuximab: NR
Tocilizumab: NR
Siltuximab: NR
Standard care: 43 (60%)

Outcomes

Primary outcome of the trial
Time to clinical improvement, defined as the time in days from randomization until either an increase of at least two points on a 6-category ordinal scale (compared with the worst status at day of randomization) or to discharge from the hospital alive, whichever occurred first. The 6-category ordinal scale was defined as 1 = death; 2 = hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 3 = hospitalized, on non-invasive ventilation or high-flow oxygen devices; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, not requiring supplemental oxygen; 6 = not hospitalized.
Note: The definition of clinical improvement extracted is "an increase of at least two points on a 6-category ordinal scale (compared with the worst status at day of randomization) or discharge from the hospital alive."

Notes

Funding: public/nonprofit (Belgian Health Care Knowledge Center; VIB Grand Challenges (Flemish Institute for Biotechnology))
Conflict of interest: yes, declared. COI of the first and last authors are: JD, KFAVD, BM, CB, VB, LH, LN, and EDL have received personal PhD training fellowships from FWO Flanders. BNL received an European Research Council Advanced Grant and several FWO grants, as well as a University of Ghent Methusalem Grant. SR has received honoraria and meeting attendance support from BMS, MSD, Pfizer, Bayer, J&J, Astellas, Roche, and Ipsen; she serves on DSMBs organized by Pfizer, J&J, BMS, and MSD. IP has received research grants from FWO and honoraria from UCB Pharma and Galapagos. She serves on advisory boards from Abbvie, Amgen, Argenx, AstraZeneca, BMS, Galapagos, and Novartis
Protocol: yes
Statistical plan: yes

In addition to the published article, the study registry, supplementary material, protocol and statistical analysis plan were used in data extraction and risk of bias assessment. WHO REACT Working Group 2021 was also consulted.
The study achieved the target sample size specified in the trial registry. There are no important changes from the trial registration in the primary outcome, procedures, intervention and control treatments. Total adverse events were not reported (but this had been prespecified). 11% were critical at study start. Overall median age was 65 years (IQR 54–73) and 77% were male.
Data presented for the outcomes mortality (D28), time to death, WHO score 7 and above (D28), serious adverse events and clinical improvement (D28) (this last only for Tocilizumab and Siltuximab) were extracted from WHO REACT Working Group 2021. The authors have been contacted in order to obtain the results.

Derde 2021

Study characteristics

Methods

RCT

Derde 2021 *(Continued)*

	Blinding: unblinded **Date of study:** 25 March 2020 to 10 April 2021 **Location:** multicenter: UK, Netherlands, Ireland, Australia, New Zealand, Canada, Finland, Italy, Saudi-Arabia **Follow-up duration (days):** 90
Participants	**Population:** patients with suspected or confirmed COVID-19 (moderate to critical) admitted to 133 centers in 9 countries **Randomized:** 2253 participants n1 = 972; n2 = 485; n3 = 378; n4 = 418 **Analyzed:** 2197 **Characteristics of participants** Mean/median age: Tocilizumab: 61 years Sarilumab: 59 years Anakinra: 60 years Standard care: 61 years 1536 males (70%) Admitted to ICU: n = 2216 Severity: mild: n = 0; moderate: n = 4; severe: n = 1482; critical: n = 730 Patients on oxygen without intubation: n = 1486; intubated: n = 730 C-reactive protein: median: 120 to 132 mg/L Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • Participants aged > 18 years • Suspected or microbiologically confirmed COVID-19 • Receiving or not respiratory or cardiovascular organ support within 24 hours in an ICU **Exclusion criteria** • Death deemed to be imminent and inevitable during the next 24 hours • One or more of the participants, substitute decision maker or attending physician are not committed to full active treatment • More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection or more than 24 hours elapsed since ICU admission • Previous participation in this REMAP within the last 90 days • Patient has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab during this hospitalization • Long-term therapy with any of these agents prior to this hospital admission • Patient has been randomized in a trial evaluating an immune modulation agent for proven or suspected COVID-19 infection where the protocol of that trial requires ongoing administration of study drug • Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization • Intention to prescribe systemic corticosteroids for any reason, other than participation in the Corticosteroid domain of this platform, is an exclusion criterion to receive IFN-β1a • Known hypersensitivity to proteins produced by *E coli* will result in exclusion criterion to receive anakinra • Known or suspected pregnancy is an exclusion criterion to receive the anakinra, IFN-β1a, tocilizumab, and sarilumab interventions • Baseline alanine aminotransferase or an aspartate aminotransferase that is more than five times the upper limit of normal is an exclusion criterion to receive tocilizumab or sarilumab • Baseline platelet count < 50 x 109 / L is an exclusion criterion to receive tocilizumab or sarilumab.
Interventions	**Intervention:** tocilizumab (8 mg/kg IV infusion single dose, maximum 800 mg, a second infusion could be administered 12 to 24 hours after the first) Sarilumab (400 mg IV single dose)

Derde 2021 *(Continued)*

	Anakinra (Initial dose: 300 mg intravenously for the first 24 hours; maintenance dose: 100 mg intravenously 4 times a day for 14 days or until either free from invasive mechanical ventilation for more than 24 hours, or discharge from ICU) **Control:** standard care **Definition of standard care:** NR **Steroid use at baseline or any time during the study** At baseline Tocilizumab: 770 (82%) Sarilumab: 422 (87%) Anakinra: 317 (87%) Standard care: 269 (66%)
Outcomes	**Primary outcome of the trial** An ordinal scale that is a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support, censored at 21 days, where all deaths within hospital and up to day 90 were assigned the worst outcome. Note: The definition of clinical improvement extracted is "Hospital discharge".
Notes	**Funding:** mixed (PREPARE consortium by the European Union; FP7-HEALTH-2013-INNOVATION-1; RECOVER consortium by the European Union Horizon 2020 research and innovation program; Australian National Health and Medical Research Council; Health Research Council of New Zealand; Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant; UK NIHR; NIHR Imperial Biomedical Research Centre; Health Research Board of Ireland; UPMC Learning While Doing Program; Translational Breast Cancer Research Consortium; Global Coalition for Adaptive Research; French Ministry of Health; Minderoo Foundation; Wellcome Trust Innovations Project; Netherlands Organization for Health Research and Development ZonMw; NIHR Research Professorship; NIHR Clinician Scientist Fellowship; Australian National Health and Medical Research Council Career Development Fellowship; Roche Products Ltd; Sanofi (Aventis Pharma Ltd); Swedish Orphan Biovitrum AB (Sobi); Faron Pharmaceuticals (drug provision in some countries)) **Conflict of interest:** yes, declared. Dr Gordon is funded by an NIHR Research Professorship. **Protocol:** yes **Statistical plan:** yes In addition to the preprint version of the article, the study registry and protocol were used in data extraction and risk of bias assessment. The report contains definite results of tocilizumab, sarilumab and anakinra from the Immune Modulation Therapy domain of the REMAP-CAP clinical trial (an international, adaptive platform trial). There is no change from the trial registration in the intervention and control treatments. The platform initially included only participants admitted to an intensive care unit and receiving respiratory or cardiovascular organ support, a moderate state enrolling hospitalized participants not receiving respiratory or cardiovascular organ support was added subsequently. A blinded International Trial Steering Committee (ITSC) closed all arms of the domain on 10 April 2021. The primary outcome indicated in the registry reflects the primary outcome reported in the paper. Adverse events are not reported.

Garcia-Vicuna 2022

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 13 April 2020 to 30 October 2020 **Location:** single center; Spain **Follow-up duration (days):** 90
Participants	**Population:** patients with confirmed COVID-19 (mild-severe) admitted to a single center in Spain. **Randomized:** 30 participants n1 = 20;/ n2 = 10 **Analyzed:** 30

Garcia-Vicuna 2022 *(Continued)*

Characteristics of participants
Mean/median age:
Sarilumab: 62 years
Standard care: 62 years
20 males (67%)
Admitted to ICU: n = NR
Severity: mild: n = 4; moderate: n = 22; severe: n=4; critical: n = 0
Patients on oxygen without intubation: n = 26; intubated: n = 0
C-reactive protein: median: 85.9 mg/L to 99.4 mg/L

Interleukin-6: median: 12 pg/mL

Number of vaccinated participants: NR
Inclusion criteria

- Age > 18, < 80 years old attending the emergency room of Hospital Universitario La Princesa in need for hospitalization or those in hospital wards
- COVID-19 infection documented by a positive positive reverse-transcriptase–PCR (RT-PCR) test or, in absence of a RT-PCR positive test, case definition of COVID 19 infection/pneumonia as per local protocol and the presence of a positive serologic test (IgM/IgA by enzyme-linked immunosorbent assay(ELISA))
- Documented interstitial pneumonia requiring admission and at least two of the following parameters:
- Fever ≥ 37.8°C (tympanic)
- IL-6 in serum ≥ 25 pg/mL (in the absence of a previous dose of prednisone or equivalent > 1 mg/kg) or PCR > 5 mg/dL
- Lymphocytes < 600 cells/mm^3
- Ferritin > 300 µg/L that doubles in 24 hours
- Ferritin > 600 µg/L in the first determination and LDH > 250 U/L
- D-dimer (> 1 mg/L)
- Informed verbal consent or requested under urgent conditions, documented in the electronic medical record

Exclusion criteria

- Patients who require mechanical ventilation at the time of inclusion
- AST/ALT values > 5-fold ULN
- Absolute neutrophil count below 500 cells/mm^3
- Absolute platelet count below 50,000 cells/mm^3
- Superimposed infection by pathogens other than COVID-19
- Complicated diverticulitis or intestinal perforation
- Immunosuppressive antirejection therapy
- Pregnancy or lactation
- Previous treatment with tocilizumab (TCZ) or sarilumab (SAR)
- Contraindication to SAR or excipients
- Comorbidities that can likely lead to an unfavorable result

Interventions

Intervention: sarilumab (200 mg subcutaneous injection twice daily)
Control: standard care
Definition of standard care: patients in both arms received drugs, including corticosteroids, or full supportive care according to the best SC updated in the local protocol for COVID-19. Patients in the SC were given the option to receive intravenous TCZ after randomization if they worsened at the investigator's discretion, as this agent had become the SC in our center when the protocol was designed. Other immunomodulators or investigational drugs in trials were prohibited.

Steroid use at baseline or any time during the study
At baseline
Sarilumab: 17 (85%)

Garcia-Vicuna 2022 *(Continued)*

	Standard care: 8 (80%)
Outcomes	**Primary outcome of the trial** 1. Mortality by 30 days 2. Mean change in functional status at day 7 on a 7-category ordinal scale as recommended by the WHO R&D Blueprint Group 3. Time to discharge from randomization Note: The definition of clinical improvement extracted is "discharged alive from the hospital by 28 days".
Notes	**Funding:** mixed (Sanofi Spain) **Conflict of interest:** yes, declared. RG-V reported receiving educational grants support from Lilly, Janssen, Pfizer, Roche, Sanofi, honoraria for presentations for Lilly, Sanofi, advisory boards for Lilly, Pfizer, Sanofi, nonfinancial support from Lilly, Pfizer, and Sanofi, all outside the present work. IG-A reported Roche provided him data for research, honoraria for presentations for Lilly, Roche, Sanofi, advisory boards for Lilly, Sanofi, non-financial support from Abbvie, BMS, MSD, Novartis, Pfizer and Roche, outside the present work. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. **Protocol:** yes **Statistical plan:** yes In addition to the published article, the study registry, protocol, statistical analysis plan and the WHO REACT Working Group 2021 were used in data extraction and risk of bias assessment. SARCOVID is an investigator-initiated open-label phase II RCT. There is no change from the trial registration in the intervention and control treatments. This study was updated on 25 April 2022 with data from the published report.

Gordon 2021

Study characteristics	
Methods	RCT- adaptive platform trial **Blinding:** unblinded **Date of study:** 19 April 2020 to 19 November 2020 **Location:** multicenter: Australia, Ireland, the Netherlands, New Zealand, Saudi Arabia, UK **Follow-up duration (days):** 90
Participants	**Population:** patients with confirmed or suspected COVID-19 (severe-critical) **Randomized:** 826 participants (n1 tocilizumab arm = 366; n2 sarilumab arm = n2 = 48; n3 control arm = 412) **Characteristics of participants** • N = 826 randomized; baseline data reported for 803 participants • Mean age: 61.4 to 63.4 years • 583 (73%) males • Admitted to ICU: n = 826 (100%) • Severity: mild: n = 0; moderate: n = 3; severe: n = 567; critical: n = 233 • Patients on oxygen without intubation: n = 570 (71%); intubated: n = 233 (29%) • C-reactive protein (median): 130 to 150 mg/L • Interleukin-6: NR; • Number of vaccinated participants: NR

Gordon 2021 *(Continued)*

Inclusion criteria

- Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (Covid-19) infection
- Severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an ICU
- Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Exclusion criteria

- Death is deemed to be imminent and inevitable during the next 24 hours AND 1 or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
- Patient is expected to be discharged from hospital today or tomorrow
- More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection
- Previous participation in this REMAP within the last 90 days
- More than 24 hours has elapsed since ICU admission
- Patient has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission
- Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization
- Patient has been randomized in a trial evaluating an immune modulation agent for proven or suspected Covid-19 infection, where the protocol of that trial requires ongoing administration of study drug
- The treating clinician believes that participation in the domain would not be in the best interests of the patient
- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known or suspected pregnancy will result in exclusion from the anakinra, IFN-β1a, tocilizumab, and sarilumab interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria
- A baseline ALT or an ASP that is more than five times the upper limit of normal will result in exclusion from receiving tocilizumab or sarilumab
- A baseline platelet count < 50 x 10^9 / L will result in exclusion from receiving tocilizumab or sarilumab

Dropouts and withdrawals: n = 34/826 (4%); withdrawal due to adverse events: NR

Interventions	**Interventions:** tocilizumab (8 mg/kg infusion, maximum 800 mg), a 2nd infusion could be administered 12 to 24 hours after the 1st at the discretion of the treating clinician. 29% received a 2nd dose. Treatment initiated within 24 hours after starting organ support in the ICU. Sarilumab (400 mg, IV). 90% received the drug. **Control:** standard care **Definition of standard care:** other aspects of patient management were provided per each site's standard care. Overall, > 80% of participants received corticosteroids. Remdesivir use was recorded in 33% (265/807) of participants. **Co-interventions:** steroid use at baseline or any time during the study in > 80% of participants.
Outcomes	**Primary outcome of the trial:** respiratory and cardiovascular organ support-free days up to day 21 Note: the definition of clinical improvement extracted is hospital discharge.
Notes	**Funding:** mixed (PREPARE consortium by the EU; FP7-HEALTH-2013-INNOVATION-1; RECOVER consortium by the EU's Horizon 2020 research & innovation programme; Australian National Health & Med-

Gordon 2021 *(Continued)*

ical Research Council; Health Research Council of New Zealand, and the Canadian Institute of Health Research, the UK National, the Health Research Board of Ireland, the UPMC Learning While Doing Program, the Breast Cancer Research Foundation, the French Ministry of Health, the Minderoo Foundation and the Wellcome Trust Innovations Project.)
Conflict of interest: yes. (Quote:) "Dr. Gordon reports grants from NIHR, grants from NIHR Research Professorship (RP-2015-06-18), non-financial support from NIHR Clinical Research Network, non-financial support from Roche Products Ltd, non-financial support from Sanofi (Aventis Pharma)"
Protocol: yes, available.

Statistical plan: yes, available

Data-sharing stated: yes, after submission of proposal to info@remapcap.org

Overall comment: in addition to the preprint article, the study registry and protocol were used in data extraction and risk of bias assessment. Appendices were not available.

The report contains early, preliminary results of tocilizumab and sarilumab from the Immune Modulation Therapy domain of the REMAP-CAP clinical trial (an international, adaptive platform trial); further follow-up and analysis are ongoing. As a result, long-term outcomes were not reported.

(Quote:) "At a scheduled interim analysis, the independent DSMB reported that tocilizumab had met the statistical trigger for efficacy (posterior probability 99.75%, odds ratio 1.87, 95%CrI 1.20, 2.76) based on an interim analysis of patients as of October 28. As per protocol, further assignment to control closed on November 19 with randomization continuing between different active immune modulation interventions (...) Following a subsequent interim analysis, the DSMB reported that sarilumab had also met the statistical trigger for efficacy and so these results are also reported"

There were no important changes from the trial registration in the population, intervention, or control treatments.

(Quote:) "Investigators at each site selected a priori at least two interventions, one of which had to be control, to which patients would be randomized...Randomization to the Corticosteroid domain for Covid-19 closed on June 17, 2020.12 Thereafter, corticosteroids were allowed as per recommended standard care."

This trial was updated on 1 March 2021 after publication of the study report.

Hermine 2021

Study characteristics

Methods

RCT
Blinding: unblinded
Date of study: 31 March 2020 to 18 April 2020
Location: multicenter: France
Follow-up duration (days): 90

Participants

Population: patients with COVID-19 (moderate-severe)

Randomized: 131 participants (n1 tocilizumab arm = 64 / n2 control arm = 67)

Characteristics of participants

- N = 131
- Mean age: 64.8 years
- 88 males
- Admitted to ICU: n = 6
- Severity: mild: n = 0; moderate: n = 55; severe: n =75; critical: n = 0
- Patients on oxygen without intubation: n = 130 (100%); intubated: n = 0

Hermine 2021 *(Continued)*

- C-reactive protein (median): 119.5 to 127.0 mg/L

Interleukin-6: NR

Number of vaccinated participants: NR

Inclusion criteria

- Confirmed SARS-CoV-2 infection (positive on RT-PCR and/or typical chest CT scan)
- Requiring more than 3L/minute of oxygen
- WHO progression scale = 5
- No NIV or high flow

Exclusion criteria

- Known hypersensitivity to tocilizumab or to any of their excipients
- Pregnancy
- Current documented bacterial infection
- Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending on the medication:
  - absolute neutrophil count (ANC) ≤ 1.0 x 10^9/L;
  - hemoglobin level: no limitation;
  - platelets (PLT) < 50 G /L;
  - SGOT or SGPT > 5N.

Dropouts and withdrawals: 1/131(1%); 0 withdrawal due to AEs

Interventions	**Intervention:** tocilizumab (8 mg/kg infusion) on day 1, an additional fixed dose of 400 mg IV on day 3 at physician discretion. The number of participants who received 2nd dose is not reported. **Control:** standard care **Definition of standard care:** usual care (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants) was provided at the discretion of the clinicians. **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 21 (33%) Standard care: 41 (61%)
Outcomes	**Primary outcome of the trial** The 2 primary outcomes were: • the proportion of patients dead or needing noninvasive or mechanical ventilation on day 4 (> 5 on the WHO-CPS); and • survival with no need for noninvasive or mechanical ventilation at day 14 Note: the definition of clinical improvement extracted is hospital discharge.
Notes	**Funding:** public/nonprofit. (This trial was publicly funded (Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research (FRM), AP-HP Foundation and the Reacting program).) **Conflict of interest:** declared. No conflict of interest. Quote: “Dr Tharaux has received honorarium fees for participation on advisory boards for Retrophin Inc not related to this work. No other disclosures are reported.” **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, with publication. philipperavaud@gmail.com

Hermine 2021 *(Continued)*

Overall comment: in addition to the published article, the trial registry, protocol and supplemental materials and the reply provided by authors were used in data extraction and assessment of risk of bias. There were no major differences between trial registry, protocol and published article in procedures and outcomes, and no changes in treatments.

Immunotherapy co-interventions consisted of anakinra (1 participant in intervention group, 3 in control) and eculizumab (1 participant in control). Remdesivir was given to 1 participant in control group.

On 23 October 2020, we received additional information from authors on this study. This study was updated with data from contact with authors.

Hermine 2022

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 30 March 2020 to 20 April 2020 **Location:** multicenter: France **Follow-up duration (days):** 90
Participants	**Population:** patients with suspected or confirmed COVID-19 (severe-critical) admitted to 12 centers in France. **Randomized:** 97 participants n1 = 46; n2 = 51 **Analyzed:** 92 **Characteristics of participants** Mean/median age: Standard care: 65 years Tocilizumab: 63 years 66 males (72%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = 0; severe: n = 25; critical: n = 67 Patients on oxygen without intubation: n = 25; intubated: n = 67 C-reactive protein: median: 182.0 to 199.0 mg/L Interleukin-6: NR Number of vaccinated participants: 0 **Inclusion criteria** • Confirmed SARS CoV-2 infection (positive on RT-PCR and/or typical chest CT scan) with critical pneumonia (O2 > 3L/min, WHO Clinical Progression Scale [WHO-CPS] score > 5 • Patients with non-invasive ventilation (NIV) or mechanical ventilation (MV) **Exclusion criteria:** • Patients with exclusion criteria to the CORIMUNO-19 cohort • Known hypersensitivity to tocilizumab or to any of their excipients • Pregnancy • Current documented bacterial infection • Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending of the medication: Absolute neutrophil count (ANC) ≤ 1.0 x 109/L • Hemoglobin level: no limitation • Platelets (PLT) < 50 G /L • SGOT or SGPT > 5N
Interventions	**Intervention:** tocilizumab (8 mg/kg single dose. Second dose of 400 mg if decrease of oxygen requirement < 50%)

Hermine 2022 *(Continued)*

	Control: standard care **Definition of standard care:** NR **Steroid use at baseline or any time during the study** At baseline Standard care: 4 (9%) Tocilizumab: 8 (16%)
Outcomes	**Primary outcome of the trial** 1. The early co-primary outcome is the proportion of patients with a decrease of WHO score of at least 1 point at day 4. 2. The longer-term co-primary outcome is the cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 if patients have been intubated before day 14 or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score 6) and remained without intubation. Note: The definition of clinical improvement extracted is "hospital discharge"
Notes	**Funding:** public/nonprofit (Assistance Publique - Hôpitaux de Paris) **Conflict of interest:** yes, declared. Conflict of interest: Olivier Hermine has nothing to disclose; Philippe Ravaud has nothing to disclose. **Protocol:** yes **Statistical plan:** yes In addition to the published article, the study registry was used in data extraction and risk of bias assessment. Data were extracted from The WHO REACT Working Group 2021. The study was updated on 16 March 2022 with data from the published report.

HMO-0224-20 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 8 April 2020 to 3 February 2021 **Location:** multicenter: Israel **Follow-up duration (days):** 90
Participants	**Population:** patients with confirmed COVID-19 (severe-critical) admitted to multiple centers in Israel. **Randomized:** 54 participants n1 = 17; n2 = 37 **Analyzed:** 54 **Characteristics of participants** Mean/median age: Placebo: 66 years Tocilizumab: 62 years 37 males (69%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = 0; severe: n = 21; critical: n = 33 Patients on oxygen without intubation: n = 21; intubated: n = 33 C-reactive protein: median: 43.3 to 118.1 mg/L Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • Any gender • Age 18 and older

HMO-0224-20 2021 *(Continued)*

- Informed consent for participation in the study
- Virological diagnosis of Sars-CoV2 infection (PCR)
- Acute respiratory failure
- Radiographic pneumonia, defined as any/ changing new lung infiltrate
- Patient breathing spontaneously, required more than 50% oxygen and Modified Early Warning Score (MEWS) > 7
- If intubated, intubated less than 24 hours with PaO2/Fio2 ratio ≤ 200 and positive end-expiratory pressure (PEEP) ≥ 5 cm H2O

Exclusion criteria:

- Known hypersensitivity to tocilizumab or its excipients
- Patient with a life expectancy of less than 6 months
- Known active infections or other clinical condition that contra-indicate tocilizumab and cannot be treated or solved according to the judgement of the clinician
- Neutrophils < 500 /mmc
- Platelets < 40.000 /mmc

Interventions	**Intervention:** tocilizumab (8 mg/kg (max 800 mg) IV single dose) **Control:** placebo **Definition of standard care:** NR **Steroid use at baseline or any time during the study** At baseline Placebo: 15 (88%) Tocilizumab: 31 (84%)
Outcomes	**Primary outcome of the trial** NR (study is unpublished) Note: The definition of clinical improvement extracted is "hospital discharge".
Notes	**Funding:** public/nonprofit (Hadassah Medical Organization) **Conflict of interest:** yes, declared. **Protocol:** NR **Statistical plan:** NR The study is not yet published. Data presented were extracted from study registry and WHO REACT Working Group 2021. The authors have been contacted in order to obtain the results.

Horby 2021b

Study characteristics

Methods	RCT **Blinding:** unblinded **Date of study:** 14 April 2020 to 24 January 2021 **Location:** multicenter (131 centres); UK **Follow-up duration (days):** 28
Participants	**Population:** patients with suspected or confirmed COVID-19 (moderate-critical) admitted to 131 centers in the UK **Randomized:** 4116 participants (n1 = 2022; n2= 2094) **Characteristics of participants** • Mean age: 63.6 years

Horby 2021b *(Continued)*

- 2772 males
- Admitted to ICU: n = NR
- Severity: mild: n = 9 / moderate: n = 1868 / severe: n = 1686 / critical = 562
- Patients on oxygen without intubation: n = 3554 (86%); intubated: n = 562 (14%)
- C-reactive protein (median): 143 to 144 mg/L
- Interleukin-6: NR
- Number of vaccinated participants: NR

Inclusion criteria

- Hospitalized adults patients (including pregnant women) with clinically suspected or laboratory-confirmed SARS-CoV-2 infection
- Hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy); evidence of systemic inflammation (C reactive protein (CRP) ≥ 75 mg/L)
- No medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial

Exclusion criteria

- A specific contra-indication to 1 of the active drug treatment arms or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomization for that patient
- Patients with known hypersensitivity to tocilizumab, evidence of active tuberculosis infection or clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19) were not eligible for randomization to tocilizumab

Dropouts and withdrawals : 0% dropout, withdrawal due to AEs: NR

Interventions	**Intervention:** tocilizumab (800 mg if weight > 90 kg; 600 mg if weight > 65 and ≤ 90 kg; 400 mg if weight > 40 and ≤ 65 kg; 8 mg/kg if weight ≤ 40 kg); a 2nd infusion could be administered 12 to 24 hours after the 1st) **Control:** standard care **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 1664 (82%) Standard care: 1721 (82%)
Outcomes	**Primary outcome of the trial** 28-day mortality Note: the definition of clinical improvement extracted is discharged alive from hospital within 28 days.
Notes	**Funding:** public/non profit (UK research and Innovation/National Institute for Health Research (NIHR); NIHR Oxford Biomedical Research Centre, Wellcome; Bill and Melinda Gates Foundation; Department for International Development; Health Data Research UK; Medical Research Council Population Health Research Unit; NIHR Clinical Trials Unit Support Funding; Abbvie (lopinavir-ritonavir); Roche Products Ltd (tocilizumab); Regeneron (REGEN-480 COV2)) **Conflict of interest:** yes, declared. The authors have no conflict of interest or financial relationships relevant to the submitted work to disclose **Protocol:** yes. In English **Statistical plan:** yes **Data-sharing stated:** yes, within 3 months of publication **Data accessibility**: ndph.ox.ac.uk/data-access **Overall comment:** in addition to the preprint article, the study registry and protocol were used in data extraction and risk of bias assessment. This article is a preliminary report on the tocilizumab arm of the ongoing RECOVERY platform study after 28 days with the main analysis planned at 6 months post-

Horby 2021b *(Continued)*

randomization. As a result, the target sample size specified in the registry was not achieved. There is no change from the trial registration in the intervention and control treatments.

IMMCOVA 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 11 June 2020 to 20 March 2021 **Location:** multicenter: Sweden **Follow-up duration (days):** 28
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) admitted to a multiple centers in Sweden **Randomized:** 49 participants n1 = 27; n2 = 22 **Analyzed:** 49 **Characteristics of participants** Mean/median age: Standard care: 62 years Tocilizumab: 64 37 males (76%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = 0; severe: n = 49; critical: n = 0 Patients on oxygen without intubation: n = 49; intubated: n = 0 C-reactive protein: median: 126.0 to 151.0 mg/L Interleukin-6: median: 24 to 26 pg/mL Number of vaccinated participants: NR **Inclusion criteria** • Age ≥ 18 years • Laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay < 7 days prior to screening • SARS-CoV-2 infection with duration at least 7 days (i e may be included on day 7) as determined by onset of symptoms (defined as day 1) • 5 liters/minute of oxygen for at least 8 hours to maintain SpO2 at ≥ 93%. A shorter duration is also accepted if presentation is acute, and the patient needs more than 10 liters/minute of oxygen, or high flow nasal cannula or non-invasive ventilation, to maintain SpO2 at ≥ 93% • C-reactive protein > 70 mg/L with no non-SARS-Cov2 infections. Values measured up to 48 hours before inclusion are accepted • Ferritin > 500 µg/L values measured up to 48 hours before inclusion are accepted • At least two points on a scale of 0 to 3 where 1 point is awarded for each value of lymphocytes < 1 x 10(9)/L, D-dimer ≥ 0.5 mg/L and lactate dehydrogenase ≥ 8 microkatal/L. The values do not have to be concurrently positive and may be up to 3 days old at inclusion • Ability to provide informed consent signed by study patient • Willingness and ability to comply with study-related procedures/assessments • In fertile females, willing to comply with effective contraceptive methods for up to 3 months after last dose of study drug. These may include surgical sterilization of patient or partner, intrauterine device or condoms. Gestagen-only birth control pills (mini-pills), which do not increase the risk of deep venous thrombosis, may also be used. Non-fertile woman is defined as more than 12 months of amenorrhea without an alternative medical cause or, in case of ambiguities, a follicle stimulating hormone (FSH) level in the postmenopausal range. **Exclusion criteria**

IMMCOVA 2021 *(Continued)*

- Pregnancy or breastfeeding
- Ongoing or completed mechanical ventilation
- In the opinion of the investigator, unlikely to survive for > 48 hours from screening
- In the opinion of the investigator, expected overall survival due to other comorbidities less than 3 months
- Severe renal dysfunction eGFR < 30 ml/min
- Medical history including chronic liver disease with inflammation, fibrosis or cirrhosis including underlying diseases such as alcoholic liver disease, non-alcoholic fatty liver disease, chronic viral hepatitis, alcoholic liver disease, autoimmune liver disease, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis, or carcinoma
- Uncontrolled hypertension Systolic BP > 180 mm Hg, Diastolic BP > 110 mm Hg
- History of hypersensitivity to the study drugs
- Presence of any of the following abnormal laboratory values at screening: absolute neutrophil count (ANC) less than 2 x 109/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5 x upper limit of normal (ULN), platelets < 100 x 109/L
- Treatment with anakinra, anti-IL 6, anti-IL-6R antagonists, Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period
- Current treatment with conventional synthetic disease-modifying antirheumatic drugs (DMARDs)/immunosuppressive agents
- Use of chronic oral corticosteroids for a non-COVID-19-related condition in a dose higher than prednisone 10 mg or equivalent per day. Ongoing acute treatment for COVID-19 with any peroral or iv steroid is permitted for up to five days before inclusion. Chronic or acute treatment with inhaled steroids is also permitted
- History of, or current autoimmune or inflammatory systemic or localized disease(s) other than rheumatoid arthritis
- Acute systemic infection, verified by blood cultures systemic bacterial infection, systemic fungi-infection or prosthesis-related infection
- History of stem-cell or solid organ transplantation
- Known active tuberculosis (TB), history of incompletely treated TB, suspected or known extrapulmonary TB, suspected or known systemic bacterial or fungal infections
- Diagnosis of, or suspicion of HIV infection, acute hepatitis A and/or chronic hepatitis B and/or C
- Previous history of gastrointestinal ulceration or diverticulitis.
- Patients who have received immunosuppressive antibody therapy within the past 3 months, including intravenous immunoglobulin or plans to receive during the study period
- Participation in any clinical research study evaluating an investigational product (IP) or therapy within 3 months and less than 5 half-lives of IP prior to the screening visit. The use of remdesivir is permitted.
- Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study

Interventions	**Intervention:** tocilizumab (8 mg/kg (max 800mg) IV single dose) **Control:** standard care **Definition of standard care:** standard care according to local recommendations at the Karolinska University Hospital. Oxygen supplementation so to achieve SpO2 > 93%. Thrombosis prophylaxis (Fragmin or Innohep and Klexane® or new oral anticoagulants including dabigatran, apixaban or rivaroxaban). Steroids (Betapred 6 mg po) broad spectrum antibiotics (for tocilizumab arm) steroids (Betapred 6 mg po) broad spectrum antibiotics (for tocilizumab arm) **Steroid use at baseline or any time during the study** At baseline Standard care: 26 (96%) Tocilizumab: 21 (95%)
Outcomes	**Primary outcome of the trial** NR (unpublished study) Note: The definition of clinical improvement extracted is "discharged at 28-days".

IMMCOVA 2021 *(Continued)*

Notes	**Funding:** public/nonprofit (Karolinska University Hospital) **Conflict of interest:** yes, declared. **Protocol:** NR **Statistical plan:** NR The study is not published yet. Data presented were extracted from study registry and WHO REACT Working Group 2021. The authors have been contacted in order to obtain the results.

Jordan 2021

Study characteristics

Methods	RCT **Blinding:** quadruple blinding **Date of study:** 28 April 2020 to 30 July 2020 **Location:** single center; USA **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) admitted to a single center in the USA. **Randomized:** 17 participants n1 = 8; n2 = 9 **Analyzed:** 16 **Characteristics of participants** Mean/median age: Clazakizumab: 59 years Placebo: 60 years 10 males (63%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = NR; severe: n = NR; critical: n = 0 Patients on oxygen without intubation: n = NR; intubated: n = 0 C-reactive protein: NR Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • Age >18 at the time of screening • Participant must be able to understand and provide informed consent • Hospitalized with COVID-19 (+) disease (confirmed by polymerase chain reaction (PCR) assay from any specimen (e.g. respiratory, blood, urine, stool, other bodily fluid)) • Not on mechanical ventilation and/or ECMO • Evidence of pulmonary involvement with at least 2 of the following: 1. Oxygen saturation (SpO2) at rest in ambient air with SpO2 ≤ 94%, 2 Tachypnea with resting respiration rate > 25 breaths/minute, 3 Partial pressure of oxygen (PaO2) / fraction of inspired oxygen (FiO2) ≤ 300 mmHg, 4 Chest imaging (radiograph, CT scan, or lung ultrasound) with abnormalities consistent COVID-19 pneumonia, 5 C-reactive protein (CRP) > 35 mg/L **Exclusion criteria** • Previous hypersensitivity or allergic reactions to clazakizumab • Lactating or pregnant females • People with latent tuberculosis (TB) and who are not receiving treatment • People with active TB • A significantly abnormal general serum screening lab result defined as a White Blood Count (WBC) < 3.0 X 103/ml, a Hgb < 8.0 g/dL, a platelet count < 50 X 103/ml, a serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) > 5 x upper limit normal

Jordan 2021 *(Continued)*

	• Participation in another clinical trial investigating COVID-19 aimed agents
Interventions	**Intervention:** clazakizumab (25 mg in 50 mL of 0.9% saline intravenously single dose. A second dose could be given after 24 hours up to day 14.) **Control:** placebo **Definition of standard care:** patients may receive standard care supportive care and off-label COVID-19 therapies. **Steroid use at baseline or any time during the study** Clazakizumab: NR Placebo: NR
Outcomes	**Primary outcome of the trial:** NR
Notes	**Funding:** Private (Vitaeris Inc.) **Conflict of interest:** NR **Protocol:** yes **Statistical plan:** yes The trial registry, protocol and statistical analysis plan were used in data extraction and assessment of risk of bias. This is an unpublished study whose results have been reported in ClinicalTrials.gov. The trial was registered prospectively and no important changes were made to primary or secondary outcomes after recruitment start. The trial (n = 17) did not achieve its target sample size (n = 60) and is underpowered to assess statistical significance between the treatment and placebo group.

Lescure 2021

Study characteristics	
Methods	RCT **Blinding:** quadruple blinding **Date of study:** 28 March 2020 to 3 July 2020 **Location:** multicenter (45 centers); Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed (any specimen) COVID-19 (moderate-critical) admitted to 45 centers in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain. **Randomized:** 420 participants (n1sarilumab 400 mg = 173; n2sarilumab 200 mg = 161; n3control = 86) **Characteristics of participants** • Mean age: 58 to 60 years • 261 males • Admitted to ICU: n = 148 • Severity: mild: n = 2; moderate: n = 304; severe: n = 60; critical = 50 • Patients on oxygen without intubation: n = 364 (87%); intubated: n = 50 (12%) • C-reactive protein (median): 94.6 (48.1 to 167.9) mg/L • Interleukin-6: median: 12.3 pg/mL • Number of vaccinated participants: NR **Inclusion criteria** • Patients aged 18 years or older at the time of signing informed consent • Hospitalized for laboratory-confirmed SARS-CoV-2 infection in any specimen within 2 weeks prior to randomization

Lescure 2021 *(Continued)*

- Evidence of pneumonia by chest imaging or chest auscultation and no alternative explanation for current clinical presentation
- Meet criteria for severe disease (defined as administration of supplemental oxygen by nasal cannula, simple face mask, or another similar device) or critical disease (defined as need for supplemental oxygen delivered by non-rebreather mask or high-flow nasal cannula, use of invasive or noninvasive ventilation, or treatment in an ICU)

Exclusion criteria

- Patients with at least 1 of the following: in the investigator's opinion, a low probability of surviving 48 hours or remaining at the investigational site beyond 48 hours
  - Dysfunction of ≥ 2 organ systems or need for extracorporeal life support or renal replacement therapy at screening
  - Absolute neutrophil count < 2000/mm3;AST or ALT exceeding 5-fold upper limit of normal (ULN) at screening
  - Platelets < 50,000/mm3 at screening
  - Known active, incompletely treated, suspected or known extrapulmonary tuberculosis
  - Prior or concurrent use of immunosuppressants at screening, including, but not limited to, IL-6 inhibitors or Janus kinase inhibitors within 30 days of baseline; Anti-CD20 agents without evidence of B-cell recovery to baseline levels or IL-1 receptor antagonist (anakinra) within 1 week of baseline
  - Abatacept within 8 weeks of baseline; tumor necrosis factor a inhibitors within 2 to 8 weeks of baseline
  - Alkylating agents, including cyclophosphamide, within 6 months of baseline
  - Cyclosporine, azathioprine, mycophenolate mofetil, leflunomide, or methotrexate within 4 weeks of baseline
  - Intravenous (IV) immunoglobulin within 5 months of baseline
  - Use of systemic chronic (e.g. oral) corticosteroids for a condition not related to COVID-19 at doses higher than prednisone 10 mg/day or equivalent at screening
  - Suspected or known active systemic bacterial or fungal infections within 4 weeks of screening

Dropouts and withdrawals: 0% dropout, withdrawal due to AEs: NR

Interventions	**Intervention** • Sarilumab 400 mg (400 mg IV infusion, a 2nd dose could be administered 24 to 48 hours after the 1st) • Sarilumab 200 mg (200 mg IV infusion, a 2nd dose could be administered 24 to 48 hours after the 1st) **Control:** placebo **Definition of standard care:** local standard care **Co-interventions** **Steroid use at baseline or any time during the study** Sarilumab 400 mg: 78 (45%) Sarilumab 200 mg: 58 (36%) Placebo: 39 (45%)
Outcomes	**Primary outcome of the trial** Time from baseline to clinical improvement of ≥ 2 points on a 7-point ordinal scale. Discharge prior to day 29 was considered as a 2-point improvement. Note: the definition of clinical improvement extracted is improvement from baseline by at least 2 categories on a 7-point ordinal scale.
Notes	**Funding:** private (Sanofi and Regeneron Pharmaceuticals, Inc) **Conflict of interest:** yes, declared. F-XL has received lecture fees from Merck Sharp & Dohme and Gilead Science. HH has nothing to disclose of relevance to this study. RF has no financial conflicts to

Lescure 2021 *(Continued)*

disclose. JSL, GS, PW, NP, and OH are employees of Sanofi and may hold stock and/or stock options in the company.
Protocol: NR
Statistical plan: NR
Data-sharing stated: yes, currently available
Data accessibility: clinicalstudydatarequest.com/

Overall comment: in addition to the preprint article, the supplementary materials, and the study registry were used in data extraction and risk of bias assessment. Neither study protocol nor statistical analysis plan were available. There were no substantive differences between the prospective registry and the preprint article. The study was an adaptive design and any changes in protocol versions are reported with rationales in the article. The study achieved its prestated sample size. As this study was conducted in 11 countries across 45 sites, standard care may have differed (supported by concomitant medication use presented in Table S2).
This study was updated on March 10th, 2021 with data from the published report.

Lomakin 2021

Study characteristics

Methods	RCT **Blinding:** double blinding **Date of study:** 29 April 2020 to 3 August 2020 **Location:** multicenter: Russian Federation **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) admitted to 12 centers in Russia **Randomized:** 206 participants n1 = 103; n2=103 **Analyzed:** 206 **Characteristics of participants** Mean/median age: Placebo: 58 years Levilimab: 59 years 109 males (53%) Admitted to ICU: n = 0 Severity: mild: n = 80; moderate: n = 123; severe: n=3; critical: n = 0 Patients on oxygen without intubation: n = 126; intubated: n = 0 C-reactive protein: median: 39.8 to 46 mg/L Interleukin-6: median: 9.4 to 11.2 pg/mL Number of vaccinated participants: NR **Inclusion criteria** • Men and non-pregnant women aged 18 years or older • Positive for SARS-CoV-2 RNA • Hospitalized with radiologically confirmed pneumonia with at least one criterion of disease severity (respiratory rate > 30/min, SpO2 ≤ 93%, PaO2/FiO2 ≤ 300 mmHg, increase of the lung involvement by more than 50% after 24 to 48 h, decreased consciousness level, agitation, unstable hemodynamics, arterial blood lactate >2 mmol/L, quick sequential organ failure assessment score (qSOFA) > 2, defined by the presence of any two symptoms of the following: systolic blood pressure ≤ 100 mm Hg, respiratory rate ≥ 22/min, Glasgow Coma Scale score ≤ 14) **Exclusion criteria** • Critical form of COVID-19 (defined by the presence of any of the following: respiratory failure and need of the invasive mechanical ventilation, septic shock, multiple organ failure) • Suspected active bacterial, fungal, viral, or other infection (besides COVID-19)

Lomakin 2021 *(Continued)*

- Confirmed active tuberculosis
- Life expectancy < 24 h, in the opinion of the investigator or who were unlikely to remain at the investigational site beyond 48 h
- Treated with other monoclonal antibodies, immunosuppressive agents or participating in a clinical trial of other drug
- History of allergic reaction to monoclonal antibodies
- Any illness or laboratory findings that, in the opinion of the study investigator, might pose an additional risk to the patient by their participation in the study
- Pregnant or breastfeeding women
- ALT and/or AST levels > 10 × ULN
- Platelet count < 50 × 10^9/L
- Absolute neutrophil count < 1.0 × 10^9/L

Interventions	**Intervention:** levilimab (162 mg subcutaneously twice on day 1; 324 mg rescue therapy allowed in case of worsening of clinical status) **Control:** placebo **Definition of standard care:** standard care therapy (SOC) in accordance with the National clinical guidelines of the Ministry of Health of the Russian Federation, which included symptomatic treatment, antiviral agents, anticoagulants, supportive care, etc. The use of other monoclonal antibodies for the treatment of COVID-19 was not allowed. **Steroid use at baseline or any time during the study** during the study Placebo: 5 (5%) Levilimab: 5 (5%)
Outcomes	**Primary outcome of the trial** ≥ 2-category improvement in clinical status relative to baseline on the 7-category ordinal scale or reaching the clinical status of categories 1 or 2 on Day 14 (amended, initially the primary outcome was overall mortality) Note: The definition of clinical improvement extracted is "≥2-category improvement in clinical status relative to baseline on the 7-category ordinal scale or reaching the clinical status of categories 1 or 2 on Day 14".
Notes	**Funding:** private (JSC BIOCAD) **Conflict of interest:** yes, declared. The research leading to these results received funding from BIOCAD under Grant Agreement No BCD-089-4/CORONA. Authors Nikita V. Lomakin, Bulat A. Bakirov, Denis N. Protsenko, Vadim I. Mazurov, Gaziyavdibir H. Musaev, Olga M. Moiseeva, Elena S. Pasechnik, Vladimir V. Popov, Elena A. Smolyarchuk, Ivan G. Gordeev, Darya S. Fomina have no conficts of interest to declare that are relevant to the content of this article. Author Mikhail Yu. Gilyarov received a speaking fee from Boehringer Ingelheim, Bayer, Pfzer и Servier. Authors Anton I. Seleznev, Yulia N. Linkova, Ekaterina A. Dokukina, Polina S. Pukhtinskaia, Anna V. Eremeeva, Maria A. Morozova, Arina V. Zinkina-Orikhan and Anton A. Lutckii, are JSC BIOCAD employees. **Protocol:** NR **Statistical plan:** NR In addition to the published article, the retrospective study registry was used in data extraction and risk of bias assessment. The protocol and analysis plan were not available. The trial had an adaptive design with the preplanned opportunity to modify the endpoints, intervention doses, sample size, or the size of the study groups. Changes were made to the primary outcome, switching from mortality to clinical improvement because the study did not have enough power to detect the difference between the groups using overall mortality. In addition, there is a minor change from the trial registration in the intervention and control treatments (same dosage, but delivered in two doses vs a single dose). Of note: The protocol allowed open label rescue administration of the intervention drug (occurred in 13 participants in the intervention group and in 42 participants in the placebo group).

Lonze 2022

Study characteristics	
Methods	RCT **Blinding:** double blinding **Date of study:** 1 April 2020 to 3 December 2020 **Location:** multicenter: USA **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe-critical) admitted to multiple centers in the USA. **Randomized:** 178 participants n1 = 78; n2 = 26; n_3= 74 **Analyzed:** 178 **Characteristics of participants** Mean/median age: Clazakizumab 25: 64 years Placebo: 60 years 123 males (69%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = 25; severe: n=90; critical: n = 37 Patients on oxygen without intubation: n=115; intubated: n = 37 C-reactive protein: median: 155.5 mg/L to 161 mg/L Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • Confirmed SARS-CoV-2 infection by reverse transcriptase-quantitative polymerase chain reaction testing and hypoxemia indicated by any of the following: Pao2/Fio2 ratio less than 200, saturation of less than 90% on at least 4 L supplemental oxygen, or increasing oxygen requirements over 24 hours preceding enrollment • Two or more indicators of hyperinflammation were required: C-reactive protein (CRP) greater than 35 mg/L, ferritin greater than 500 mg/mL, d-dimer greater than 1000 ng/mL, neutrophil:lymphocyte ratio greater than 4, lactate dehydrogenase greater than 200 U/L, or elevated troponin absent cardiac disease • Subjects with capacity provided written consent, consent was otherwise obtained from legally authorized representatives **Exclusion criteria** • Irreversible conditions deemed nonsurvivable • Active inflammatory bowel disease • Active untreated diverticulitis • Untreated bacteremia • Pregnancy • Known hypersensitivity to clazakizumab
Interventions	**Intervention:** clazakizumab 25 (25 mg IV single dose. If the CRP does not decrease by 50% within 36 to 48 hours after the first dose, a second dose of 25 mg clazakizumab will be given no later than day 3.) **Control:** placebo **Definition of Standard care:** NR **Steroid use at baseline or any time during the study** At baseline Clazakizumab 25: 59 (76%) Placebo: 55 (74%)
Outcomes	**Primary outcome of the trial** 28-day ventilator-free survival

Lonze 2022 *(Continued)*

	Note: The definition of clinical improvement extracted is "Change in clinical status defined by an improvement in status by at least 2 score points on WHO 11-point ordinal scale, where 0 = uninfected; no viral RNA detected, 1 = asymptomatic; viral RNA detected, 2 = symptomatic; independent, 3 = symptomatic; assistance needed, 4 = hospitalized; no oxygen therapy, 5 = hospitalized; oxygen by mask or nasal prongs, 6 = hospitalized; oxygen by NIV or high flow, 7 = intubation and mechanical ventilation, pO2/FiO2 >/= 150 or SpO2/FiO2 >/= 200, 8 = mechanical ventilation pO2/FiO2 < 150 (SpO2/FiO2 < 200) or vasopressors, 9 = mechanical ventilation pO2/FiO2 < 150 and vasopressors, dialysis, or ECMO, and 10 = Dead"
Notes	**Funding:** mixed (This study was funded by a grant from the Jack Rudin Family Foundation to Dr. Lonze. Clazakizumab was provided at no cost to the investigators by Vitaeris, recently acquired by CSL Behring. No corporate monetary support was provided. Vitaeris provided advice on the study design but had no role in conduct of the study, data collection, analysis, or interpretation. CSL Behring had no role in the study design, study conduct, data collection, analysis, or interpretation.) **Conflict of interest:** yes, declared. Drs. Lonze's, Spiegler's, Petkova's, Dieter's, Li's, S. M. Cohen's, and Hochman's institutions received funding from The Jack Rudin Family Foundation. Drs. Lonze, Spiegler, Alachkar, Dieter, Quinn, Mattoo, Soomro, S. M. Cohen, Leung, Landrum, D. J. Cohen, Sen, Chong, and Montgomery disclosed the off-label product use of Clazakizumab. Dr. Weldon's institution received funding from a private donation for research related to COVID therapy. Dr. Dieter disclosed that her spouse is employed by Daiichi Sankyo (2019 to present) and Bristol Myers Squibb (2008–2009). Dr. Soomro received support for article research from The Jack Rudin Family Foundation. Drs. Leung's and Ali's institutions received funding from New York University Langone. Drs. D. J. Cohen's and Troxel's instructions received funding from Vitaeris. Dr. D. J. Cohen's institution received funding from Alexion Pharmaceuticals; he received funding from Natera and Veloxis. Dr. Chong received funding from Vitaeris. Dr. Hochman disclosed that she is a principal investigator (PI) for the ISCHEMIA trial for which, in addition to support by National Heart, Lung, and Blood Institute grant, devices and medications were provided by Medtronic; Abbott Vascular (formerly St. Jude Medical); Royal Philips NV (formerly Volcano Corporation); Arbor Pharmaceuticals, LLC; AstraZeneca Pharmaceuticals LP; Merck Sharp & Dohme Corp.; Omron Healthcare; Sunovion Pharmaceuticals; Espero BioPharma; and Amgen; and financial donations from Arbor Pharmaceuticals, LLC and AstraZeneca Pharmaceuticals LP, and PI for the National Institutes of Health International Study of Comparative Health Effectiveness with Medical and Invasive Approaches EXTENDed Follow-up (ISCHEMIA-EXTEND) trial. Dr. Montgomery disclosed that he is listed on a patent claim for Clazakizumab. The remaining authors have disclosed that they do not have any potential conflicts of interest. **Protocol:** yes **Statistical plan:** yes In addition to the published article, the study registry, protocol/SAP were used in data extraction and risk of bias assessment. The study achieved the target sample size specified in the trial registry. There is no change from the trial registration in the intervention and control treatments. The registry original primary outcome does not reflect the current primary outcome. This study reports on the results of the high-dose clazakizumab only since the Safety and Monitoring Board (DSMB) recommended dropping of the low-dose arm after interim analysis.

Mariette 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 27 March 2020 to 6 April 2020 **Location:** multicenter: France **Follow-up duration (days):** 90
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) admitted to six centers in France **Randomized:** 148 participants n1 = 68; n2 = 80 **Analyzed:** 144 **Characteristics of participants**

Mariette 2021 *(Continued)*

	Mean/median age: Sarilumab: 62 years Standard care: 63 years 108 males (75%) Admitted to ICU: n = 0 Severity: mild: n = 0; moderate: n = NR; severe: n = NR; critical: n = 0 Patients on oxygen without intubation: n = 144; intubated: n = 0 C-reactive protein: median: 155.0 to 160.0 mg/L **Inclusion criteria** • Hospitalized patients 18 years or older • Confirmed SARS CoV-2 infection (positive on RT-PCR or typical chest CT scan) with mild-to-moderate, severe, or critical pneumonia (receiving > 3L/min of oxygen and having a WHO Clinical Progression Scale [CPS] score > 5 • Moderate-to-severe pneumonia with a WHO CPS score of 5, receiving at least 3 L/min of oxygen, but without ventilation assistance that included high-flow oxygen, non-invasive ventilation, or mechanical ventilation **Exclusion criteria** • ICU at admission • Pregnant women
Interventions	**Intervention:** sarilumab (400 mg IV infusion single dose, second infusion at day 3 in absence of clinical response) **Control:** standard care **Definition of standard care:** antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants **Steroid use at baseline or any time during the study** At baseline Sarilumab: 3 (4%) Standard care: 4 (5%)
Outcomes	**Primary outcome of the trial** The proportion of patients dead or needing non-invasive ventilation or mechanical ventilation on day 4 (patients with a WHO-CPS score of > 5) to be analyzed as a binary outcome and survival with no need for non-invasive ventilation (including high-flow oxygen) or mechanical ventilation at day 14, to be analyzed as a time-to-event outcome. Note: The definition of clinical improvement extracted is "Discharged".
Notes	**Funding:** public/nonprofit (Ministry of Health, Programme Hospitalier de Recherche Clinique and Assistance Publique – Hôpitaux de Paris Foundation and Foundation for Medical Research.) **Conflict of interest:** yes, declared. We declare no competing interests. **Protocol:** yes **Statistical plan:** yes Data presented were extracted from study registry and WHO REACT Working Group 2021. The authors have been contacted in order to obtain the results. Data extraction was updated on 23 December 2021, after the publication of the report. There is no change from the trial registration in the intervention and control treatments. The registry primary outcome reflects the reported primary outcome. Some outcomes (adverse and serious adverse events) were not prespecified in the registry.

Merchante 2021

Study characteristics

Merchante 2021 *(Continued)*

Methods	RCT **Blinding:** unblinded **Date of study:** 13 July 2020 to 5 March 2021 **Location:** multicenter: Spain **Follow-up duration (days):** 28
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) treated in ten hospitals in Andalusia, Southern Spain. **Randomized:** 197 participants **Analyzed:** 191 **Characteristics of participants** Mean/median age: Sarilumab 200 mg: 65 years Sarilumab 400 mg: 57 years Standard care: 57 years 88 males (46%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = 93; severe: n = 22; critical: n = 0 Patients on oxygen without intubation: n = 104; intubated: n = 0 C-reactive protein: median: 67 to 96 mg/L Interleukin-6: median: 56 pg/mL Number of vaccinated participants: NR **Inclusion criteria** • Age ≥ 18 years • Hospitalization due to COVID-19 with SARS-CoV-2 infection confirmed by a positive antigen detection test or a polymerase chain reaction assay • Interstitial pneumonia confirmed by the presence of infiltrates on chest radiograph or a computer tomography scan • IL-6 levels ≥ 40 pg/mL and/or D-dimer > 1500 ng/mL or ≥ 1000 if progressive increments were documented in at least two determinations after admission **Exclusion criteria** • Presence of ARDS requiring HFNO or mechanical ventilation at randomization (or expected to be started in the first 24 hours after randomization as deemed by decision of the investigator) • Patients in which the decision was made to not progress to mechanical ventilation in the event of clinical deterioration
Interventions	**Intervention** Sarilumab 200 mg (200 mg subcutaneously single dose) Sarilumab 400 mg (400 mg subcutaneously single dose) **Control:** standard care **Definition of standard care:** patients received standard care according to local practice, which included any individual drug or combination of drugs listed in the protocol of the Spanish Ministry of Health (www.mscbs.gob.es) and the Spanish Agency of Medicines and Medical Products (www.aemps.gob.es) during the study period. Dexamethasone was the preferred backbone therapy since the press release of the Recovery trial, but high and/or pulse doses (> 1 mg methylprednisolone or equivalent per kilogram of body weight) of corticosteroids were also permitted. **Steroid use at baseline or any time during the study** At baseline Sarilumab 200 mg: 33 (89%) Sarilumab 400 mg: 36 (92%) Standard care: 34 (87%)
Outcomes	**Primary outcome of the trial**

Merchante 2021 *(Continued)*

	Development of ARDS requiring high low nasal oxygen (HFNO), non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation (IMV) during the first 28 days after randomization. Note: The definition of clinical improvement extracted is "Clinical improvement was defined as a 2-point rise in a 7-category ordinal scale or hospital discharge, whichever occurred first."
Notes	**Funding:** mixed (Consejeria de Salud y Familias, Junta de Andalucia, Spain (COVID-19 Research Program); General Sub-Directorate of Networks and Cooperative Research Centers, Ministry of Science and Innovation, Spanish Network for Research in Infectious Diseases; European Regional Development Fund; Spanish Clinical Research Network; ISCIII-Sub-Directorate General for Research Assessment and Promotion) **Conflict of interest:** yes, declared. The authors have no conflict of interest or financial relationships relevant to the submitted work to disclose. No form of payment was given to anyone to produce the manuscript. **Protocol:** yes **Statistical plan:** yes In addition to the published article, the REACT meta-analysis and study registry was used in data extraction and risk of bias assessment. There is no change from the trial registration in the intervention and control treatments. The registry primary outcome reflects the reported primary outcome.

Rosas 2022

Study characteristics	
Methods	RCT **Blinding:** double-blinding **Date of study:** 3 April 2020 to 28 July 2020 **Location:** multicenter: Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, UK, USA **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed COVID-19 (mild to critical) **Randomized:** 452 participants (n1 tocilizumab arm = 301 / n2 control arm = 151) **Characteristics of participants** • N = 452 • Mean age: 60.8 years • 306 males • Admitted to ICU: n = 247 (56%) • Severity: mild: n = 15 / moderate: n = 122/ severe: n = 133/ critical: n = 168 • Patients on oxygen without intubation n = 255 (56%); intubated n = 168 (37%) • C-reactive protein (median): 150.3 to 157.2 mg/L • interleukin-6: median: 150.3 to 157.2 pg/mL • Number of vaccinated participants: 0 **Inclusion criteria** Patients 18 years or older with severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test in any body fluid and evidenced by bilateral chest infiltrates on chest x-ray or CT were enrolled. Eligible patients had blood oxygen saturation ≤ 93% or partial pressure of oxygen/fraction of inspired oxygen < 300 mm/Hg. Informed consent was obtained for all enrolled patients. **Exclusion criteria** Patients were excluded if the treating physician determined that death was imminent and inevitable within 24 hours or if they had active tuberculosis or bacterial, fungal, or viral infection other than SARS-CoV-2.

Rosas 2022 *(Continued)*

	Dropouts and withdrawals :14/452 (3%); 0 withdrawal due to AEs
Interventions	**Intervention:** tocilizumab (8 mg/kg infusion, maximum 800 mg), a second infusion could be administered 8 to 24 hours after the first) **Control:** placebo **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 57 (19%) Placebo: 41 (28%)
Outcomes	**Primary outcome of the trial** Clinical status assessed on a 7-category ordinal scale at day 28 Note: the definition of clinical improvement extracted is improvement from baseline by at least 2 categories on the ordinal scale
Notes	**Funding:** mixed (F. Hoffmann-La Roche Ltd; Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority) **Conflict of interest:** yes. (Quote:) "I.O.R. received a grant from Roche/Genentech during the conduct of the study; a grant and personal fees from Genentech outside the submitted work; and personal fees from Boehringer and Bristol-Myers Squibb outside the submitted work. A.M.'s institution received grant support from Roche/Genentech during the conduct of the study; he has received funding from the National Institutes of Health outside the submitted work and medical education from Merck and Livanova outside the submitted work." **Protocol:** yes, available **Statistical plan:** yes, available **Data-sharing stated:** yes, through vivli.org **Overall comment:** in addition to all available versions of the preprint article, the study registry and supplementary appendix, as well as responses from contact with authors were used in data extraction and 'Risk of bias' assessment. The protocol and statistical analysis plan were not available although it was sent by authors after requested. The full data could not be accessed. Patients in the tocilizumab group received a 2nd dose only if their condition did not improve or worsened. The study achieved the target sample size prespecified in the registry. There is no change from the trial registration in the intervention and control treatments as well as primary outcome. Some secondary outcomes in the registry were not reported in the preprint article, particularly regarding the 60-day time point as well. The sponsor (Hoffman-La Roche Ltd.) played a prominent role, with writing support for the authors provided by Sara Duggan, Ph.D., of ApotheCom, funded by F. Hoffmann-La Roche Ltd. 3 authors were employees of Roche Products Ltd. On 7 December 2020, we received additional information from authors on this study. This study was updated with data from contact with authors on 13 January 2021. This trial was updated on 1 March 2021 after publication of the study report. This study was updated on May 27th, 2022 after a recent publication with longer term follow up outcomes.

Rutgers 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 6 April 2020 to 12 January 2021 **Location:** multicenter: The Netherlands **Follow-up duration (days):** 90
Participants	**Population:** patients with confirmed COVID-19 (moderate-critical) admitted to 11 centers in the Netherlands. **Randomized:** 354 participants n1 = 174; n2 = 180 **Analyzed:** 354 **Characteristics of participants** Mean/median age: Tocilizumab: 67 years Standard care: 66 years 237 males (67%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = 257; severe: n = 82; critical: n = 3 Patients on oxygen without intubation: n = 339; intubated: n = NR C-reactive protein: median 75 to 85 mg/L Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • 18 years or older • Capable of providing informed consent • SARS-CoV-2 infection confirmed by nasopharyngeal swab polymerase chain reaction • Admitted to a ward • Have at least one of the following signs compatible with hyperinflammation: 1) a need for supplemental oxygen (inspired by the ASTCT consensus grade 2 for CRS, generally matching a saturation < 94%) and/or 2) ferritin > 2000 ug/l or a doubling of serum ferritin in 20 to 48 hrs. **Exclusion criteria** • Pregnancy • Allergy to tocilizumab
Interventions	**Intervention:** tocilizumab (8 mg/kg IV infusion single dose, maximum 800 mg. A second infusion could be administered 8 hours after the first) **Control:** standard care **Definition of standard care:** standard care. The majority of patients (88%) received dexamethasone as a concomitant treatment. All other concomitants were permitted, including remdesivir and hydroxychloroquine. **Steroid use at baseline or any time during the study** At baseline Tocilizumab: 151 (87%) Standard care: 162 (90%)
Outcomes	**Primary outcome of the trial:** Mortality after randomization, assessed as a time-to-event endpoint
Notes	**Funding:** mixed (participating hospitals; Roche (drug supplier)) **Conflict of interest:** yes, declared. None to declare. **Protocol:** NR **Statistical plan:** NR

Rutgers 2021 *(Continued)*

In addition to the preprint article, the prospective trial registry was used in data extraction and assessment of risk of bias. Neither protocol nor statistical analysis plan was available. The study achieved it target sample size. There is no change from the trial registration in the intervention and control treatments. The registry primary outcome does reflect the reported primary outcome. Some outcomes in the registry (normalization of HRCT, seroconversion 14 days after randomization) were not reported in the preprint paper. Some outcomes are reported in the paper, but were not prespecified in the trial registry (for example time to death, time to WHO score 7 and above). Considered an interim analysis since only 30-day outcomes are reported. A 3-month endpoint is included in the registry, which reports study status as recruitment completed with follow up continuing.

Salama 2020

Study characteristics

Methods

RCT
Blinding: double-blind
Date of study: 14 May 2020 to 18 August 2020
Location: multicenter: Brazil, Kenya, Mexico, Peru, South Africa, USA
Follow-up duration (days): 60

Participants

Population: patients with confirmed COVID-19 (mild to severe)

Randomized: 388 participants (n1 tocilizumab arm = 259 / n2 control arm = 129)
Characteristics of participants

- N = 388
- Mean age: 55.9 years
- 223 males
- Admitted to ICU: n = 58
- Severity: mild: n = 35 / moderate: n = 242/ severe: n = 100/ critical: n = 0
- Patients on oxygen without intubation: n = 342 (88%); intubated: n = 0
- C-reactive protein (median) : 124.5 to 143.4 mg/L
- Interleukin-6: NR
- Number of vaccinated participants: 0

Inclusion criteria

- Patients ≥18 years of age (with no upper age limit)
- Hospitalized with Covid-19 pneumonia confirmed by a positive polymerase chain reaction test and radiographic imaging
- Blood oxygen saturation < 94% on ambient air

Exclusion criteria

- If they required continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation
- If progression to death was imminent and inevitable within 24 hours as determined by the treating physician
- Active tuberculosis or suspected active bacterial, fungal, or viral infection (other than SARS-CoV-2 or well-controlled HIV)
- Patients with comorbidities were not excluded unless the investigator determined it would preclude safe patient participation

Dropouts and withdrawals: 11/388 (3%); 0 withdrawal due to AEs

Interventions

Intervention: tocilizumab (8 mg/kg up to 800 mg max infusion)
Control: placebo

Salama 2020 *(Continued)*

	Co-interventions **Steroid use at baseline or any time during the study** Tocilizumab: 200 (77%) Placebo: 112 (87%)
Outcomes	**Primary outcome of the trial:** Mechanical ventilation (invasive mechanical ventilation or extracorporeal membrane oxygenation) or death by day 28 Note: the definition of clinical improvement extracted is improvement from baseline by at least 2 categories on the ordinal scale
Notes	**Funding:** private (Genentech, Inc.) **Conflict of interest:** yes, declared. Quote "C.S. reports personal fees from Genentech, Inc. J.H., L.Y., W.G.R., B.K., and S.V.M are employees and shareholders of Genentech, Inc. and have filed a patent for a method of treating pneumonia, including COVID-19 pneumonia, with an IL-6 antagonist." **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, through vivli.org/ **Overall comment**: in addition to the published article, the preprint article, study registry, protocol, statistical analysis plan and supplementary appendix were used in data extraction and 'Risk of bias' assessment. The study achieved the target sample size specified in the trial registry. There is no change from the trial registration in the intervention and control treatments. The registry and protocol version 1 primary outcome (cumulative proportion of mechanical ventilation) does not reflect the primary outcome reported in the paper and protocol version 2 (cumulative proportion of mechanical ventilation or death). Some secondary outcomes reported in the registry were not reported in the manuscript. On 21 December 2020, we received additional information from authors on this study, we updated the study results based on authors reply. The study was also updated on 13 January 2021 with data from the New England Journal of Medicine publication. The definition for clinical improvement was 'at least a two-category improvement in clinical status relative to baseline on the seven-category ordinal scale (for patients in category 2 at baseline, those with a clinical status of category 1 were considered to have met the threshold)' and the data now corresponds to this definition. This study was updated on May 27th, 2022 with results extracted from the registry.

Salvarani 2020

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 31 March 2020 to 11 June 2020 **Location:** multicenter: Italy **Follow-up duration (days):** 30
Participants	**Population:** patients with confirmed COVID-19 (severe) **Randomized:** 126 participants (n1 tocilizumab arm = 60 / n2 control arm = 66) **Characteristics of participants** • N = 126 • Mean/median age: 60 years • 77 males • Admitted to ICU: n = 0

Salvarani 2020 *(Continued)*

- Severity: mild: n = 0 / moderate: n = 0/ severe: n = 126 / critical: n = 0
- Patients on oxygen without intubation: n = NR; intubated: n = 0
- C-reactive protein (median): 6.5 to 10.5 mg/L
- Interleukin-6: median: 42.1 pg/mL
- Number of vaccinated participants: NR

Inclusion criteria

Patients 18 years and older, with an instrumental diagnosis of COVID-19 pneumonia confirmed by a positive reverse-transcriptase polymerase chain reaction assay for SARS-CoV-2 in a respiratory tract specimen. Other inclusion criteria were the presence of acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FIO_2) ratio between 200 mm Hg and 300 mm/Hg, an inflammatory phenotype defined by a temperature greater than 38 ‘C during the last 2 days, and/or serum C-reactive protein (CRP) levels of 10mg/dL or greater and/or CRP level increased to at least 2 times the admission measurement.

Exclusion criteria included

- ICU admission
- Known hypersensitivity to tocilizumab
- Any condition preventing future admission to ICU, such as advanced age with multiple comorbidities, as well as the patient’s expressed will to avoid future intubation.

Dropouts and withdrawals: 3/126 (2%); 0 withdrawals due to AEs

Interventions	**Intervention:** tocilizumab (8 mg/kg) on day 1 up to a maximum of 800 mg, followed by a 2nd dose after 12 hours **Control:** standard care **Definition of standard care:** supportive care following the treatment protocols of each centre. All drugs were allowed but IL-1 blockers, Jak inhibitors, and tumour necrosis factor inhibitors. Steroids were allowed if already taken before hospitalization. In case of occurrence of documented clinical worsening, patients randomized in both arms could receive any therapy, including steroids, and, for patients randomized in the control arm, tocilizumab. **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 6 (10%) Standard care: 7 (11%)

Outcomes	**Primary outcome of the trial**
	
	• Clinical worsening within 14 days since randomization, defined by occurrence of 1 of the following events:
	  ◦ admission to ICU with mechanical ventilation;
	  ◦ death;
	  ◦ PaO_2/FIO_2 ratio > 150 mm Hg
	
	Note: the definition of clinical improvement extracted is discharge.

Notes	**Funding:** mixed (local resources, the Italian Ministry of Health and Roche) **Conflict of interest:** yes, declared. Quote “Dr Costantini reported receiving nonfinancial support (provision of experimental drug and distribution to clinical sites) from Roche during the conduct of the study. Dr Angheben reported receiving grants from Italian Ministry of Health” **Protocol: y**es, available **Statistical plan:** yes, available **Data-sharing stated:** yes, after approval of a proposal

Salvarani 2020 *(Continued)*

Overall comments: in addition to the published article, the trial registries, protocol and supplemental material were used in data extraction and assessment of risk of bias. The trial was terminated on the decision of the Scientific Committee due to lack of effect and poor enrolment because of the dramatic decrease in the incidence of the disease in Italy at the time. There were some differences between trial registration and published article in inclusion and exclusion criteria. There was no difference in study treatments between trial registration and published article. 14 participants in the standard care group crossed over and received tocilizumab after clinical worsening

Samsonov 2022

Study characteristics

Methods	RCT **Blinding:** double-blind **Date of study:** 23 April 2020 to 24 July 2020 **Location:** multicenter: Russia **Follow-up duration (days):** 28
Participants	**Population:** patients with suspected or confirmed COVID-19 (severe-critical) admitted to 16 centers in Russia **Randomized:** 372 participants n1 = 124; n2 = 124; n3= 124 **Analyzed:** 372 **Characteristics of participants** Mean/median age: RPH-104: 58 years Olokizumab: 60 years Placebo: 60 years 196 males (53%) Admitted to ICU: n = NR Severity: mild: n = 0; moderate: n = NR; severe: n = NR; critical: n = NR Patients on oxygen without intubation: n = NR; intubated: n = NR C-reactive protein: NR Interleukin-6: NR Number of vaccinated participants: NR **Inclusion criteria** • The presence of a voluntarily signed and dated Patient Informed Consent Form for participation in this study, or a record of an Medical Consilium decision justifying patient's participation in case of patient is unable to state his/her will • Having either of the following COVID-associated respiratory syndromes:pneumonia with oxygenation saturation SpO2 ≤ 93% (on room air) or respiratory rate greater than 30/min or acute respiratory distress syndrome (ARDS) (PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 315 if PaO2 is not available) • COVID-19 diagnosis based on:laboratory-confirmed SARS-CoV-2 infection as determined by Polymerase Chain Reaction method (PCR) or bilateral changes in the lungs typical for COVID-19, based on chest computed tomography results. **Exclusion criteria** • A history of hypersensitivity to the study drugs (RPH-104 and/or OKZ), and/or their components • The presence of any of the following laboratory abnormalities:absolute neutrophil counts < 0.5 x 10^9 L,white blood cell count < 2 x 10^99 L, platelet count < 50 x 10^9 L, ALT and/or AST ≥ 3.0 x Upper Limit of Normal (ULN) • Severe renal failure: creatinine clearance < 30 mL/min • Septic shock (vasopressors are required to maintain mean arterial pressure ≥ 65 mm Hg and lactate ≥ 2 mmol/L in the absence of hypovolemia)

Samsonov 2022 *(Continued)*

- The disease progresses to death over the next 24 hours, regardless of treatment, according to Investigator
- Perforation of the gastrointestinal tract, a history of diverticulitis
- Administration of plasma from COVID-19 convalescent donors within 4 weeks before study enrollment and/or planned administration during the study
- Recent (less then 5 half-lives) administration of tocilizumab or sarilumab
- Recent (less then 5 half-lives) or planned during the current study period use of the following drugs: biologics (except RPH-104 or OKZ) with immunosuppressive effect, including, but not limited to: Interleukin-1 (IL-1) inhibitors (anakinra, rilonacept, canakinumab), IL- 6 inhibitors (except tocilizumab and sarilumab), IL-17A inhibitors (secukinumab), tumor necrosis factor α (TNFα) inhibitors (infliximab, adalimumab, etanercept, etc.), antiB-cell drugs, etc. other immunosuppressive drugs (with the exception of methotrexate in a dose of up to 25 mg/week), including, but not limited to:high doses of glucocorticoids (equivalent to prednisolone > 1 mg/kg) orally or parenterally. JAK inhibitor, cyclophosphamide, etc.
- Concurrent participation in another clinical trial
- Pregnancy, breastfeeding
- A history of active tuberculosis, or active tuberculosis suspected by the Investigator

Interventions	**Intervention** RPH-104 (80 mg subcutaneously single dose) olokizumab (64 mg subcutaneously single dose) **Control:** placebo **Definition of standard care:** throughout the study, it is allowed to use standard COVID-19 therapy accepted at the institution, with the exception of drugs that are not allowed by this protocol throughout the study, as well as tocilizumab and sarilumab during the first 24 hours after administration of the study drugs. Tocilizumab or sarilumab at the doses recommended for the treatment of this disease may be added to concomitant therapy in the absence, in the Investigator's opinion, of improvement in the patient's condition within 24 hours after the administration of one of the study drugs. The following medications are prohibited throughout the study: immunosuppressive biologics (with the exception of RPH-104 or OKZ), including, but not limited to: IL-1 inhibitors (anakinra, rilonacept, canakinumab), IL-6 inhibitors (except tocilizumab and sarilumab), IL-17A inhibitors (secukinumab), tumor necrosis factor α. **Steroid use at baseline or any time during the study** At baseline RPH-104: 0 (0%) Olokizumab: 0 (0%) Placebo: 0 (0%)
Outcomes	**Primary outcome of the trial** NR Note: The definition of clinical improvement extracted is "The proportion of patients with an improvement in clinical status by 2 or more points on the 6-point ordinal scale (where 1 was the most favorable outcome and 6 was the most undesirable outcome) during the study with no use of tocilizumab or sarilumab. The 6-point ordinal scale included the following categories: Not hospitalized, no activity limitations. Not hospitalized, limited activity. Hospitalized, not requiring supplemental oxygen. Hospitalized, supplemental oxygen, with independent breathing. Hospitalized, mechanical ventilation (invasive/non-invasive) or ECMO. Death."
Notes	**Funding:** private (R-Pharm International, LLC, Data Management 365 LLC and K-Research, LLC) **Conflict of interest:** NR **Protocol:** yes **Statistical plan:** yes The trial registry, protocol and statistical analysis plan were used in data extraction and assessment of risk of bias. This is an unpublished study whose results have been reported in ClinicalTrials.gov. The

Samsonov 2022 *(Continued)*

study achieved the target sample size specified in the trial protocol. The protocol was prospective and no important changes were made to primary or secondary outcomes after the start of the recruitment.

Sancho-Lopez 2021

Study characteristics

Methods	RCT **Blinding:** unblinded **Date of study:** 4 August 2020 to 23 March 2021 **Location:** multicenter: Spain **Follow-up duration (days):** 28
Participants	**Population:** patients with confirmed COVID-19 (moderate) admitted to 5 centers in Spain **Randomized:** 201 participants n1 = 99; n2 = 102 **Analyzed:** 201 **Characteristics of participants** Mean/median age: Sarilumab: 60 years Standard care: 60 years 141 males (70%) Admitted to ICU: n = 0 Severity: mild: n = 0; moderate: n = 201; severe: n = 0; critical: n = 0 Patients on oxygen without intubation: n = 201; intubated: n 0 C-reactive protein: median: 95.25 to 98.55 mg/L Interleukin-6: median: 13.25 to 19.20 pg/mL Number of vaccinated participants: NR **Inclusion criteria** • Patients at least 18 years of age and hospitalized due to COVID-19 confirmed by positive RT-PCR or antigen test • Presented with pneumonia defined by the radiographic evidence of pulmonary infiltrates by imaging, or rales/crackles on examination, and required standard oxygen supplement due to SpO2 ≤ 94% on room air • Time from symptom onset to inclusion must be at least 7 days • Patients must present elevation of IL-6 more than 40 pg/mL, or d-dimer more than 1.0 mcg/ml, or at least two of the following analytical inflammatory parameters: elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, or lymphopenia **Exclusion criteria** • Patients with high oxygen requirements (including face mask with reservoir bag, non-invasive mechanical ventilation or high flow nasal cannula, or mechanical ventilation) • Had been on treatment with weight-adjusted corticosteroids (CS) for more than 1 day • Were admitted to the intensive care unit (ICU) • Pregnant or lactating • Had allergy or hypersensitivity to sarilumab or CS • Had received immunosuppressive monoclonal antibody therapy within the past 5 months • AST/ALT values more than 10 x ULN • Neutropenia (less than 0.5 x 109/L) • Severe thrombocytopenia (less than 50 x 109/L) • Sepsis caused by an alternative pathogen • Diverticulitis with risk of perforation • Ongoing infectious dermatitis

Sancho-Lopez 2021 *(Continued)*

Interventions	**Intervention:** sarilumab (200 mg IV infusion single dose for 1 hour (if body weight < 75 kg); 400 mg IV infusion for 1 hour (if body weight >= 75 kg)) **Control:** standard care **Definition of standard care:** corticosteroids were given to all patients at a 1 mg/kg/day of methylprednisolone for at least 3 days as part of the standard care background medication. Standard care also included antibiotic agents, antiviral agents, steroid boluses, vasopressor support, and anticoagulants that were provided at the discretion of the investigators. **Steroid use at baseline or any time during the study** At baseline Sarilumab: 99 (100%) Standard care: 102 (100%)
Outcomes	Primary outcome: proportion of patients progressing to severe respiratory failure (Brescia-COVID equal or higher than 3, defined by the need for high-frequency nasal ventilation, continuous positive airway pressure (CPAP), noninvasive ventilation, or mechanical ventilation), admission to the ICU, or death. Note: The definition of clinical improvement extracted is "discharge at day 28.
Notes	**Funding:** private (Biomedical Research Foundation of the Puerta de Hierro Majadahonda University Hospital; Sanofi (drug donation)) **Conflict of interest:** yes, declared. Aranzazu Sancho-Lopez, Antonio F Caballero-Bermejo, Belen Ruiz-Antoran, Elena Munez Rubio, Mercedes Garcıa Gasalla, Juan Buades, Marta Gonzalez Rozas, Marıa Lopez Veloso, Ana Munoz Gomez, Ana Cuenca Abarca, Pedro Duran del Campo, Fatima Ibanez, Alberto Dıaz de Santiago, Yolanda Romero, Jorge Calderon, Ilduara Pintos, Adrian Ferre, Beltran, Gustavo Centeno Soto, Jose Campos, Antonio Ramos Martınez, Cristina Avendano Sola, Ana Fernandez Cruz have nothing to disclose. **Protocol:** yes **Statistical plan:** yes In addition to the published article, the study registry and supplementary file were used in data extraction and risk of bias assessment. WHO REACT Working Group 2021 was also available. The registry primary outcome does not reflect the reported primary outcome. Outcomes from the registry were specified at 15 days as a time point vs the outcomes in report are reported at 28 days as a time point. The study achieved the target sample size specified in the trial registry. There is no change from the trial registration in the intervention and control treatments. This study was updated on 18 November 2021 with data from the published journal report.

Sivapalasingam 2022

Study characteristics	
Methods	RCT **Blinding:** double blinding **Date of study:** 18 March 2020 to 2 July 2020 **Location:** multicenter: USA **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed COVID-19 (moderate-critical) admitted to 56 centers in the USA **Randomized:** NR **Analyzed:** 457 **Characteristics of participants** Mean/median age: Sarilumab 400mg: NR Sarilumab 200mg: NR Placebo: NR 331 males (72%) Admitted to ICU: n = NR

Sivapalasingam 2022 *(Continued)*

Severity: mild: n = 0; moderate: n = NR; severe: n = NR; critical: n = NR
Patients on oxygen without intubation: n = NR; intubated: n = NR
C-reactive protein: NR

Interleukin-6: median: 67.1 to 254.9 pg/mL

Number of vaccinated participants: NR
Inclusion criteria

- ≥18 years of age
- Hospitalized with laboratory-confirmed SARS-CoV-2 infection
- Requiring supplemental oxygen and/or assisted ventilation

Exclusion criteria:

- In the opinion of the investigator, not expected to survive for more than 48 hours from screening
- Presence of any of the following abnormal laboratory values at screening: absolute neutrophil count < 2000 mm3, aspartate aminotransferase or alanine aminotransferase > 5 x upper limit of normal, platelets < 50,000 per mm3
- Treatment with anti-IL 6, anti-IL 6R antagonists, or with Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period
- Current treatment with the simultaneous combination of leflunomide and methotrexate
- Exclusion criteria related to tuberculosis (TB): Known active TB or a history of incompletely treated TB and Suspected or known extrapulmonary TB
- Patients with suspected or known active systemic bacterial or fungal infections Note: Patients with a history of positive bacterial or fungal cultures but on enrollment do not have suspected or known active systemic bacterial or fungal infections may be enrolled
- Participation in a double-blind clinical research study evaluating an investigational product or therapy within 3 months and less than 5 half-lives of investigational product prior to the screening visit Exception: The use of remdesivir, hydroxychloroquine, or other treatments being used for COVID-19 treatments in the context of an open-label study, emergency use authorization, compassionate use protocol, or open-label use is permitted
- Any physical examination findings, and/or history of any illness, concomitant medications, or recent live vaccines that, in the opinion of the study investigator,might confound the results of the study or pose an additional risk to the patient by their participation in the study
- Known systemic hypersensitivity to sarilumab or the excipients of the drug product

Interventions	**Intervention** Sarilumab 400 mg (400 mg IV infusion single dose or weekly up to 4 doses) Sarilumab 200 mg (200 mg IV infusion single dose or weekly up to 4 doses) **Control:** placebo **Definition of standard care:** all patients received local standard care (SOC), including corticosteroids and open-label use of putative treatments for Covid-19 **Steroid use at baseline or any time during the study** Sarilumab 400mg: NR Sarilumab 200mg: NR Placebo: NR
Outcomes	**Primary outcome of the trial** Per cent change from baseline in CRP level at day 4 (phase 2) Note: The definition of clinical improvement extracted is "Proportion with 1-point improvement in clinical status using a 7-point ordinal scale on day 22".
Notes	**Funding:** private (Regeneron Pharmaceuticals, Inc.; Sanofi; Biomedical Advanced Research and Development Authority; Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority) **Conflict of interest:** yes, declared. ICMJE forms for all authors available at www.medrxiv.org/content/10.1101/2021.05.13.21256973v1.supplementary-material. Several authors, including first corresponding author, are employees and own stock by the sponsor, Regeneron Pharmaceuticals, Inc.

Sivapalasingam 2022 *(Continued)*

Protocol: no
Statistical plan: no

In addition to the published/preprint articles, the data supplement and study registry were used in data extraction and risk of bias assessment. Study authors report that the phase 2 and 3 trial was designed with an adaptive trial design allowing for changes to enrolment, interventions, and outcomes while the trial was ongoing. Several post-hoc changes were thus made to severity eligible for enrolment, interventions, and outcomes. Here we extracted phase 2 data. Phase 3 cohort 1 was also reported in this paper but extracted separately.
The study was updated on 13 April 2022 with data from the published report.
The study was updated on 27 May 2022 with data extracted from the registry.

Soin 2021

Study characteristics

Methods

RCT
Blinding: unblinded
Date of study: 30 May 2020 to 31 August 2020
Location: Multicenter: India
Follow-up duration (days): 30

Participants

Population: patients with confirmed COVID-19 (moderate-critical) admitted to 12 centers in India
Randomized: 180 participants n1 = 90; n2 = 90
Analyzed: 179
Characteristics of participants
Mean/median age:
Tocilizumab: 56 years
Standard care: 54 years
152 males (85%)
Admitted to ICU: n = 118
Severity: mild: n = 0; moderate: n = NR; severe: n = NR; critical: n = 9
Patients on oxygen without intubation: n = 161; intubated: n = 9
C-reactive protein: mean: 88.1 to 110.7 mg/L

Interleukin-6: mean: 85.2 to 115.5 pg/mL

Number of vaccinated participants: NR
Inclusion criteria

- Patients aged 18 years or older
- Admitted to hospital with SARS-CoV-2 infection confirmed by WHO criteria (positive PCR test on any specimen)
- Moderate to severe disease defined according to the Indian MoHFW clinical management protocol for COVID-19. Moderate defined as respiratory rate 15 to 30 per min [revised to 24 per min on 13 June 2020] and blood oxygen saturation [SpO2] 90 to 94% and Severe defined as respiratory rate ≥ 30 per min or SpO2 < 90% in ambient air, or ARDS or septic shock

Exclusion criteria:

- Known severe allergic reaction to tocilizumab or other monoclonal antibodies
- Active tuberculosis infection
- Suspected or active bacterial, fungal, or viral infection (except treated hepatitis C or B), or any other infection except COVID-19
- Investigator deemed that the patient death was imminent and inevitable within 24 hours or judged that the patient had any serious medical conditions or laboratory abnormalities that precluded safe participation in and completion of the study

Soin 2021 *(Continued)*

	• Patients could not have received any oral anti-rejection or immunomodulatory drugs in the previous 6 months or treatment with any investigational agent (including antivirals, cell-depleting therapies, biologics, and Janus kinase inhibitors) within five half-lives or 30 days before randomization, whichever was longer • Patients could not have a diagnosis of immune related rheumatic disease or be receiving corticosteroids equivalent to methylprednisolone at a dose of more than 1 mg/kg per day at screening or baseline Absolute neutrophil count less than 500 cells per mcL, platelet count less than 50,000 cells per mcL, and alanine aminotransferase or aspartate aminotransferase concentrations more than ten times the upper limit of normal within 24 h of screening or baseline.
Interventions	**Intervention:** tocilizumab (6 mg/kg IV infusion, maximum 480 mg/day, a second infusion could be administered within 12 hours to 7 days after the first dose.) **Control:** standard care **Definition of standard care:** standard care was provided according to the protocols at the individual study sites. Corticosteroids equivalent to methylprednisolone at a dose of 1 mg/kg or less were permitted if deemed necessary by the treating physician. Supplemental oxygen was recommended to treat hypoxia, and high-flow nasal cannula, non-invasive ventilation, and mechanical ventilation could be considered if hypoxia and respiratory distress progressed. Treatments for shock or hypovolemia, symptoms such as fever and myalgia, and comorbid conditions could be administered if deemed necessary by the treating physician. **Steroid use at baseline or any time during the study** During the study Tocilizumab: 83 (91%) Standard care: 80 (91%)
Outcomes	**Primary outcome of the trial** Proportion of patients with progression of COVID-19 from moderate to severe or from severe to death up to day 14 Note: The definition of clinical improvement extracted is "Clinical improvement was defined as National Early Warning Score2 of ≤ 2 maintained for 24 hours or COVID-19 grade up to 28 days."
Notes	**Funding:** mixed (Medanta Institute of Education and Research; Roche India; Cipla India; Action COVID-19 India) **Conflict of interest:** yes, declared. AVR reports personal speaker fees, honoraria, and advisory board fees from Roche outside of the submitted work and is a member of the pediatric steering committee of the RECOVERY trial. All other authors declare no competing interests. **Protocol:** yes **Statistical plan: y**es In addition to all available version of the published article, the study registry and protocol were used in data extraction and risk of bias assessment. This is an unmasked study with no placebo. There is no change from the trial registration in the intervention and control treatments. Primary and secondary efficacy analyses were done in the modified intention-to-treat population (i.e. 179 patients), which included all randomly assigned patients who had at least one post-baseline assessment for the primary endpoint. Overall safety (mortality, adverse and serious adverse events) was assessed in all randomly assigned patients (i.e. 180 patients). Conversion to negative RT-PCR, stated as an outcome in the protocol and article, was not reported.

Stone 2020

Study characteristics	
Methods	RCT **Blinding:** double-blind **Date of study:** 20 April 2020 to 15 June 2020

Stone 2020 *(Continued)*

Location: multicenter: USA
Follow-up duration (days): 28

Participants

Population: patients with COVID-19 (mild to severe)

Randomized

243 participants (n1 tocilizumab arm = 161; n2 control arm = 82)

Characteristics of participants

- Mean / median age: 60 years
- 141 males
- Admitted to ICU: n = 11 (4%)
- Severity: mild: n = 38; moderate: n = 194; severe: n = 10; critical: n = 1
- Patients on oxygen without intubation: n = 204 (84%)
- Intubated: n = 1
- C-reactive protein (median): 94.3 to 116 mg/L
- Interleukin-6: median: 24.4 pg/mL
- Number of vaccinated participants: 0

Inclusion criteria

- Patients were eligible for enrolment if they were 19 to 85 years of age and had SARS-CoV-2 infection confirmed by either nasopharyngeal swab polymerase chain reaction or serum IgM antibody assay
- Patients had to have at least 2 of the following signs:
  - fever (body temperature > 38°C) within 72 hours before enrolment;
  - pulmonary infiltrates; or
  - a need for supplemental oxygen in order to maintain an oxygen saturation higher than 92%.
- At least one of the following laboratory criteria also had to be fulfilled:
  - C-reactive protein level higher than 50 mg per liter;
  - ferritin level higher than 500 ng per milliliter;
  - D-dimer level higher than 1000 ng per milliliter; or
  - lactate dehydrogenase level higher than 250 U per liter.

Exclusion criteria

Unable to provide verbal informed consent or have verbal agreement to participate through attestation and signature of a witness required, as outlined in the Partners IRB's Table for Consenting in COVID Research that is More than Minimal Risk. Patients between the ages of 79 and 86 will be excluded if they have:

- NYHA Class III/IV heart 32 of 92;
- pulmonary infiltrate on chest X ray;
- need for supplemental O_2 to maintain saturation > 92% AND at least 1 of the following:
  - ferritin > 500 ng/mL;
  - CRP > 50 mg/L;
  - LDH > 250 U/L.
- D-dimer > 1000 ng/mL failure, insulin-dependent diabetes mellitus, angina, or treatment of a malignancy (excluding nonmelanoma skin cancer) within 6 months
- uncontrolled bacterial, fungal, or non-COVID viral infection
- active tuberculosis (see appendix B)
- any prior investigational immunosuppressive therapy within 28-days or 3 half-lives of the agent (for instance with biologic or JAK inhibitor)
- any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk
- receipt of intravenous tocilizumab for the treatment of a non-COVID condition within 3 weeks of the first COVID symptom

Stone 2020 *(Continued)*

	• history of hypersensitivity to tocilizumab • any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk • treatment with other biologic or small-molecule immunosuppressive therapy such as IL1R-antagonism, JAK inhibition, or other agents. • treatment with convalescent plasma • history of diverticulitis or bowel perforation • ANC < 500, platelets < 50,000 • AST/ALT > 5X ULN **Dropouts and withdrawals:** 1/243 (1%); 0 withdrawal due to AEs
Interventions	**Intervention:** tocilizumab (8 mg/kg infusion up to 800 mg max) single dose **Control:** placebo
Outcomes	**Primary outcome of the trial:** the primary outcome was intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo, assessed in a time-to-event analysis. Note: improvement was defined as an decrease in score by at least 2 points on the ordinal clinical improvement scale.
Notes	**Funding:** private (supported by Genentech) **Conflict of interest:** yes, declared. Quote: "Dr. Stone reports grants from Genentech, during the conduct of the study; grants and personal fees from Principia Biopharma and Roche, grants from Viela, personal fees from Sanofi, Chemocentryx, Celgene, Abbvie, Chugai, Grunenthal, Glaxo Smith Kline, InflaRx, INSmed, Regeneron, Roivant, outside of submitted work." **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, following approval of proposal. **Overall comment**: in addition to the published article, the trial registry, study protocol and statistical analysis plan were used in data extraction and assessment of risk of bias. The study did not achieve the sample size recorded in the trial registry. There were no other notable differences in study population, procedures, treatments or outcomes between the published article and the trial registry, study protocol and statistical analysis plan. This study was updated on 11 May 2022, with data extracted from the registry.

Talaschian 2021

Study characteristics	
Methods	RCT **Blinding:** double blinding **Date of study:** 10 July 2020 to 10 October 2020 **Location:** Single center; Iran **Follow-up duration (days):** 28
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) admitted to a single center in Iran **Randomized:** 40 participants n1 = 20; n2 = 20 **Analyzed:** 36 **Characteristics of participants** Mean/median age: Tocilizumab: 60 years

Talaschian 2021 *(Continued)*

Standard care: 64 years
19 males (53%)
Admitted to ICU: n = NR
Severity: mild: n = 0; moderate: n = NR; severe: n = NR; critical: n=0
Patients on oxygen without intubation: n = 36; intubated: n = 0
C-reactive protein: mean: 64.6 mg/L to 71.8 mg/L

Interleukin-6: mean: 437.3 pg/mL

Number of vaccinated participants: NR
Inclusion criteria

- Confirmed COVID-19 infection (RT-PCR)
- Elevated C-reactive protein (CRP higher than 10mg/L) or IL-6 (higher than 18 pg/ml) or lymphopenia (lymphocyte count under 1100/ MCL)
- At the pulmonary stage of the disease with blood oxygen saturation < 93% or respiratory rate (RR) higher than 24
- Not connecting to the mechanical ventilator
- Not responding to standard COVID-19 treatment
- Informed consent before enrollment

Exclusion criteria

- Allergic or intolerant to any therapeutic factors used in this study
- With positive pro-calcitonin (PCT) and had an active infection (including latent or active tuberculosis (TB) infection)
- Had a history of receiving immunosuppressive drugs and corticosteroids
- With a history of active malignancies

Interventions	**Intervention:** tocilizumab (8 mg/kg IV infusion single dose, maximum 800 mg, a second infusion could be administered 12 hours after first) **Control:** standard care **Definition of standard care:** all patients received usual care for the disease based on the Iranian protocol for diagnosis and treatment of COVID-19. **Steroid use at baseline or any time during the study** At baseline Tocilizumab: 5 (29%) Standard care: 7 (37%)
Outcomes	**Primary outcome of the trial** Improvement and discharge or death after administration of intervention whichever came first. Note: The definition of clinical improvement extracted is "Hospital discharge".
Notes	**Funding:** public/nonprofit (Tehran University of Medical Sciences) **Conflict of interest:** yes, declared. The authors declare that they have no conflicts of interest. **Protocol:** NR **Statistical plan:** NR In addition to the preprint article, the study registry was used in data extraction and risk of bias assessment. The protocol or statistical analysis plan were not available. The study achieved the target sample size specified in the trial registry. The trial registry was updated after study completion to reflect changes made in inclusion and exclusion criteria and control intervention (changed from placebo to standard care only). The registry stated the trial to be quadruple blinded however, no placebo was used during the study. Quote: "In this study, patients, investigators, and outcome assessors did not inform which group received an intervention. Besides, a placebo was not used in the control group." Hence it is unclear if participants and personnel/carers were blinded. The registry primary outcome does not reflect the reported primary outcome. Some outcomes reported in the preprint paper and used in the NMA are not prespecified in the registry (clinical improvement

Talaschian 2021 *(Continued)*

and SAEs). The study was assessed to be at a high risk of bias because of some concerns in four domains.

Veiga 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** from 8 May 2020 to 17 July 2020 **Location:** multicenter (9 centres): Brazil **Follow-up duration (days):** 29

Participants	**Population:** patients with confirmed COVID-19 (moderate-critical)
	
	Randomized: 129 participants (n1 tocilizumab arm = 65 / n2 control arm = 64)
	
	Characteristics of participants
	
	• N= 129
	• Mean age: 57.4 years
	• 88 males
	• Admitted to ICU: n = NR
	• Severity: mild: n = 0; moderate: n = 67; severe: n = 41; critical = 21
	• Patients on oxygen without intubation: n = 108 (84%); intubated: n = 21(16%)
	• C-reactive protein (mean): 160 to 193 mg/L
	• Interleukin-6: NR
	• Number of vaccinated participants: NR
	
	Inclusion criteria
	
	• Confirmed diagnosis of SARS-CoV-2 infection
	• CT (or chest X-ray) of the chest consistent with COVID-19
	• More than 3 days of symptoms related to COVID-19
	• 18 years or older;
	• Need for oxygen supplementation to maintain SpO_2 > 93% OR need for mechanical ventilation less than 24 hours before the randomization
	• 2 or more of the following inflammatory tests:
	  ◦ D-dimer > 1000 ng/mL;
	  ◦ C reactive protein (CRP) > 5 mg/dL;
	  ◦ ferritin > 300 mg/dL;
	  ◦ lactate dehydrogenase (LDH) > upper limit of normal.
	
	Exclusion criteria
	
	• Need for mechanical ventilation for 24 hours or more before the randomization
	• Hypersensitivity to tocilizumab
	• Patients without therapeutic perspective or in palliative care
	• Active non-controlled infections (other than COVID-19)
	• Neutrophil count < 0.5 x 10^9/L
	• Platelet count < 50 x 10^9/L
	• Liver disease, cirrhosis or elevated AST or ALT above 5 times the upper limit of normal
	• Renal disease with estimate glomerular filtration below 30 mL/min/1.72 m^2 (MDRD or CKD-EPI scores)
	• Breastfeeding women

Veiga 2021 *(Continued)*

	• Pregnancy • Other clinical conditions that contraindicate tocilizumab, according to the attending physician **Dropouts and withdrawals:** (0%); 0 withdrawal due to AEs
Interventions	**Intervention:** tocilizumab (8 mg/kg, IV) on day 1 up to a maximum of 800 mg. **Control:** standard care **Definition of standard care:** standard care (best supportive care), according to the local protocol. The concomitant use of hydroxychloroquine, azithromycin, corticosteroids, and antibiotics was allowed according to standard care per local institutional guidelines for patients with covid-19. Remdesivir was not available in Brazil. **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 56 (86%) Standard care: 55 (86%)
Outcomes	**Primary outcome of the trial** Clinical status at 15 days evaluated with the use of a 7-level ordinal scale Note: the definition of clinical improvement extracted is discharge alive
Notes	**Funding:** mixed (the hospitals and research institutes participating in Coalition covid-19 Brazil; Fleury Laboratory (laboratory analysis); Instituto Votorantim (donation for drug provision)) **Conflict of interest:** yes, declared. "Support from hospitals and research institutes participating in the Coalition covid-19 Brazil, Fleury Laboratory in São Paulo, Brazil, and Instituto Votorantim for the submitted work. JAGGP reports support from Pfizer, Jansen, Sanofi,..." **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, 3 months after publication. Request to the corresponding author. **Overall comment:** in addition to the published article and its supplementary materials, the trial registry, published protocol and statistical analysis plan were used in data extraction and 'Risk of bias' assessment. Viral clearance was an exploratory outcome in the protocol but results were not reported. There were no other substantive differences between the protocol, registry and published report in study population, procedures or interventions. Unblinded study. The trial was terminated early after the first interim analysis owing to an excess number of deaths at 15 days in the tocilizumab group. Quote: "The trial registration on Clinicaltrials.gov was finalised only after enrolment of the first patient because of an administrative error by the research team. Thus, the study did not achieve the sample size recorded in the trial registry. On May 8th, an eligible patient was identified at our centre and enrolment offered to the patient. At the same day, the protocol was included in ClinicalTrials.gov but could not be registered. On May 11th, we received a response with a modified Protocol Registration and Results System for registration. On May 12th, we uploaded our protocol information in ClinicalTrials.gov as approved by the Brazilian Ethics authorities. As we did not receive a reply from ClinicalTrials.gov in subsequent days, a new contact was made on May 24th and the protocol as initially submitted was published." Quote. "In the first version of the trial protocol, need of mechanical ventilation was an exclusion criterion. On June 4th, 2020, after the study was initiated, an amendment was made to allow inclusion of patients under mechanical ventilation for less than 24 hours. On July 7th, 2020 chest X-ray evidence of COVID-19 was included as an alternative to computed tomography in the inclusion criteria"

Wang 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** 13 February 2020 to 13 March 2020 **Location:** multicenter: China **Follow-up duration (days):** 14
Participants	**Population:** patients with confirmed COVID-19 (moderate-severe) to 6 **Randomized:** 65 participants (n1 Tocilizumab arm = 33 / n2 control arm = 32) **Characteristics of participants** • N = 65 • Mean/median age: 63 years • 33 males • Admitted to ICU: n = NR • Severity: mild: n = 0; moderate: n = 37; severe: n = 28; critical: n = 0 • Patients on oxygen without intubation: n = 65 (100%); intubated: n = 0 • C-reactive protein (median): 6.28 to 9.95 mg/L • Interleukin-6: median: 25.13 pg/mL • Number of vaccinated participants: NR **Inclusion criteria** • 18 to 85 years old • Plasma IL-6 levels elevated • Moderate (with bilateral pulmonary lesions) or severe in disease degree **Exclusion criteria** • Woman who is pregnant or lactating • ALT or AST > 5 times the upper limit of normal (ULN; neutropenia < 0.5×10^9/L; platelet < 50×10^9/L; • People diagnosed with rheumatism- and immunity-related diseases, cancer and other related diseases • People who are taking antirejection or immunomodulatory drugs • People who are allergic to tocilizumab or any excipients • Patients with active hepatitis and tuberculosis, associated with specific bacterial and fungal infections • Patients who have had organ transplantation • People with mental disorders **Dropouts and withdrawals:** 0/65 (0%); 0 withdrawal due to AEs
Interventions	**Intervention:** tocilizumab (400 mg infusion). Patients received a 2nd dose only if their condition did not improve or worsened. The number of patients received 2nd dose is not reported. **Control:** standard care **Definition of standard care:** standard care was given according to the “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or update version)”. **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: NR Standard care: NR
Outcomes	**Primary outcome of the trial:**

Wang 2021 *(Continued)*

- Cure rate of the enrolled patients (defined as:
  - fever attenuated for continuously 7 days;
  - 2 times COVD-19 nucleolus acid detections negative;
  - CT scan shows chest effusion absorbed more than 50% percent when the patient is discharged from hospital.

Notes	**Funding:** public/nonprofit (Department of Science and Technology of Anhui Province and Health Commission of Anhui Province, China National Center for Biotechnology Development) **Conflict of interest:** declared. No conflict of interest (quote:9 “We declare no competing interests.” **Protocol:** NR **Statistical plan:** NR **Data-sharing stated:** Yes, to qualifying researchers who submit a proposal with a valuable research question. **Overall comment:** in addition to all available versions of the preprint article, the study registry was used in data extraction and 'Risk of bias' assessment. The study did not achieve the target sample size specified in the registry. Quote: "Because of the rapid decline in the number of COVID-19 patients in China, finally a total of 65 pneumonia patients with laboratory confirmed SARS-CoV-2 infection underwent randomization." There is no change from the trial registration in the intervention and control treatments, nor in the primary outcome. Mortality was stated as a secondary outcome in the registry but not in the report. Conversely, some secondary outcomes in the report (recovery rate of hypoxia over 14 days and the time to negative virus load) were not in the registry. The study was judged to raise some concerns for 4 out of 5 domains which substantially lowered the confidence in the result, hence it was deemed an overall high risk of bias. The study was updated on March 11th, 2021 with data from the published report.

AE: adverse event; **ALT**: alanine aminotransferase; **ARDS**: acute respiratory distress syndrome; **AST**: aspartate aminotransferase; **CKD-EPI score**: Chronic Kidney Disease Epidemiology Collaboration; **CT**: computed tomographic; **DSMB**: Data and Safety Monitoring Board; **EU**: European Union; **HCV**: hepatitis C virus; **ICU**: intensive care unit; **IL**: interleukin; **IMV**: invasive mechanical ventilation; **IV**: intravenous; **JAK**: janus kinase; **LDH**: lactate dehydrogenase; **MDRD score**: Modification of Diet in Renal Disease; **NIHR**: National Institute for Health Research; **n1:** n in experimental arm; **n2**: n in control arm; **NIV:** non-invasive ventilation; **NR**: not reported; **NYHA:** New York Heart Association; **PCR**: polymerase chain reaction; **RCT**: randomized controlled trial; **SAE**: serious adverse event;**SGOT:** Serum glutamic oxaloacetic transaminase;**SGPT:** serum glutamic pyruvic transaminase; **WHO**: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albuquerque 2021	Secondary analysis
Rossotti 2020	Not randomized
Smieszek 2021	Secondary analysis
Tom 2022	Prognosis study
Zafar 2021	Secondary analysis

ADDITIONAL TABLES

Table 1. Risk of bias table: tocilizumab vs standard care/placebo. Clinical improvement (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	**Some concerns**	Low	**Some concerns**	Low	**Some concerns**
Salama 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns**	Low	**Some concerns**	**Some concerns**	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
ARCHITECTS 2021	Low	Low	Low	Low	Low	Low
COVIDOSE-2 2021	Low	Low	Low	Low	Low	Low
Declercq 2021	Low	Low	Low	**Some concerns**	Low	**Some concerns**
HMO-0224-20 2021	**High**	Low	Low	Low	Low	**High**
Horby 2021b	Low	Low	Low	**Some concerns**	Low	**Some concerns**
IMMCOVA 2021	Low	Low	Low	Low	Low	Low
Talaschian 2021	**Some concerns**	**Some concerns**	**Some concerns**	Low	**Some concerns**	**High**
Veiga 2021	Low	**Some concerns**	Low	**Some concerns**	Low	**Some concerns**
Broman 2022	Low	**Some concerns**	Low	**Some concerns**	**Some concerns**	**Some concerns**
Hermine 2022	Low	Low	**Some concerns**	**Some concerns**	**Some concerns**	**Some concerns**
Rosas 2022	Low	Low	Low	Low	Low	Low

Hermine 2021. **Rob 2. Deviations from intervention**:
Quote: “Open-label study”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross over.
Administration of co-interventions of interest (antivirals, corticosteroids, and biologics) were reported. The proportions of patients receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced.
Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Hermine 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).

Mortality is an observer-reported outcome not involving judgement.
Salvarani 2020. **Rob 2. Deviations from intervention**:
Quote: "the trial was open label"
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
Cross over: 15 (23%) patients in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context.
Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%).
These deviations could affect the outcome. Nevertheless, this domain was rated as Some Concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Salvarani 2020.**Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of clinical improvement probably does not differ between groups.
Unblinded study.
Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.
Salvarani 2020. **Rob 5. Selection of the reported results**:
Comment: The protocol and statistical analysis plan were available.
Clinical improvement (defined as discharge) is not present in the protocol or registry.
No information on whether the results were selected from multiple outcome measurements or analyses of the data.
Declercq 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
HMO-0224-20 2021. **Rob 1. Randomization**:
RoB assessment consulted from The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group "Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis." JAMA. 2021;326(6):499–518 due to unavailability of trial details.
Horby 2021b. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Talaschian 2021.**Rob 1. Randomization**:
Quote: "Eligible patients (one or two days after hospitalization) were randomly distributed to the control and intervention groups by block randomization (1:1 ratio."
Comment: Allocation sequence probably random. Unclear allocation concealment.
Talaschian 2021. **Rob 2. Deviations from intervention**:
*Quote: "In this study, patients, investigators, and outcome assessors did not inform which group received an intervention. Besides, a placebo was not used in the control group."
Comment: Unclear blinding (unclear if participants and personnel/carers blinded)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Biologics were the intervention.
Corticosteroids reported and balanced between groups. Antivirals reported and not balanced between groups: 35% in the Tocilizumab versus 10% in the standard care arm.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were ana lysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Talaschian 2021. **Rob 3. Missing outcome data**:
Comment: 40 participants randomized; 36 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
3 participants in the treatment arm and 1 in the standard care arm refused to participate before start of the intervention.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome

Talaschian 2021**. Rob 5. Selection of the reported results**:
Comment: The trial registry was available.
clinical improvement outcome (D28) (defined as discharge) not pre-specified.
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.
Veiga 2021. **Rob 2. Deviations from intervention**:
Quote: “open label” trial.
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
Cross over: 2/64 (3%) of the control arm received tocilizumab.
Co-interventions of interest, corticosteroids, and antivirals were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Data for the outcome were analyzed using intention-to-treat analysis for this outcome. This method was considered appropriate to estimate the effect of assignment to intervention.
Veiga 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study.
Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Broman 2022.**Rob 2. Deviations from intervention**:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: corticosteroids. Antivirals were not administered.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention
Broman 2022.**Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Broman 2022. **Rob 5. Selection of the reported results**:
Comment: The protocol and statistical analysis plan were not available, and the registry was retrospective (dated October 8, 2021).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as prespecified.
Hermine 2022. **Rob 3. Missing outcome data**:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022.**Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Hermine 2022.**Rob 5. Selection of the reported results**:
Comment: The prospective registry was available (dated March 31st, 2020).
Outcomes not pre-specified in the registry (time point not reported/different).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial not analyzed as pre-specified.

Table 2. Risk of bias table: tocilizumab vs standard care/placebo. Clinical improvement (D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	**Some concerns**	Low	**Some concerns**
Hermine 2022	Low	Low	**Some concerns**	**Some concerns**	Low	**Some concerns**

Declercq 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Hermine 2022. **Rob 3. Missing outcome data**:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022.**Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.

Table 3. ROB table: tocilizumab vs standard care (SC)/placebo. WHO Clinical Progression Score level 7 or above (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Salama 2020	Low	Low	Low	Low	Low	Low
Stone 2020	Low	Low	Low	Low	Low	Low
ARCHITECTS 2021	Low	Low	Low	Low	Low	Low
COVIDOSE-2 2021	Low	Low	Low	Low	Low	Low
COVITOZ-01 2021	Low	Low	Low	Low	Low	Low
Declercq 2021	Low	Low	Low	Low	Low	Low
HMO-0224-20 2021	High	Low	Low	Low	Low	**High**
IMMCOVA 2021	Low	Low	Low	Low	Low	Low

Table 3. ROB table: tocilizumab vs standard care (SC)/placebo. WHO Clinical Progression Score level 7 or above (D28) *(Continued)*

Rutgers 2021	Some concerns	Low	Low	Low	Low	**Some concerns**
Veiga 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Broman 2022	Low	Some concerns	Low	Low	Some concerns	**Some concerns**
Rosas 2022	Low	Low	Low	Low	Low	Low

Hermine 2020. Rob 2. Deviation from Intervention:
Quote: “Open-label study”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross over.
Administration of co-interventions of interest (antivirals, corticosteroids, and biologics) were reported. The proportions of patients receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced.
Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
HMO-0224-20 2021. Rob 1. Randomization:
RoB assessment consulted from The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group "Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis." JAMA. 2021;326(6):499–518 due to unavailability of trial details.
Rutgers 2021.Rob 1. Randomization:
Quote: “Randomization was stratified according to the use of hydroxychloroquine and to (on admission) agreed restrictions for ICU eligibility (ICU eligible or ICU non-eligible).”
Comment: Allocation sequence probably random. No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Veiga 2021.Rob 2. Deviation from Intervention:
Quote: “open label” trial.
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
Cross over: 2/64 (3%) of the control arm received tocilizumab.
Co-interventions of interest, corticosteroids, and antivirals were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Data for the outcome were analyzed using intention-to-treat analysis for this outcome. This method was considered appropriate to estimate the effect of assignment to intervention.
Broman 2022. Rob 2. Deviation from Intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: corticosteroids. Antivirals were not administered.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Broman 2022. Rob 5. Selection of the reported results:
Comment: The protocol and statistical analysis plan were not available, and the registry was retrospective (dated October 8, 2021).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 4. ROB table: tocilizumab vs standard care (SC)/placebo. All-cause mortality (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Salama 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	Some concerns	Low	Low	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
ARCHITECTS 2021	Low	Low	Low	Low	Low	Low
Declercq 2021	Low	Low	Low	Low	Low	Low
COVIDOSE-2 2021	Low	Low	Low	Low	Low	Low
COVITOZ-01 2021	Low	Low	Low	Low	Low	Low
Gordon 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
HMO-0224-20 2021	High	Low	Low	Low	Low	**High**
Horby 2021b	Low	Low	Low	Low	Low	Low
IMMCOVA 2021	Low	Low	Low	Low	Low	Low
Rosas 2021	Low	Low	Low	Low	Low	Low
Rutgers 2021	Some concerns	Low	Low	Low	Low	**Some concerns**
Soin 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Talaschian 2021	Some concerns	Some concerns	Some concerns	Low	Some concerns	**High**
Veiga 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Broman 2022	Low	Some concerns	Low	Low	Some concerns	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Low	Low	**Some concerns**

Hermine 2020.Rob 2. Deviations from intervention:
Quote: "Open-label study"
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross over.
Administration of co-interventions of interest (antivirals, corticosteroids, and biologics) were reported. The proportions of patients receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced.
Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.

Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

Salvarani 2020. Rob 2. Deviations from intervention:

Quote: "the trial was open label"

Comment: Unblinded study.

Deviations from intended intervention arising because of the study context:

Cross over: 15 (23%) patients in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical

worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context.

Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations

could affect the outcome. Nevertheless, this domain was rated as Some Concern as it is impossible to distinguish deviation because of trial context and

deviation because of intervention effect.

Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to

intervention.

Gordon 2021.Rob 2. Deviations from intervention:

Quote: “open-label”

Comment: Unblinded study.

Deviations from intended intervention arising because of the study context:

No participant cross-over.

Administration of co-interventions of interest: corticosteroids (252/272 vs 46/48 vs 293/312) were administered and balanced; antivirals (remdesivir: 107/341 vs 21/48 vs 133/389) were reported and imbalanced.

This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.

Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

HMO-0224-20 2021.Rob 1. Randomization:

RoB assessment consulted from The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group "Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis." JAMA. 2021;326(6):499–518 due to unavailability of trial details.

Rutgers 2021.Rob 1. Randomization:

Quote: “Randomization was stratified according to the use of hydroxychloroquine and to (on admission) agreed restrictions for ICU eligibility (ICU eligible or ICU non-eligible).”

Comment: Allocation sequence probably random. No information on allocation concealment.

Imbalances in baseline characteristics appear to be compatible with chance.

Soin 2021.Rob 2. Deviations from intervention:

Quote: "After randomization, none of the study personnel or patients was masked to treatment assignment in this open-label trial."

Comment: Unblinded study (participants and personnel/carers).

Deviations from intended intervention arising because of the study context.

One patient randomly assigned to the standard care group inadvertently received tocilizumab at baseline and was included in the tocilizumab group for all analyses (one cross-over)

Information on the administration of co-interventions of interest was provided: antivirals and corticosteroids. Biologics were not reported.

Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.

Participants were not analyzed according to their randomized groups for the outcome.

Of note, 1 participant randomized to the control group was analyzed in the intervention group. Nevertheless, we considered the analysis to be probably appropriate to estimate the effect of assignment to intervention.

Talaschian 2021.Rob 1. Randomization:

Quote: "Eligible patients (one or two days after hospitalization) were randomly distributed to the control and intervention groups by block randomization (1:1 ratio."

Comment: Allocation sequence probably random. Unclear allocation concealment.

Talaschian 2021.Rob 2. Deviations from intervention:

Quote: "In this study, patients, investigators, and outcome assessors did not inform which group received an intervention. Besides, a placebo was not used in the control group."

Comment: Unclear blinding (unclear if participants and personnel/carers blinded)

Deviations from intended intervention arising because of the study context:

No participant cross-over.

Biologics were the intervention.

Corticosteroids reported and balanced between groups. Antivirals reported and not balanced between groups: 35% in the Tocilizumab versus 10% in the standard care arm.

This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Talaschian 2021.Rob 3. Missing outcome data:
Comment: 40 participants randomized; 36 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
3 participants in the treatment arm and 1 in the standard care arm refused to participate before start of the intervention.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome
Talaschian 2021.Rob 5. Selection of the reported results:
Comment: The trial registry was available.
Outcome has different time point listed in the registry.
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.
Veiga 2021.Rob 2. Deviations from intervention:
Quote: “open label” trial.
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
Cross over: 2/64 (3%) of the control arm received tocilizumab.
Co-interventions of interest, corticosteroids, and antivirals were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Data for the outcome were analyzed using intention-to-treat analysis for this outcome. This method was considered appropriate to estimate the effect of assignment to intervention.
Broman 2022. Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: corticosteroids. Antivirals were not administered.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Broman 2022. Rob 5. Selection of the reported results:
Comment: The protocol and statistical analysis plan were not available, and the registry was retrospective (dated October 8, 2021).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.
Hermine 2022. Rob 3. Missing outcome data:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.

Table 5. ROB table: tocilizumab vs standard care (SC)/placebo. All-cause mortality (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	**Some concerns**	Low	Low	Low	**Some concerns**
Salama 2020	Low	Low	Low	Low	Low	Low
ARCHITECTS 2021	Low	Low	Low	Low	Low	Low

Table 5. ROB table: tocilizumab vs standard care (SC)/placebo. All-cause mortality (≥ D60) *(Continued)*

COVITOZ-01 2021	Low	Low	Low	Low	Low	Low
Declercq 2021	Low	Low	Low	Low	Low	Low
Derde 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
HMO-0224-20 2021	High	Low	Low	Low	Low	**High**
Broman 2022	Low	Low	Low	Low	Low	Low
Hermine 2022	Low	Low	Some concerns	Low	Low	**Some concerns**
Rosas 2022	Low	Low	Low	Low	Low	Low

Hermine 2020.Rob 2. Deviations from intervention:
Quote: "Open-label study"
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross over.
Administration of co-interventions of interest (antivirals, corticosteroids, and biologics) were reported. The proportions of patients receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced.
Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Derde 2021.Rob 2. Deviations from intervention:
Quote: "Open-label design"
Comment: Unblinded study (participants and personnel/carers).
No participant cross-over.
No information on administration of co-interventions of interest, antivirals, biologics, and corticosteroids were reported.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
HMO-0224-20 2021. Rob 1. Randomization:
RoB assessment consulted from The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group "Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis." JAMA. 2021;326(6):499–518 due to unavailability of trial details.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.

Table 6. ROB table: tocilizumab vs standard care (SC)/placebo. Incidence of any adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	**Some concerns[1]**	Low	**Some concerns[2]**	Low	**Some concerns**
Rosas 2022	Low	Low	Low	Low	Low	Low

Table 6. ROB table: tocilizumab vs standard care (SC)/placebo. Incidence of any adverse events *(Continued)*

Salama 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns[3]**	Low	**Some concerns[4]**	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Wang 2021	**Some concerns[5]**	**Some concerns[6]**	Low	**Some concerns[7]**	**Some concerns[8]**	High
Veiga 2021	Low	**Some concerns[9]**	Low	**Some concerns$_{10}$**	Low	**Some concerns**
Soin 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Some concerns	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concerns' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[2] Comment: method of measuring the outcome probably appropriate. Measurement of outcome probably does not differ between groups. Unblinded study. The outcome may contain both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.
[3] Quote: "the trial was open label" Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 15 (23%) participants in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context. Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome and were not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[4] Comment: method of measuring the outcome probably appropriate. Measurement of outcome probably does not differ between groups. Unblinded study. The outcome may contain both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.
[5] Quote: "Randomisation numbers were generated using SAS statistical software package (SAS Institute, Cary, USA). A computer- generated 1:1 block randomization scheme was used to assign participants to either treatment group or control one. Each consecutively coded participant was randomly enrolled by the sub-site investigators until the total number of cases allocated to the site was reached." Comment: Allocation sequence random. Allocation concealment unclear.
[6] Quote: "One case in the control group aggravated on day three after randomization was transferred to the tocilizumab group according to the rules of the study protocol." Comment: unblinded study. Deviations from intended intervention arising because of the study context: one participant cross-over. No information on administration of any co-interventions of interest: antivirals, corticosteroids, biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were not analyzed according to their randomized groups for the outcome. Of note, 1 participant randomized to the control group was analyzed in the intervention group. Nevertheless, we considered the analysis to be probably appropriate to estimate the effect of assignment to intervention.
[7] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study. The outcome contains both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.
[8] Comment: the protocol and statistical analysis plan were not available. The registry was available. Adverse events were not mentioned in the registry but reported in the paper. No information on whether results were selected from multiple outcome measurements or analyses of the data.
9 Quote: “open label” trial. Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 2/64 (3%) of the control arm received tocilizumab. Co-interventions of interest (corticosteroids and antivirals) were reported, but no information on another co-intervention of interest:

biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[10] Comment: method of measuring the outcome probably appropriate. Measurement of outcome probably does not differ between groups. Unblinded study. The outcome contains both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.
Soin 2021.Rob 2. Deviations from intervention:
Quote: "After randomization, none of the study personnel or patients was masked to treatment assignment in this open-label trial."
Comment: Unblinded study (participants and personnel/carers).
Deviations from intended intervention arising because of the study context.
One patient randomly assigned to the standard care group inadvertently received tocilizumab at baseline and was included in the tocilizumab group for all analyses (one cross-over)
Information on the administration of co-interventions of interest was provided: antivirals and corticosteroids. Biologics were not reported.
Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Participants were not analyzed according to their randomized groups for the outcome.
Of note, 1 participant randomized to the control group was analyzed in the intervention group. Nevertheless, we considered the analysis to be probably appropriate to estimate the effect of assignment to intervention.
Soin 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor)
The authors reported on adverse events and serious adverse events that may contain both clinically- and laboratory-detected events. All these outcomes can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.

Table 7. ROB table: tocilizumab vs standard care (SC)/placebo. Incidence of serious adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Salama 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
ARCHITECTS 2021	Low	Low	Low	Low	Low	Low
COVIDOSE-2 2021	Low	Low	Low	Low	Low	Low

Table 7. ROB table: tocilizumab vs standard care (SC)/placebo. Incidence of serious adverse events *(Continued)*

COVITOZ-01 2021	Low	Low	Low	Low	Low	Low
Declercq 2021	Low	Low	Low	Low	Low	Low
Gordon 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
IMMCOVA 2021	Low	Low	Low	Low	Low	Low
Talaschian 2021	Some concerns	Some concerns	Some concerns	Low	Some concerns	**High**
Veiga 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Wang 2021	Some concerns	Some concerns	Low	Some concerns	Low	**Some concerns**
Broman 2022	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Some concerns	Low	**Some concerns**
Rosas 2022	Low	Low	Low	Low	Low	Low

Hermine 2020.Rob 2. Deviations from intervention:
Quote: “Open-label study”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross over.
Administration of co-interventions of interest (antivirals, corticosteroids, and biologics) were reported. The proportions of patients receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced.
Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Hermine 2020.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Salvarani 2020.Rob 2. Deviations from intervention:
Quote: "the trial was open label"
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
Cross over: 15 (23%) patients in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context.
Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome. Nevertheless, this domain was rated as Some Concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Salvarani 2020.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.

Unblinded study.
The outcome contains both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Gordon 2021.Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest: corticosteroids (252/272 vs 46/48 vs 293/312) were administered and balanced; antivirals (remdesivir: 107/341 vs 21/48 vs 133/389) were reported and imbalanced.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Gordon 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ among groups.
Unblinded study (outcome assessor)
Outcome may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Soin 2021.Rob 2. Deviations from intervention:
Quote: "After randomisation, none of the study personnel or patients was masked to treatment assignment in this open-label trial."
Comment: Unblinded study (participants and personnel/carers).
Deviations from intended intervention arising because of the study context.
One patient randomly assigned to the standard care group inadvertently received tocilizumab at baseline and was included in the tocilizumab group for all analyses (one cross-over)
Information on the administration of co-interventions of interest was provided: antivirals and corticosteroids. Biologics were not reported.
Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Participants were not analyzed according to their randomized groups for the outcome.
Of note, 1 participant randomized to the control group was analyzed in the intervention group. Nevertheless, we considered the analysis to be probably appropriate to estimate the effect of assignment to intervention.
Soin 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor)
The authors reported on adverse events and serious adverse events that may contain both clinically- and laboratory-detected events. All these outcomes can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Talaschian 2021.Rob 1. Randomization:
Quote: "Eligible patients (one or two days after hospitalization) were randomly distributed to the control and intervention groups by block randomization (1:1 ratio."
Comment: Allocation sequence probably random. Unclear allocation concealment.
Talaschian 2021.Rob 2. Deviations from intervention:
Quote: "In this study, patients, investigators, and outcome assessors did not inform which group received an intervention. Besides, a placebo was not used in the control group."
Comment: Unclear blinding (unclear if participants and personnel/carers blinded)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Biologics were the intervention.
Corticosteroids reported and balanced between groups. Antivirals reported and not balanced between groups: 35% in the Tocilizumab versus 10% in the standard care arm.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Talaschian 2021.Rob 3. Missing outcome data:
Comment: 40 participants randomized; 36 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
3 participants in the treatment arm and 1 in the standard care arm refused to participate before start of the intervention.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome

Talaschian 2021.Rob 5. Selection of the reported results:
Comment: The trial registry was available.
Serious adverse events outcomes not pre-specified.
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.
Veiga 2021.Rob 2. Deviations from intervention:
Quote: “open label” trial.
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
Cross over: 2/64 (3%) of the control arm received tocilizumab.
Co-interventions of interest, corticosteroids, and antivirals were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Data for the outcome were analyzed using intention-to-treat analysis for this outcome. This method was considered appropriate to estimate the effect of assignment to intervention.
Veiga 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study.
Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Wang 2021.Rob 1. Randomization:
Quote: "Randomization numbers were generated using SAS statistical software package (SAS Institute, Cary, USA). A computer- generated 1:1 block randomization scheme was used to assign patients to either treatment group or control one. Each consecutively coded patient was randomly enrolled by the sub-site investigators until the total number of cases allocated to the site was reached."
Allocation sequence random. Allocation concealment unclear.
Wang 2021.Rob 2. Deviations from intervention:
Quote: "One case in the control group aggravated on day 3 after randomization was transferred to the tocilizumab group according to the rules of the study protocol."
Comment: Unblinded study (participants and personnel/carers).
Deviations from intended intervention arising because of the study context:
One participant cross-over.
No information on administration of any co-interventions of interest: antivirals, corticosteroids, biologics.
Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Participants were not analyzed according to their randomized groups for the outcome.
Of note, 1 participant randomized to the control group was analyzed in the intervention group. Nevertheless, we considered the analysis to be probably appropriate to estimate the effect of assignment to intervention.
Wang 2021. Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The outcome may contain both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.
Broman 2022. Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: corticosteroids. Antivirals were not administered.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention
Broman 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Broman 2022.Rob 5. Selection of the reported results:
Comment: The protocol and statistical analysis plan were not available, and the registry was retrospective (dated October 8, 2021).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.

No information on whether the trial was analyzed as pre-specified.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.

Table 8. ROB table: tocilizumab vs standard care (SC)/placebo. Time to clinical improvement

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Salama 2020	Low	Some concerns	Low	Low	Low	**Some concerns**
Salvarani 2020	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Declercq 2021	Low	Low	Low	Some concerns	Low	**Some concerns**
Derde 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Some concerns	Low	**Some concerns**
Rosas 2022	Low	Some concerns	Low	Low	Low	**Some concerns**

Hermine 2020. **Rob 2. Deviations from intervention**:
Quote: “Open-label study”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross over.
Administration of co-interventions of interest (antivirals, corticosteroids, and biologics) were reported. The proportions of patients receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced.
Nevertheless, this domain was rated as some Concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Participants were analyzed according to their randomized groups for the time-to-event outcome. Of note, 1 vs 0 participants were excluded from the analysis because of consent withdrawal which will be assessed in domain 3. Nevertheless, we consider the analysis appropriate to estimate the effect of assignment to intervention.
Hermine 2020.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Mortality is an observer-reported outcome not involving judgement.
Salama 2020.Rob 2. Deviations from intervention:

Quote: “double-blind, placebo-controlled trial”
"A site blinding plan was established at each site to identify which personnel would be blinded or unblinded at a site level. A pharmacy manual and specific training in addition to completion of a site blinding plan was provided to each site. Each site had an unblinded pharmacist that randomised the patient and prepared and labelled study medication in the same method for both tocilizumab and placebo. The remainder of the study team was blinded to treatment assignment. There was no communication during the study between unblinded and blinded members. In addition, there was an unblinded medical monitor available to answer questions from the unblinded site staff. Placebo was not provided and consisted of an unaltered saline infusion bag, the same as would be used to prepare tocilizumab. The volume of tocilizumab diluted in saline appears colorless and matches saline."
Comment: Blinded study. Participants were blinded. Carers were probably blinded.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 10 vs 1 participants were excluded from the analysis post-randomization because they did not receive the drug. This method was considered inappropriate to estimate the effect of assignment to intervention for this time-to-event outcome. There was probably no substantial impact of failure to analyze participants according to their randomized groups.
Salvarani 2020.Rob 2. Deviations from intervention:
Quote: "the trial was open label"
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
Cross over: 15 (23%) patients in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context.
Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome. Nevertheless, this domain was rated as Some Concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Salvarani 2020.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of time to clinical improvement probably does not differ between groups.
Unblinded study.
Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Salvarani 2020.Rob 5. Selection of the reported results:
Comment: The protocol and statistical analysis plan were available.
Time to clinical improvement (defined as discharge) is not present in the protocol or registry.
No information on whether the results were selected from multiple outcome measurements or analyses of the data.
Declercq 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Derde 2021. Rob 2. Deviations from intervention:
Quote: "Open-label design"
Comment: Unblinded study (participants and personnel/carers).
No participant cross-over.
No information on administration of co-interventions of interest, antivirals, biologics and corticosteroids were reported.
Hence, no information on whether deviations arose because of the trial context.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 9 (tocilizumab), 2 (sarilumab), 8 (anakinra) participants were excluded from the analysis post-randomization because outcome data were not available which is accounted for in domain 3.
This method was considered appropriate to estimate the effect of assignment to intervention for this outcome.
Derde 2021. Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome does not differ among groups.
Unblinded study (outcome assessor)
Clinical improvement (defined as hospital discharge) require clinical judgement and could be affected by knowledge of intervention receipt.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.

Not likely that missingness depended on the true value of the outcome.
Hermine 2022. Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Rosas 2022.Rob 2. Deviations from intervention:
Quote: "Masking: Double (Participant, Investigator)"
Comment: Blinded study (participants and personnel/carers)
Participants were analyzed according to their randomized groups for the time-to-event outcome.
Of note, 2 vs 1 participants were excluded from the (time to clinical improvement) analysis post-randomization for reasons other than missing data. 1 vs 1 were excluded from the (time to death) analysis post randomization because of a randomization error. 11 vs 12 participants were excluded from the (time to viral negative conversion) analysis post-randomization because they did not have at least one virology assessment.
This method was considered inappropriate to estimate the effect of assignment to intervention for this outcome. There was probably no substantial impact of failure to analyze participants according to their randomized groups.

Table 9. ROB table: tocilizumab vs standard care (SC)/placebo. Time to WHO score 7 or above

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	**Some concerns** [1]	Low	Low	Low	**Some concerns**
Salama 2020	Low	**Some concerns** [2]	Low	Low	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Rutgers 2021	Some concerns	Low	Low	Low	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: 3 participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between 2 arms (> 10% absolute difference between the 2 arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as Some Concerns as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Participants were analyzed according to their randomized groups for the outcome. Of note, 1 vs 0 participants were excluded from the analysis because of consent withdrawal. Nevertheless, we consider the analysis appropriate to estimate the effect of assignment to intervention.
[2] Quote: “double-blind, placebo-controlled trial.” “A site blinding plan was established at each site to identify which personnel would be blinded or unblinded at a site level. A pharmacy manual and specific training in addition to completion of a site blinding plan was provided to each site. Each site had an unblinded pharmacist that randomized the participant and prepared and labeled study medication in the same method for both tocilizumab and placebo. The remainder of the study team was blinded to treatment assignment. There was no communication during the study between unblinded and blinded members. In addition, there was an unblinded medical monitor available to answer questions from the unblinded site staff. Placebo was not provided and consisted of an unaltered saline infusion bag, the same as would be used to prepare tocilizumab. The volume of tocilizumab diluted in saline appears colorless and matches saline.”
Comment: Blinded study. Participants were blinded. Carers were probably blinded. Participants were analyzed according to their randomized groups for the outcome. Of note, 10 vs 1 participants were excluded from the analysis post-randomization because they did not receive the drug. This method was considered inappropriate to estimate the effect of assignment to intervention for this time-to-event outcome. There was probably no substantial impact of failure to analyze participants according to their randomized groups
Rutgers 2021.Rob 1. Randomization:
Quote: “Randomization was stratified according to the use of hydroxychloroquine and to (on admission) agreed restrictions for ICU eligibility (ICU eligible or ICU non-eligible).”
Comment: Allocation sequence probably random. No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.

Table 10. ROB table: tocilizumab vs standard care (SC)/placebo. Time to death

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Broman 2022	Low	Low	Low	Low	Low	Low
Declercq 2021	Low	Low	Low	Low	Low	Low
Derde 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Rutgers 2021	Some concerns	Low	Low	Low	Low	**Some concerns**
Talaschian 2021	Some concerns	Some concerns	Some concerns	Low	Some concerns	**High**
Hermine 2022	Low	Low	Some concerns	Low	Low	**Some concerns**
Rosas 2022	Low	Some concerns	Low	Low	Low	**Some concerns**

Hermine 2020. Rob 2. Deviations from intervention:
Quote: “Open-label study”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross over.
Administration of co-interventions of interest (antivirals, corticosteroids, and biologics) were reported. The proportions of patients receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced.
Nevertheless, this domain was rated as some Concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Participants were analyzed according to their randomized groups for the time-to-event outcome. Of note, 1 vs 0 participants were excluded from the analysis because of consent withdrawal which will be assessed in domain 3. Nevertheless, we consider the analysis appropriate to estimate the effect of assignment to intervention.
Derde 2021.Rob 2. Deviations from intervention:
Quote: "Open-label design"
Comment: Unblinded study (participants and personnel/carers).
No participant cross-over.
No information on administration of co-interventions of interest, antivirals, biologics, and corticosteroids were reported.
Hence, no information on whether deviations arose because of the trial context.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 9 (tocilizumab), 2 (sarilumab), 8 (anakinra) participants were excluded from the analysis post-randomization because outcome data were not available which is accounted for in domain 3.
This method was considered appropriate to estimate the effect of assignment to intervention for this outcome.
Rutgers 2021.Rob 1. Randomization:
Quote: “Randomization was stratified according to the use of hydroxychloroquine and to (on admission) agreed restrictions for ICU eligibility (ICU eligible or ICU non-eligible).”
Comment: Allocation sequence probably random. No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Talaschian 2021.Rob 1. Randomization:

Quote: "Eligible patients (one or two days after hospitalization) were randomly distributed to the control and intervention groups by block randomization (1:1 ratio."
Comment: Allocation sequence probably random. Unclear allocation concealment.
Talaschian 2021.Rob 2. Deviations from intervention:
Quote: "In this study, patients, investigators, and outcome assessors did not inform which group received an intervention. Besides, a placebo was not used in the control group."
Comment: Unclear blinding (unclear if participants and personnel/carers blinded)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Biologics were the intervention.
Corticosteroids reported and balanced between groups. Antivirals reported and not balanced between groups: 35% in the Tocilizumab versus 10% in the standard care arm.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 3 vs 1 participants were excluded from the analysis post-randomization due to missing data which is accounted for in domain 3.
This method was considered appropriate to estimate the effect of assignment to intervention for this outcome.
Talaschian 2021. **Rob 3. Missing outcome data**:
Comment: 40 participants randomized; 36 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
3 participants in the treatment arm and 1 in the standard care arm refused to participate before start of the intervention.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome
Talaschian 2021.Rob 5. Selection of the reported results:
Comment: The trial registry was available.
Outcome has different timepoint listed in the registry.
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 97 participants randomized; 92 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 3 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Rosas 2022.Rob 2. Deviations from intervention:
Quote: "Masking: Double (Participant, Investigator)"
Comment: Blinded study (participants and personnel/carers)
Participants were analyzed according to their randomized groups for the time-to-event outcome.
Of note, 2 vs 1 participants were excluded from the (time to clinical improvement) analysis post-randomization for reasons other than missing data. 1 vs 1 were excluded from the (time to death) analysis post randomization because of a randomization error. 11 vs 12 participants were excluded from the (time to viral negative conversion) analysis post-randomization beca use they did not have at least one virology assessment.
This method was considered inappropriate to estimate the effect of assignment to intervention for this outcome. There was probably no substantial impact of failure to analyse participants according to their randomized groups.

Table 11. ROB table: sarilumab vs standard care (SC)/placebo. Clinical improvement (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Mariette 2021	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**
Merchante 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Sancho-Lopez 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**

Table 11. ROB table: sarilumab vs standard care (SC)/placebo. Clinical improvement (D28) *(Continued)*

Branch-Elliman 2022	Low	Low	Low	Some concerns	Some concerns	**Some concerns**
Garcia-Vicuna 2022	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Some concerns	Some concerns	**Some concerns**

Mariette 2021.Rob 2. Deviations from intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Mariette 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Mariette 2021.Rob 5. Selection of the reported results:
Comment: The protocol, statistical analysis plan and registry were available (dated March 27, 2020).
Outcome not pre-specified (timepoint not reported/different).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial not analyzed as pre-specified.
Merchante 2021.Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: corticosteroids and biologics. Antivirals (3 vs 7 vs 4) and anticoagulant were reported (37 vs 39 vs 39) and were balanced between groups.
Hence, no sufficient information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Merchante 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unclear blinding (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Sancho-Lopez 2021.Rob 2. Deviations from intervention:
Quote: "Our clinical trial was a national, multicenter, randomized, open label, controlled clinical study".
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Corticosteroids were administered for all patients. Antiviral were provided but no numbers are reported.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Sancho-Lopez 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.

Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Branch-Elliman 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Branch-Elliman 2022.Rob 5. Selection of the reported results:
Comment: The protocol, statistical analysis plan, and registry (submitted April 20, 2020) were available.
Outcome not pre-specified.
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.
Garcia-Vicuna 2022.Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest: antivirals, corticosteroids and biologics are reported: lopinavir/Ritonavir: 4 vs 1, methylprednisolone bolus: 14 vs 3 and tocilizumab: 0 vs 3.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Garcia-Vicuna 2022. Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Hermine 2022.Rob 5. Selection of the reported results:
Comment: The prospective registry was available (dated March 25th, 2020).
Outcomes not pre-specified in the registry (timepoint not reported/different).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial not analyzed as pre-specified.

Table 12. ROB table: sarilumab vs standard care (SC)/placebo. Clinical Improvement (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Mariette 2021	Low	Some concerns	Low	Some concerns	Some concerns	**Some concerns**

Table 12. ROB table: sarilumab vs standard care (SC)/placebo. Clinical Improvement (≥ D60) *(Continued)*

Hermine 2022	Low	Low	Some concerns	Some concerns	Low	**Some concerns**

Mariette 2021. Rob 2. Deviations from interventions:
Quote: "open-label study"
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Mariette 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Mariette 2021.Rob 5. Selection of the reported results:
Comment: The protocol, statistical analysis plan and registry were available (dated March 27, 2020).
Outcome not pre-specified (timepoint not reported/different).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial not analyzed as pre-specified.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.

Table 13. ROB table: sarilumab vs standard care (SC)/placebo. WHO Clinical Progression Score level 7 or above (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Mariette 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Sancho-Lopez 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Branch-Elliman 2022	Low	Low	Low	Low	Low	Low
Garcia-Vicuna 2022	Low	Some concerns	Low	Low	Low	**Some concerns**
Sivapalasingam 2022a	Some concerns	Low	Some concerns	Low	Low	**Some concerns**

Mariette 2021.Rob 2. Deviation from Intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Sancho-Lopez 2021.Rob 2. Deviation from Intervention:
Quote: "Our clinical trial was a national, multicenter, randomized, open label, controlled clinical study".
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Corticosteroids were administered for all patients. Antiviral were provided but no numbers are reported.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Garcia-Vicuna 2022.Rob 2. Deviation from Intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest: antivirals, corticosteroids and biologics are reported: Lopinavir/Ritonavir: 4 vs 1, methylprednisolone bolus: 14 vs 3 and Tocilizumab: 0 vs 3.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Sivapalasingam 2022a.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022a. Rob 3. Missing outcome data:
Comment: 463 participants randomized; 436 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: randomized but not treated (n=6), withdrew consent(n=5), death before start of treatment(n=1) and lost to follow up (n=21).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.

Table 14. ROB table: sarilumab vs standard care (SC). All-cause mortality (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Gordon 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Lescure 2021	Low	Low	Low	Low	Low	Low
Mariette 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Merchante 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Sancho-Lopez 2021	Low	Some concerns	Low	Low	Low	**Some concerns**

Table 14. ROB table: sarilumab vs standard care (SC). All-cause mortality (D28) *(Continued)*

Branch-Elliman 2022	Low	Low	Low	Low	Low	Low
Garcia-Vicuna 2022	Low	Some concerns	Low	Low	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Low	Low	**Some concerns**
Sivapalasingam 2022a	Some concerns	Low	Some concerns	Low	Low	**Some concerns**
Sivapalasingam 2022b	Some concerns	Low	Some concerns	Low	Low	**Some concerns**

Gordon 2021. Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest: corticosteroids (252/272 vs 46/48 vs 293/312) were administered and balanced; antivirals (remdesivir: 107/341 vs 21/48 vs 133/389) were reported and imbalanced.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Mariette 2021.Rob 2. Deviation from Intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Merchante 2021. Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: corticosteroids and biologics. Antivirals (3 vs 7 vs 4) and anticoagulant were reported (37 vs 39 vs 39) and were balanced between groups.
Hence, no sufficient information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Sancho-Lopez 2021.Rob 2. Deviation from Intervention:
Quote: "Our clinical trial was a national, multicenter, randomized, open label, controlled clinical study".
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Corticosteroids were administered for all patients. Antiviral were provided but no numbers are reported.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Garcia-Vicuna 2022.Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.

Administration of co-interventions of interest: antivirals, corticosteroids and biologics are reported: Lopinavir/Ritonavir: 4 vs 1, methylprednisolone bolus: 14 vs 3 and Tocilizumab: 0 vs 3.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Hermine 2022. Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Sivapalasingam 2022a.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022a. Rob 3. Missing outcome data:
Comment: 463 participants randomized; 436 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: randomized but not treated (n=6), withdrew consent(n=5), death before start of treatment(n=1) and lost to follow up (n=21).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Sivapalasingam 2022b.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022b.Rob 3. Missing outcome data:
Comment: 1407 participants randomized; 1330 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons for potential missing data: randomized but not treated (n=42), discontinuation due to investigator/sponsor decision (n=1), withdrawal of consent (n=9) and loss to follow-up (n=75).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.

Table 15. ROB table: sarilumab vs standard care (SC). All-cause mortality (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Derde 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Lescure 2021	Low	Low	Low	Low	Low	Low
Mariette 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Garcia-Vicuna 2022	Low	Some concerns	Low	Low	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Low	Low	**Some concerns**
Sivapalasingam 2022a	Some concerns	Low	Some concerns	Low	Low	**Some concerns**

Table 15. ROB table: sarilumab vs standard care (SC). All-cause mortality (≥ D60) *(Continued)*

Sivapalasingam 2022b	Some concerns	Low	Some concerns	Low	Low	**Some concerns**

Derde 2021.Rob 2. Deviations from intervention:
Quote: "Open-label design"
Comment: Unblinded study (participants and personnel/carers).
No participant cross-over.
No information on administration of co-interventions of interest, antivirals, biologics and corticosteroids were reported.
Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Mariette 2021. Rob 2. Deviations from intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Garcia-Vicuna 2022.Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest: antivirals, corticosteroids and biologics are reported: Lopinavir/Ritonavir: 4 vs 1, methylprednisolone bolus: 14 vs 3 and Tocilizumab: 0 vs 3.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Sivapalasingam 2022a.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022a. Rob 3. Missing outcome data:
Comment: 463 participants randomized; 436 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: randomized but not treated (n=6), withdrew consent(n=5), death before start of treatment(n=1) and lost to follow up (n=21).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Sivapalasingam 2022b.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022b.Rob 3. Missing outcome data:
Comment: 1407 participants randomized; 1330 participants analyzed.

Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons for potential missing data: randomized but not treated (n=42), discontinuation due to investigator/sponsor decision (n=1), withdrawal of consent (n=9) and loss to follow-up (n=75).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.

Table 16. ROB table: sarilumab vs standard care (SC). Incidence of adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lescure 2021	Low	Low	Low	Low	Some concerns	**Some concerns**
Mariette 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Sancho-Lopez 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Some concerns	Low	**Some concerns**
Sivapalasingam 2022a	Some concerns	Low	Some concerns	Low	Some concerns	**Some concerns**
Sivapalasingam 2022b	Some concerns	Low	Some concerns	Low	Some concerns	**Some concerns**

Lescure 2021.Rob 5. Selection of the reported results:
Comment: The trial registry was available and consulted (up to version dated April 3rd, 2020).
Outcome not pre-specified
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.
Mariette 2021.Rob 2. Deviations from intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Mariette 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Sancho-Lopez 2021.Rob 2. Deviations from intervention:
Quote: "Our clinical trial was a national, multicenter, randomized, open label, controlled clinical study".
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Corticosteroids were administered for all patients. Antiviral were provided but no numbers are reported.

Hence, no information on whether deviations arose because of the trial context.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Sancho-Lopez 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that contains both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Sivapalasingam 2022a. Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022a.Rob 3. Missing outcome data:
Comment: 463 participants randomized; 436 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: randomized but not treated (n=6), withdrew consent(n=5), death before start of treatment(n=1) and lost to follow up (n=21).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Sivapalasingam 2022a.Rob 5. Selection of the reported results:
Comment: The trial registry was available and consulted (up to version dated March 26th, 2020).
Outcome not pre-specified
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.
Sivapalasingam 2022b.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022b.Rob 3. Missing outcome data:
Comment: 1407 participants randomized; 1330 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons for potential missing data: randomized but not treated (n=42), discontinuation due to investigator/sponsor decision (n=1), withdrawal of consent (n=9) and loss to follow-up (n=75).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Sivapalasingam 2022b. Rob 5. Selection of the reported results:
Comment: The trial registry was available and consulted (up to version dated March 26th, 2020).
Outcome not pre-specified
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial probably not analyzed as pre-specified.

Table 17. ROB table: sarilumab vs standard care (SC). Incidence of serious adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Gordon 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Lescure 2021	Low	Low	Low	Low	Low	Low
Mariette 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Garcia-Vicuna 2022	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Some concerns	Low	**Some concerns**
Sivapalasingam 2022a	Some concerns	Low	Some concerns	Low	Low	**Some concerns**
Sivapalasingam 2022b	Some concerns	Low	Some concerns	Low	Low	**Some concerns**

Gordon 2021.Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study.
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest: corticosteroids (252/272 vs 46/48 vs 293/312) were administered and balanced; antivirals (remdesivir: 107/341 vs 21/48 vs 133/389) were reported and imbalanced.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Gordon 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ among groups.
Unblinded study (outcome assessor).
Outcome may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Mariette 2021.Rob 2. Deviations from intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Mariette 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).

The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Sivapalasingam 2022a.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022a.Rob 3. Missing outcome data:
Comment: 463 participants randomized; 436 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: randomized but not treated (n=6), withdrew consent(n=5), death before start of treatment(n=1) and lost to follow up (n=21).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Sivapalasingam 2022b.Rob 1. Randomization:
Quote: "patients were randomized in a 2:2:1 ratio to IV sarilumab 400 mg, sarilumab 200 mg, or placebo"
Comment: Allocation sequence probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Sivapalasingam 2022b.Rob 3. Missing outcome data:
Comment: 1407 participants randomized; 1330 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons for potential missing data: randomized but not treated (n=42), discontinuation due to investigator/sponsor decision (n=1), withdrawal of consent (n=9) and loss to follow-up (n=75).
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Garcia-Vicuna 2022. Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest: antivirals, corticosteroids and biologics are reported: lopinavir/Ritonavir: 4 vs 1, methylprednisolone bolus: 14 vs 3 and tocilizumab: 0 vs 3.
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Garcia-Vicuna 2022.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.
Hermine 2022. Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022. Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
The authors reported on this outcome that may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment but is not likely in the context of the pandemic.

Table 18. ROB table: sarilumab vs standard care (SC). Time to clinical improvement

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Derde 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Lescure 2021	Low	Low	Low	Low	Low	Low
Mariette 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Merchante 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Sancho-Lopez 2021	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Some concerns	Low	**Some concerns**

Derde 2021.Rob 2. Deviations from intervention:
Quote: "Open-label design"
Comment: Unblinded study (participants and personnel/carers).
No participant cross-over.
No information on administration of co-interventions of interest, antivirals, biologics, and corticosteroids were reported.
Hence, no information on whether deviations arose because of the trial context.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 9 (tocilizumab), 2 (sarilumab), 8 (anakinra) participants were excluded from the analysis post-randomization because outcome data were not available which is accounted for in domain 3.
This method was considered appropriate to estimate the effect of assignment to intervention for this outcome.
Derde 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome does not differ among groups.
Unblinded study (outcome assessor)
Clinical improvement (defined as hospital discharge) require clinical judgement and could be affected by knowledge of intervention receipt.
Mariette 2021.Rob 2. Deviations from intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 0 vs 4 participants were excluded from the analysis post-randomization because they withdrew consent which will be taken into account in ROB 3.
Mariette 2021. Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Merchante 2021.Rob 2. Deviations from intervention:
Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.

No information on administration of co-interventions of interest: corticosteroids and biologics. Antivirals (3 vs 7 vs 4) and anticoagulant were reported (37 vs 39 vs 39) and were balanced between groups.
Hence, no sufficient information on whether deviations arose because of the trial context.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 1 vs 1 vs 0 participants were excluded from the analysis post-randomization because [1 in group (sarilumab 200) did not comply with protocol, 1 in group (sarilumab 400) they did not receive the drug. This method was considered inappropriate to estimate the effect of assignment to intervention for this outcome. There was probably no substantial impact of failure to analyse participants according to their randomized groups.
Merchante 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unclear blinding (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Sancho-Lopez 2021.Rob 2. Deviations from intervention:
Quote: "Our clinical trial was a national, multicenter, randomized, open label, controlled clinical study".
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Corticosteroids were administered for all patients. Antiviral were provided but no numbers are reported.
Hence, no information on whether deviations arose because of the trial context.
Our analysis is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
Sancho-Lopez 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.
Hermine 2022. Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.

Table 19. ROB table: sarilumab vs standard care (SC)/placebo. Time to WHO Score 7 or above

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Mariette 2021	Low	Some concerns	Low	Low	Some concerns	**Some concerns**
Sancho-Lopez 2021	Low	Some concerns	Low	Low	Low	**Some concerns**

Mariette 2021. Rob 2. Deviations from interventions
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.

Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 0 vs 4 participants were excluded from the analysis post-randomization because they withdrew consent which will be taken into account in ROB 3.
Mariette 2021. Rob 5. Selection of the reported results
Comment: The protocol, statistical analysis plan and registry were available (dated March 27, 2020).
Outcomes not pre-specified.
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
Trial not analyzed as pre-specified.
Sancho-Lopez 2021.Rob 2. Deviations from intervention:
Quote: "Our clinical trial was a national, multicenter, randomized, open label, controlled clinical study".
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Corticosteroids were administered for all patients. Antiviral were provided but no numbers are reported.
Hence, no information on whether deviations arose because of the trial context.
Our analysis is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

Table 20. ROB table: sarilumab vs standard care (SC). Time to death

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Derde 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Mariette 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Merchante 2021	Low	Some concerns	Low	Low	Low	**Some concerns**
Hermine 2022	Low	Low	Some concerns	Low	Low	**Some concerns**

Derde 2021.Rob 2. Deviations from intervention:
Quote: "Open-label design"
Comment: Unblinded study (participants and personnel/carers).
No participant cross-over.
No information on administration of co-interventions of interest, antivirals, biologics, and corticosteroids were reported.
Hence, no information on whether deviations arose because of the trial context.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 9 (tocilizumab), 2 (sarilumab), 8 (anakinra) participants were excluded from the analysis post-randomization because outcome data were not available which is accounted for in domain 3.
This method was considered appropriate to estimate the effect of assignment to intervention for this outcome.
Mariette 2021.Rob 2. Deviations from intervention:
Quote: “open-label study”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
Administration of co-interventions of interest were reported in Table S2: anticoagulants (41 vs 45), hydroxychloroquine (2 vs 8), antibiotics (42 vs 43), antivirals (2 vs 3), immuno-modulators (0 vs 3) and corticosteroids (9 vs 17).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 0 vs 4 participants were excluded from the analysis post-randomization because they withdrew consent which will be taken into account in ROB 3.
Merchante 2021.Rob 2. Deviations from intervention:

Quote: “open-label”
Comment: Unblinded study (participants and personnel/carers)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: corticosteroids and biologics. Antivirals (3 vs 7 vs 4) and anticoagulant were reported (37 vs 39 vs 39) and were balanced between groups.
Hence, no sufficient information on whether deviations arose because of the trial context.
Participants were analyzed according to their randomized groups for the outcome.
Of note, 1 vs 1 vs 0 participants were excluded from the analysis post-randomization because [1 in group (sarilumab 200) did not comply with protocol, 1 in group (sarilumab 400) they did not receive the drug. This method was considered inappropriate to estimate the effect of assignment to intervention for this outcome. There was probably no substantial impact of failure to analyse participants according to their randomized groups.
Hermine 2022.Rob 3. Missing outcome data:
Comment: 91 participants randomized; 81 participants analyzed.
Data not available for all or nearly all participants randomized.
No evidence that the result is not biased.
Reasons: 2 vs 8 participants withdrew consent.
Missingness could depend on the true value of the outcome.
Not likely that missingness depended on the true value of the outcome.

Table 21. ROB table: clazakizumab vs placebo. Clinical improvement (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lonze 2022	Low	Low	Low	Low	Some concerns	**Some concerns**

Lonze 2022. Rob 5. Selection of the reported results:
Comment: The protocol, statistical analysis plan and retrospective registry were available (dated April 9th, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 22. ROB table: clazakizumab vs placebo. Clinical improvement (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lonze 2022	Low	Low	Low	Low	Some concerns	**Some concerns**

Lonze 2022. Rob 5. Selection of the reported results:
Comment: The protocol, statistical analysis plan and retrospective registry were available (dated April 9th, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 23. ROB table: clazakizumab vs placebo. WHO Score 7 or above (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lonze 2022	Low	Low	Low	Low	Some concerns	**Some concerns**

Lonze 2022. Rob 5. Selection of the reported results:
Comment: The protocol, statistical analysis plan and retrospective registry were available (dated April 9th, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 24. ROB table: clazakizumab vs placebo. All-cause mortality (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Jordan 2021	Some concerns	Low	Low	Low	Low	**Some concerns**
Lonze 2022	Low	Low	Low	Low	Low	Low

Jordan 2021.Rob 1. Randomization:
Quote: "Randomized, double-blind, placebo-controlled, exploratory phase II study."
Comment: Allocation sequence probably random. No information on allocation concealment.

Table 25. ROB table: clazakizumab vs placebo. All-cause mortality (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Jordan 2021	Some concerns	Low	Low	Low	Low	**Some concerns**
Lonze 2022	Low	Low	Low	Low	Low	Low

Jordan 2021.Rob 1. Randomization:
Quote: "Randomized, double-blind, placebo-controlled, exploratory phase II study."
Comment: Allocation sequence probably random. No information on allocation concealment.

Table 26. ROB table: clazakizumab vs placebo. Incidence of any adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Jordan 2021	Some concerns	Low	Low	Low	Low	**Some concerns**

Jordan 2021.Rob 1. Randomization:
Quote: "Randomized, double-blind, placebo-controlled, exploratory phase II study."
Comment: Allocation sequence probably random. No information on allocation concealment.

Table 27. ROB table: clazakizumab vs placebo. Incidence of serious adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias

Table 27. ROB table: clazakizumab vs placebo. Incidence of serious adverse events *(Continued)*

Jordan 2021	Some concerns	Low	Low	Low	Low	**Some concerns**
Lonze 2022	Low	Low	Low	Low	Some concerns	**Some concerns**

Jordan 2021.Rob 1. Randomization:
Quote: "Randomized, double-blind, placebo-controlled, exploratory phase II study."
Comment: Allocation sequence probably random. No information on allocation concealment.
Lonze 2022. Rob 5. Selection of the reported results:
Comment: The protocol, statistical analysis plan and retrospective registry were available (dated April 9th, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 28. ROB table: olokizumab vs placebo. Clinical improvement (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Samsonov 2022	Some concerns	Some concerns	Low	Low	Low	**Some concerns**

Samsonov 2022.Rob 1. Randomization:
Quote: "Eligible patients were randomized to one of three treatment groups"
Comment: Allocation probably random.
No information on allocation concealment
Imbalances in baseline characteristics appear to be compatible with chance.
Samsonov 2022.Rob 2. Deviations from intervention:
Quote: "Masking: Double (Participant, Investigator)"
Comment: Unclear blinding (unclear if personnel/carers blinded)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: antivirals and corticosteroids. Biologics (Tocilizumab and Sarilumab) were reported: 5 (Olokizumab arm) vs 15 (placebo arm).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

Table 29. ROB table: olokizumab vs placebo. All-cause mortality (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Samsonov 2022	Some concerns	Some concerns	Low	Low	Low	**Some concerns**

Samsonov 2022.Rob 1. Randomization:
Quote: "Eligible patients were randomized to one of three treatment groups"
Comment: Allocation probably random.
No information on allocation concealment
Imbalances in baseline characteristics appear to be compatible with chance.
Samsonov 2022.Rob 2. Deviations from intervention:
Quote: "Masking: Double (Participant, Investigator)"
Comment: Unclear blinding (unclear if personnel/carers blinded)

Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: antivirals and corticosteroids. Biologics (Tocilizumab and Sarilumab) were reported:5 (Olokizumab arm) vs 15 (placebo arm).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concerns as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

Table 30. ROB table: olokizumab vs placebo. Incidence of serious adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Samsonov 2022	Some concerns	Some concerns	Low	Low	Low	**Some concerns**

Samsonov 2022.Rob 1. Randomization:
Quote: “Eligible patients were randomized to one of three treatment groups"
Comment: Allocation probably random.
No information on allocation concealment.
Imbalances in baseline characteristics appear to be compatible with chance.
Samsonov 2022.Rob 2. Deviations from intervention:
Quote: “Masking: Double (Participant, Investigator)”
Comment: Unclear blinding (unclear if personnel/carers blinded)
Deviations from intended intervention arising because of the study context:
No participant cross-over.
No information on administration of co-interventions of interest: antivirals and corticosteroids. Biologics (Tocilizumab and Sarilumab) were reported: 5 (Olokizumab arm) vs 15 (placebo arm).
This deviation was not balanced and could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Our analysis for the binary outcome is an intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

Table 31. ROB table: siltuximab vs placebo. Clinical improvement (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	Some concerns	Low	**Some concerns**

Declercq 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.

Table 32. ROB table: siltuximab vs placebo. Clinical Improvement (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias

Table 32. ROB table: siltuximab vs placebo. Clinical Improvement (≥ D60) *(Continued)*

Declercq 2021	Low	Low	Low	Some concerns	Low	**Some concerns**

Declercq 2021. **Rob 4. Measurement of the outcome**:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.

Table 33. ROB table: siltuximab vs placebo. All-cause mortality (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	Low	Low	Low

Table 34. ROB table: siltuximab vs placebo. All-cause mortality (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	Low	Low	Low

Table 35. ROB table: siltuximab vs placebo. WHO Score 7 or above (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	Low	Low	Low

Table 36. ROB table: siltuximab vs placebo. Incidence of serious adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	Low	Low	Low

Table 37. ROB table: siltuximab vs placebo. Time to clinical improvement

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	Some concerns	Low	**Some concerns**

Declercq 2021.Rob 4. Measurement of the outcome:
Comment: Method of measuring the outcome probably appropriate.
Measurement or ascertainment of outcome probably does not differ between groups.
Unblinded study (outcome assessor).
Clinical improvement requires clinical judgement and could be affected by knowledge of intervention receipt, but it is not considered likely in the context of a pandemic.

Table 38. ROB table: siltuximab vs placebo. Time to death

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Declercq 2021	Low	Low	Low	Low	Low	Low

Table 39. ROB table: levilimab vs placebo. Clinical improvement (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lomakin 2021	Low	Low	Low	Low	Some concerns	**Some concerns**

Lomakin 2021.Rob 5. Selection of the reported results:
Comment: The registry was retrospective (dated May 21, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 40. ROB table: levilimab vs placebo. All-cause mortality (D28)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lomakin 2021	Low	Low	Low	Low	Some concerns	**Some concerns**

Lomakin 2021.Rob 5. Selection of the reported results:
Comment: The registry was retrospective (dated May 21, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 41. ROB table: levilimab vs placebo. All-cause mortality (≥ D60)

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lomakin 2021	Low	Low	Low	Low	Low	Low

Table 42. ROB table: levilimab vs placebo. Incidence of any adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lomakin 2021	Low	Low	Low	Low	Some concerns	**Some concerns**

Lomakin 2021. **Rob 5. Selection of the reported results**:
Comment: The registry was retrospective (dated May 21, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

Table 43. ROB table: levilimab vs placebo. Incidence of serious adverse events

Study	1.Randomization	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lomakin 2021	Low	Low	Low	Low	Some concerns	**Some concerns**

Lomakin 2021.Rob 5. Selection of the reported results:
Comment: The registry was retrospective (dated May 21, 2020).
No information on whether the result was selected from multiple outcome measurements or analyses of the data.
No information on whether the trial was analyzed as pre-specified.

APPENDICES

Appendix 1. Living process of the review

Steering committee

We set up a steering committee of epidemiologists, methodologists, statisticians and clinicians with content expertise. This committee meet regularly, discuss the conduct of the project, difficulties encountered and possible changes in the protocol according to new knowledge available on COVID-19 disease. Changes in the protocol could consist for example of changes in the search strategy, eligibility criteria (e.g. study design), research questions for the pairwise meta-analyses, outcomes.

Process and quality control

Our aim is to update the synthesis at least every week. For this purpose, we will search, screen and extract data every day. The updated synthesis will be reported online every two weeks during the period of the project from March 2020- December 2022 with a last search date set up to September 27, 2022 for pharmacological treatments in hospitalized COVID-19 patients .

To standardize the process and ensure both rapidity and quality, we will proceed as follows.

1. We will separate the process into different tasks and set up a team for each task (i.e. a researcher/volunteer will be involved in a single task). Each team will be led by a senior researcher ensuring the quality and standardization of the task.

2. For some tasks, we will develop a short training program for researchers/volunteers joining the team. This program will involve:
   a. reading a manual detailing the task;
   b. performing the task on a sample as an exercise (e.g. evaluating the risk of bias of three studies) and contacting the team leader to ask about difficulties; and
   c. after a successful training, the newcomer will perform the double data extraction with a senior well-trained researcher.
3. Each team will hold a weekly meeting to discuss difficulties and ensure standardization. All decisions and changes will be recorded.
4. We will set-up an internal quality control process where a senior researcher, and former editor in chief of Cochrane, (D Tovey) will check the data extracted and reported on the website. All points will be discussed with the data extraction team and modifications recorded for transparency.
5. We will develop an external quality control process for data collection involving senior researchers who will check a random sample of the data collected (e.g. member of the Cochrane Bias Methods Group for risk of bias)

We will consider the following tasks:

1. research mapping: screening and extracting data from registries;
2. screening of databases from title/abstract to full text;
3. data extraction;
4. data analyses;
5. assessment of evidence certainty.

The core team will perform the analysis, presentation and interpretation of the results.

Evolution of the protocol over time

The process will also evolve over time according to the new knowledge available regarding COVID-19.

The steering committee will systematically discuss and achieve consensus on the changes of protocol proposed.

Appendix 2. Case definitions

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g. cough, shortness of breath)), AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days before onset of symptoms.

OR

C. A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g. cough, shortness breath)) AND requiring hospitalization AND no other etiology that fully explains the clinical presentation.

Probable case

A suspect case for whom testing for COVID-19 is inconclusive (inconclusive being the result of the test reported by the laboratory).

Confirmed case

A person with laboratory confirmation of COVID-19 infection, regardless of clinical signs and symptoms.

Of note, when the definition used to classify cases was not clearly reported, we will rely on the classification provided by authors.

Appendix 3. Search strategies

Cochrane COVID-19 Study Register

The **Cochrane Covid-19 Study Register** (covid-19.cochrane.org/) has been searched on a regular basis (last search 7 June 2022). The Cochrane Covid-19 Study Register is a specialized register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. The register contains study reports from several sources, including:

- daily searches of PubMed;
- daily searches of ClinicalTrials.gov;

- weekly searches of Embase.com;
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP);
- weekly searches of medRxiv;
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL).

Complete data sources and search methods for the register are available at: community.cochrane.org/about-covid-19-study-register. In covid-19.cochrane.org/ we:

1. Select new studies “Last week”
2. Select results available “Report results”
3. Select study characteristics, study type “Interventional”
4. Select study characteristics, intervention assignment “Randomized”
5. Select All
6. Export the results in a.ris file

Below is the search strategy used by the Cochrane COVID-19 Study Register.

Current strategy (last updated 2 September 2021)

PubMed

(2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARS-CoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "COVID-19"[Mesh] OR "COVID-19 Testing"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "Coronavirus"[Mesh:NoExp] OR "SARS-CoV-2"[Mesh] OR "COVID-19"[nm] OR "COVID-19 drug treatment"[nm] OR "COVID-19 diagnostic testing"[nm] OR "COVID-19 serotherapy"[nm] OR "COVID-19 vaccine"[nm] OR "LAMP assay"[nm] OR "severe acute respiratory syndrome coronavirus 2"[nm] OR "spike protein, SARS-CoV-2"[nm]) NOT ("animals"[mh] NOT "humans"[mh]) NOT (editorial[pt] OR newspaper article[pt])

Embase.com

((('coronaviridae'/de OR 'coronavirinae'/de OR 'coronaviridae infection'/de OR 'coronavirus disease 2019'/exp OR 'coronavirus infection'/de OR 'SARS-related coronavirus'/de OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR '2019 nCoV':ti,ab,kw OR 2019nCoV:ti,ab,kw OR ((corona* OR corono*) NEAR/1 (virus* OR viral* OR virinae*)):ti,ab,kw OR coronavir*:ti,ab,kw OR coronovir*:ti,ab,kw OR COVID:ti,ab,kw OR COVID19:ti,ab,kw OR HCoV*:ti,ab,kw OR 'nCov 2019':ti,ab,kw OR 'SARS CoV2':ti,ab,kw OR 'SARS CoV 2':ti,ab,kw OR SARSCoV2:ti,ab,kw OR 'SARSCoV 2':ti,ab,kw) NOT (('animal experiment'/de OR 'animal'/exp) NOT ('human'/exp OR 'human experiment'/de))) NOT 'editorial'/it) NOT ([medline]/lim OR [pubmed-not-medline]/lim) AND [1-12-2019]/sd

CENTRAL

1 ("2019 nCoV" OR 2019nCoV OR "corona virus*" OR coronavirus* OR COVID OR COVID19 OR "nCov 2019" OR "SARS-CoV2" OR "SARS CoV-2" OR SARSCoV2 OR "SARSCoV-2"):TI,AB AND CENTRAL:TARGET

2 Coronavirus:MH AND CENTRAL:TARGET

3 Coronavirus:EH AND CENTRAL:TARGET

4 #1 OR #2 OR #3

5 2019 TO 2021:YR AND CENTRAL:TARGET

6 #5 AND #4

7 INSEGMENT

8 #6 NOT #7

(Continued)

ClinicalTrials.gov

COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR coronavirus

WHO ICTRP

We screen the entire COVID-19.csv file available from www.who.int/emergencies/diseases/novel-coronavirus-2019.

medRxiv

We screen the entire COVID-19 results identified by the Stephen B. Thacker CDC Library.

Epistemonikos L·OVE

The **Epistemonikos L·OVE COVID-19 platform (Epistemonikos)**, (app.iloveevidence.com/). This platform is a digital repository built by systematic searches in multiple databases, trial registries and preprint servers.

Complete data sources and search methods are available here. In app.iloveevidence.com/ we:

1. Select “COVID-19 L-OVE”
2. Select population “COVID 19”
3. Select “Primary studies”
4. Filter results by “RCT” and “Reporting data”
5. Export the results in a.ris file

Below is the search strategy used by COVID-19 L-OVE.

Source	Search strategy
Epistemonikos Database	*COVID* OR *coronavir* OR *coronovir* OR *betacoronavir* OR *beta-coronavirus* OR “corona virus” OR “virus corona” OR “corono virus” OR “virus corono” OR *neocoronavir* OR hcov* OR *2019-ncov* OR *cv19* OR *cv-19* OR “cv 19” OR n-cov* OR ncov* OR (wuhan* AND (virus OR viruses OR viral)) OR *cv-19* OR sars* OR sari OR “severe acute respiratory syndrome” OR antisars* OR anti-sars* OR “corona patients” OR *pandemi*

Other sources

We also systematically searched for updates or publications of the preprints using a preprint tracker developed in collaboration with a research team from the French National Centre for Scientific Research (CNRS) (Cabanac 2021); see dbrech.irit.fr/pls/apex/.

Other resources searched are listed below.

- **European Medicine Agency** (**EMA) clinical data website** (clinicaldata.ema.europa.eu/web/cdp/home) to identify trials submitted to the EMA and search for the Clinical Study Report (CSR) of eligible studies (www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments) and (www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines).
- **FDA website** to identify FDA approval trials (www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19).

In addition, we searched **Retraction Watch Database** for retracted studies (retractionwatch.com/retracted-coronavirus-covid-19-papers/).

For the Retraction Watch Website

1. Click in « Retracted coronavirus (COVID-19) papers »
2. Check the list of news Retracted papers

Previous search strategy

The initial search strategy was developed with an information specialist (Robin Featherstone). We conducted an evaluation of two secondary sources the L-OVE platform and the Cochrane COVID-19 Study Register. We found that searching both secondary sources allowed the identification of 100% of the reports of RCTs (preprint or peer-reviewed publication) assessing treatment or preventive interventions for COVID-19 (see Appendix 3). We updated our search on 7 September 2020 and now only search the L-OVE platform, the Cochrane COVID-19 Study Register, the Retraction Watch Database and all other resources listed below. The last search date was 3 June 2022.

- **PubMed** was searched every working day up to 7 September 2020.
- **ChinaXiv** (chinaxiv.org/) is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in Chinese. Searched every working day from 1 March 2020 to 7 September 2020.
- **MedRxiv** (www.medrxiv.org) is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in the medical, clinical, and related health sciences. A curated list of records for COVID-19 and SARS-CoV-2 is available at connect.biorxiv.org/relate/content/181. Note that this list also includes sources listed in bioRxiv, but we only screened the sources published on MedRxiv. Searched every working day from 1 March 2020 to 7 September 2020.
- **CNKI** (China National Knowledge Infrastructure; www.cnki.net/) database and journal.yiigle.com/. Searched on 17 April 2020.
- **LitCOVID** (www.ncbi.nlm.nih.gov/research/coronavirus/), a curated database that tracks scientific evidence on COVID-19 published in PubMed. The hub is updated daily and studies are categorized by domain (e.g. "transmission" or "treatment" (www.nature.com/articles/d41586-020-00694-1)). We screened studies listed under "treatment" from 1 March 2020 to 1 June 2020. We decided to stop searching LitCOVID because it did not identify any trials that were not already identified in the primary source.
- **WHO database of publications on coronavirus disease** (COVID-19) (www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov) from 1 March 2020 to 28 August 2020. We decided to stop searching these secondary sources because they did not identify any trials that were not already identified in the primary source.
- We screened other sources such as the **EPPI-Centre living map of evidence** (eppi.ioe.ac.uk/COVID19_MAP/COVID_map_v5.html) and **Meta-evidence**, developed by Campbell UK & Ireland (meta-evidence.co.uk/) from 1 March 2020 to 28 August 2020. We decided to stop searching these secondary sources because they did not identify any trials that were not already identified in the primary source.

Appendix 4. GRADE methods used for assessing certainty of evidence

Data from RCTs start at high certainty. Evidence certainty can be downgraded for the following reasons.

- Limitations in study design or execution (risk of bias)
  - In general, if there is no or only one risk of bias domain with "some concerns", we do not downgrade
  - Downgrade by 1 level: if there are at least two risk of bias domains with some concerns or one domain with high risk
  - Downgrade by 2 levels: if all studies reporting on the outcome have domains at high risk of bias
  - For each of these decisions, we consider the contribution (i.e. "weight") of the study to the pooled estimate. If most of the weight (> 75%) comes from studies at low risk of bias, we did not downgrade.
- Inconsistency of results
  - In general, we usually downgrade by 1 level when $I^2 > 50\%$ and by two levels if $I^2 > 90\%$
  - We do not downgrade if the I^2 is high but all in the same direction (showing appreciable benefit/appreciable harm) visually in the forest plot
  - Where results are inconsistent in other ways, this can also be downgraded, e.g. if there are inconsistent results across subgroups in the primary study.
  - Inconsistency can also arise from the pooled effect being different (in direction and size) to the effect from the largest study and we will consider downgrading for this reason
- Indirectness of evidence
  - In general, we downgrade for indirectness in cases where results may not be generalizable to other countries/settings
  - We downgrade one level for outcomes with data from: only single-centre studies; pooled effects based on single-centre studies from the same country; multi-centre studies from only one country.
  - We do not downgrade if multiple (single- or multi-centre) studies are included from different countries, or if a multi-centre trial based in different countries.
  - We do not downgrade adverse effects outcomes for the above reasons because we consider these to be similar across settings.
- Imprecision
  - The level of precision will depend on the outcome, the number of events and participants, the size of the effect and the width of the confidence intervals, and the size of the absolute effect.
  - We usually downgrade by 1 level when about < 400 events (dichotomous outcomes) or < 2000 participants per group (continuous outcomes).
  - We consider the absolute risk in assessing imprecision and downgrade by 1 level when the minimal important difference (MID) threshold is crossed (Schünemann 2022). For outcomes clinical improvement, time to clinical improvement, and adverse events we

considered a 5% difference in the absolute risk (50 events per 1000) as the MID threshold. Absolute differences smaller than 5% will be considered as a trivial effect/no effect. For the outcomes of mortality, time to death, WHO score 7 and above, time to WHO score 7 and above, and serious adverse events the minimal important difference (MID) threshold is 1% difference in the absolute risk (10 per 1000).
    - We usually downgrade by two levels if both MIDs (for benefit and harm) in the absolute risk are crossed or the number of participants and/or events is low.
    - We will also consider the final effect estimate and what the interpretation will be (i.e. no effect/trivial effect, benefit, harm) alongside the absolute effects and each end of the confidence intervals.
- Publication bias
    - If an outcome is prespecified in a clinical trial registry or protocol but no results are reported, we will add a footnote under 'other considerations'.
- Studies reporting no events
    - If studies report zero event for an outcome, we do not consider these in the respective GRADE assessment as they do not contribute to the pooled effect. We add the respective studies in 'comments' in the Summary of findings
- These are only general rules for making decisions to downgrade the certainty of the evidence. In many cases the review team will need to discuss decisions for specific outcomes. The different levels of certainty that result from the GRADE approach will be interpreted as follows:
- **High**: we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low**: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 5. Summary of baseline characteristics of studies included in the meta-analysis

	Reference	Experimental arm(s)	Control	Sample size	Dose	Severity	Number of vaccinated participants	Publication status	Conflict of interest (COI)	Funding	Country	Overall risk of bias
1	Hermine 2021	Tocilizumab	Standard care	131	8 mg/kg	Moderate/severe	NA	Published paper	no COI	Public/non-profit	France	Some concerns
2	Salama 2020	Tocilizumab	Placebo	388	8 mg/kg	Mild to severe	0	Published paper	COI	Private	Brazil, Kenya, Mexico, Peru, South Africa, USA	Some concerns
3	Salvarani 2020	Tocilizumab	Standard care	126	8 mg/kg	Severe	NA	Published paper	COI	Mixed	Italy	Some concerns
4	Stone 2020	Tocilizumab	Placebo	243	8 mg/kg	Mild to severe	0	Published paper	COI	Private	USA	Low
5	ARCHITECTS 2021	Tocilizumab	Placebo	21	8 mg/kg	Critical	NA	Unpublished results	NR	Public/non-profit	USA	Low
6	COVIDOSE-2 2021	Tocilizumab	Standard care	28	4 0mg or 120 mg	Moderate/severe	NR	Unpublished results	NR	Public/non-profit	USA	Low
7	COVITOZ-01 2021	Tocilizumab	Standard care	26	8 mg/kg	Mild to severe	NA	Unpublished results	NR	Public/non-profit	Spain	Low
8	Declercq 2021	Tocilizumab; Siltuximab	Standard care	154	8 mg/kg	Moderate to critical	NA	Published paper	no COI	Public/non-profit	Belgium	Some concerns

(Continued)

9	Derde 2021	Tocilizumab; Sarilumab	Standard care	1390	8 mg/kg	Severe/critical	NR	Preprint	no COI	Mixed	UK, Netherlands, Ireland, Australia, New Zealand, Canada, Finland, Italy, Saudi-Arabia	Some concerns
9	Gordon 2021	Tocilizumab; Sarilumab	Standard care	778	8 mg/kg	Severe/critical	NA	Published paper	COI	Mixed	Australia, Ireland, the Netherlands, New Zealand, Saudi Arabia, UK	Some concerns
10	HMO-0224-20 2021	Tocilizumab	Placebo	54	8 mg/kg	Severe/critical	NR	Unpublished results	NR	Public/non-profit	Israel	High
11	Horby 2021b	Tocilizumab	Standard care	4116	maximum 800 mg	Moderate to critical	NR	Published paper	no COI	Public/non-profit	UK	Some concerns
12	IMMCOVA 2021	Tocilizumab	Standard care	49	8 mg/kg	Moderate/severe	NR	Unpublished results	NR	Public/non-profit	Sweden	Low
13	Jordan 2021	Clazakizumab	Placebo	17	25 mg	Moderate/severe	NA	Results posted on registry	NR	Private	USA	Some concerns
14	Lescure 2021	Sarilumab	Placebo	420	2 arms merged: 400 mg/200 mg once off	Moderate to critical	NA	Published paper	COI	Private	Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy,	Some concerns

(Continued)

											Japan, Russia, and Spain	
15	Lomakin 2021	Levil-imab	Placebo	206	324 mg/ day	Moder-ate/severe	NA	Published paper	COI	Private	Russia	Some concern
16	Mariette 2021	Sarilum-ab	Stan-dard care	148	400mg	Moder-ate/severe	NA	Published paper	No COI	Pub-lic/non-profit	France	Some concerns
17	Merchante 2021	Sarilum-ab	Stan-dard care	118	2 arms merged: 200/400 mg	Moder-ate/severe	NR	Published paper	No COI	Mixed	Spain	Some concerns
18	Rutgers 2021	Tocilizum-ab	Stan-dard care	354	8 mg/kg	Moderate to critical	NR	Preprint	no COI	Mixed	The Nether-lands	Some concerns
19	San-cho-Lopez 2021	Sarilum-ab	Stan-dard care	201	200 to 400mg	Moderate	NR	Published paper	No COI	Private	Spain	Some concerns
20	Soin 2021	Tocilizum-ab	Stan-dard care	180	6 mg/kg	Moderate to critical	NA	Published paper	COI	Mixed	India	Some concerns
21	Talaschian 2021	Tocilizum-ab	Stan-dard care	40	8 mg/kg	Moder-ate/severe	NA	Preprint	no COI	Pub-lic/non-profit	Iran	High
22	Veiga 2021	Tocilizum-ab	Stan-dard care	129	8 mg/kg	Moderate to critical	NA	Published paper	COI	Mixed	Brazil	Some concerns
23	Wang 2021	Tocilizum-ab	Stan-dard care	65	400 mg	Moder-ate/severe	NA	Published paper	no COI	Pub-lic/non-profit	China	Some concerns
24	Branch-Elliman 2022	Sarilum-ab	Stan-dard care	50	400 mg	Mild to se-vere	NR	Published paper	COI	Pub-lic/non-profit	USA	Some concerns

(Continued)

25	Broman 2022	Tocilizumab	Standard care	88	400 to 800 mg	Moderate/severe	0	Published paper	COI	No specific funding	Finland	Some concerns
26	Garcia-Vicuna 2022	Sarilumab	Standard care	30	400 mg once-off	Mild to severe	NA	Published paper	No COI	Mixed	Spain	Some concerns
27	Hermine 2022	Tocilizumab	Standard care	97	8 mg/kg once-off	Severe/critical	0	Published paper	no COI	Public/non-profit	France	Some concerns
28	Hermine 2022	Sarilumab	Standard care	91	400 mg	Severe/critical	0	Published paper	No COI	Public/non-profit	France	Some concerns
29	Lonze 2022	Clazakizumab	Placebo	152	25 mg	Moderate to critical	NA	Published paper	COI	Mixed	USA	Some concerns
30	Rosas 2022	Tocilizumab	Placebo	452	8 mg/kg	Mild to critical	0	Published paper	COI	Mixed	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	Some concerns
31	Samsonov 2022	Olokizumab	Placebo	248	64 mg	Severe/critical	NA	Results posted on registry	NR	Private	Russia	Some concerns
32	Sivapalasingam 2022	Sarilumab	Placebo	457	2 arms merged: 400 mg/200 mg once-off	Moderate to critical	NA	Published paper	COI	Private	USA	Some concerns
	Sivapalasingam 2022	Sarilumab	Placebo	1330	2 arms merged: 400	Moderate to critical	NA	Published paper	COI	Private	USA	Some concerns

(Continued)

		mg/200mg once off

Abbreviations

NA: not applicable (study conducted in 2020, vaccines were not available); NR: not reported.

Appendix 6. Characteristics of unpublished registered studies

Tocilizumab vs placebo/standard care

Registration number	Status	Registration date	Design	Estimated sample size	Interventions	Control interventions
NCT04690920	Completed	December 2020	Parallel	200	Tocilizumab	standard care
IRCT20200510047383N1	Recruitment Completed	May 2020	Parallel	100	Tocilizumab	standard care
IRCT20200525047570N1	Recruitment Completed	July 2020	Parallel	60	Tocilizumab	standard care
IRCT20201024049134N2	Recruitment Completed	June 2021	Parallel	60	Tocilizumab	standard care
EUCTR2020-001770-30-BE	Terminated	April 2020	Parallel	60	Tocilizumab	standard care
NCT04335071	Terminated	April 2020	Parallel	5	Tocilizumab	Placebo
EUCTR2020-001275-32-DK	Terminated	March 2020	Parallel	200	Tocilizumab	standard care
EUCTR2020-001408-41-DE	Terminated	April 2020	Parallel	200	Tocilizumab	Placebo
EUCTR2020-001767-86-IE	Ongoing	April 2020	Parallel	90	Tocilizumab	standard care
CTRI/2020/12/029793	Not recruiting	December 2020	Parallel	54	Tocilizumab	Placebo
ACTRN12620000580976	Not recruiting	May 2020	Parallel	150	Tocilizumab	standard care
NCT04361552	Cancelled	April 2020	Parallel	0	Tocilizumab	standard care

Sarilumab vs placebo/standard care

Registration number	Status	Registration date	Design	Estimated sample size	Interventions	Control interventions
EUCTR2020-001290-74-ES	Terminated	April 2020	Parallel	216	Sarilumab	standard care
EUCTR2020-001275-32-DK	Terminated	March 2020	Parallel	200	Sarilumab	standard care
EUCTR2020-001390-76-IT	Ongoing	June 2020	Parallel	171	Sarilumab	standard care

Clazakizumab vs placebo/standard care

Registration number	Status	Registration date	Design	Estimated sample size	Interventions	Control interventions
NCT04381052	Terminated	May 2020	Adaptive	1	Clazakizumab	Placebo
NCT04494724	Ongoing	July 2020	Parallel	60	Clazakizumab	Placebo

Olokizumab vs placebo/standard care

Registration number	Status	Registration date	Design	Estimated sample size	Interventions	Control interventions
NCT05187793	Ongoing	January 2022	Parallel	204	Olokizumab	standard care
NCT04452474	Cancelled	June 2020	Parallel	0	Olokizumab	Placebo

Siltuximab vs placebo/standard care

Registration number	Status	Registration date	Design	Estimated sample size	Interventions	Control interventions
NCT04616586	Terminated	November 2020	Parallel	555	Siltuximab	Placebo

Appendix 7. Details on the request for information sent to authors of published IL 6-blocking agent trials

Study ID	Author's contact name	Treatment	Date of contact	Reply (last check 21/07/2022)
Hermine 2021	Xavier Mariette	Tocilizumab	9 October 2020	Publication received + all requested data 23 October 2020
Salama 2020	Shalini V. Mohan	Tocilizumab	3 November 2020	E-mail received with some of the data requested on 3 December 2020
Salvarani 2020	Carlo Salvarani	Tocilizumab	3 November 2020	No response
Stone 2020	John Stone	Tocilizumab	3 November 2020	No response
ARCHITECTS 2021	Todd Seto and May Vawer	Tocilizumab	19 July 2022	19 July 2022 "Data for our study is already published in the meta-analysis"
COVIDOSE-2 2021	Pankti D Reid and Garth W Strohbehn	Tocilizumab	19 July 2022	No response

(Continued)

COVITOZ-01 2021	No available contact	Tocilizumab	No contact information available.	No response
Declercq 2021	Bart Lambrecht	Anakinra	30 December 2021	No response
Derde 2021	Lennie P G Derde	Tocilizumab	23 July 2021	No response
Gordon 2021	Anthony Gordon	Sarilumab Tocilizumab	25 January 2021	No response
HMO-0224-20 2021	Reuven Pizov and Eithan Galun	Tocilizumab	19 July 2022	No response
Horby 2021b	Peter W Horby and Martin J Landray	Tocilizumab	Contacted	Response received, no additional data available.
IMMCOVA 2021	Jonas Sundén-Cullberg	Tocilizumab	19 July 2022	No response
Jordan 2021	Stanley Jordan	Clazakizumab	30 December 2021	No response
Lescure 2021	Francois X Lescure	Sarilumab	12 February 2021	No response
Lomakin 2021	Polina S. Pukhtinskaia	Levilimab	19 July 2022	No response
Mariette 2021	Xavier Mariette	Sarilumab	19 July 2022	No response up to 21 July 2022
Merchante 2021	Julián de la Torre Cisneros	Sarilumab	20 January 2022	No response
Rutgers 2021	T van Meerten	Tocilizumab	31 May 2021	Willing to share but no data received.
Sancho-Lopez 2021	Aránzazu Sancho-López and Belén Ruiz-Antorán	Sarilumab	19 July 2022	No response up to 21 July 2022
Soin 2021	Pooja Sharma	Tocilizumab	12 April 2022	No response
Talaschian 2021	Mahdi Mahmoudi	Tocilizumab	31 May 2021	No response
Veiga 2021	Viviane C Veiga	Tocilizumab	1 February 2021	No response
Wang 2021	Xiaoling Xu and Xiaodong Mei	Tocilizumab	25 September 2020	Cannot share before publication.
Branch-Elliman 2022	Westyn Branch-Elliman	Sarilumab	12 April 2022	Willing to share, but no data received yet.
Broman 2022	Jarmo Oksi	Tocilizumab	19 July 2022	No response
Garcia-Vicuna 2022	Rosario García-Vicuña	Sarilumab	19 July 2022	21 July 2022: willing to share in August
Hermine 2022	Olivier Hermine	Tocilizumab	12 April 2022	No response
Hermine 2022	Olivier Hermine	Sarilumab	12 April 2022	No response
Lonze 2022	Bonnie Lonze	Clazakizumab	07 June 2022	No response

(Continued)

Rosas 2022	Ivan O. Rosas	Tocilizumab	25 September 2020	Missing data requested received on7 December 2020. Protocol and statistical plan still not available.
Samsonov 2022	Sergey Grishin	Olokizumab	19 July 2022	No response up to 21 July 2022
Sivapalasingam 2022	Sumathi Sivapalasingam	Sarilumab	16 June 2021	No response

Appendix 8. Prevalence of variants of concern (VOC) during the period of the study

Study	Location	Start date	End date	Prevalence (min-max)
Hermine 2021	France	31 March 2020	18 April 2020	No VOC during the recruitment period.
Salama 2020	Brazil, Kenya, Mexico, Peru, South Africa, USA	14 May 2020	18 August 2020	No VOC during the recruitment period.
Salvarani 2020	Italy	31 March 2020	11 June 2020	No VOC during the recruitment period.
Stone 2020	USA	20 April 2020	15 June 2020	No VOC during the recruitment period.
ARCHITECTS 2021	USA	12 June 2020	28 August 2020	No VOC during the recruitment period.
COVIDOSE-2 2021	USA	10 September 2020	31 January 2021	No VOC during the recruitment period.
COVITOZ-01 2021	Spain	04 May 2020	21October 2021	Alpha: 1-90%
Declercq 2021	Belgium	04 April 2020	06 December 2020	No VOC during the recruitment period.
Derde 2021	UK, Netherlands, Ireland, Australia, New Zealand, Canada, Finland, Italy, Saudi-Arabia	25 March 2020	NR	End date unclear. No VOC during the recruitment period.
Gordon 2021	Australia, Ireland, the Netherlands, New Zealand, Saudi Arabia, UK	19 April 2020	19 November 2020	No VOC during the recruitment period.
HMO-0224-20 2021	Israel	08 April 2020	03 February 2021	Alpha: 1-70%
Horby 2021b	UK	23April 2020	24 January 2021	No VOC during the recruitment period.
IMMCOVA 2021	Sweden	11 June 2020	March 2021	No VOC during the recruitment period.

(Continued)

Jordan 2021	USA	28 April 2020	30 July 2020	No VOC during the recruitment period.
Lescure 2021	Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain	28 March 2020	03 July 2020	No VOC during the recruitment period.
Lomakin 2021	Russia	29 April 2020	03 August 2020	No VOC during the recruitment period.
Mariette 2021	France	27 March 2020	06 April 2020	No VOC during the recruitment period.
Merchante 2021	Spain	13 July 2020	05 March 2021	Alpha: 1-65%
Rutgers 2021	The Netherlands	06 April 2020	12 Jan 2021	No VOC during the recruitment period.
Sancho-Lopez 2021	Spain	04 August 2020	23 March 2021	Alpha: 1-80%
Soin 2021	India	30 May 2020	31 August 2020	No VOC during the recruitment period.
Talaschian 2021	Iran	10 July 2020	10 October 2020	No VOC during the recruitment period.
Veiga 2021	Brazil	08 May 2020	17 July 2020	No VOC during the recruitment period.
Wang 2021	China	13 February 2020	13 March 2020	No VOC during the recruitment period.
Branch-Elliman 2022	USA	10 April 2020	03 February 2021	No VOC during the recruitment period.
Broman 2022	Finland	12 August 2020	16 June 2021	No VOC during 2020. Alpha was dominant during first half of 2021 and delta as of June 2021[a].
Garcia-Vicuna 2022	Spain	13 April 2020	30 October 2020	No VOC during the recruitment period.
Hermine 2022	France	27 March 2020	07 April 2020	No VOC during the recruitment period.
Hermine 2022	France	30 March 2020	20 April 2020	No VOC during the recruitment period.
Lonze 2022	USA	01April 2020	03 December 2020	No VOC during the recruitment period.
Rosas 2022	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	03 April 2020	28 May 2020	No VOC during the recruitment period.
Samsonov 2022	Russia	23 April 2020	24 July 2020	No VOC during the recruitment period
Sivapalasingam 2022	USA	18 March 2020	02 July 2020	No VOC during the recruitment period.
Sivapalasingam 2022	USA	18 March 2020	02 July 2020	No VOC during the recruitment period.

[a]No information on VOC in outbreak.com for Finland until after December 2021. Information retrieved from: thl.fi/en/web/infectious-diseases-and-vaccinations/what-s-new/coronaviru[…]ates/transmission-and-protection-coronavirus/coronavirus-variants

Appendix 9. Matrices indicating availability of trial results for critical and important outcomes

10.1.1 Matrix indicating availability of trial results for the critical and important outcomes of the review. Tocilizumab compared to standard care/placebo

Trial ID	Study follow-up (in days)	Tocilizumab	Standard care or placebo	Critical outcomes							
				All-cause mortality		Clinical improvement		WHO SCORE 7 and above		AE	SAE
				Day 28	Day ≥60	Day 28	Day ≥60	Day 28	Day ≥60		
Hermine 2021 (NCT04331808)	90	64	67	✓	✓	✓	*	✓	*	✓	✓
Salama 2020 (NCT04372186)	60	259	129	✓	✓	✓	*	✓	*	✓	✓
Salvarani 2020 (NCT04346355)	30	30	66	✓	*	✓	*	*	*	✓	✓
Stone 2020 (NCT04356937)	28	161	82	✓	*	✓	*	✓	*	✓	✓
ARCHITECTS 2021[a] (NCT04412772)	90	10	11	✓	✓	✓	*	✓	*	*	✓
COVIDOSE-2 2021[a](NCT04479358)	28	20	8	✓	*	✓	*	✓	*	*	✓
COVITOZ-01 2021[a] (NCT04435717)	90	17	9	✓	✓	*	*	✓	*	*	✓
Declercq 2021 (NCT04330638; EudraCT2020-001500-41)	90	82	72	✓	✓	✓	*	✓	*	*	✓
Derde 2021; Gordon 2021 (NCT02735707)	90	972	418	*	✓	*	*	*	*	*	✓
HMO-0224-20 2021[a] (NCT04377750)	90	37	17	✓	✓	✓	*	✓	*	*	*
Horby 2021b (NCT04381936; ISRCTN50189673)	28	2022	2094	✓	*	✓	*	✓	*	*	*
IMMCOVA 2021[a] (NCT04412291; EudraCT 2020-001748-24)	28	22	27	✓	*	✓	*	✓	*	*	✓
Rutgers 2021 (NL8504)	90	174	180	✓	*	*	*	✓	*	*	*
Soin 2021 (CTRI/2020/05/025369)	30	90	90	✓	*	*	*	*	*	✓	✓

(Continued)

Talaschian 2021 (IRCT20081027001411N4)	28	20	20	✓	*	✓	*	*	*	*	✓
Veiga 2021 (NCT04403685)	29	65	64	✓	*	✓	*	✓	*	✓	✓
Wang 2021 (ChiCTR2000029765)	14	33	32	**X**	*	*	*	*	*	✓	✓
Broman 2022 (NCT04577534)	90	29	29	✓	✓	✓	*	✓	*	*	✓
Hermine 2022 (NCT04324073)	90	51	46	✓	✓	✓	✓	✓	*	✓	✓
Rosas 2022 (NCT04320615)	60	301	151	✓	✓	✓	*	✓	*	✓	✓

[a]For the outcomes that were prespecified in the registry but no data were reported in the REACT meta-analysis, the overall reporting outcome bias could not be assessed since the published report was not available.

Trial ID	Study follow-up (in days)	Tocilizumab	Standard care or Placebo	Important outcomes		
				Time to death	Time to clinical improvement	Time to WHO score 7 and above
Hermine 2021 (NCT04331808)	90	64	67	✓	✓	✓
Salama 2020 (NCT04372186)	60	259	129	*	✓	✓
Salvarani 2020 (NCT04346355)	30	30	66	*	✓	*
Stone 2020 (NCT04356937)	28	161	82	✓	✓	✓
ARCHITECTS 2021[b] (NCT04412772)	90	10	11	*	*	*
COVIDOSE-2 2021[b] (NCT04479358)	28	20	8	*	*	*
COVITOZ-01 2021[b] (NCT04435717)	90	17	9	*	*	*
Declercq 2021 (NCT04330638; EudraCT2020-001500-41)	90	82	72	✓	*	*
Derde 2021; Gordon 2021 (NCT02735707)	90	972	418	✓	✓	*
HMO-0224-20 2021[b] (NCT04377750)	90	37	17	*	*	*
Horby 2021b (NCT04381936; ISRCTN50189673)	28	2022	2094	*	*	*
IMMCOVA 2021[b] (NCT04412291, EudraCT 2020-001748-24)	28	22	27	*	*	*
Rutgers 2021 (NL8504)	90	174	180	✓	*	✓
Soin 2021 (CTRI/2020/05/025369)	30	90	90	*	*	*
Talaschian 2021 (IRCT20081027001411N4)	28	20	20	✓	*	*
Veiga 2021 (NCT04403685)	29	65	64	*	*	*
Wang 2021 (ChiCTR2000029765)	14	33	32	*	*	*
Broman 2022 (NCT04577534)	90	29	29	✓	*	*
Hermine 2022 (NCT04324073)	90	51	46	✓	✓	*
Rosas 2022 (NCT04320615)	60	301	151	✓	✓	*

[b]For the outcomes that were prespecified in the registry but no data were reported in the REACT meta-analysis, the overall reporting outcome bias was not assessed since the published report was not available.

AE: Adverse event

SAE: Serious adverse event

Key:
✓ A study result is available for inclusion in the synthesis.
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavorable by the study investigators.
– No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results.
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study.

* Outcome not assessed for the respective trial

10.2.1 Matrix indicating availability of trial results for the critical and important outcomes of the review. Sarilumab compared to standard care/placebo

Trial ID	Study follow-up (in days)	Sarilumab	Standard care or placebo	Critical outcomes							
				All-cause mortality		Clinical improvement		WHO SCORE 7 and above		AE	SAE
				Day 28	Day ≥60	Day 28	Day ≥60	Day 28	Day ≥60		
Derde 2021; Gordon 2021 (NCT02735707)	90	485	418	*	✓	*	*	*	*	*	✓
Lescure 2021 (NCT04327388; EudraCT2020-001162-12-FR; U1111-1249-602)	60	334	86	✓	✓	*	*	*	*	*	*
Mariette 2021 (NCT04324073)	90	68	80	✓	✓	✓	✓	✓	*	✓	✓
Merchante 2021 (NCT04357860; EudraCT2020-001531-27)	28	79	39	✓	*	✓	*	*	*	*	*
Sancho-Lopez 2021 (EU-CTR 2020-002037-15)	28	99	102	✓	*	✓	*	✓	*	✓	*
Branch-Elliman 2022 (NCT04359901)	30	20	30	✓	*	✓	*	✓	*	*	*
Garcia-Vicuna 2022(NCT04357808)	90	20	10	✓	✓	*	✓	*	✓	*	✓
Hermine 2022 (NCT04324073)	90	50	41	✓	✓	✓	✓	*	*	✓	✓
Sivapalasingam 2022 (NCT04315298) (results from phase 2)	60	*	*	✓	✓	✓	*	✓	*	✓	✓
Sivapalasingam 2022 (NCT04315298) (results from phase 3 cohort 1)	60	*	*	✓	✓	✓	*	*	*	✓	✓

Trial ID	Study follow-up (in days)	Sarilumab	standard care or Placebo	Important outcomes		
				Time to death	Time to clinical improvement	Time to WHO score 7 and above
Derde 2021;Gordon 2021 (NCT02735707)	90	485	418	✓	✓	*
Lescure 2021 (NCT04327388; EudraCT2020-001162-12; U1111-1249-602)	60	334	86	*	✓	*
Mariette 2021 (NCT04324073)	90	68	80	✓	✓	✓
Merchante 2021 (NCT04357860; EudraCT2020-001531-27)	28	39	39	✓	✓	*
Sancho-Lopez 2021 (EU-CTR 2020-002037-15)	28	99	102	*	✓	✓
Branch-Elliman 2022 (NCT04359901)	30	20	30	*	*	*
Garcia-Vicuna 2022(NCT04357808)	90	20	10	*	*	*
Hermine 2022 (NCT04324073)	90	50	41	✓	✓	*
Sivapalasingam 2022 (NCT04315298)	60	*	*	*	*	*
Sivapalasingam 2022 (NCT04315298)	60	*	*	*	*	*

11.3.1 Matrix indicating availability of trial results for the critical and important outcomes of the review. Clazakizumab compared to placebo

Trial ID	Study follow-up (in days)	Clazakizumab	Standard care or placebo	Critical outcomes							
				All-cause mortality		Clinical improvement		WHO SCORE 7 and above		AE	SAE
				Day 28	Day ≥60	Day 28	Day ≥60	Day 28	Day ≥60		
Lonze 2022 (NCT04343989; NCT04659772)	60	78	74	✓	✓	✓	✓	✓	*	*	✓

Trial ID	Study follow-up (in days)	Clazakizumab	Standard care or placebo	Important outcomes		
				Time to death	Time to clinical improvement	Time to WHO score 7 and above
Lonze 2022 (NCT04343989; NCT04659772)	60	78	74	*	*	*

10.4.1 Matrix indicating availability of trial results for the critical and important outcomes of the review. Olokizumab compared to placebo

Trial ID	Study follow-up (in days)	Olokizumab	Placebo	Important outcomes		
				Time to death	Time to clinical improvement	Time to WHO score 7 and above
Samsonov 2022 (NCT04380519)	28	124		*	**X**	*

10.5.1 Matrix indicating availability of trial results for the critical and important outcomes of the review. Siltuximab compared to standard care

Trial ID	Study follow-up (in days)	Siltuximab	Standard care	Critical outcomes							
				All-cause mortality		Clinical improvement		WHO SCORE 7 and above		AE	SAE
				Day 28	Day ≥60	Day 28	Day ≥60	Day 28	Day ≥60		
Declercq 2021 (NCT04330638; EudraCT2020-001500-41)	90	76	72	✓	✓	✓	*	✓	*	*	✓

Trial ID	Study follow-up (in days)	Siltuximab	standard care	Important outcomes		
				Time to death	Time to clinical improvement	Time to WHO score 7 and above
Declercq 2021 (NCT04330638; EudraCT2020-001500-41)	90	76	72	✓	*	*

10.6.1 Matrix indicating availability of trial results for the critical and important outcomes of the review. Levilimab compared to placebo

Trial ID	Study follow-up (in days)	Levilimab	Placebo	Critical outcomes							
				All-cause mortality		Clinical improvement		WHO SCORE 7 and above		AE	SAE
				Day 28	Day ≥60	Day 28	Day ≥60	Day 28	Day ≥60		
Lomakin 2021 (NCT04397562)	60	103	103	✓	✓	✓	*	*	*	✓	✓

Trial ID	Study follow-up (in days)	Levilimab	Placebo	Important outcomes		
				Time to death	Time to clinical improvement	Time to WHO score 7 and above
Lomakin 2021 (NCT04397562)	60	103	103	*	*	*

AE: Adverse event

SAE: Serious adverse event

Key:
✓ A study result is available for inclusion in the synthesis
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavorable by the study investigators
– No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study

* Outcome not assessed for the respective trial

Appendix 10. Summary of findings: Tocilizumab compared to standard care/placebo - Important outcomes

Tocilizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: worldwide

Intervention: tocilizumab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with tocilizumab				
Time to clinical improvement follow-up: range 28 days to 90 days	644 per 1000[b]	**716 per** 1000 (679 to 749)	**HR 1.22** (1.10 to 1.34) [Time to clinical improvement]	2827 (7 RCTs)[c]	⊕⊕⊖⊖ Low[d,e]	
Time to WHO progression score (level 7 and above) follow-up: range 28 days to 90 days	212 per 1000[f]	**139 per** 1000 (108 to 181)	**HR 0.63** (0.48 to 0.84) [Time to WHO progression score (level 7 and above)]	1116 (4 RCTs)[g]	⊕⊕⊕⊕ High	
Time to death	244 per 1000[h]	**194 per** 1000 (166 to 225)	**HR 0.77** (0.65 to 0.91)	2949 (9 RCTs)[i]	⊕⊕⊕⊖ Moderate[j]	

(Continued)

follow-up: range 28 days to 90 days	[Time to death]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; D: day; HR: hazard ratio; RCT: randomized controlled trial; WHO: World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]Last updated: 27 January 2023
[b]Baseline risk calculated from Hermine 2021; Hermine 2022; Rosas 2022; Salama 2020; Salvarani 2020; Stone 2020.
[c]Derde 2021; Hermine 2021; Hermine 2022; Rosas 2022; Salama 2020; Salvarani 2020; Stone 2020.
[d]Risk of bias downgraded by 1 level: some concerns regarding deviation from intended intervention, missing data, outcome measurement and selection of the reported result.
[e]Imprecision downgraded by 1 level: wide confidence interval consistent with the possibility for benefit and the possibility for a trivial/no effect.
[f]Baseline risk calculated from Hermine 2021; Rutgers 2021; Salama 2020; Stone 2020.
[g]Hermine 2021; Rutgers 2021; Salama 2020; Stone 2020.
[h]Baseline risk calculated from Broman 2022; Declercq 2021; Derde 2021; Hermine 2021; Hermine 2022; Rosas 2022; Rutgers 2021; Stone 2020; Talaschian 2021.
[i]Broman 2022; Declercq 2021; Derde 2021; Hermine 2021; Hermine 2022; Rosas 2022; Rutgers 2021; Stone 2020; Talaschian 2021.
[j]Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviations from intended interventions, missing data, and selection of the reported results.

Appendix 11. Summary of findings: Sarilumab compared to standard care/placebo - Important outcomes

Sarilumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19[a]

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: worldwide

Intervention: sarilumab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with sarilumab				
Time to clinical improvement	752 per 1000[b]	**793 per** 1000 (752 to 834)	**HR 1.13** (1.00 to 1.29)	1881 (6 RCTs)[c]	⊕⊕⊖⊖ Low[d,e]	

(Continued)

follow-up: range 28 days to 90 days			[Time to clinical improvement]		
Time to WHO progression score (level 7 and above) follow-up: 28 days	159 per 1000[f]	**145 per** 1,000 (49 to 391)	**HR 0.90** (0.29 to 2.86) [Time to WHO progression score (level 7 and above)]	349 (2 RCTs)[g]	⊕⊖⊖⊖ Very low[h,i,j]
Time to death follow-up: range 28 days to 90 days	316 per 1000[k]	**236 per** 1000 (192 to 290)	**HR 0.71** (0.56 to 0.90) [Time to death]	1260 (4 RCTs)[l]	⊕⊕⊕⊕ High[m]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; D: day; HR: hazard ratio; RCT: randomized controlled trial; WHO: World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]Last updated: 27 January 2023

[b]Control risk calculated from Hermine 2022; Mariette 2021; Merchante 2021; Sancho-Lopez 2021.
[c]Derde 2021; Hermine 2022; Lescure 2021; Mariette 2021; Merchante 2021; Sancho-Lopez 2021.
[d]Risk of bias downgraded by 1 level: some concerns regarding deviations from intended interventions, missing data, and outcome measurement.

[e]Imprecision downgraded by 1 level: wide confidence interval consistent with the possibility for benefit and the possibility for no effect/trivial effect.

[f]Control risk calculated from Mariette 2021; Sancho-Lopez 2021.
[g]Mariette 2021; Sancho-Lopez 2021.
[h]Risk of bias downgraded by 1 level: some concerns regarding deviation from intended intervention, and selection of the reported results.
[i]Inconsistency downgraded by 1 level: $I^2 = 66.9\%$.
[j]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm.

[k] Control risk calculated from Derde 2021; Hermine 2022; Mariette 2021; Merchante 2021.
[l]Derde 2021; Hermine 2022; Mariette 2021; Merchante 2021.
[m]Despite some concerns regarding deviations from intended intervention and missing data, not downgraded for risk of bias because the studies with these concerns contributed only a small proportion of weight to the effect estimate.

Appendix 12. Summary of findings: Siltuximab compared to standard care/placebo - Important outcomes

Siltuximab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Patient or population: people with mild/moderate/severe/critical COVID-19

Setting: worldwide

(Continued)

Intervention: siltuximab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/placebo	Risk with siltuximab				
Time to clinical improvement - not reported	-	-	-	-	-	
Time to WHO progression score (level 7 and above) - not reported	-	-	-	-	-	
Time to death follow-up: 90 days	125 per 1000[b]	**183 per 1000** (83 to 373)	**HR 1.51** (0.65 to 3.50) [Time to death]	148 (1 RCT)[c]	⊕⊖⊖⊖ Very low[d,e]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; D: day; HR: hazard ratio; RCT: randomized controlled trial; WHO: World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]Last updated: 2 February 2023
[b]Control risk calculated from Declercq 2021.
[c]Declercq 2021
[d]Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings.
[e]Imprecision downgraded by 2 levels: very wide confidence interval consistent with the possibility for benefit and the possibility for harm.

Appendix 13. Sensitivity analyses

Sensitivity 1: participants randomized

Sensitivity 2: high risk of bias excluded

Sensitivity 3: only published studies

Comparison	Outcomes	Clinical improvement D28	Clinical improvement D60 or more	WHO progression score (level 7 or above) D28	All-cause mortality D28	All-cause mortality D60 or more	Adverse events	Serious adverse events
		RR (95%CI) N trials (N participants) I^2	RR (95%CI) N trials (N participants) I^2	RR (95%CI) N trials (N participants) I^2	RR (95%CI) N trials (N participants) I^2	RR (95%CI) N trials (N participants) I^2	RR (95%CI) N trials (N participants) I^2	RR (95%CI) N trials (N participants) I^2
Tocilizumab vs. standard care or placebo	**Main analysis**	**1.05 (1.00,1.11) 15 RCTs 6116 24.1%**	**1.10 (0.81,1.48) 1 RCT 97 -**	**0.90 (0.72,1.12) 13 RCTs 2217 19.9%**	**0.88 (0.81,0.94) 19 RCTs 7454 0.0%**	**0.91 (0.80, 1.04) 10 RCTs 7454 0.0%**	**1.03 (0.95, 1.12) 9 RCTs 1811 0.0%**	**0.93 (0.81, 1.07) 17 RCTs 2995 0.0%**
	Sensitivity 1	1.05 (1.00,1.11) 15 RCTs 6074 27.5%	1.07 (0.80, 1.42) 1 RCT 92	0.90 (0.72, 1.11) 13 RCTs 2087 16.9%	0.88 (0.81, 0.94) 19 RCTs 7380 0.0%	0.91 (0.80, 1.04) 10 RCTs 2725 0.0%	1.02 (0.94, 1.10) 9 RCTs 1775 0.0%	0.92 (0.80, 1.06) 17 RCTs 2921 0.0%
	Sensitivity 2	1.06 (1.01, 1.11) 13 RCTs 6022 25.7%	1.10 (0.81, 1.48) 1 RCT 97 -	0.88 (0.70, 1.10) 12 RCTs 2063 21.2%	0.88 (0.81, 0.95) 17 RCTs 7360 0.0%	0.92 (0.81, 1.05) 9 RCTs 2747 0.0%	1.03 (0.95, 1.12) 9 RCTs 1811 0.0%	0.92 (0.80, 1.07) 16 RCTs 2955 0.0%
	Sensitivity 3	1.06 (1.00, 1.11) 10 RCTs 5924	1.10 (0.81, 1.48) 1 RCT	0.99 (0.81, 1.21) 7 RCTs	0.89 (0.82, 0.96) 12 RCTs 6882	0.93 (0.73, 1.20) 6 RCTs 1310	1.03 (0.95, 1.12) 9 RCTs	0.94 (0.81, 1.08) 12 RCTs 2831

(Continued)		33.1%	97 -	1585 0.0%	0.0%	0.0%	1811 0.0%	0.0%
Sarilumab vs. standard care or placebo	**Main analysis**	**0.99 (0.94, 1.05) 8 RCTs 2425 0.01%**	**1.50 (1.01, 2.24) 1 RCTs 91 -**	**1.10 (0.90, 1.33) 5 RCTs 886 0.0%**	**1.06 (0.86, 1.30) 10 RCTs 3305 10.3%**	**1.12 (0.97, 1.28) 4 RCTs 860 0.0%**	**1.10 (1.01, 1.19) 6 RCTs 2647 0.0%**	**1.09 (0.97, 1.21) 7 RCTs 2936 0.0%**
	Sensitivity 1	0.99 (0.94, 1.05) 8 RCTs 2408 0.0%	1.06 (0.92, 1.26) 2 RCTs 226 0.0%	1.09 (0.90, 1.32) 5 RCTs 882 0.0%	1.03 (0.83, 1.29) 10 RCTs 3266 14.7%	1.08 (1.00, 1.17) 4 RCTs 852 0.0%	1.08 (1.00, 1.17) 6 RCTs 2629 0.0%	1.07 (0.96, 1.19) 7 RCTs 2900 0.0%
	Sensitivity 2					1.12 (0.97, 1.28) 4 RCTs 2647 0.0%		
	Sensitivity 3					1.10 (1.01, 1.19) 4 RCTs 860 0.0%		
Clazakizumab vs. placebo	**Main analysis**	**1.28 (0.97, 1.70) 1 RCT 152**	**1.28 (0.99, 1.66) 1 RCT 152**	**0.66 (0.43, 1.01) 1 RCT 152**	**0.91 (0.54, 1.55) 2 RCTs 169 0.0%**	**0.77 (0.49, 1.19) 2 RCTs 169 0.0%**	**1.12 (0.20, 6.24) 1 RCT 17**	**0.69 (0.46, 1.04) 2 RCTs 169 0.0%**

(Continued)

	Sensitivity 1	1.28 (0.97, 1.70) 1 RCT 152	1.28 (0.99, 1.66) 1 RCT 152	0.66 (0.43, 1.01) 1 RCT 152	0.91 (0.53, 1.54) 2 RCTs 168 0.0%	0.76 (0.49, 1.18) 2 RCTs 168 0.0%	1.00 (0.18, 5.46) 1 RCT 16	0.69 (0.46, 1.03) 2 RCTs 168 0.0%
	Sensitivity 2	-	-	-	-	-	-	-
	Sensitivity 3	-	-	-	0.90 (0.52, 1.55) 1 RCT 152	0.75 (0.47, 1.18) 1 RCT 152	-	0.69 (0.45, 1.05) 1 RCT 152
Olokizumab vs. placebo[a]	**Main analysis**	**1.10 (0.96, 1.24)** **1 RCT** **248**	**-**	**-**	**1.50 (0.55, 4.09)** **1 RCT** **248**	**-**	**-**	**1.25 (0.51, 3.06)** **1 RCT** **248**
	Sensitivity 1	1.10 (0.96, 1.24) 1 RCT 248	-	-	1.50 (0.55, 4.09) 1 RCT 248	-	-	1.25 (0.51, 3.06) 1 RCT 248
Siltuximab vs. standard care[b]	**Main analysis**	**0.97 (0.79, 1.18)** **1 RCT** **148**	**-**	**1.97 (1.07, 3.63)** **1 RCT** **148**	**1.35 (0.54, 3.36)** **1 RCT** **148**	**1.58 (0.74, 3.38)** **1 RCT** **148**	**-**	**1.29 (0.64, 2.62)** **1 RCT** **148**
Levilimab vs. placebo[a]	**Main analysis**	**1.53 (1.26, 1.85)** **1 RCT** **206**	**-**	**-**	**1.00 (0.26, 3.89)** **1 RCT** **206**	**1.00 (0.26, 3.89)** **1 RCT** **206**	**1.17 (0.73, 1.87)** **1 RCT** **206**	**0.50 (0.05, 5.43)** **1 RCT** **206**

(Continued)

	Sensitivity 1	1.53 (1.26, 1.85) 1 RCT 206	-	-	1.00 (0.26, 3.89) 1 RCT 206	1.00 (0.26, 3.89) 1 RCT 206	1.17 (0.73, 1.87) 1 RCT 206	0.50 (0.05, 5.43) 1 RCT 206

WHO progression score (level 7 or above) D60 was not reported in any of the included trials.

[a] Sensitivity 2 and sensitivity 3 were not possible.

[b] Sensitivity 1, sensitivity 2 and sensitivity 3 were not possible.

WHAT'S NEW

Date	Event	Description
1 June 2023	New search has been performed	Search updated on 7 June 2022.
1 June 2023	New citation required and conclusions have changed	This update includes 22 additional trials, for a total of 32 trials (n = 12,160) involving people hospitalized for COVID-19 disease. In hospitalized people with COVID-19, this updated review found a beneficial effect of tocilizumab on all-cause mortality in the short term and probably little or no difference in the risk of adverse events compared to standard care alone or placebo. Tocilizumab and sarilumab probably result in little or no increase in clinical improvement at D28.

HISTORY

Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

- Conception and design of the original review: LG, AC, DD, JJM, GR, AH, GG, DT, PR, IB
- Coordination of the review: LG, AC, IB
- Search and selection of studies for inclusion in the review update: CR, HB, RA, CA, GF, LG
- Collection of data for the review update: BB, HB, KP, CG, HB, MD, PK, LG
- Assessment of the risk of bias in the included studies: BB, HB, KP, CG, HB, MD, LG, CHN, IB
- Analysis of data: AC, TE
- Assessment of the certainty in the body of evidence: KP, NH
- Interpretation of data: LG, TE, AJ, DD, DT, JJM, GG, GR, AH, NH, PR, AC, IB
- Writing of and commenting on/revising the review update: LG, RA, AJ, AC, TE, BB, KP, NH, CR, MD, CG, HB, CA, CHN, GF, PK, CS, CB, YS, TVN, DD, SM, JJM, GR, AH, GG, DT, PR, IB

All authors made substantial contributions to the refined scope/direction of this 2023 update, approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DECLARATIONS OF INTEREST

Lina Ghosn: none known.

Rouba Assi: none known.

Theodoros Evrenoglou: none known.

Brian Buckley: no relevant interests; employed as a systematic reviewer by Cochrane Response during the conduct of the review (with funding from the World Health Organization).

Nicholas Henschke: none known.

Katrin Probyn: none known.

Carolina Riveros: no relevant interests; works as a health professional (epidemiologist).

Mauricia Davidson: none known.

Carolina Graña: none known.

Hillary Bonnet: none known.

Alexander Jarde: none known.

Camila Ávila: none known.

Camilla Hansen Nejstgaard: none known.

Sonia Menon: P95 (consultant).

Gabriel Ferrand: none known.

Philipp Kapp: none known.

Christine Scmucker: none known.

Claudia Breuer: none known

Yanina Sguassero: Cochrane Response (employment); editor of Cochrane Clinical Answers.

Thu Van Nguyen: none known.

Declan Devane: Health Research Board (grant/contract); Registered Midwife but no longer in clinical practice; Editor of Cochrane Pregnancy and Childbirth.

Joerg Meerpohl: none known.

Gabriel Rada: none known.

Asbjørn Hróbjartsson: no relevant interests; Editor of Cochrane Methodology.

Giacomo Grasselli: Pfizer (speaker arrangement).

David Tovey: no relevant interests; Emeritus Editor in Chief and Feedback Editors for two Cochrane Review Groups.

Philippe Ravaud: no relevant interests; involved in Mariette CORIMUNO-19 Collaborative 2021 (The Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research, and AP-HP Foundation).

Anna Chaimani: none known.

Isabelle Boutron: no relevant interests; member of Cochrane Editorial Board.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Below are the changes made since the last update compared to the protocol (CRD42020214700).

- Outcomes: to avoid multiplicity, we reduced the number of outcomes. For the selected outcome domains, we now consider only two time points (day 28 (D28) and ≥ D60). We no longer evaluate the outcome domain WHO Clinical Progression Score level 6 or above as IL-6 blocking agents, as the definition used in the studies appears to be subject to variation due to local guidelines and resources. It is therefore an unreliable or inconsistent indicator when assessed across studies.
- Risk of bias assessment: we did not consider anticoagulants as a relevant co-intervention for assessing risk of bias in the domain deviations from intervention after discussion with content experts.
- Subgroup analyses: the subgroup analyses planned to explore age, severity, sex, severity of the disease, comorbidity status and time after the beginning of the outbreak were not conducted because of the limited number of RCTs providing relevant data and the absence of variation across trials in some variables such as age and gender. Severity was possible only for some outcomes for tocilizumab. We decided to conduct post hoc subgroup analysis to explore the impact of the funding source (public or non-profit/mixed or private) and conflict of interests.
- Prospective registration assessment: we have amended our method of assessment for prospective registration on the registry to consider the date submitted using history of changes instead of date first posted on the registry.
- As of April 2021, and due to limited resources, we discontinued attempts to contact authors of completed or terminated trials with no results posted or published. We nonetheless continued to contact authors of studies included in the meta-analyses for missing data.
- In the assessment of imprecision in GRADE, we no longer considered the relative risk and standard MIDs of 0.75 and 1.25 as effect thresholds. We considered the size of the absolute risk and its confidence intervals and set minimal important difference thresholds at 5% (50 per 1000) for the outcomes of clinical improvement, time to clinical improvement, and adverse events. For mortality outcomes, time to death, WHO score 7 and above, time to WHO score 7 and above, and serious adverse events, we set the threshold at 1% (10 per 1000). Absolute differences smaller than 5% (or 1% respectively) are considered to indicate trivial/no effect, and differences of more than 5% (or 1% respectively) are considered clinically important benefit/harm.
- Since the last update, we no longer considered studies with no events in GRADE because they do not contribute to the pooled effect estimate.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized [adverse effects] [*therapeutic use]; Bias; COVID-19 [mortality]; *COVID-19 Drug Treatment; Disease Progression; Interleukin-6 [*antagonists & inhibitors]; Multicenter Studies as Topic; Randomized Controlled Trials as Topic

MeSH check words

Aged; Female; Humans; Male; Middle Aged