Tocilizumab for COVID-19

Review information

Authors

[Empty name][1]

[1][Empty affiliation]

Citation example: [Empty name]. Tocilizumab for COVID-19. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

History

Date / Event	Description

Characteristics of studies

Characteristics of included studies

Hermine 2020

Methods	Parallel RCT
Participants	Randomised: 131 patients with moderate or severe pneumonia requiring at least 3 L/min oxygen but not ventilation or admission to ICU Age (median [IQR]): 64 years [57.1-74.3] tocilizumab; 63.3 years [57.1-72.3]) usual care Male (n %): 44/63 (70%) tocilizumab; 44/67 (66%) usual care Confirmed SARS-CoV-2 infection: 56/63 (89%) tocilizumab; 61/67 (100%) usual care Respiratory rate (median [IQR]): 24 [22-300 tocilizumab; 26 [24-30] usual care Comorbidities: Chronic cardiac disease: 20/61 (33%) tocilizumab; 20.67 (30%) usual care Diabetes: 20/61 (33%) tocilizumab; 23/67 (34%) usual care Chronic kidney disease: 5/61 (8%) tocilizumab; 13/67 (19%) usual care Asthma: 5/61 (8%) tocilizumab; 3/67 (5%) usual care
Interventions	Tocilizumab was administered intravenously at 8 mg/kg on day 1. Administration of an additional fixed dose of tocilizumab, 400 mg IV on day 3 was recommended if oxygen requirement was not decreased by more than 50%, but decision was left to the treating physician. Usual care was provided at the discretion of the clinicians, and included antibiotic agents, antiviral agents, corticosteroids, vasopressor support and anticoagulants.
Outcomes	All-cause mortality; respiratory failure or ARDS; admission to ICU; serious averse events; adverse events; discharge from hospital
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

RECOVERY [critical]

Methods	
Participants	
Interventions	
Outcomes	All cause morality (day 28) [critical] All cause mortality [subgrouped]
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

RECOVERY [invasive mech vent]

Methods	
Participants	
Interventions	
Outcomes	
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

RECOVERY [moderate-severe]

Methods	
Participants	
Interventions	
Outcomes	All cause mortality (day 28) [moderate-severe] All cause mortality [subgrouped]
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

RECOVERY [non-invasive vent]

Methods	
Participants	
Interventions	
Outcomes	
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

RECOVERY [oxygen only]

Methods	
Participants	
Interventions	
Outcomes	
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

RECOVERY [total]

Methods	Parallel RCT (n=4116)
Participants	**Baseline characteristics** Intervention Age: 63.3 Feamle (%): 34 Diabetes (%):28 Heart disease (%):22 Chronic lung disease (%):23 Control Age:63.9 Feamle (%): 31 Diabetes (%): 29 Heart disease (%): 24 Chronic lung disease (%): 23 **Incusion criteria:** **Exclusion criteria:**

Interventions	**Intervention**: usual standard of care plus tocilizumab single intravenous infusion over 60 min. The dose of tocilizumab was established by bodyweight (800 mg if weight >90 kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg). A second dose could be given 12–24 h later if, in the opinion of the attending clinician, the patient's condition had not improved. **Control:** usual standard of care alone
Outcomes	All cause mortality (day 21-28) [All patients] Mechanical ventilation No. of patients discharged from hospital
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

REMAP-CAP IL6

Methods	N/A
Participants	
Interventions	
Outcomes	All cause mortality (day 21-28) [All IL6 Ag] All cause mortality (day 21-28) [critilcal IL6 Ag]
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

REMAP-CAP sarilumab

Methods	N/A
Participants	
Interventions	
Outcomes	All cause mortality (21 days) [critical] Serious adverse events
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

REMAP-CAP tocilizumab

Methods	randomised multifactorial, adaptive platform trial
Participants	**Baseline** Age (Mean SD): 61.5 (12.5) TCZ; 61.1 (12.8) Control Male (n %): 261/353 (73.9%) TCZ; 283/402 (73.8%) Control Confirmed SARS-CoV-2: 284/345 (82.3%) TCZ; 334/394 (84.8%) Control Comorbidities: Diabetes: 123/349 (35.2%) TCZ; 150/401 (37.4%) Control Kidney disease: 30/312 (9.6%) TCZ; 43/372 (11.6%) Control Severe cardiovascular disease: 34/339 (10%) TCZ; 47/395 (11.9%) Control **Inclusion criteria**: critically ill patients, aged 18 years or over, with suspected or confirmed COVID-19, admitted to an intensive care unit and receiving respiratory or cardiovascular organ support. **Exclusion criteira**: presumption that death was imminent with lack of commitment to full support, prior participation in REMAP-CAP within 90 days.
Interventions	**Intervention:** Tocilizumab, at a dose of 8mg/kg of actual body weight (up to a maximum of 800mg), was administered as an intravenous infusion over 1 hour. Dose could be repeated 12-24 hours later at the discretion of treating clinician.
Outcomes	All cause mortality at day 21, serious adverse events, discharge from ICU (day 30)
Notes	NB: most patients recruited after publication of RECOVERY trial results (610/654; 93.3%) also received corticosteroids; 107/158 patients enrolled prior to publication received corticosteroids. **We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Rosas [critical]

Methods	N/A
Participants	
Interventions	
Outcomes	All cause mortality (day 21-28) [critical] All cause mortality [subgrouped] All cause mortality [undergrouped]
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Rosas [moderate-severe]

Methods	N/A
Participants	
Interventions	
Outcomes	All cause mortality (day 21-280 [moderate-severe] All cause mortality [subgrouped] All cause mortality [undergrouped]
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Rosas 2020

Methods	Parallel RCT
Participants	Randomised: 452 patients hospitalised with COVID-19 mITT population: n=294 (TCZ); n=144 (SC) Age (Mean SD): 60.9 (14.6) TCZ; 60.6 (13.7) SC Male (n %): 205/295 (69.7%) TCZ; 101/144 (70.1%) SC Disease severity (see notes): Ordinal scale [2]: 9 (3.1%) TCZ; 6 (4.2%) SC [Mild] Ordinal scale [3]: 78 (26.5%) TCZ; 44 (30.6%) SC [Moderate] Ordinal scale [4]: 94 (32%) TCZ; 39 (27.1%) SC [Moderate/Severe] Ordinal scale [5]: 45 (15.3%) TCZ; 15 (10.4%) SC [Severe] Ordinal scale [6]: 68 (23.1%) TCZ; 40 (27.8%) SC [Critical] Comorbidities: Cardiovascular impairment: 88 (29/9%) TCZ; 35 (24.3%) SC Diabetes: 105 (35.7%) TCZ; 62 (43.1%) SC Obesity: 63 (21.4%) TCZ; 27 (18.8%) SC Hypertension: 178 (60.5%) TCZ; 94 (65.3%) SC
Interventions	**Intervention**: intravenous tocilizumab (8 mg/kg infusion, maximum 800 mg); if clinical signs or symptoms did not improve or worsened (defined as sustained fever or worsened ordinal scale clinical status), a second infusion could be administered 8 to 24 hours after the first. **Standard care**: NR; however authors report that the 'lack of standardised treatment across study sites and countries is an important limitation of this study'.
Outcomes	All cause mortality day 28, mechanical ventilation, admission to ICU, serious adverse events, adverse events, septic shock,
Notes	NB: within 'Trial Design and Oversight', authors specify "Patients 18 years or older wth severe COVID-19 pneumonia..... were enrolled"; however table 1 demonstrates that ~30% of patients (categories 2 and 3) only had mild or moderate disease. 7-category ordinal scale: 1, discharged or ready for discharge; 2, non–ICU hospital ward, not requiring supplemental oxygen; 3, non–ICU hospital ward

	requiring supplemental oxygen; 4, ICU or non–ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death. **We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Rosas 2021

Methods	RCT (n=649)
Participants	**Baseline Characteristics** **[Remdesivir plus Tocilizumab]No. randomised (N): 434** **[Remdesivir]No. randomised (N): 215** **Remdesivir plus Tocilizumab** Participants with laboratory confirmed COVID-19 (%) **100** Participants with severe or critical illness (%) 100 Age (mean [SD]) **60.1 [13.3]** Female participants (%) **38.1** Paediatric participants (%) Pregnant participants (%)0 Pregnant and/or breastfeeding participants (%)0 Frailty index or similar Participants with hypertension (%) 62.1 Participants with diabetes (%) 40 Participants with chronic heart disease (%) 24.4 **Tocilizumab** Participants with laboratory confirmed COVID-19 (%) 100 Participants with severe or critical illness (%) 100 Age (mean [SD]) **58.2 [13.3]** Female participants (%) **33.8**

	Paediatric participants (%) Pregnant participants (%) 0 Pregnant and/or breastfeeding participants (%)0 Frailty index or similar Participants with hypertension (%) 61 Participants with diabetes (%) 38.6 Participants with chronic heart disease (%) 21.4 Included criteria: Aged 12 years and older hospitalized with severe COVID-19 pneumonia Positive SARS-CoV-2 polymerase chain reaction test result within 7 days of randomization Pneumonia confrmed by chest x-ray or computed tomography Hypoxemia requiring>6 L/min supplemental oxygen Excluded criteria: Estimated glomerular fltration rate was5Ã—the upper limit of normal within 24 h of screening Suspected active bacterial, fungal, viral, or other infection except COVID19 were excluded Corticosteroids for treatment of COVID-19 pneumonia were permitted Treatment with convalescent plasma, chloroquine or hydroxychloroquine, antivirals, biologics, and Janus kinase inhibitors during the trial was prohibited.
Interventions	Remdesivir was administered intravenously as a 200 mg IV loading dose followed by 100 mg once-daily IV maintenance dose of remdesivir from Days 2 to 10. Remdesivir will be discontinued at the time of hospital discharge even if 10 days of remdesivir dosing have not been completed. Tocilizumab 8 mg/kg (maximum, 800 mg) or placebo on day 1. Patients with sustained fever or clinically signifcant worsening of signs and symptoms of COVID-19 (e.g., increased supplemental oxygen requirement) could receive a second infusion of blinded tocilizumab or placebo within 8 to 24 h of the frst infusion.
Outcomes	All-cause mortality (day 28) All-casue mortality (day 60) Adverse events Serious adverse events Hospital discharge (day 28)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	

Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Salama 2020

Methods	Parallel RCT
Participants	**Baseline** Age (Mean SD): 56.0 (14.3) TCZ; 55.6 (14.9) Placebo Male (n %): 150/249 (60.2%) TCZ; 73/128 (57%) Placebo Disease severity (see notes): Ordinal scale [2]: 24 (9.6%) TCZ; 11 (8.6%) Placebo Ordinal scale [3]: 161 (64.7%) TCZ; 81 (63.3%) Placebo Ordinal scale [4]: 64 (25.7%) TCZ; 36 (28.1) Placebo Comorbidities: Asthma: 27 (10.8%) TCZ; 16 (12.6%) Placebo COPD: 12 (4.8%) TCZ; 5 (3.9%) Placebo Diabetes: 105 (42%) TCZ; 48 (37.8%) Placebo Hypertension: 119 (47.6%) TCZ; 63 (49.6%) Placebo **Inclusion criteria**: Patients 18 years of age or older, hospitalised with COVID-19 pneumonia confirmed by positive PCR and radiographic imaging, blood oxygen saturation <94% on ambient air. **Exclusion criteria**: Patients that required continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation. Randomised: 389 nonventilated patients hospitalised with COVID-19 pneumonia
Interventions	**Intervention**: Tocilizumab, 8 mg/kg (maximum 800 mg) **Standard care**: as per local practice, which could include antiviral treatment, limited systemic corticosteroids and supportive care.
Outcomes	All cause mortality day 28, serious advserse events, adverse events, septic shock
Notes	7 category ordinal scale: 2 - non-ICU hospital ward (or ready for hospital ward), not requiring supplemental oxygen; 3 - non-ICU hospital ward (or ready for hospital ward), requiring supplemental oxygen; 4 - ICU or non-ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen. **We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	

Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Salvarini 2020

Methods	Parallel RCT
Participants	**Baseline** Randomised: 126 adults hospitalised with COVID-19 pneumonia. Age (Median [IQR]): 61.5 [51.5-73.5] TCZ; 60.0 [54.0-69.0] Standard care Male (n %): 40/60 (66.7%) TCZ; 37/66 (56.1%) Standard care Days from symptom onset to randomization (median [IQR]): 7 days [4-11] TCZ; 8 days [6-11] Standard care Comorbidities: Diabetes: 10/60 (16.7%) TCZ; 9/66 (13.6%) Standard care Hypertension: 27/60 (45%) TCZ; 29/66 (43.9%) Standard care COPD: 2/60 (3.3%) TCZ; 2/66 (3%) Standard care **Inclusion criteria**: Confirmed COVID-19 by RT-PCR; presence of acute respiratory failure with partial pressure of arterial oxygen to fraction of inspired oxygen ratio between 200 and 300 mm/Hg; an inflammatory phenotype defined by a temperature greater than 38 degrees celsius during the last two days. **Exclusion criteria**: ICU admission, known hypersensitivity to tocilizumab, any condition preventing future admission to ICU, such as advanced age with multiple comorbidities.
Interventions	**Intervention**: 8 mg/kg tocilizumab intravenously administered within 8 hours of randomisation, up to a maximum of 800 mg, followed by a second dose after 12 hours. **Standard care**: all drugs were allowed but IL-1 blockers, ak inhibitors, and tumor necrosis factor inhibitors. Steroids were allowed if already taken before hospitalisation.
Outcomes	All cause mortality day 28, Admission to ICU, clinical progression, discharge from hospital,
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	

Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Soin 2021

Methods	
Participants	
Interventions	
Outcomes	All cause mortality (day 21-28) [All patients] Mechanical ventialtion Admission to ICU Serious adverse events Adverse events
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Stone 2020

Methods	Parallel RCT
Participants	Randomised: 243 adults hospitalised with confirmed COVID-19 in a hyperinflammatory state. Age (Median [IQR]): 61.6 years [46.4-69.7] TCZ; 56.5 years [44.7-67.8] Placebo Men (n %) 96/161 {60%) TCZ; 45/82 (55%) Placebo Disease severity (see notes): Ordinal scale [2]: 23/161 (14%) TCZ; 15/82 (18%) Placebo Ordinal scale [3]: 133/161 (83%) TCZ; 61/82 (74%) Placebo

	Ordinal scale [4]: 5/161 (3%) TCZ; 5/82 (6%) Placebo Ordinal scale [5]: 0 TCZ; 1/82 (1%) Placebo Comorbidities: Diabetes: 45/161 (28%) TCZ; 30/82 (37%) Placebo Hypertension: 80/161 (50%) TCZ; 38/82 (46%) Placebo Asthma: 15/161 (9%) TCZ; 7/82 (9%) Placebo
Interventions	Intervention: tocilizumab 8 mg/kg body weight, administered intravenously. **Comparator**: placebo
Outcomes	All-cause mortality at day 28, mechanical ventilation, serious adverse events, adverse events, clinical improvement, clinical progression, discharge from hospital
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Veiga 2021

Methods	**Study design:** Randomized controlled trial **Study grouping:**
Participants	**Baseline Characteristics** Tocilizumab ● *No. randomised (N)*: 65 ● *Age (mean [range])*: 57.4 (15.7) ● *Female (N [%])*: 21 (32%) ● *No. of paediatric patients (N [%])*: 0 ● *No. of pregnant patients (N [%])*: 0 ● *No. of pregnant and/or breastfeeding patients (N [%])*: 0

	Standard of Care ● *No. randomised (N)*: 64 ● *Age (mean [range])*: 57.5 (13.5) ● *Female (N [%])*: 20 (31%) ● *No. of paediatric patients (N [%])*: 0 ● *No. of pregnant patients (N [%])*: 0 ● *No. of pregnant and/or breastfeeding patients (N [%])*: 0 **Included criteria:** Inclusion Criteria:Male and females with 18 years and olderConfirmed diagnosis of SARS-CoV 2 infectionMore than 3 days of symptoms related to COVID-19Computed tomography (or Chest X-Ray) with COVID-19 alterationsBoth of the criteriaNeed for oxygen supplementation to keep SPO2 > 93% OR need for mechanical ventilation for less than 24 hours before the randomizationAt least two of the following inflammatory tests above the cutoff :D-dimer > 1,000 ng/mLReactive C protein > 5 mg/dLFerritin > 300 mg/dLLactate dehydrogenase > upper level limit **Excluded criteria:** Exclusion Criteria:Need for mechanical ventilation for 24 hours or more before the randomizationHypersensitivity to tocilizumabPatients without therapeutic perspective or in palliative careActive non controlled infectionsOther clinical conditions that contraindicate tocilizumab, according to the assistant physicianLow neutrophils count (< 0.5 x 109/L)Low platelets count (< 50 x 109/L)Liver disease, cirrhosis or elevated AST or ALT above 5 times the upper level limitRenal disease with estimate glomerular filtration below 30 mL/min/1.72 m2 (MDRD or CKD-EPI scores)Active diverticulitisBreastfeeding womenPregnancy
Interventions	**Intervention Characteristics** Tocilizumab ● *Intervention (including dosage, route of administration, loading and maintenance phases)*: Single intravenous infusion at a dose of 8 mg/kg (maximum 800 mg). ● *Co-intervention (including description of standard care)*: Theconcomitant use of hydroxychloroquine, azithromycin,corticosteroids, and antibiotics was allowed accordingto standard care per local institutional guidelines forpatients with covid-19. ● *Duration of treatment (days)*: 1 ● *Follow up after randomisation (days)*: 29 Standard of Care ● *Intervention (including dosage, route of administration, loading and maintenance phases)*: ● *Co-intervention (including description of standard care)*: Theconcomitant use of hydroxychloroquine, azithromycin,corticosteroids, and antibiotics was allowed accordingto standard care per local institutional guidelines forpatients with covid-19. ● *Duration of treatment (days)*: 1 ● *Follow up after randomisation (days)*: 29
Outcomes	All cause mortality day 28, duration of hospital stay (days), serious adverse events, adverse events, all-cause mortality or mechanical ventilation (composite)
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Wang 2020

Methods	Parallel RCT
Participants	**Baseline Characteristics** Randomised: 65 hospitalised adults with confirmed COVID-19 and moderate to severe illness. Age (Median [IQR]): 63.5 years [58-71] TCZ; 63 years [54-69] Control Males (n %): 18/34 (53%) TCZ; 15/31 (48%) Control Disease severity: Moderate: 20/34 (58.8%) TCZ; 17/31 (54.8%) Control Severe: 14/34 (41.2%) TCZ; 14/31 (45.2%) Control Comorbidities: Hypertension: 10/34 (29.4%) TCZ; 10/31 (32.3%) Control Diabetes: 4/34 (11.8%) TCZ; 6/31 (19.4%) Control **Inclusion criteria**: Adults aged 18-85 years old, elevated plasma IL-6 levels, moderate (with bilateral pulmonary lesions) or severe in disease degree. **Exclusion criteria**: pregnant or lactating women, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal; people diagnosed with rheumatism; allergic to tocilizumab or any excipients; organ transplantation and mental disorders.
Interventions	**Intervention**: The first dose of tocilizumab was 400 mg, diluted in 100 ml 0.9% saline, and intravenous dripped for more than 1 hour. A second dose was given if a patient remained febrile for 24 hours after the first dose. **Control:** Standard care was given according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or update version)"
Outcomes	Serious adverse events, adverse events, length of hospitalisation
Notes	**We have used version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the risk of bias for this study. Refer to Main text > Published notes for more details.**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Risk of bias arising from the randomization process	Unclear risk	
Risk of bias due to deviations from the intended interventions	Unclear risk	
Missing outcome data	Unclear risk	
Risk of bias in measurement of the outcome	Unclear risk	
Risk of bias in selection of the reported result	Unclear risk	
Overall risk of bias	Unclear risk	

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Hermine 2020

[Empty]

RECOVERY [critical]

[Empty]

RECOVERY [invasive mech vent]

[Empty]

RECOVERY [moderate-severe]

[Empty]

RECOVERY [non-invasive vent]

[Empty]

RECOVERY [oxygen only]

[Empty]

RECOVERY [total]

[Empty]

REMAP-CAP IL6

[Empty]

REMAP-CAP sarilumab

[Empty]

REMAP-CAP tocilizumab

[Empty]

Rosas [critical]

[Empty]

Rosas [moderate-severe]

[Empty]

Rosas 2020

[Empty]

Rosas 2021

Ivan O. Rosas , George Diaz, Robert L. Gottlieb , Suzana M. Lobo , Philip Robinson, Bradley D. Hunter, Adilson W. Cavalcante, J. Scott Overcash, Nicola A. Hanania, Alan Skarbnik, Julia Garcia-Diaz, Ivan Gordeev, Jordi CarratalÃ , Oliver Gordon, Emily Graham, Nicholas Lewin-Koh, Larry Tsai, Katie Tuckwell, Huyen Cao, Diana Brainard and Julie K. Olsson. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med. [DOI: https://doi.org/10.1007/s00134-021-06507-x]

Salama 2020

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Salvarini 2020

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Soin 2021

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Stone 2020

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Veiga 2021

Veiga, Viviane C; Prats, JoÃ£o A G G; Farias, Danielle L C; Rosa, Regis G; Dourado, Leticia K; Zampieri, Fernando G; Machado, FlÃ¡via R; Lopes, Renato D; Berwanger, Otavio; Azevedo, Luciano C P; Avezum, Ã□lvaro; Lisboa, Thiago C; Rojas, SalomÃ³n S O; Coelho, Juliana C; Leite, Rodrigo T; Carvalho, JÃºlio C; Andrade, Luis E C; Sandes, Alex F; PintÃ£o, Maria C T; Castro, Claudio G; Santos, Sueli V; de Almeida, Thiago M L; Costa, AndrÃ© N; Gebara, OtÃ¡vio C E; de Freitas, FlÃ¡vio G Rezende; Pacheco, Eduardo S; Machado, David J B; Martin, Josiane; ConceiÃ§Ã£o, FÃ¡bio G; Siqueira, Suellen R R; Damiani, Lucas P; Ishihara, Luciana M; Schneider, Daniel; de Souza, Denise; Cavalcanti, Alexandre B; Scheinberg, Phillip. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021;372:n84. [DOI: 10.1136/bmj.n84]

Wang 2020

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Excluded studies

Data and analyses

5 Tocilizumab vs Standard care UPDATE 15_10_21

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 All-cause mortality (Day 21-28) [All patients]	10	7121	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.80, 0.93]
5.2 All-cause mortality (Day 28) [moderate-severe]	6	4756	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.80, 0.97]
5.3 All-cause mortality (Day 21-28) [critical]	3	1417	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.14]
5.4 All-cause mortality [subgrouped]	9	6173	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.83, 0.97]
5.4.1 Moderate-severe	6	4756	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.98]
5.4.2 Critical	3	1417	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.14]
5.5 All-cause mortality [ungrouped]	7	2057	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.05]

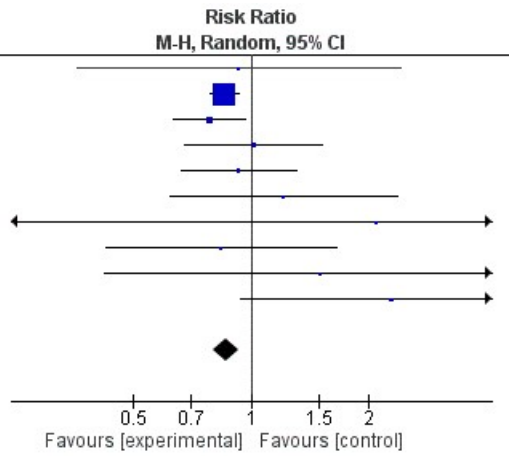
5.6 Duration of hospital stay	1	129	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-6.20, -0.60]
5.6.1 Days	1	129	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-6.20, -0.60]
5.7 Mechanical ventilation	4	4248	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.70, 0.90]
5.8 Respiratory failure or ARDS	1	130	Risk Ratio (IV, Random, 95% CI)	0.50 [0.25, 1.03]
5.9 Admission to ICU	4	699	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.54, 1.23]
5.10 All cause mortality or no. of patients requiring mechanical ventilation (composite)	2	371	Risk Ratio (IV, Random, 95% CI)	1.12 [0.70, 1.80]
5.11 Serious adverse events	9	2951	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.77, 1.02]
5.12 Adverse events	8	2204	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.90, 1.21]
5.14 Septic shock	3	1457	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.44, 1.33]
5.16 Clinical recovery (end of follow-up)	1	65	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.27]
5.17 Clinical improvement	1	242	Risk Ratio (IV, Random, 95% CI)	1.03 [0.94, 1.12]
5.18 Clinical progression	2	365	Risk Ratio (IV, Random, 95% CI)	1.08 [0.72, 1.62]
5.19 Discharge from ICU (Day 30) [critical]	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.20 Time to improvement	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.21 No. of patients discharged from hospital	5	5251	Risk Ratio (IV, Random, 95% CI)	1.05 [0.98, 1.13]
5.22 Length of hospitalisation	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.23 Duration of mechanical ventilation	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.24 Median time to discharge	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Figures

Figure 1 (Analysis 5.1)

Study or Subgroup	Tocilizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hermine 2020	7	63	8	67	0.6%	0.93 [0.36, 2.42]
RECOVERY [total]	621	2022	754	2094	75.0%	0.85 [0.78, 0.93]
REMAP-CAP tocilizumab	98	350	142	397	12.4%	0.78 [0.63, 0.97]
Rosas 2020	58	294	28	144	3.5%	1.01 [0.68, 1.52]
Rosas 2021	78	430	41	210	4.9%	0.93 [0.66, 1.31]
Salama 2020	26	249	11	128	1.3%	1.22 [0.62, 2.38]
Salvarini 2020	2	60	1	63	0.1%	2.10 [0.20, 22.56]
Soin 2021	13	91	15	88	1.2%	0.84 [0.42, 1.66]
Stone 2020	9	161	3	81	0.3%	1.51 [0.42, 5.42]
Veiga 2021	14	65	6	64	0.7%	2.30 [0.94, 5.61]
Total (95% CI)		**3785**		**3336**	**100.0%**	**0.87 [0.80, 0.93]**
Total events	926		1009			

Heterogeneity: Tau² = 0.00; Chi² = 8.63, df = 9 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.77 (P = 0.0002)

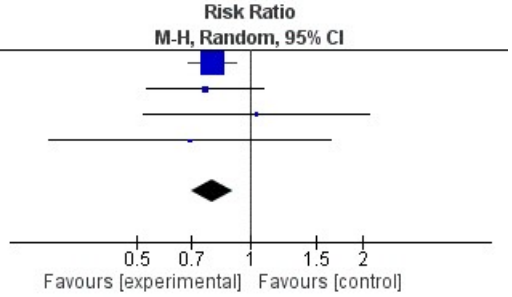


Forest plot of comparison: 5 Tocilizumab vs Standard care UPDATE 15_10_21, outcome: 5.1 All-cause mortality (Day 21-28) [All patients].

Figure 2 (Analysis 5.7)

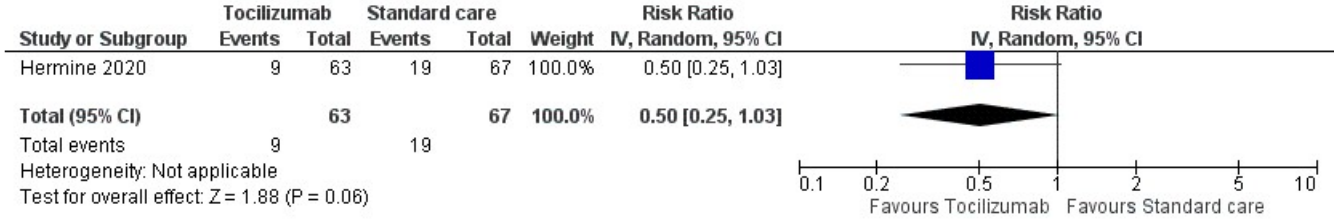
Study or Subgroup	Tocilizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RECOVERY [total]	265	1754	343	1800	80.7%	0.79 [0.69, 0.92]
Rosas 2020	51	183	33	90	13.5%	0.76 [0.53, 1.09]
Soin 2021	14	91	13	88	3.6%	1.04 [0.52, 2.09]
Stone 2020	11	161	8	81	2.3%	0.69 [0.29, 1.65]
Total (95% CI)		**2189**		**2059**	**100.0%**	**0.79 [0.70, 0.90]**
Total events	341		397			

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.45 (P = 0.0006)



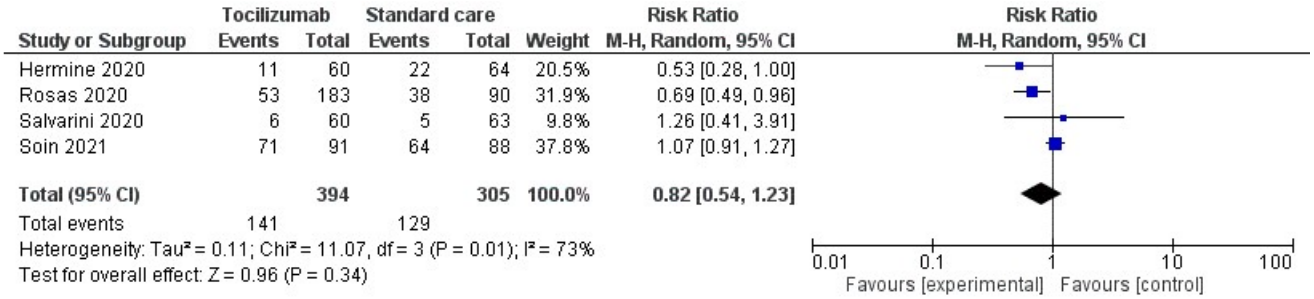
Forest plot of comparison: 5 Tocilizumab vs Standard care UPDATE 15_10_21, outcome: 5.7 Mechanical ventilation.

Figure 3 (Analysis 1.8)



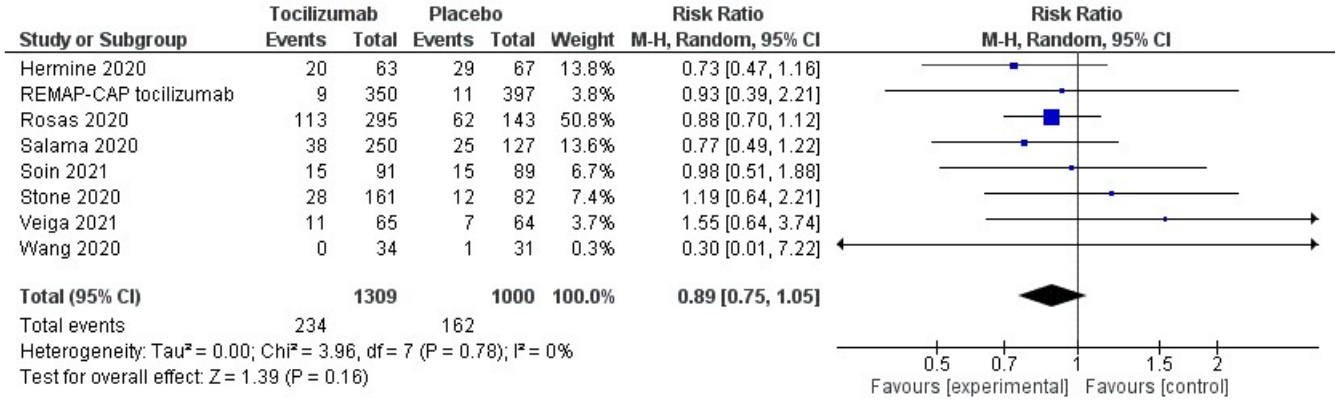
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.8 Respiratory failure or ARDS.

Figure 4 (Analysis 1.9)



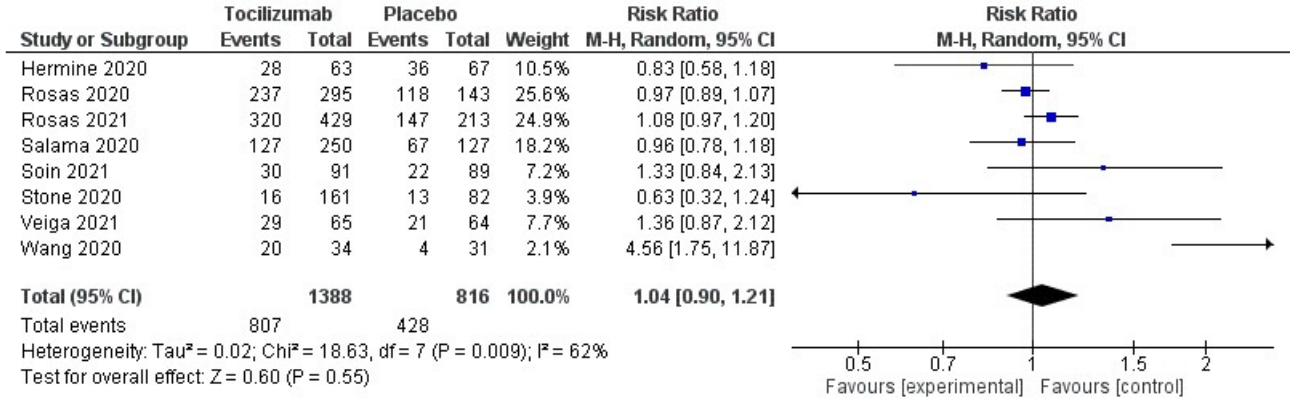
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.9 Admission to ICU.

Figure 5 (Analysis 1.11)



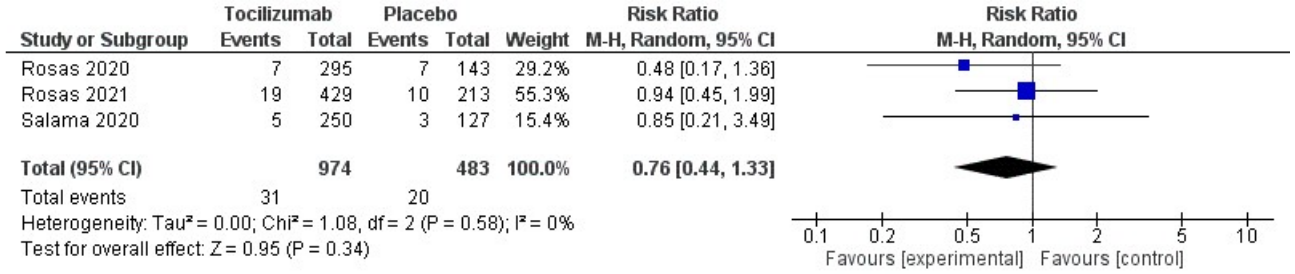
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.11 Serious adverse events.

Figure 6 (Analysis 5.12)



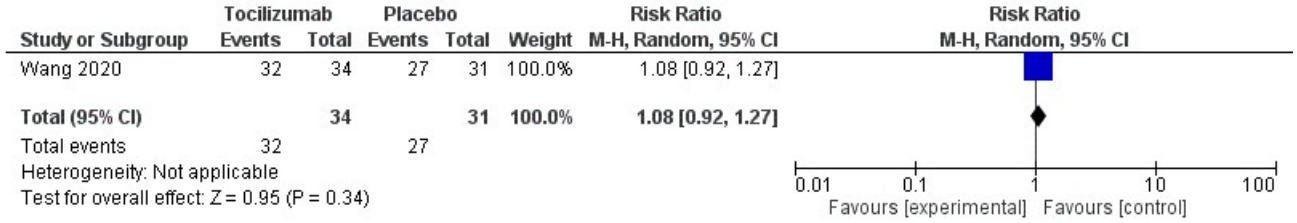
Forest plot of comparison: 5 Tocilizumab vs Standard care UPDATE 15_10_21, outcome: 5.12 Adverse events.

Figure 7 (Analysis 5.14)



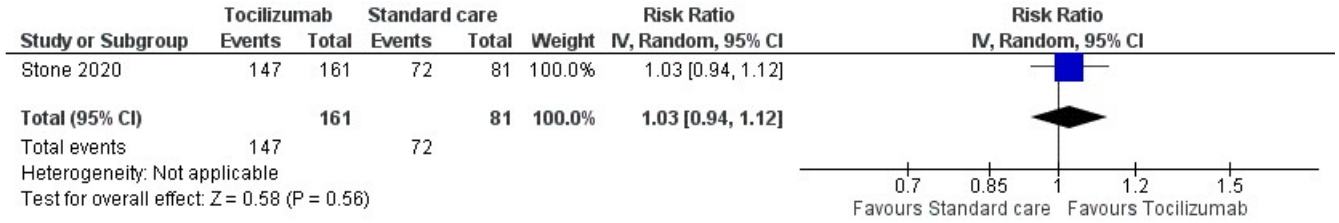
Forest plot of comparison: 5 Tocilizumab vs Standard care UPDATE 15_10_21, outcome: 5.14 Septic shock.

Figure 8 (Analysis 5.16)



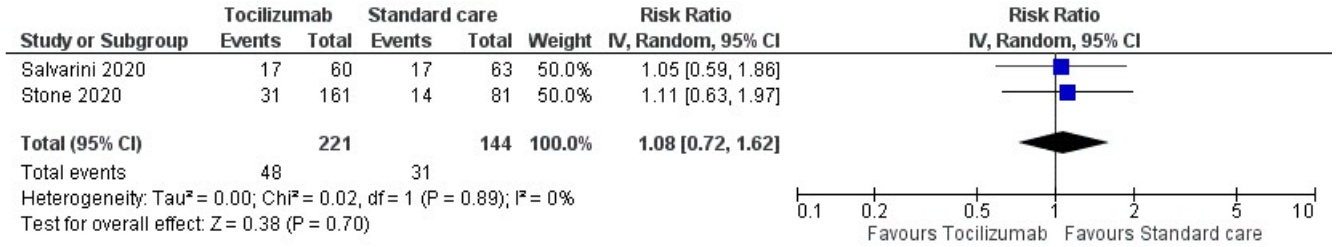
Forest plot of comparison: 5 Tocilizumab vs Standard care UPDATE 15_10_21, outcome: 5.16 Clinical recovery (end of follow-up).

Figure 9 (Analysis 5.17)



Forest plot of comparison: 5 Tocilizumab vs Standard care UPDATE 15_10_21, outcome: 5.17 Clinical improvement.

Figure 10 (Analysis 5.18)



Forest plot of comparison: 5 Tocilizumab vs Standard care UPDATE 15_10_21, outcome: 5.18 Clinical progression.