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].

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	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomised via a web-based secure centralised system.
Allocation concealment (selection bias)	Low risk	An independent statistician provided a computer-generated assignment randomisation list stratified by center and blocked with varying block sizes unknown to the investigators.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	130/131 randomised patients comprised the analysis set.
Selective reporting (reporting bias)	Low risk	All relevant outcomes provided within protocol were reported.
Other bias	Unclear risk	None identified.

RECOVERY [critical]

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	

Other bias	Unclear risk	

RECOVERY [invasive mech vent]

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

RECOVERY [moderate-severe]

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

RECOVERY [non-invasive vent]

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

RECOVERY [oxygen only]

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

RECOVERY [total]

Methods	Parallel RCT (n=4116)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

REMAP-CAP IL6

Methods	N/A
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

REMAP-CAP sarilumab

Methods	N/A
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

REMAP-CAP tocilizumab

Methods	randomised multifactorial, adaptive platform trial
Participants	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. 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
Interventions	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.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised via centralised computer program to each intervention.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	Data reported for all included patients.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes of interest reported.
Other bias	Unclear risk	None identified.

Rosas [critical]

Methods	N/A
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	

Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Rosas [moderate-severe]

Methods	N/A
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other 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.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using an interactive voice or web-based response system and permuted-block randomisation.
Allocation concealment (selection bias)	Low risk	Patients were randomised using an interactive voice or web-based response system.
Blinding of participants and personnel (performance bias)	Unclear risk	States that the trial is 'double-blind' but provides no further information.
Blinding of outcome assessment (detection bias)	Unclear risk	States that the trial is 'double-blind' but provides no further information.
Incomplete outcome data (attrition bias)	Unclear risk	438 of 452 patients represented the mITT population and provided data for final analysis. No information was provided regarding the missing 14 patients.
Selective reporting (reporting bias)	Low risk	All relevant prespecified outcomes of interest were reported.
Other bias	Low risk	None identified.

Salama 2020

Methods	Parallel RCT
Participants	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 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
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.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised through permuted-block randomisation and an interactive voice or web-based response system.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias)	Unclear risk	States that the trial is 'double-blind' but provides no further information.
Blinding of outcome assessment (detection bias)	Unclear risk	States that the trial is 'double-blind' but provides no further information.
Incomplete outcome data (attrition bias)	Low risk	377 of 389 randomised patients included in mITT population.
Selective reporting (reporting bias)	Low risk	All relevant outcomes as per protocol included in analysis.
Other bias	Low risk	None identified.

Salvarini 2020

Methods	Parallel RCT
Participants	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. 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
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	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using a web-based system, stratified by centre.
Allocation concealment (selection bias)	High risk	"It has been consistently reported and clinically observed that this monoclonal antibody rapidly lowers fever and serup CRP level in patients with COVID-19, thus making allocaiton concealment unlikely"
Blinding of participants and personnel (performance bias)	High risk	Trial was open label.
Blinding of outcome assessment (detection bias)	High risk	Trial was open label.
Incomplete outcome data (attrition bias)	Low risk	123 of 126 randomised patients provided outcome data.

Selective reporting (reporting bias)	Low risk	Relevant outcomes as per protocol were assessed.
Other bias	Low risk	None identified.

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	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed with randomly permuted locks of sizes 3 and 6.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	States that the trial is 'double-blind' but provides no further information.
Blinding of outcome assessment (detection bias)	Unclear risk	States that the trial is 'double-blind' but provides no further information.
Incomplete outcome data (attrition bias)	Low risk	242 of 243 randomised patients included in mITT analysis; one patient required intubation before receiving placebo.
Selective reporting (reporting bias)	Low risk	All relevant pre-specified outcomes reported
Other bias	Low risk	None identified

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 **Pretreatment:**
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	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with random blocks of sizes 2, 4, 6 and 8 according to a computer generated schedule using the sample function software R 3.6.3
Allocation concealment (selection bias)	Low risk	Randomised with random blocks of sizes 2, 4, 6 and 8 according to a computer generated schedule using the sample function software R 3.6.3
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	All 129 randomised patients included in ITT analysis.
Selective reporting (reporting bias)	Unclear risk	
Other bias	Low risk	None identified

Wang 2020

Methods	Parallel RCT
Participants	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. 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
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	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation numbers were generated using SAS statistical software package. A computer-generated 1:1 block randomisation scheme was used. 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 concealment (selection bias)	Low risk	Randomisation numbers were generated using SAS statistical software package. A computer-generated 1:1 block randomisation scheme was used. Each consecutively coded patient was randomly enrolled by the sub-site investigators until the total number of cases allocated to the site was reached.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias)	Low risk	All randomised patients included in ITT and safety populations
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided.
Other bias	Low risk	None identified.

Footnotes

Characteristics of excluded studies

Footnotes

Data and analyses

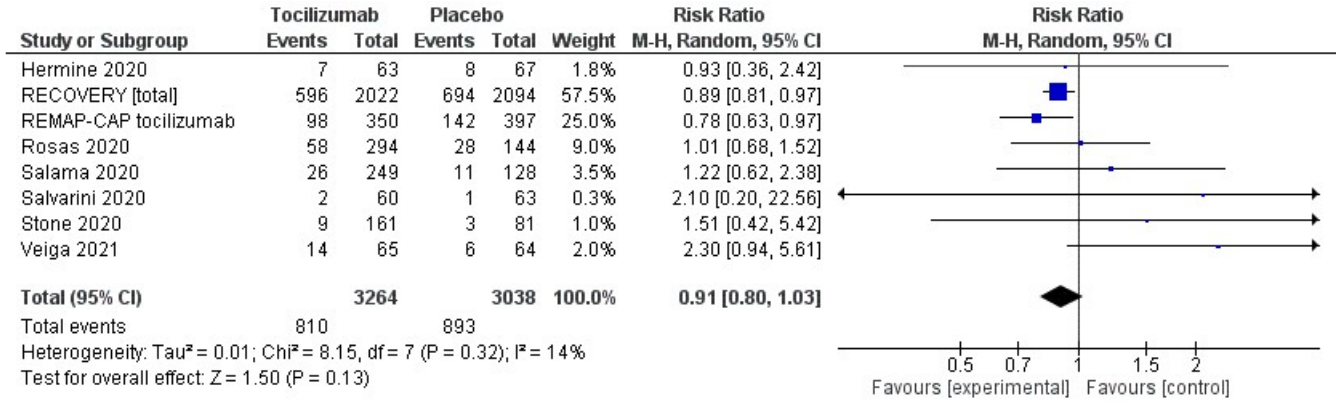
1 Tocilizumab vs Standard care

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 All-cause mortality (Day 21-28) [All patients]	8	6302	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.03]
1.2 All-cause mortality (Day 28) [moderate-severe]	6	4756	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.98]
1.3 All-cause mortality (Day 21-28) [critical]	3	1417	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.14]
1.4 All-cause mortality [subgrouped]	9	6173	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.83, 0.97]
1.4.1 Moderate-severe	6	4756	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.98]
1.4.2 Critical	3	1417	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.14]
1.5 All-cause mortality [ungrouped]	7	2057	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.05]
1.6 Duration of hospital stay	1	129	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-6.20, -0.60]
1.6.1 Days	1	129	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-6.20, -0.60]
1.7 Mechanical ventilation	3	4069	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.69, 0.92]
1.8 Respiratory failure or ARDS	1	130	Risk Ratio (IV, Random, 95% CI)	0.50 [0.25, 1.03]
1.9 Admission to ICU	3	520	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.90]
1.10 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]
1.11 Serious adverse events	7	2129	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.05]
1.12 Adverse events	6	1382	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.82, 1.28]
1.14 Septic shock	2	815	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.26, 1.35]
1.16 Clinical recovery (end of follow-up)	1	65	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.92, 1.27]
1.17 Clinical improvement	1	242	Risk Ratio (IV, Random, 95% CI)	1.03 [0.94, 1.12]
1.18 Clinical progression	2	365	Risk Ratio (IV, Random, 95% CI)	1.08 [0.72, 1.62]

1.19 Discharge from ICU (Day 30) [critical]	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20 Time to improvement	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.21 No. of patients discharged from hospital	4	4611	Risk Ratio (IV, Random, 95% CI)	1.07 [0.99, 1.16]
1.22 Length of hospitalisation	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.23 Duration of mechanical ventilation	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.24 Median time to discharge	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

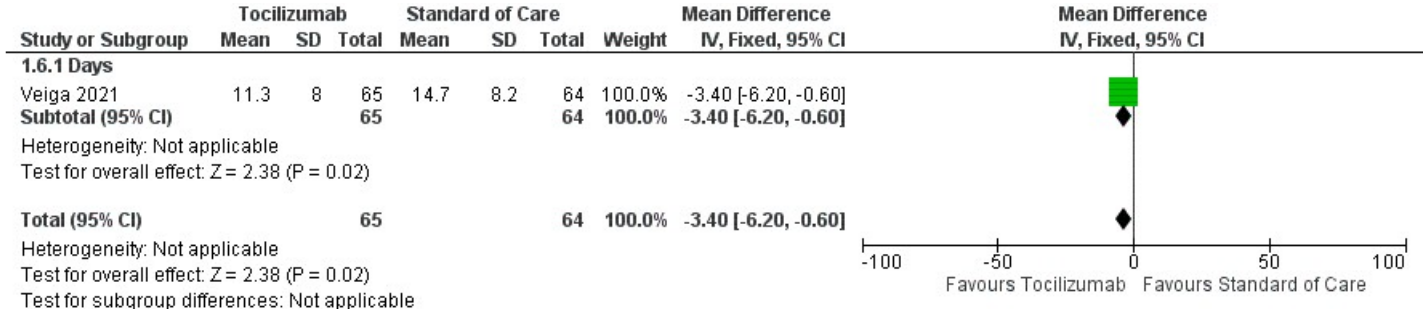
Figures

Figure 1 (Analysis 1.1)



Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.1 All-cause mortality (Day 21-28) [All patients].

Figure 2 (Analysis 1.6)

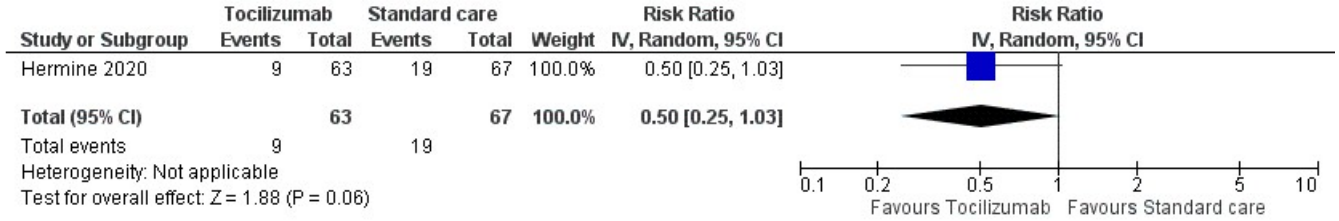


Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.6 Duration of hospital stay.

Figure 3 (Analysis 1.7)

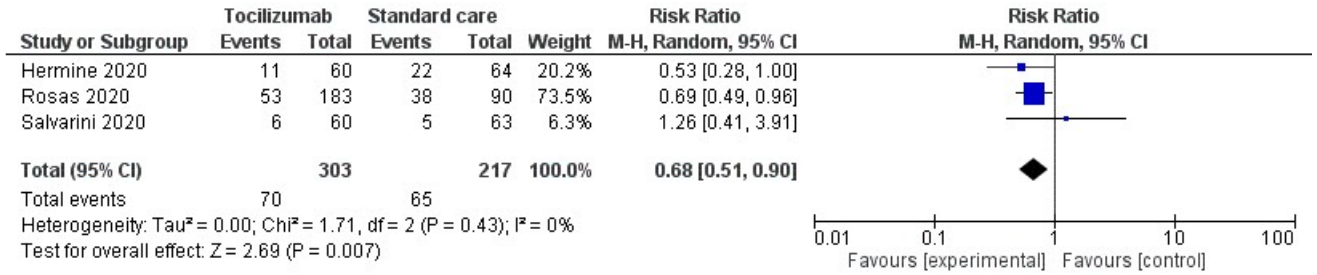
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.7 Mechanical ventilation.

Figure 4 (Analysis 1.8)



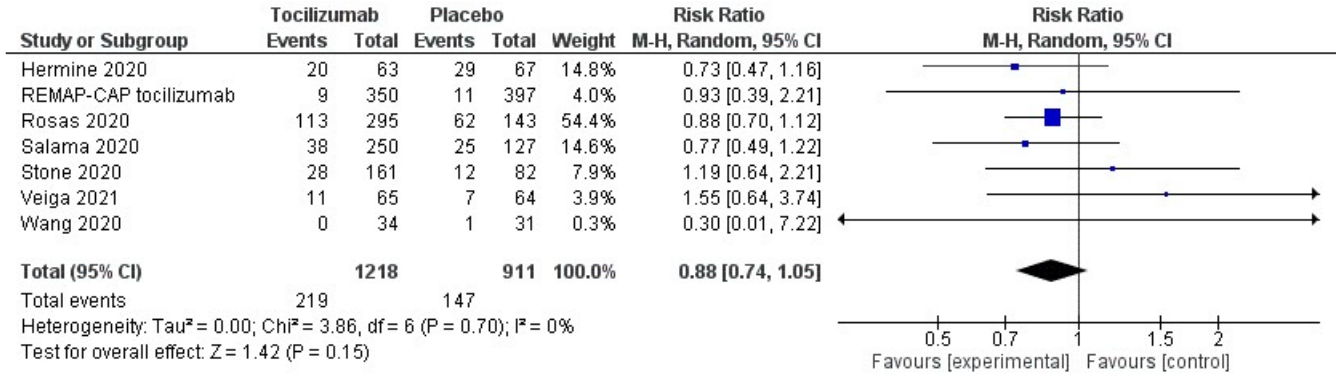
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.8 Respiratory failure or ARDS.

Figure 5 (Analysis 1.9)



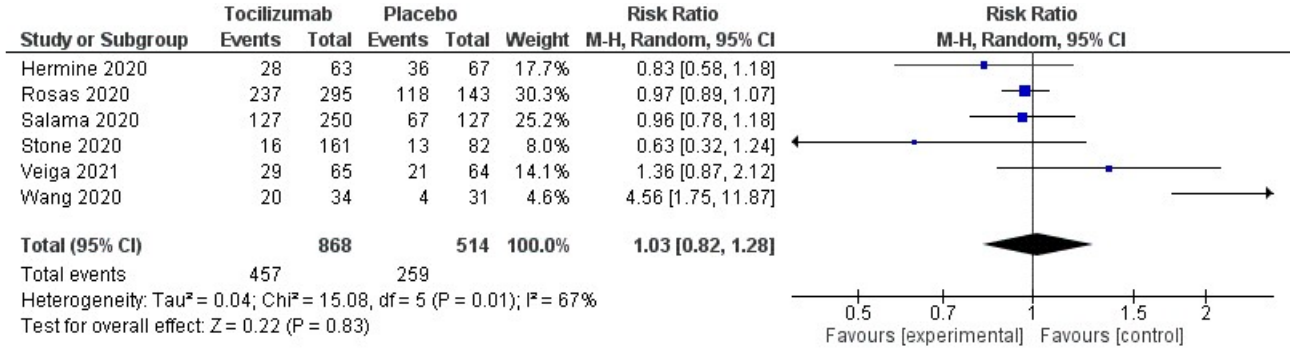
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.9 Admission to ICU.

Figure 6 (Analysis 1.11)



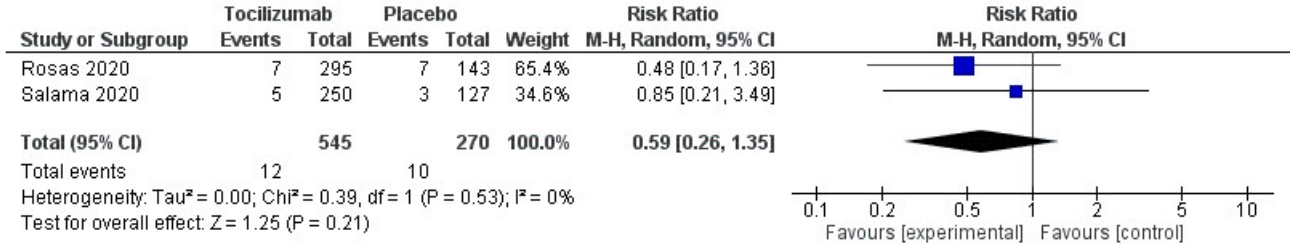
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.11 Serious adverse events.

Figure 7 (Analysis 1.12)



Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.12 Adverse events.

Figure 8 (Analysis 1.14)

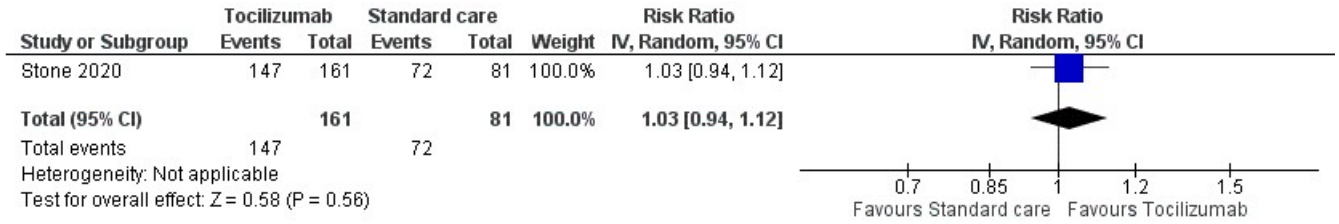


Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.14 Septic shock.

Figure 9 (Analysis 1.16)

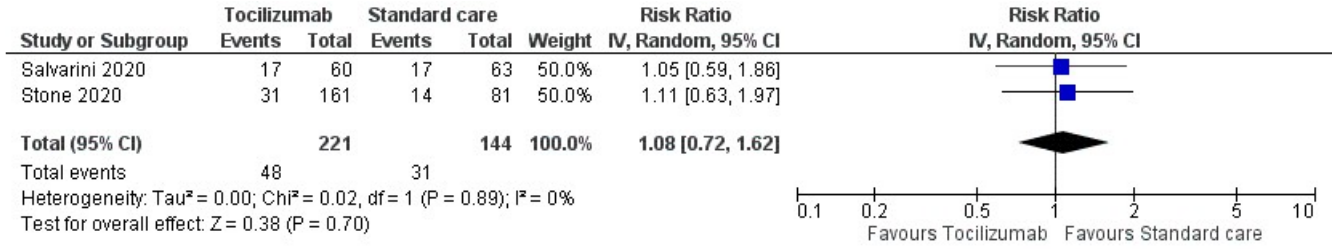
Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.16 Clinical recovery (end of follow-up).

Figure 10 (Analysis 1.17)



Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.17 Clinical improvement.

Figure 11 (Analysis 1.18)



Forest plot of comparison: 1 Tocilizumab vs Standard care, outcome: 1.18 Clinical progression.