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Research Article

Tocilizumab and Mortality in Hospitalised Patients with Covid-19. A Systematic Review Comparing Randomised Trials with Observational Studies

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Abstract

Background: Early observational studies suggested that tocilizumab might produce clinical improvement in covid-19 patients leading to the use of tocilizumab. Early underpowered randomised controlled trials (RCTs) however did not show benefit until the most recent largest trial. RECOVERY trial. We aimed to compare the evidence from RCTs and observational studies of the effect of tocilizumab on in-hospital mortality in patients with covid-19.

Materials and Methods: Embase and PubMed were searched from July 2020 until 1 March 2021. Observational studies and RCTs assessing in-hospital mortality in patients receiving tocilizumab compared with standard care or placebo were included. The primary outcome was in-hospital mortality closest to 30 days. The risk of bias in observational studies was assessed using the ROBINS-I tool. A fixed effect meta-analysis was used to combine relative risks, with random effects and risk of bias as a sensitivity analysis.

Results: Of 5,792 publications screened for inclusion, eight RCTs and 33 observational studies were identified. The RCTs showed an overall relative risk reduction in in-hospital mortality at 30 days of 0.86 (95% confidence interval (CI) 0.78 to 0.96) with no statistically significant heterogeneity. 23 of the observational studies had a severe risk of bias, 10 of which did not adjust for potential confounders. The 10 observational studies with moderate risk of bias reported a larger reduction in mortality at 30-days (relative risk 0.72, 95% CI 0.64 to 0.81) but with significant heterogeneity (P<0.01).

Conclusion: This meta-analysis provides strong evidence from RCTs that tocilizumab reduces the risk of mortality in hospitalised covid-19 patients. Observational studies with moderate risk of bias exaggerated the benefits on mortality two-fold and showed heterogeneity. Collectively observational studies provide a less reliable evidence base for evaluating treatments for covid-19.

Keywords: monoclonal antibodies; epidemiology; randomised clinical trials; covid-19

Abbreviations

CI	Confidence interval
FE	Fixed effect
ICU	Intensive care unit
IL-6	Interleukin-6
IPW	Inverse probability weighting
RCT	Randomised controlled trial
RE	Random effect
TCZ	Tocilizumab

Introduction

Tocilizumab, currently licensed for treatment of rheumatoid arthritis, is a monoclonal antibody that inhibits the interleukin-6 (IL-6) receptor and is being used to treat patients with severe covid-19 [1].

IL-6 is a cytokine that is released by macrophages as part of the immune response to infection. Circulating IL-6 concentrations correlate with covid-19 severity [2]. However, in severe covid-19 there is vascular inflammation and dysfunction, and IL-6 promotes endothelial dysfunction and impairs vascular permeability [3]. Tocilizumab inhibits this inflammatory process. Treatments are needed that improve survival in severely ill covid-19 patients. Severely ill patients with covid-19 have high short-term mortality rates ranging from 35% [26] to 61% [54].

At the start of the covid-19 pandemic, early case reports suggested that tocilizumab might produce clinical and biochemical improvement in covid-19 [4-6]. This was followed by reports of observational studies using retrospective data, largely supporting clinicians' impressions of benefit in severe covid-19. This led to the use of tocilizumab, despite failure to show benefit on all-cause mortality from early underpowered randomised controlled trials (RCTs) in severe covid-19 [7]. The RECOVERY trial, the largest RCT of tocilizumab, has recently shown clear overall benefit in hospitalised patients with covid-19 of all degrees of severity, in addition to the benefit achieved with systematic corticosteroids [8].

We therefore conducted a systematic review and meta-analysis comparing both randomised trials and observational studies in the effect of tocilizumab on in-hospital mortality.

Materials and Methods

Search Strategy

A search of PubMed and Embase was conducted monthly from July 2020 until 1 March 2021, written in English, Spanish, French, and German, of treatment comparisons in hospitalised covid-19 patients and clinical outcomes. Search terms for treatment comparisons including tocilizumab and clinical outcomes were combined with search terms for study design (randomised controlled trials and observational studies separately). Where possible MeSH or index terms were used. We also searched the references in the retrieved papers for any additional relevant publications.

Eligibility

All titles, abstracts, and selected full-text articles were reviewed for eligibility by five reviewers (KA, AC, AR, MH, JM). We included observational studies (either prospective or retrospective) and RCTs that reported the effect of tocilizumab on in-hospital mortality closest to 30 days in-patients with covid-19. Observational studies were eligible if they compared tocilizumab with standard care. Earlier publications that used the same data source over the same study period as a later publication were excluded as duplicates. RCTs were eligible if they compared tocilizumab against standard care or placebo. Studies that reported only mortality at 14 days or less were excluded.

Data Extraction and Risk of bias assessment

For each RCT, data were extracted on study design (randomisation and blinding), comparator (placebo or standard care), the relative risk estimate, 95% confidence intervals (CI), p values and analytic method. For each eligible observational study, information on study design, data source, population characteristics, outcome, analytical methods and covariate adjustments were extracted. A single measure was extracted from each study with adjusted measures in preference to unadjusted measures, where available. Where no measure of association was reported, the numbers of events were extracted. Data extraction was conducted by six reviewers (KA, JM, AC, AR, AL, MH) and any discrepancies were resolved by three separate senior reviewers (BP, SP, NQ).

The risk of bias was appraised using the Cochrane ROBINS-I ('Risk Of Bias In Non-randomised Studies of Interventions') tool for observational studies [9]. Three reviewers (NQ, BP, IU) rated studies as being of low, moderate, serious or critical risk in each of the seven domains (see supplementary file 3). Immortal time bias was assessed in the Bias due to Selection domain of the ROBINS-I tool. Any discrepancies in the assessment of the risk of bias were resolved with two senior reviewers (SP, NQ).

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Based on Maximum Criterion
ADJUSTED								
Ruiz-Antorán et al.	−	−	+	+	+	+	+	Moderate
Gupta et al.	−	−	−	+	+	+	+	Moderate
Biran et al.	−	−	+	+	+	+	+	Moderate
Owen et al.	−	−	+	+	+	+	+	Moderate
Ignatius et al.	−	−	+	+	+	+	+	Moderate
Canziani et al.	−	−	+	+	−	+	+	Moderate
Buzón-Martín et al.	−	+	−	−	+	+	+	Moderate
Rajendram et al.	−	+	+	+	+	−	−	Moderate
De Rossi et al.	−	−	+	+	−	+	+	Moderate
Rodríguez-Baño et al.	−	+	+	+	−	+	+	Moderate
Somers et al.	−	×	+	+	+	+	−	Serious
Narain et al.	−	−	×	+	−	+	NA	Serious
Tian et al.	−	×	+	+	+	+	+	Serious
Rossotti et al.	−	+	+	+	+	+	NA	Serious

Rossi et al.	⊖	⊕	⊖	⊕	⊗	⊕	⊗	Serious
Guisado-Vasco et al.	⊖	⊗	⊗	⊖	⊕	⊖	⊗	Serious
Menzella et al.	⊗	⊖	⊖	⊕	NA	⊕	⊕	Serious
Patel et al.	⊗	⊗	⊕	⊖	NA	⊕	⊕	Serious
Eimer et al.	⊖	⊖	⊕	⊕	NA	⊕	⊕	Moderate
Galván-Román et al.	⊖	⊖	⊖	⊗	⊖	⊖	⊕	Serious
Fisher et al.	⊖	⊗	⊕	⊕	NA	⊕	⊕	Serious
Okoh et al.	⊖	⊕	⊕	⊗	NA	⊖	⊗	Serious
Pereira et al.	⊗	⊗	⊕	NA	NA	⊕	⊕	Critical
UNADJUSTED								
Campochiaro et al.	⊗	⊗	⊕	⊕	NA	⊕	⊕	Serious
Klopfenstein et al.	⊗	⊗	⊕	NA	NA	⊕	⊖	Serious
Masia et al.	⊗	⊖	⊕	⊕	NA	⊕	⊖	Serious
Vazquez Guillamet et al.	⊗	NA	NA	NA	NA	⊕	⊕	Critical
Rojas-Marte et al.	⊗	⊗	⊕	⊕	⊖	⊗	⊖	Critical
Huang et al.	⊗	⊗	⊕	⊕	⊕	⊖	⊖	Critical
Khamis et al.	⊗	⊗	⊗	⊕	NA	⊖	⊕	Critical
Nasa et al.	⊖	⊖	⊗	⊕	⊕	⊗	⊖	Critical
Salvati et al.	⊗	⊖	⊕	⊕	NA	⊗	⊕	Critical
Quartuccio et al.	⊗	⊗	⊕	⊕	NA	⊕	⊕	Critical

⊕ - Low; ⊖ - Moderate; ⊗ - Serious; ⊗ - Critical; NA- No information

Supplementary File 3 – *Risk of Bias assessment*

Data synthesis and analysis

The first stage of data synthesis involved ensuring that a measure of association was available from each study. For studies in which no relative risk measure was reported, an unadjusted odds ratio was calculated. Owing to heterogeneity in the reporting of relative risks (rate ratio, hazard ratio, odds ratio), and the inclusion of both adjusted and unadjusted estimates from observational studies, the risk estimation methods could not be homogenised, and the reported relative risk estimates, were used as reported in each study.

The relative risk estimates from RCTs and observational studies were combined using both the inverse variance-weighted method for a fixed effect model and the Der Simonian-Laird random effect model. Heterogeneity was assessed using the I^2 statistic and an interaction test p value, and corresponding forest plots were constructed. A sensitivity analysis to assess the effect of the risk of bias on the reported relative risk estimates was conducted. All analyses were conducted using R software [10].

Results

The full search results are presented in the flow chart (see Figure 1). We have included 41 published comparative studies that evaluated the effect of tocilizumab on mortality in patients hospitalised with covid-19. These comprised eight randomised controlled trials (RCTs) (1-8) and 33 observational studies (9-42) (see supplementary file 2). Study sizes ranged from 123 to 4,116 patients in RCTs and 33 to 3,924 patients in observational studies. The 41 studies came from 10 countries; the highest number (14 (34%)) came from the USA.

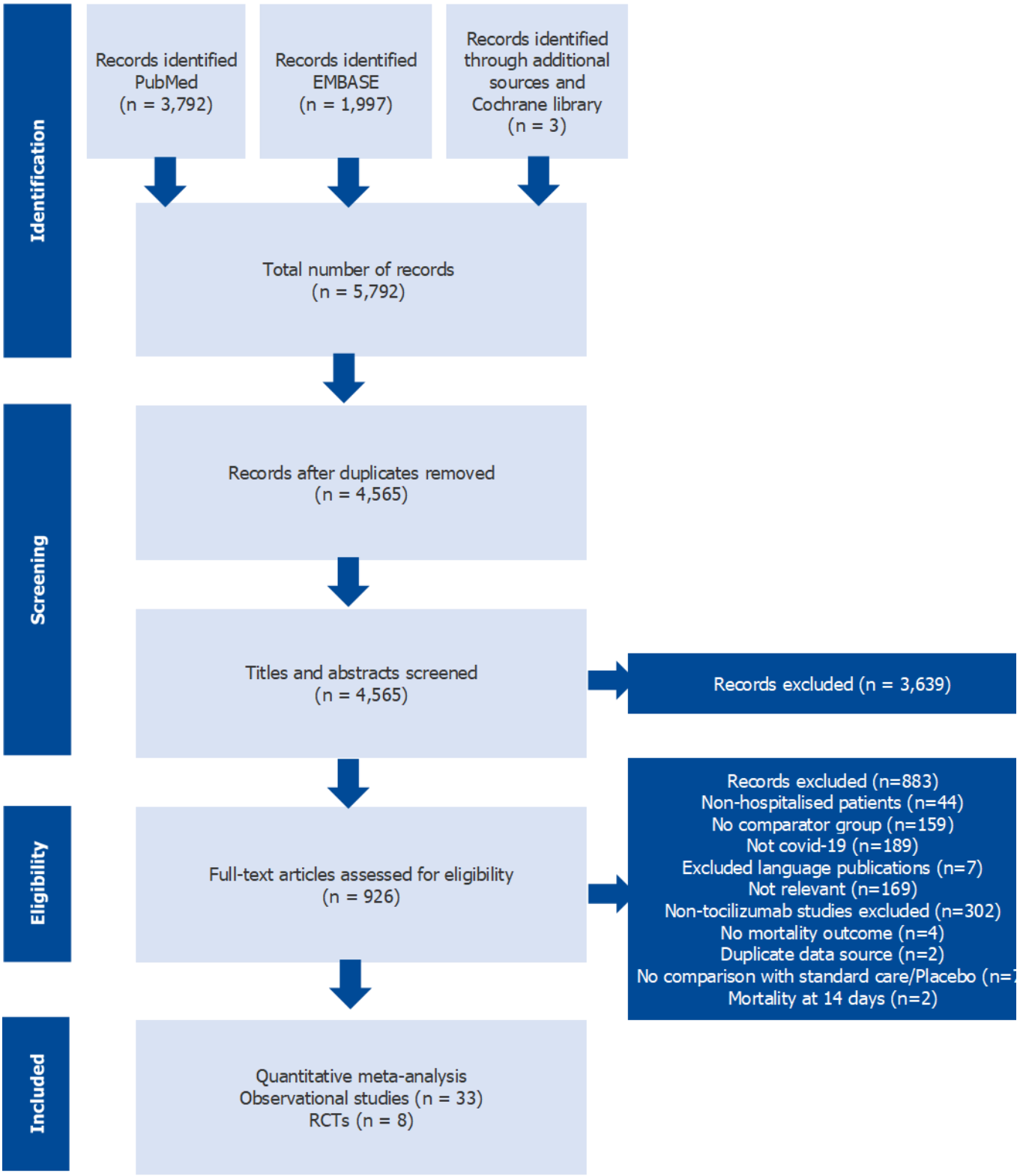
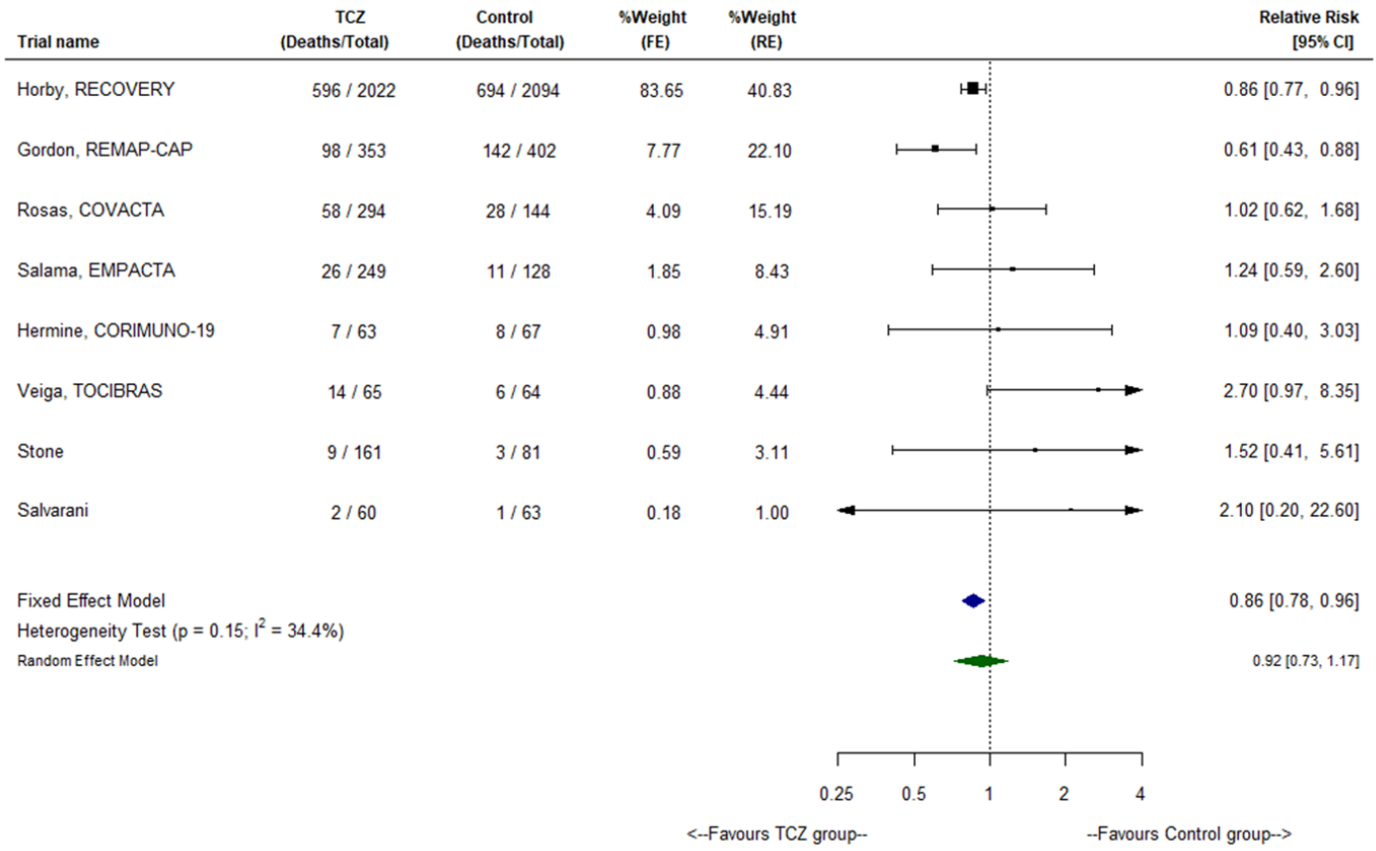


Figure 1 – *PRISMA flowchart*

The Randomised Evidence

Figure 2 presents a meta-analysis of the eight RCTs regarding the estimated relative risk effect of tocilizumab compared with standard care on 30-day mortality. In all cases, the dosage regimen was 8 mg/kg intravenously given once or twice (see supplementary file 2: Table 1). Using a fixed effect model, the combined estimate is a relative risk of 0.86 (95% CI 0.78 to 0.96, P=0.15).



FE: Fixed effect; RE: Random effect; TCZ: Tocilizumab

Figure 2 – *Fixed effects meta-analysis of RCTs reporting a relative risk for 30-day mortality*

Trial name	Study design	Number of patients	Study setting	Inclusion criteria	Exclusion criteria	Tocilizumab dosage regimen	Outcome	Analytical method
Horby et al. - RECOVERY	Randomized controlled open-label platform trial	2,022 TCZ 2,094 SC	UK	- Hospitalised - SARS-Cov-2 infection (clinically suspected or laboratory confirmed)	- Medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	IV TCZ (400-800 mg). A second dose may be given ≥ 12 and < 24 h later if, in the opinion of the attending clinician, the patient's condition has not improved	28-day mortality	Rate Ratio

Gordon et al. - REMAP-CAP	Multifactorial adaptive platform trial	353 TCZ 402 SC	Global	Critically ill patients, aged >18 years, with suspected or confirmed covid-19, admitted to an ICU and receiving respiratory or cardiovascular organ support	- Presumption that death was imminent with lack of commitment to full support
					- Participated in REMAP-CAP within 90 days
					- Known hypersensitivity to TCZ 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:
					  - ANC ≤ 1.0×10^9/L
					  - Haemoglobin level: no limitation
					  - PLT < 50 G/L
					  - SGOT or SGPT > 5 N
						IV TCZ (8 mg/kg, max. 800 mg). Additional dose could be administered 12-24 h later at the discretion of the treating clinician	Primary hospital survival	Bayesian cumulative logistic model (OR)

Rosas et al. - COVACTA	Randomized double-blind placebo-controlled trial	294 TCZ 144 PBO	Global	Patients ≥ 18 years with severe covid-19 pneumonia confirmed by RT-PCR in any body fluid and evidenced by bilateral chest infiltrates on chest X-ray or CT-scan were enrolled. Eligible patients had blood O_2 saturation ≤ 93% or PaO_2/FiO_2 < 300 mm Hg	Treating physician determined that: - Death was imminent and inevitable within 24 h - Patient had active tuberculosis or bacterial, fungal, or viral infection other than SARS-CoV-2	IV TCZ (8mg/kg infusion, max. 800 mg)	28-day mortality	Weighted difference in %
Salama et al. - EMPACTA	Randomized double-blind placebo-controlled trial	249 TCZ 128 PBO	Global	Patients ≥ 18 years (with no upper age limit) hospitalised with covid-19 pneumonia confirmed by a positive PCR test and radiographic imaging were	- Patient received CPAP - Patient received bilevel positive airway pressure - Patient received MV	IV TCZ (8 mg/kg, max. 800 mg). Additional dose could be administered 8-24 h after the first	28-day mortality	Weighted difference in %

				eligible. Patients had a blood O_2 saturation < 94% on ambient air				
Hermine et al. – CORIMUNO-19	Randomized cohort-embedded investigator-initiated multicentre open-label Bayesian trial	63 TCZ 67 SC	France	Patients not requiring ICU at admission with moderate and severe pneumopathy according to the WHO Criteria of severity of covid pneumopathy. Moderate cases: - Showing fever and respiratory symptoms with radiological findings of pneumonia and requiring between 3 L/min and 5 L/min of O_2 to maintain an O_2 saturation (SaO_2) of ≥ 97% Severe cases meeting any of the following criteria: - Respiratory distress (≥30 breaths/min) - O_2 saturation of ≤93% at rest in ambient air - O_2 saturation of ≤97% with O_2 > 5 L/min - PaO_2/FiO_2 ≤300 mm Hg	Exclusion criteria included: - Known hypersensitivity to TCZ - Pregnancy - Current documented bacterial infection - Patients with any of following laboratory results out of the ranges detailed below at screening: ANC 1.0 × 10^9/L or less or PLT < 50 G/L	IV TCZ (8 mg/kg, max. 800 mg). One dose on day one, additional 400 mg dose on day 3 if O_2 requirement was not decreased by >50%	28-day survival	Age and centre adjusted multivariable Cox regression (HR)
Veiga et al. - TOCIBRAS	Randomized multicentre open-label parallel group superiority trial	65 TCZ 64 SC	Brazil	Hospital in-patients aged ≥ 18 years with SARS-CoV-2 infection, confirmed by RT-PCR, and with symptoms >3 days. Eligible patients had severe or critical covid-19 with evidence of pulmonary infiltrates confirmed by chest CT scan or X-ray and were receiving supplemental O_2 to maintain O_2 saturation > 93% or had been receiving MV for < 24 h before analysis In addition, at least two of the following criteria had to be met: - D dimer > 2.74 nmol/L (> 1000 ng/mL)	Exclusion criteria included: - Active uncontrolled infection - Raised AST or ALT levels > 5 times the ULN - Renal disease with an eGFR of < 30 mL/min/1.72 m^2	IV TCZ (8 mg/kg max. 800 mg). Single dose	28-day hospital mortality	Logistic regression (OR)

				- CRP > 50 mg/L (> 5 mg/dL) - Ferritin >300 µg/L, or - LDH > ULN				
Stone et al. – BACC Bay TCZ Trial	Randomized double-blind placebo-controlled trial	161 TCZ 81 PBO	USA	Individuals 19-85 years-old RT-PCR or IgM antibody assay confirmed SARS-CoV-2 Patients had >2 of the following signs: - Fever (body temperature >38°C) within 72 h before enrolment - Pulmonary infiltrates - Need for supplemental O_2 to maintain an O_2 saturation > 92% >1 of the following laboratory criteria also had to be fulfilled: - CRP level > 50 mg/L - Ferritin level > 500 ng/mL - D-dimer level > 1000 ng/mL - LDH level > 250 U/L	- Receiving supplemental O_2 at a rate > 10 L/min - If they had a recent history of treatment with biologic agents or small molecule immunosuppressive therapy - Receiving other immunosuppressive therapy that the investigator believed placed them at higher risk for an infection - Individuals had had diverticulitis	IV TCZ (8 mg/kg, max. 800 mg). Single dose	28-day mortality	stratified Cox regression (HR)
Salvarani et al.	Randomized multicentre open-label trial	60 TCZ 63 SC	Italy	Patients ≥ 18 years, with an instrumental diagnosis of covid-19 pneumonia confirmed by a positive RT-PCR for SARS-CoV-2 in a respiratory tract specimen Other inclusion criteria were: - Acute respiratory failure with a PaO_2/FiO_2 ratio between 200-300 mm Hg - Inflammatory phenotype defined by a temperature > 38 °C during the last 2 days, and/or serum CRP levels of ≥ 10mg/dL and/or CRP level ≥ 2	- ICU admission - Known hypersensitivity to TCZ - Any condition preventing future admission to ICU (e.g. advanced age with multiple comorbidities) - Patients expressed will to avoid future intubation - Patients were not allowed to receive invasive or non-invasive MV	IV TCZ (8 mg/kg, max. 800 mg). First dose <8 h from randomization, second dose <12 h	30-day mortality	Chi-square test in an asymptotic form and the relative risk with its bilateral 95% CI

				the admission measurement				

Table 1. *Summary of RCT studies*

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
Adjusted										
Ruiz-Antorán et al.	Retrospective observational study	254 TCZ 235 SC	Spain (18 tertiary Spanish hospitals)	Patients ≥ 18 years with covid-19, confirmed by PCR on nasopharyngeal swab, who were consecutively admitted outside the ICU with documented pneumonia (by either imaging and/or the presence of rales/crackles on physical examination) with severe respiratory failure	- Patients < 18 years old - Those who died within 24 h after admission to hospital or after developing inclusion criteria	IV TCZ	Standard care	In-hospital mortality	IPTW-adjusted regression (HR)	Inverse probability weighting based on propensity score matching based on age, gender, HT, neurological exploration, diabetes mellitus, WHO ordinal scale, time from symptoms, confirmed infection, lymphocytes, neutrophils, PLT, prothrombin activation, temperature, LDH, and baseline medication use of ACE-inhibitors, LPV/r, HCQ, CCT, IFN, NSAID, moxifloxacin, remdesivir, and AZT
Gupta et al.	Retrospective observational study	433 TCZ 3,491 SC	USA (STOP-covid study 68 hospitals across USA)	Patients aged ≥ 18 years with laboratory-confirmed covid-19 admitted to an ICU directly attributable to covid-19	- Enrolment in a RCT involving TCZ or other IL-6 antagonists - Hospitalisation for ≥ 1 week before ICU admission - Liver disfunction (AST/ ALT > 500 U/L) - Receipt of an IL-6 antagonist other than TCZ during the first 2 days of ICU admission - Receipt of TCZ before ICU admission	TCZ	Standard care	Mortality	Inverse probability weighted Cox regression (HR)	Inverse probability weighted using age, sex, race, ethnicity, BMI, HT, diabetes, CAD, congestive HF, current tobacco use, active cancer, home medications (statin, ACE inhibitor, ARB-2), days from symptom onset to ICU admission (≤3 vs >3), severity-of-illness covariates assessed on ICU admission and concurrent therapies received on ICU admission

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
Biran et al.	Retrospective observational study	210 TCZ 420 SC	USA (13 hospitals in Hackensack Meridian Health Network)	Patients ≥ 18 years with laboratory-confirmed covid-19 who needed support in the ICU Patients receiving TCZ for chronic rheumatological conditions were not excluded	- Pregnancy - Individuals participating in a clinical therapeutic trial	IV TCZ (400 mg). Second dose was permitted at worsening oxygenation and before mechanical ventilation	Standard care	Hospital-related mortality	Multivariable Cox regression (HR)	Age, gender, diabetes, COPD or asthma, HT, cancer, renal failure, obesity, oxygenation < 94%, qSOFA score, use of steroids, CRP > 15 mg/dL, intubation or MV support and time to TCZ treatment after admission
Owen et al.	Retrospective observational study	440 TCZ 2,107 SC	Spain (17 Grupo HM Hospitals)	Admitted to any of the participating hospitals with a diagnosis of covid POSITIVE or covid PENDING	None reported	Tocilizumab	Standard care	28-day all-cause in hospital mortality	Multivariable Fine & Gray Model	Age, sex, Confirmed covid-19 diagnosis, supplemental O_2, treatment with steroids, temperature (c), heart rate (bpm), SaO_2 (%), SBP, DBP, CCI, Prior MI, congestive HF, PVD, cerebrovascular disease, dementia, pulmonary disease, renal disease, HT, diabetes, cancer, liver disease, prior stroke, ischemic heart disease, obesity, ALT, AST, creatinine, CRP, D-dimer, eosinophils, glucose, LDH, lymphocytes, monocytes, neutrophils, PLT count, potassium, sodium, urea, WBC count
Ignatius et al.	Retrospective observational study	90 TCZ 90 SC	USA (John Hopkins Health System, Washington DC)	Patients > 18 years with confirmed covid-19, hospitalised The intervention group was patients who received TCZ for off-label treatment of covid-19, and the comparator arm was drawn from patients with covid-19 who did not receive TCZ	Patients were excluded if they were < 18 years old or if they died or were discharged within 24 hours after hospitalisation	IV TCZ (usually 8 mg/kg, range 6–8 mg/kg, max. 800 mg). Single dose	Standard care (HCQ, AZT, CCT, heparin, remdesivir)	28-day mortality	Inverse-probability weighted Cox regression (HR)	Age, sex, race, BMI, CCI, $SpO_2/FiO2$, respiratory rate, temperature, SBP, DBP, pulse, O_2 supplementation device, code status, CRP, WBC, ALC, Hgb, albumin, ALT, GFR, D-dimer, ferritin, and IL-6
Canziani et al.	Retrospective	64 TCZ 64 SC	Italy	Adult patients with covid-19 in need of respiratory support Criteria for receiving TCZ:	- Late intubation (> 24h)	IV TCZ (8 mg/kg). Second dose 24 h later	Standard care (SB ENX, direct	30-day Mortality	Multivariable Cox	Matching variable (matched according to the respiratory support) and multivariable

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
	observational study		(Two general hospitals in Milan and Bergamo)	- Clinical worsening in the previous 24 h with increasing need for O_2 or ventilatory support - Absence of clinical or biochemical signs of an active bacterial infection - Elevated CRP - A higher risk for mortality at blood tests including lymphocyte count, ferritin, creatine kinase, ALT, and D-dimer		if no clinical worsening had occurred between infusions	antivirals including LPV/r, DRV + CBT, HCQ)		regression (HR)	adjustment (variables were selected if the rate of missing values was very low (<5%) and proved significant in the univariable Cox analysis (P value < 0.1)
Buzón-Martín et al.	Retrospective observational study	163 TCZ 211 SC	Spain (University hospital of Burgos, Burgos)	Patients ≥ 18 years and admitted presenting covid-19 related respiratory insufficiency upon clinical and blood gas parameters	- Patients who died within 48 h of admission - Those testing positive but asymptomatic were excluded	TCZ	Standard care (respiratory support, LPV/r, AZT, HCQ, ENX, IFN 1-β and methylprednisolone)	Mortality	Multivariate Cox regression (HR)	Adjustment not listed
Rajendram et al.	Retrospective observational study	82 TCZ 82 SC	USA (Ten hospitals within the Cleveland Clinic Enterprise)	Patients with RT-PCR confirmed SARS-CoV-2 and admitted to the ICU at the time of TCZ administration	- Received additional doses of TCZ more than 48 h after the initial dose - Received TCZ through an RCT	IV TCZ (4–8 mg/kg max. dose 400 mg). Single dose - additional doses discouraged	Standard care	28-day mortality	Multivariable logistic regression (OR)	Propensity score matching based on ICU admission source, max. CRP, SOFA score at ICU admission, vasopressor use, age, race, weight, and the use of MV during hospital admission and multivariate adjustment (not listed)
De Rossi et al.	Retrospective observational study	90 TCZ 68 SC	Italy (Montichiari Hospital)	- Confirmed covid-19 infection by a positive RT-PCR collected on a nasopharyngeal swab - Bilateral pulmonary interstitial opacities on chest imaging that were not fully explained by congestive HF or other forms of volume overload - Respiratory failure ≥ 1 of the following conditions:	- Presence of a critical respiratory syndrome that requires IMV or MV at hospital admission - Presence of severe clinical conditions as revealed by ALT 5x ULN	IV TCZ (400 mg) or SB TCZ (324 mg)	Standard care (HCQ, LPV/r)	Death	Multivariable Cox regression (HR)	Age, gender, diabetes, HT, heart diseases, serum CRP, respiratory support needed at hospital admission, and time elapsed from symptoms onset to hospital admission

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				○ Respiratory rate ≥ 30 breaths/min ○ $SpO_2 \leq 93\%$ while breathing ambient air ○ $PaO_2/FiO_2 \leq 300$ mm Hg	- Neutrophils <500 mmc and/or PLT <50.000 mmc					
Rodríguez-Baño et al.	Retrospective observational study	88 TCZ 344 SC	Spain (60 Spanish hospitals)	Presenting on a specific date (day 0) with > 1 clinical and 1 laboratory criterion suggestive of a hyperinflammatory state: - Temperature ≥ 38°C - Increase in O_2 support required to achieve O_2 saturation > 92% - Laboratory criteria were ferritin > 2000 ng/mL or increase >1000 ng/mL since admission, D-dimers > 1500 mg mL (or doubled in 24 h), and IL6 > 50 pg/mL	- Being under MV at day 0 - Occurrence of the primary endpoint in ≤ 2 day after day 0 - Written decision to avoid any escalation in medical treatment before day 0 - Previous use of systemic CCT, TCZ, other immunomodulatory drugs or immunoglobulins - Treatment with immunomodulatory drugs other than CCT or TCZ, or with immunoglobulins during the first 48 h after day 0	TCZ	Standard care	21-day mortality	Inverse probability weighted Cox regression (HR)	Inverse probability weighting calculated using propensity score matching based on age, gender, ethnicity, comorbidities (cardiac disease, HT, chronic pulmonary disease, chronic renal disease, liver cirrhosis, malignancy, diabetes mellitus, obesity, HIV infection), laboratory data (lymphocytes, LDH, ALT, ferritin, D-dimers, IL-6), previous treatments, radiographic findings, 7-point scale and type of O_2 requirement
Somers et al.	Retrospective observational study	78 TCZ 76 SC	USA (Covid-19 Rapid Response Registry)	- Admitted for severe covid-19 pneumonia, had a RT-PCR positive SARS-CoV-2 test, and required IMV - Individualized decisions on TCZ usage were made by the attending infectious diseases physician	- < 16 years - Intubated for conditions unrelated to covid-19 - Enrolled in an RCT for sarilumab	IV TCZ (8 mg/kg max. 800 mg). Single dose - additional doses discouraged	Standard care	28-day Mortality	Inverse probability weighted Cox regression (HR)	Inverse probability weighting based propensity score matching (age, congestive HF, chronic pulmonary disease, chronic renal disease, therapeutic anticoagulation, ferritin, LDH, and AST)

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
Narain et al.	Retrospective observational study	73 TCZ 3,076 SC	USA (12 hospitals and emergency departments within Northwell Health system)	- Patients > 18 year with covid-19 positivity as determined by PCR testing of nasopharyngeal swabs - Meeting CCS criteria of ferritin > 700 ng/mL or CRP > 30 mg/dL or LDH > 300 U/L	- Received any prespecified immunomodulatory drug (steroids, anakinra, TCZ) before the patient met the inclusion criteria	TCZ	Standard care (i.e. AZN, HCQ, colchicine and ascorbic acid)	In-hospital mortality	Multivariable Cox proportional hazards (HR)	Age, sex, race or ethnicity, smoking history, insurance status, treated in a tertiary vs community medical centre, chronic lung disease, CV disease, HT, diabetes, renal disease, haemodialysis, liver disease, cancer, autoimmune disease, CCI, BMI, CRP, ferritin, D-dimer, LDH, haemoglobin, PLT, serum sodium, serum transaminases, neutrophil-to-lymphocyte ratio, use of IMV and vasopressor use within 24 h
Tian et al.	Retrospective observational study	65 TCZ 130 SC	China (Tongji Hospital, Wuhan Pulmonary Hospital, and Renmin Hospital of Wuhan University, Wuhan)	Patients ≥ 18 years with covid-19 admitted to hospitals Criteria for administering TCZ: - Diagnosis of covid-19 confirmed upon RT-PCR positivity for SARS-CoV-2 - Patients with extensive lung lesions - Severe cases who also show an increased level of IL-6 in laboratory testing	- Incomplete medical records (e.g., transfer to any other hospital) - Evidence of concomitant bacterial infection, and pregnancy	IV TCZ (400 mg max. 800 mg). Second dose within 12 h in case of fever. Third dose 24 h apart based on clinician response	Standard care (i.e., antiviral, antibiotics, immunoglobulin therapy, CCT)	In-hospital death	Multivariable Cox regression (HR)	Propensity score matching based on age, sex, and comorbidities (HT, diabetes, tumour, coronary heart disease, chronic obstructive pulmonary disease, cerebral infarction, liver cirrhosis, hepatitis, and tuberculosis) and adjustment using time to death, controlling for treatment group and potential confounders, including age, gender, and comorbidities
Rossotti et al.	Retrospective observational study	74 TCZ 148 SC	Italy (ASST Grande Ospedale Metropolitano Niguarda, Milan)	Patients ≥ 18 years with a RT-PCR SARS-CoV-2 with a diagnosis of severe or critical covid-19 according to the Chinese Guidelines for the management of covid-19 Criteria for administering TCZ: - CT scan findings of severe, bilateral interstitial pneumonia	- ALT value > 5 x ULN; neutrophil cell count < 500 cell/mmc; PLT count < 50,000 cell/mmc - An active bacterial infection or a complicated intestinal diverticulitis	IV TCZ (8 mg/kg infused max. dose of 800 mg). Second dose after 12 h in case of fever persistence	Standard care	In-hospital mortality	Cox regression (HR)	Matching based on age, sex, severity of disease, P/F, CCI, and length of time between symptoms onset and hospital admittance

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				- Presence of an active inflammatory status alternatively defined by abnormal CRP levels (> 1 mg/dL), IL-6 > 40 pg/mL, d -dimer > 1.5 mcg/mL, or ferritin > 500 ng/mL)	- A positive pregnancy test - A positive HBsAg status - Any concomitant disease not defined as "under control"					
Rossi et al.	Retrospective observational study	84 TCZ 84 SC	France (Primary care centre regional hospital)	- Severe covid-19 pneumonia defined as pulse $SpO_2 \leq 96\%$ despite O_2 support ≥ 6 L/min with O_2 mask, for > 6 h - TCZ was administered at discretion of the attending physician	- Patients with invasive MV (i.e., intubated) - Patients in the critical care medicine department	IV TCZ (400 mg). Single dose	Standard care	28-day Mortality	Cox regression (HR)	Inverse probability weighting based on propensity score matching based on age, sex, smoking status, history of CAD, stroke, HF or PAD, HT, chronic kidney disease with estimated GFR < 60 mL/min/1.73 m^2, cancer, long-term CCT treatment, use of antibiotics, antivirals, CCT or baricitinib after admission, SpO_2/FiO_2 ratio at admission, time between admission and inclusion, and SpO_2/FiO_2 ratio and CRP at inclusion
Guisado-Vasco et al.	Retrospective observational study	132 TCZ 475 SC	Spain (Hospital Universitario Quirón salud Madrid)	Those admitted to the hospital with covid-19 pneumonia: - Clinical criteria: o Pneumonia confirmed by chest imaging o $SaO_2 \leq 94\%$ while breathing ambient air or ratio of the $PaO_2/FiO_2 \leq 300$ mm Hg or SaO_2/FiO_2 of 235 and 315 mm Hg - Microbiological criteria: o PCR confirmed SARS-CoV-2 by nasopharyngeal	- Pregnancy or breast-feeding - < 18 years old - Known allergy or hypersensitivity to any drug in the protocol, advanced dementia, vital prognosis < 6 months, chronic renal insufficiency with a filtration rate < 25 ml/min/1.73m2, untreated hepatitis	TCZ	Standard care (HCQ, AZT, LPV/r, DRV–CBT and LMWH for prophylaxis)	In-hospital mortality	Binary logistic regression model (OR)	Multivariate adjustment (adjustment variables not listed)

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				swab during admission o After an initial negative PCR result, but a typical clinical scenario of SARS-CoV-2 infection o Distinguished clinical picture even without conducting a PCR assay, according to local epidemiology	B or C infection, known severe liver disease, previous uncontrolled arterial HT, prolonged QTc interval at triage - Any concomitant medication that contraindicated any of the selected drugs in the protocol - Patients who were only under supportive care owing to their severe condition					
Menzella et al.	Retrospective observational study	41 TCZ 38 SC	Italy (IRCCS of Reggio Emilia, Reggio Emilia)	Patients with SARS-CoV-2 infection confirmed by a positive RT-PCR assay in a respiratory tract specimen and clinical and radiological findings compatible with covid-19 severe pneumonia. The criteria for administering TCZ were strictly based on drug availability	None reported	IV TCZ (8 mg/kg max. 800 mg) by two consecutive infusions 12 h apart. SC TCZ (162 mg) ranging from 2 to 4 doses depending on drug availability and body weight due to a temporary unavailability of IV formulation	Standard care (antimicrobial and/or immunomodulatory therapy containing LPV/r, HCQ, AZT, interferon, remdesivir, methylprednisolone)	In-hospital mortality	Multivariable Cox proportional hazards (HR)	Age, sex
Patel et al.	Retrospective observational study	42 TCZ 41 SC	USA (Swedish Medical Centre, Washington)	Patients ≥ 18 years old hospitalised for covid-19 and treated with TCZ and a comparative matched cohort that did not receive TCZ	Patients enrolled in RCTs of TCZ	TCZ	Standard care	Mortality	Not reported	Matching based on exact WHO score at hospital administration and TCZ administration, day of TCZ administration and age

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
Eimer et al.	Retrospective observational study	22 TCZ 22 SC	Sweden (Karolinska University Hospital Huddinge, Stockholm)	Patients > 18 years with confirmed SARS-CoV-2 infection admitted to the ICU for severe ARDS Criteria for receiving TCZ (at discretion of the physician): - Rising O_2 requirements with > 5 L/min on O_2 mask to maintain SpO_2 at 94% - ≥ 7 days from symptom onset - Hyperinflammation characterized by > 1 of the following: o CRP > 100 mg/L or doubled in the last 24 h o LDH > 8 µkat/L o IL-6 > 40 ng/L o D-Dimer > 2mg/L o Rising, high sensitivity troponin T > 15 ng/L o Ferritin > 500 µg/L o No contraindication to TCZ o AST/ALT at > 5 times of the upper limit of normal, o Neutropenia with < 500 cells/mm3, o Thrombocytopenia < 50 cells/mm3) Patients were eligible as controls if they were admitted to ICU with covid-19 and ARDS did not fulfil the TCZ treatment criteria	Patients with positive PCR for SARS-CoV-2 admitted for a primary diagnosis other than ARDS	IV TCZ (8 mg/kg). Single dose	Standard care	30-day mortality	Not reported (HR)	Propensity score matched using age, diabetes, HT, obesity, D-dimer, IL-6, troponin T and PaO_2/FiO_2 ratio
Galván-	Retrospective	28 TCZ 59 SC	Spain (Hospital Universitario La Princesa, Madrid)	Patients with confirmed detection of SARS-CoV-2, baseline IL-6 serum level	IL-6 > 40 pg / ml	IV TCZ (8 mg/kg max. 800	Standard care	Mortality	Multivariable Cox	Total lymphocyte count, D-dimer, LDH, PaO2/FiO2,

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
Román et al.	observational study			measurement and admitted to hospital with severe to critical covid-19 Criteria for administering TCZ: - Interstitial pneumonia with severe respiratory failure (score = 2) - Rapid respiratory worsening requiring MV/IMV (score ≥ 3 on the covid respiratory severity scale) - Presence of extrapulmonary organ failure (shock or score ≥ 3 on the SOFA scale) - Severe systemic inflammatory response (IL-6 (> 40 pg/mL increased levels of D-dimer (> 1500 ng / mL); progressively increasing D-dimer) - Patients who, according to their baseline clinical condition, would be IMV subsidiary		mg). Second dose after 12h			Regression (HR)	COPD, obesity, HT, CRP, and IL-6
Fisher et al.	Retrospective observational study	45 TCZ 70 SC	USA (Stony Brook University Hospital, New York)	Covid-19 pneumonia confirmed by nasal swab and required IMV in any ICU during their hospitalisation The criteria for receiving TCZ (at discretion of primary healthcare provider): Respiratory support in the form of high-flow nasal cannula or higher	None reported	IV TCZ (400 mg). Second dose after 24 h if there was a perceived lack of response to the initial dose	Standard care	30-day Mortality	Multivariate logistic regression (OR)	Age, sex, BMI, SOFA score, CCI, baseline IL-6, CRP, ferritin, and CCT therapy
Okoh et al.	Retrospective observational study	20 TCZ 40 SC	USA (Newark Beth Israel Medical Centre, New Jersey)	Patients > 18-years with laboratory-confirmed SARS-CoV-2 with full clinical data who had completed their	None reported	IV TCZ (8 mg/kg max. 800 mg). Second dose ≥ 12 h in patients who	Standard care (HCQ, LPV/r, favipiravir)	In-hospital mortality	Chi-squared Fishers Exact test	Propensity score matching based on age, gender, race, BMI, laboratory markers such as white cell count, haemoglobin, platelets,

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				hospitalisation Criteria for administering TCZ: - Decrease in WBC count, serum haemoglobin and PLT count - Elevation in baseline inflammatory markers: serum ferritin, LDH, procalcitonin, ESR and CRP - Patients who did not receive TCZ in addition to the standard care could not be treated with TCZ because: o admitted to the general medical ward and managed as mild cases o Existing bacterial infection o chronic immunosuppression o Unavailability of TCZ at the time of request		remain febrile within 24 h of initial dose				ferritin, CRP, LDH, ESR, procalcitonin, albumin and medications (HCQ, antibiotics, steroid)
Pereira et al.	Retrospective observational study	29 TCZ 29 SC	USA (Columbia University Irving Medical Centre Hospital, New York)	Patients >18 years with solid organ transplant ≥ 90 days of potential observation Criteria for administering TCZ: - Patients with > 7 days of symptoms - Progressive respiratory distress - Rising levels of inflammatory markers including CRP, ferritin, or IL-6	None reported	IV TCZ (4-8 mg/kg max. 800 mg). Additional doses of TCZ when the primary team deemed the initial response to be insufficient	Standard care	Mortality	Not reported	Matching based on age (> or < 60 years), HT, CKD, and receipt of high dose CCT
Unadjusted										

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
Campochiaro et al.	Retrospective observational study	32 TCZ 33 SC	Italy (San Raffaele Hospital, Milan)	Criteria for receiving TCZ: - Diagnosis of covid-19 confirmed upon positive RT-PCR for SARS-CoV-2 on nasopharyngeal swab - Hyper-inflammation (CRP, ≥ 100 mg/L, normal values <6 mg/L) or ferritin (≥ 900 ng/mL), in the presence LDH > 220 U/L) - Severe respiratory involvement defined by typical radiological findings at chest X-ray and/or CT scan, in the presence of an SaO_2 ≤92% while breathing ambient air or PaO_2/FiO_2 ≤300 mm Hg - Patients admitted to hospital before or after the time period of TCZ availability who retrospectively fulfilled eligibility criteria for TCZ treatment were used as a comparison group	- Evidence of concomitant bacterial infection - History of diverticular disease - Neutropenia < 1500×10^9 cells/L - Concomitant use of other immunosuppressive biologic drugs - Baseline elevation of AST/ALT levels > 5x ULN range - No concomitant CCT therapy	IV TCZ (400 mg). Second dose (400 mg) after 24 h in case of respiratory worsening	Standard care (HCQ, LPV/r, ceftriaxone, AZT, anti-coagulation prophylaxis with SB ENX)	28-day Mortality	Two tailed Fisher's exact	No
Klopfenstein et al.	Retrospective observational study	20 TCZ 25 SC	France (Nord Franche-Comté Hospital, Trévenans)	Adult patients who received TCZ for confirmed COVID-19 by SARS-CoV-2 RT-PCR or diagnosis confirmed during the tocilizumab multidisciplinary team meeting. Criteria for administering TCZ: - No contraindication to TCZ - Confirmed covid-19 with SARS-CoV-2 RT-PCR (or high suspicion of covid-19 with obvious clinical, biological, and	Control group: - Patients with treatment not routinely administered in the hospital (remdesivir and immunoglobulins) - Patients with moderate disease - Those hospitalised < 48 h and/or who did not receive the	TCZ. Single dose or two doses	Standard care	Death	Chi-squared or Fishers exact test	No

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				imaging data and without differential diagnosis despite a negative SARS-CoV-2 RT-PCR) - Failure of standard care - Time to symptom onset > 7 days - O_2 therapy ≥ 5 l/min, - > 25% of lung damages on CT scan - ≥ 2 parameters of inflammation or biological markers of mortality (with a high level) such as ferritin, CRP, D-dimers, lymphopenia, and LDH - The standard care included patients receiving standard treatment but without TCZ Control group: adult patients with confirmed COVID19 by SARS-CoV-2 RT-PCR receiving standard treatment but without tocilizumab	standard treatment and/or O_2 therapy)					
Masiá et al.	Retrospective observational study	76 TCZ 62 SC	Spain (University Hospital of Elche, Elche)	All patients admitted confirmed or suspected covid-19 Criteria for administering TCZ: - CURB-65 ≥ 2, O_2 saturation < 93% - Respiratory frequency > 30 per min Chest X-ray with bilateral multilobar infiltrates - D-dimer ≥ 0.7 µg/L; IL-6 ≥ 40, pg/mL; lymphocyte count <800 × 10^9/L; ferritin ≥ 700 µg/L;		IV TCZ (600 mg if ≥75 kg or 400 mg if <75kg). Second dose after 24 h if persistence of fever; no improvement in tachypnoea; no improvement in SaO_2 ≥ 5%; no decrease in CRP > 25%;	Standard care (antimicrobial and/or immunomodulatory therapy containing LPV/r, HQC, AZT, IFN-β-1b or remdesivir ± methylprednisolone	Death	Chi-squared or Fishers exact test	No

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				fibrinogen > 700 mg/dl; CRP > 25 mg/L		radiological progression)				
Vazquez Guillamet et al.	Retrospective observational study	12 TCZ 31 SC	USA (Washington University-Barnes Jewish Hospital, Washington)	Consecutive patients infected with SARS-CoV-2 requiring MV. Criteria for administering TCZ was at discretion of treating physician.	None reported	IV TCZ (8 mg/kg). Second dose 12–24 hours later, if the clinical circumstances persisted	Standard care	30-day mortality	Chi squared/Fishers exact test	No
Rojas-Marte et al.	Retrospective observational study	96 TCZ 97 SC	USA (Maimonides Medical Centre, New York)	Adult patients hospitalised with severe to critical SARS-CoV-2 infection - Severe disease: defined as requiring O_2 supplementation via face mask up to 10 L/min to maintain an O_2 saturation of ≥ 95% - Very severe disease: defined by requiring a non-rebreather mask or HFNC to maintain an O_2 saturation of ≥ 95% - Critical disease: defined by the need for intubation and MV Control group: patients required to be on supplemental O_2 that matched the treatment group	- Died < 24h of admission - Included in clinical trials with other biologic agents or convalescent plasma	IV TCZ. Single dose	Standard care	Mortality	Chi-squared or Fishers exact test	No
Huang et al.	Retrospective observational study	55 TCZ 41 SC	USA (Cedars Sinai Medical Centre, California)	Patients admitted for a covid-19-related admission with diagnosis confirmed by a positive nasopharyngeal RT-PCR test for SARS-CoV-2 Criteria for administering TCZ: - Signs of respiratory compromise consisting of tachypnoea, dyspnoea OR	- Patients administered investigational IL-6 antagonist, clazakizumab - Non- covid related death	IV TCZ (400mg). Single dose	Standard care (HCQ, AZT, remdesivir, dexamethasone)	Mortality	Chi-squared/ Fisher's exact test	No

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				- Peripheral capillary SpO_2 < 90% on at least 4 L of O_2 - Increasing oxygen requirements over 24 h, PLUS - > 2 of the following predictors for severe disease: o IL-6 > 10 pg/mL o CRP > 35 mg/L o Ferritin > 500 ng/mL o D-dimer > 1 mcg/L o Neutrophil-Lymphocyte Ratio > 4 o LDH > 200 U/L o Increased troponin in a patient without known cardiac disease						
Khamis et al.	Retrospective observational study	62 TCZ 48 SC	Oman (Tertiary care hospital, Muscat)	Patients hospitalised with confirmed or imminent respiratory failure and any one of the following conditions: - ARDS; Severe pneumonia; Pneumonia; Critical respiratory condition requiring HFNC, IMV, MV, or rapidly increasing O_2 requirement; Sepsis; Septic shock; MODS Criteria for administering TCZ: - Confirmed critical respiratory condition, rapidly increasing O_2 requirements or severe	- Coexistent infection other than covid-19 - History of severe allergic reactions to mAb - Long-term oral medication of anti-rejection drugs or immunoregulatory drugs, - Neutrophils < 500/μL or platelets < 50×10^9	IV TCZ (4–8 mg/kg) followed by an additional dose after 12 h if no clinical response without exceeding a total of 800 mg	Standard care (including HCQ, LPV/r and IV steroids and O_2 therapy)	Death	Chi-squared or Fisher's exact test	No

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				covid-19 pneumonia as evidenced wit chest X-ray or CT scan and >1 of the following: o Blood O_2 saturation ≤ 93% o PaO_2/FiO_2 < 300 mm Hg, - And: o Established presence of hyperinflammation as per serial monitoring of serum ferritin, CRP, fibrinogen, d-dimer, LDH and IL-6 ▪ Ferritin > 300 µg/L (or surrogate) and doubling within 24 h ▪ Ferritin > 600 µg/L at presentation and LDH > 250 U/L ▪ Elevated d-dimer (> 1 µg/mL) ▪ IL-6 > 80 pg/mL	- Active diverticulitis, IBD, or another symptomatic GI tract condition that might predispose patients to bowel perforation; - Severe haematological, renal or liver function impairment (ALT/AST ratio > 5 ULN) - Active tuberculosis or other active infection					
Nasa et al.	Retrospective observational study	22 TCZ 63 SC	United Arab Emirates (2 centres in Dubai)	Severe and critical covid-19 patients who developed severe or critical CRS and no contraindications: - Severe cases (New organ dysfunction: liver test dysfunction, acute kidney injury, sepsis: IVF for resuscitation, low dose vasopressor, supplemental	None reported	IV TCZ (8 mg/kg max. 800 mg). Two divided doses 12 h apart	Standard care	28-day Mortality	Chi-squared Fishers Exact test	No

Study	Study design	Number of patients	Study setting	Study population	Exclusion criteria	Tocilizumab dosage regimen	Comparator	Outcome	Analytical method	Covariate adjustments
				O_2 (HFNC HFNBM, FiO_2 ≥ 40%, NIV) - Critical (Life-threatening, MV, high dose vasopressors)						
Salvati et al.	Retrospective observational study	20 TCZ 13 SC	Italy (Careggi University Hospital, Florence)	Adult patients admitted for covid-19 pneumonia	- Patients with evidence of bacterial sepsis - ANC < 500/mm^3, thrombocytopenia (< 50,000 PLT/mm^3), liver impairment (ALT > 2.5 times ULN), medical history positive for GI perforation - Known hypersensitivity to TCZ	IV TCZ (8 mg/kg max. 800 mg). Two doses twice 12−24 h	Standard care (Supplemental O_2 therapy, LMWH, HCQ and LPV/r (or darunavir/cobicistat)	28-day Mortality	Not reported	No
Quartuccio et al.	Retrospective observational study	42 TCZ 69 SC	Italy (Single centre hospital)	Patients with covid-19 pneumonia who provided oral or written consent	None reported	IV TCZ (8 mg/kg). Single dose	Standard care (IV methylprednisolone at 1 mg/kg/day)	Mortality	Chi-squared Fishers Exact test	No

ACE inhibitor: angiotensin-converting enzyme inhibitor; ALT: alanine aminotransferase levels; ANC: absolute neutrophil count; ARB-2: angiotensin 2 receptor blocker; ARDS: acute respiratory distress syndrome; AST: aspartate aminotransferase; AZT: azathioprine; CAD: coronary artery disease; CBT: cobicistat; CCI: Charlson Morbidity Index; CCS: coronavirus disease 2019 cytokine storm; CCT: corticosteroids; COPD: chronic pulmonary obstructive disorder; CPAP: continuous positive airway pressure; CRP- c-reactive protein; CT: computed tomography; CV: cardiovascular; DBP: diastolic blood pressure; DRV: darunavir; GFR: glomerular filtration rate; ENX: enoxaparin; ESR: estimated sedimentation rate; GI: gastrointestinal; Hgb: haemoglobin; HCQ: hydroxychloroquine; HF: heart failure; HFNBM: high flow (> 10 L) Nonrebreathing mask; HFNC: high flow nasal canula; HR: hazard ratio; HT: hypertension; IBD: inflammatory bowel disease; ICU: intensive care unit; IFN: interferon; IL-6: interleukin-6; IMV: invasive mechanical ventilation; IV: intravenous; LDH: lactate dehydrogenase; LMWH: low molecular weight heparin; LPV/r: lopinavir + ritonavir; mAb: monoclonal antibodies; MI: myocardial infarction; MODS: Multiple Organ Dysfunction Syndrome; MV: mechanical ventilation; NIV: non-invasive ventilation; NSAID: non-steroidal anti-inflammatory drugs; O_2: oxygen; OR: odds ratio; PAD: peripheral artery disease; PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; PBO: placebo; PLT: platelets; PVD: peripheral vascular disease; qSOFA: quick sequential organ failure assessment; RT-PCR: reverse-transcriptase polymerase chain reaction; SaO_2: oxygen saturation; SB: subcutaneous; SBP: systolic blood pressure; SC: standard of care; SGOT/SGPT: serum glutamic-oxalacetic transaminase/glutamic-pyruvic transaminase; SOFA: sequential Organ Failure Assessment; SPO_2: oxygen saturation; TCZ: tocilizumab; ULN: upper limit of normal; WBC: white blood cell; WHO: World Health Organization.

Table 2. *Summary of Observational studies*

Supplementary File 2 – *Summary of RCT and Observational Studies*

The RECOVERY trial is the largest, contributing 83.7% of the total weight. Hence, the meta-analysis produces a very similar treatment effect estimate to that in RECOVERY: relative risk 0.86 (95% CI 0.77 to 0.96). The next largest trial REMAP-CAP, weighted 7.8% and produced large treatment effect, relative risk 0.61 (95% CI 0.43 to 0.88). The other six smaller trials all had non-significant effect estimates, in the opposite direction.

The test for heterogeneity of effect sizes across trials was non-significant (interaction P=0.15). Nevertheless, this hint of apparent heterogeneity is sufficient to generate somewhat different results for a random-effects meta-analysis: the combined relative risk estimate of 0.92 comes nearer the null, with a wider 95% CI (0.73 to 1.17) and is non-significant. This arises because the random effect model gives increased weight to the six smaller studies (combined weight 37% compared with 8.8% in the fixed-effects model), and this pulls the overall estimate away from the highly positive RECOVERY result and increases the uncertainty.

While the absolute treatment benefit; the percentage reduction in mortality is of interest, it is hard to summarise. Since the mortality risk depends on the severity of the disease at the time of randomisation, it is plausible that the absolute treatment benefit will be more marked in patients with more severe disease. This could be explored in future subgroup analyses.

In RECOVERY, the percentage mortality reduction was 3.6% (95% CI 0.8 to 6.3) (3), while in REMAP-CAP (1) it was 7.3% (95% CI 0.95 to 13.2) (see supplementary file 4). Although the latter recruited more high-risk patients from intensive care units, the mortality rates in the control groups were similar (33% versus 35% respectively). We note that the five smallest RCTs all had much lower mortality rates (collectively 7.2%); it is, therefore, likely that they lacked the power to show a survival benefit of tocilizumab.

Evidence from Observational Studies

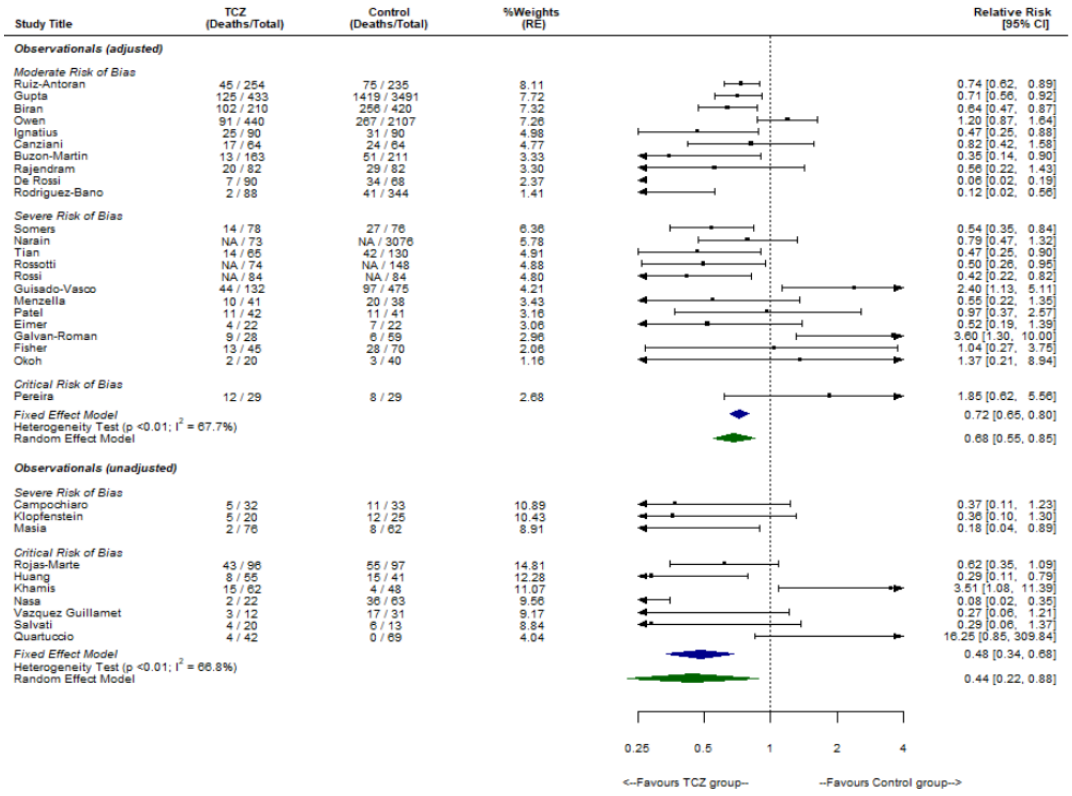


Figure 3 – *Fixed effects meta-analysis of observational studies reporting a relative risk of 30-day mortality by risk of bias.*

The 33 observational studies comparing patients receiving tocilizumab against standard care are summarised in Figure 3. In all studies the dosage regimen was 4-8 mg/kg, to a maximum of 800 mg intravenously, given once or twice (see supplementary file 2: Table 2). We concentrate on the 23 studies that adjusted for potential confounders, separating the 10 other unadjusted studies as providing intrinsically unreliable evidence (see supplementary file 3). Overall, the 23 adjusted observational studies produce a larger effect of tocilizumab on mortality than the RCTs. There is also significant heterogeneity among them (interaction P<0.01). Using a fixed effect model the overall relative risk is 0.72 (95% CI 0.65 to 0.80), whereas the random effect model estimate is 0.68 (95% CI 0.68 to 0.85).

Observational studies vary in their methodological quality. Of the 23 adjusted studies, 10 studies have a moderate risk of bias and 13 studies a severe or critical risk of bias. In Figure 4, we compared the treatment effect estimates for the RCTs with those for observational studies, split according to their risk of bias (moderate or severe). For the 10 observational studies with a moderate risk of bias the overall mortality relative risk from a fixed-effects model is 0.72 (95% CI 0.64 to 0.81), an apparently larger treatment effect than for the meta-analysis of RCTs (about twice as large a relative risk reduction).

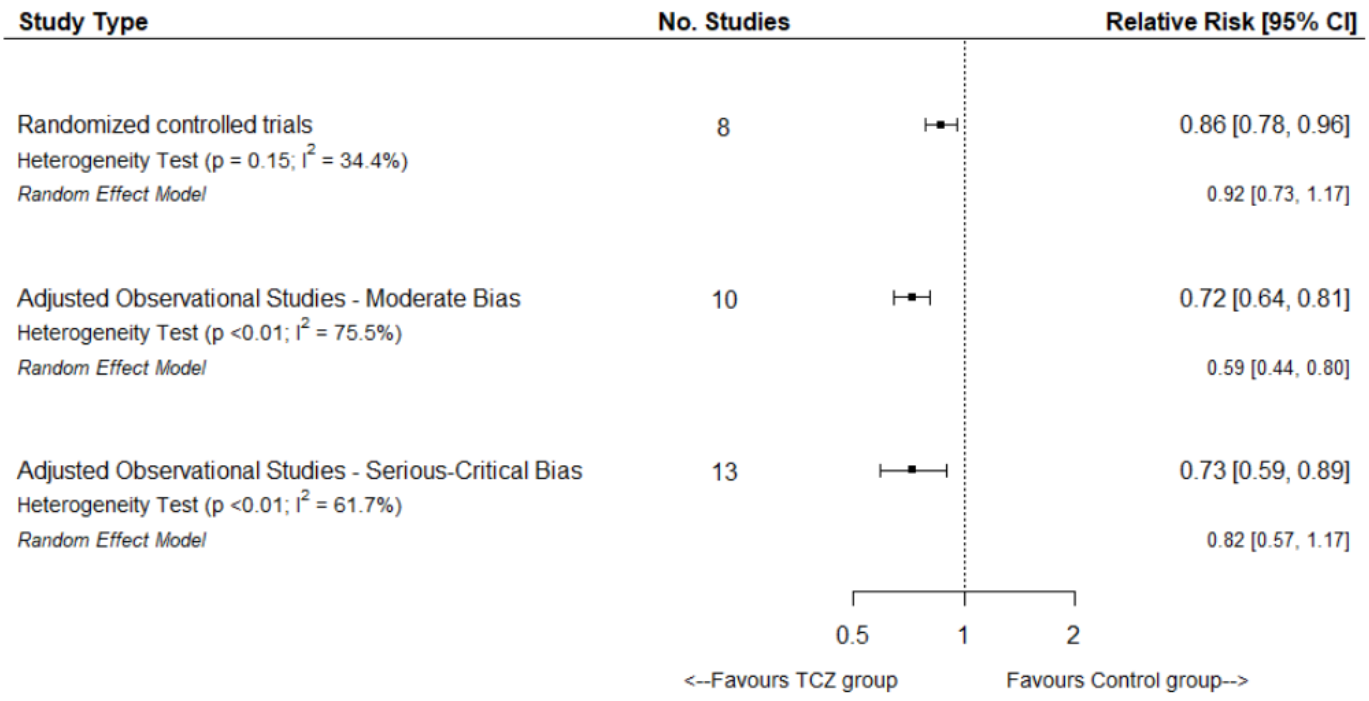


Figure 4 – *Forest plot of relative risk of 30-day mortality by study type and risk of bias*

Four of the 10 studies dominate this overall estimate, with a combined weight of 66% in the fixed-effects meta-analysis. It is therefore worth exploring their methods. The largest cohort study (17) in patients admitted to 68 US intensive care units compared 433 patients who received tocilizumab within 2 days of admission, of whom 125 (29%) died with 3,491 patients who did not, of whom 1,419 (41%) died. Adjustment for over 20 potential confounders, using a propensity score with inverse probability weighting (IPW), resulted in a mortality hazard ratio of 0.71 (95% CI 0.56 to 0.92).

The second largest study (9), in patients admitted to 13 US intensive care units, included 210 patients who received tocilizumab, of whom 102 (49%) died. Of the 554 patients who did not receive tocilizumab, 420 were matched for propensity scores and 256 (61%) died. This involved adjustment for 13 potential confounders and correction for immortal time bias. The primary analysis yielded a mortality hazard ratio of 0.64 (95% CI 0.47 to 0.87).

The third study [51] was a retrospective cohort study of all patients with covid-19 in 17 Spanish hospitals. The 440 patients treated with tocilizumab had markedly higher unadjusted 28-day mortality than the other 2,107 patients (hazard ratio 2.35) but also had a poorer risk profile. After covariate adjustment for 22 factors (including corticosteroids) of which 13 were time-updated covariates, the hazard ratio became 1.20 (95% CI 0.87 to 1.64, P=0.26).

The fourth study [42] was in patients admitted to 18 tertiary hospitals in Spain with severe covid-19; 254 patients who received tocilizumab, of whom 45 (18%) died in hospital were compared with 235 patients who did not, of whom 75 (32%) died in hospital. Adjustment for over 20 potential confounders, using a propensity score with inverse probability weighting, resulted in a mortality hazard ratio of 0.74 (95% CI 0.62 to 0.89). It is puzzling that this study produces a substantially more precise treatment effect estimate (i.e., a narrower CI) than that of Gupta et al [26], even though it was around one-third the size. We suspect that this contradiction arises because the latter study correctly used a robust variance estimator to account for potential replication of patients induced by inverse probability, whereas the former did not.

Discussion

It is generally recognised that RCTs provide the highest quality of evidence on which to base therapeutic recommendations, while evidence from observational studies requires much more cautious interpretation. Hence, in interpreting this systematic review of the effect of tocilizumab on survival of patients with covid-19, it is appropriate that we first concentrate on the randomised evidence.

Overall, based on a fixed effect meta-analysis of eight RCTs, we see a 14% relative risk reduction in mortality with tocilizumab (95% CI 4-22%). This is very similar to the findings in the RECOVERY trial, which dominates the analysis, owing to its size.

We have also presented a random effect meta-analysis, since it is conventional to do so. It provides a weaker overall effect estimate, an 8% relative risk reduction with a wider 95% CI that includes no effect on mortality. However, this is likely to be a misleading analysis. There is no significant heterogeneity of effect across randomised trials (interaction P=0.15), yet the random effect model increases the weight given to the six smaller trials, none of which point in the direction of treatment benefit. This undue influence of small studies appears to dilute a treatment effect and generate increased uncertainty. There is a long-standing debate on the relative merits of fixed effect and random effect meta-analyses. In this case, we think that a random effect model is less trustworthy.

A key question is whether the overall survival benefit from tocilizumab relates to all hospitalised patients with covid-19 or if there are specific subgroups in whom the benefit is greater or absent. The RECOVERY trial reports that these benefits were seen in all patient subgroups, including those requiring oxygen, and those requiring mechanical ventilation in an intensive care unit (ICU) (3). The combination of tocilizumab and a systemic corticosteroid (e.g., dexamethasone) appears to reduce mortality to a greater extent. It is also plausible that the reduction in mortality due to tocilizumab is more marked in more severe disease, in which IL-6 release may be more marked. For instance, the second largest RCT, the REMAP-CAP trial, was in critically ill patients in an ICU and reported a 39% relative reduction in in-hospital mortality, although with a wide 95% CI (12-57%) [11]. However, in the RECOVERY trial [8], patients requiring non-invasive

ventilation and invasive mechanical ventilation (each subgroup having more deaths than in the REMAP-CAP trial) did not have larger relative reductions in in-hospital mortality than patients who did not require ventilatory support.

Interpretation of the evidence from observational studies presents more of a challenge. For the sake of completeness, we have included all 33 observational studies that evaluated the association between tocilizumab treatment and mortality (see Figure 3), but we feel it best to ignore the findings of most of them, owing to their unreliability. 10 studies did not adjust for confounders in their mortality analyses and a further 13 studies were classified as having a severe risk of bias. Reasons for such a poor rating include lack of adjustment for key covariates and bias in the selection of patients.

This leaves 10 observational studies classified as having a moderate risk of bias. Their combined data (2,093 patients given tocilizumab, of whom 460 died in hospital) amounted to a slightly lower mortality than in the RCTs. Overall, these 10 studies showed a stronger association between tocilizumab treatment and survival than the RCTs, with a relative reduction in mortality of 29% (95% CI 20-36%). The four largest were all retrospective cohort studies based on multiple hospitals, two in the USA and two in Spain. While the pooled 95% confidence interval in these studies at moderate risk of bias overlapped with the pooled estimate from the RCTs, it is noteworthy that only two observational studies had point estimates that fell within the 95% confidence interval of the pooled RCTs or the RECOVERY trial, the largest RCT.

The diversity of statistical methods across these studies is a challenge: propensity adjustment with IPW, propensity matching, and covariate adjustment were all used to account for potential confounders. Inevitably, one doubts whether any study has adequately corrected for the selection bias involved in the clinical decisions about who received tocilizumab and who did not. Unmeasured confounders may well play an important role. Hence, the extent to which one can trust the adjusted relative risk estimate in each observational study is open to debate, and the overall effect estimate across the 10 observational studies with moderate bias may have been overestimated two-fold (14% in RCTs versus 29% in observational studies).

Our systematic review has some limitations. We have only evaluated treatment effects on mortality, whereas other outcomes such as time to recovery and need for mechanical ventilation may have an important bearing on the overall benefit profile of tocilizumab and its cost-effectiveness by reducing the duration of illness. We believe that in-hospital mortality, as well as being the most important outcome, provides the least scope for bias in comparing RCTs and observational studies. We have concentrated on overall mortality in all patients, whereas there could be subgroups for whom the survival benefit is more (or less) marked, although subgroup analyses according to severity in the RECOVERY trial suggest that that is not the case.

The role of observational studies of treatments in covid-19, and more generally, is controversial. For tocilizumab, the pooled observational studies agree with the RCTs in the direction of benefit on mortality but exaggerated its magnitude two-fold. The large observational studies may seem to have been more informative motivation than the early underpowered RCTs which even when pooled showed no evidence of tocilizumab's efficacy. We did not combine RCTs and observational studies with network meta-analysis, which may produce highly misleading results [52]. The results of observational studies should be used mainly to generate hypotheses and to inform the design of RCTs and not as a basis for treating patients, except when RCTs are not reliable, as recently reported for the efficacy of prophylactic anticoagulation in covid-19 patients [53].

Conclusion

This systematic review of all reported RCTs of tocilizumab versus standard care shows strong evidence that tocilizumab reduces mortality in severe covid-19. Observational studies of adequate methodological quality also provided evidence of efficacy, but the effect size was exaggerated two-fold. Collectively observational studies provide a less reliable evidence base for evaluating treatment for covid-19.

Conflict of Interest Statement

OXON Epidemiology is a scientific service provider of observational research, pragmatic trials and meta-analysis to the pharmaceutical industry.

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Data sharing

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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