Supplementary Table S1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page#
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review-level (e.g. incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009): Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097.

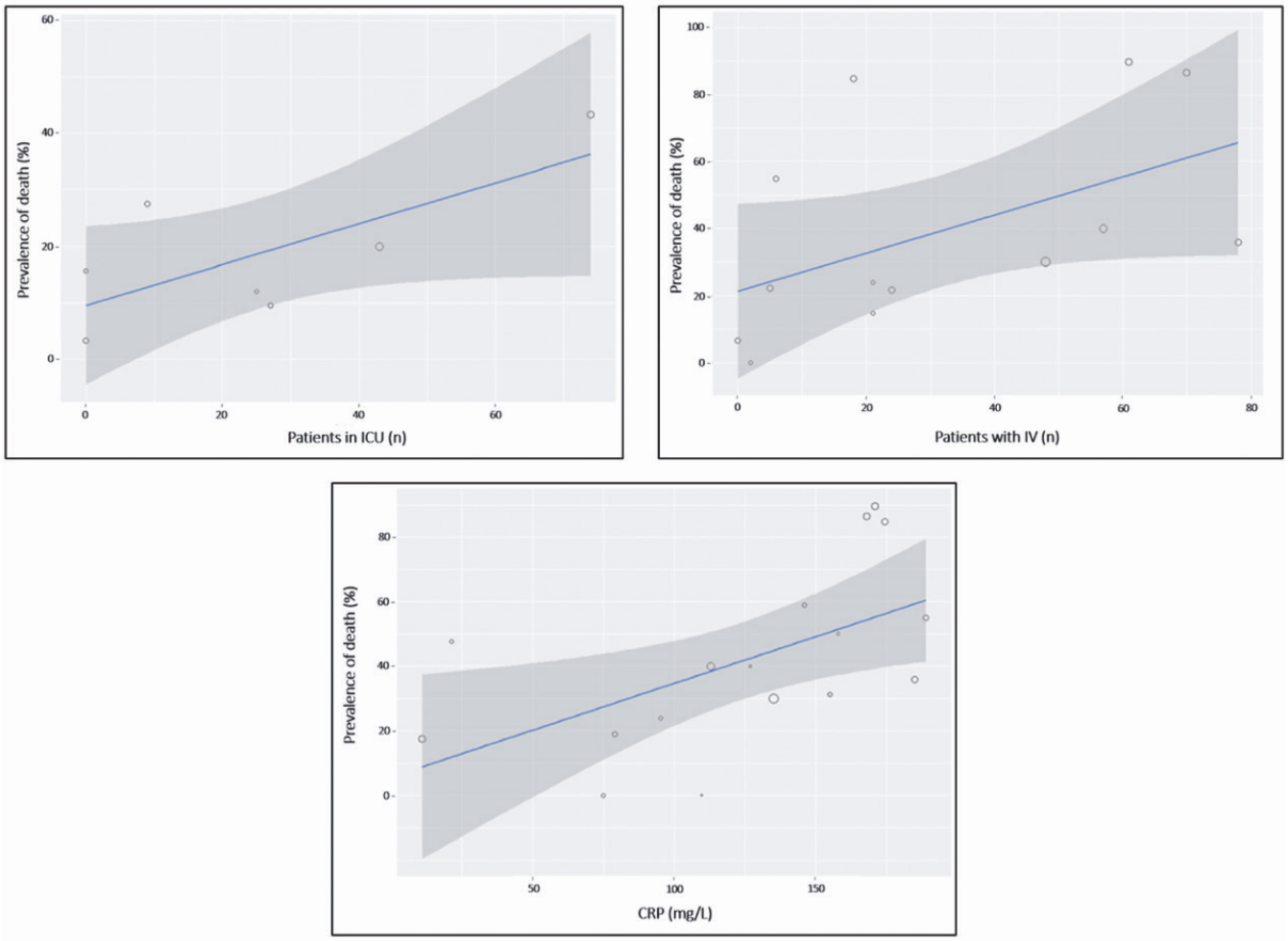
Supplementary Table S2. Papers excluded from the analysis with the main reason.

First author	Year	Title	Main reason for exclusion
Rilinger J	2020	A prospective, randomised, double blind placebo-controlled trial to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia (TOC-COVID): a structured summary of a study protocol for a randomised controlled trial	out of interest
Kaushik S	2020	Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome Coronavirus 2 infection: a multi-institutional study from New York City.	out of interest
Comel AC	2020	Rapid radiological improvement of COVID-19 pneumonia after treatment with tocilizumab.	case report
Tadepalli S	2020	The role of interleukin-6 inhibitors in the treatment of COVID-19 infections: a case series.	case report
Madenidou AV	2020	Real-life experience of tocilizumab use in COVID-19 patients.	letter to the editor
Belladonna M	2020	Potential benefits of tryptophan metabolism to the efficacy of tocilizumab in COVID-19.	review
Guner R	2020	COVID-19 experience of the major pandemic response center in the capital: results of the pandemic's first month in Turkey.	out of interest
Ayanian S	2020	The association between biomarkers and clinical outcomes in novel coronavirus pneumonia in a US cohort.	out of interest
Derespina KS	2020	Clinical manifestations and outcomes of critically ill children and adolescents with COVID-19 in New York City.	out of interest
Carlino MV	2020	Predictors of intensive care unit admission in patients with coronavirus disease 2019 (COVID-19).	out of interest
Wu Y	2020	Clinical characteristics and immune injury mechanisms in 71 patients with COVID-19.	out of interest
Gupta S	2020	Factors associated with death in critically ill patients with Coronavirus disease 2019 in the US.	out of interest
Pérez-Sáez MJ	2020	Use of tocilizumab in kidney transplant recipients with COVID-19.	out of interest
Keam S	2020	Immunopathology and immunotherapeutic strategies in severe acute respiratory syndrome coronavirus 2 infection.	review
Potere N	2020	Interleukin-6 receptor blockade with subcutaneous tocilizumab in severe COVID-19 pneumonia and hyperinflammation: a case–control study.	letter to the editor
Luo M	2020	IL-6 and $CD8^+$ T cell counts combined are an early predictor of in-hospital mortality of patients with COVID-19.	out of interest
Gatti M	2020	Serious adverse events with tocilizumab: pharmacovigilance as an aid to prioritise monitoring in COVID-19	out of interest
Sheianov MV	2020	Pulse therapy with corticosteroids and intravenous immunoglobulin in the management of severe tocilizumab-resistant COVID-19: a report of three clinical cases.	out of interest
Gade A	2020	Interleukin 6 levels after tocilizumab administration in transplant recipients with COVID-19.	out of interest
Farooqi F	2020	Treatment of severe COVID-19 with tocilizumab mitigates cytokine storm and averts mechanical ventilation during acute respiratory distress: a case report and literature review	case report, review
Frigault M	2020	Tocilizumab not associated with increased infection risk after CAR T-cell therapy: implications for COVID-19?	letter to the editor
Naqvi M	2020	Tocilizumab and Remdesivir in a pregnant patient with Coronavirus disease 2019 (COVID-19).	out of interest
Ranger A	2020	Interleukin-6 blockade treatment for COVID-19 associated cytokine release syndrome in a patient with poorly controlled chronic myeloid leukaemia.	letter to the editor
Portsmore S	2020	Combined IL-6 and JAK-STAT inhibition therapy in COVID-19 related sHLH, potential game changer.	out of interest
Antony SJ	2020	Early use of tocilizumab in respiratory failure associated with acute COVID -19 pneumonia in recipients with solid organ transplantation.	out of interest
Shabani S	2020	Tocilizumab administration in patients with SARS-CoV-2 infection: Subcutaneous injection vs intravenous infusion.	letter to the editor
Allam SR	2020	Interleukin-6 receptor antagonist therapy to treat SARS-CoV-2 driven inflammatory syndrome in a kidney transplant recipient.	out of interest
Andrianopoulos I	2020	Tocilizumab's efficacy in patients with Coronavirus disease 2019 (COVID-19) is determined by the presence of cytokine storm.	letter to the editor
Rojo M	2020	Gastrointestinal perforation after treatment with tocilizumab: an unexpected consequence of COVID-19 pandemic.	case report
Maes B	2020	Treatment of severely ill COVID-19 patients with anti-interleukin drugs (COV-AID): a structured summary of a study protocol for a randomised controlled trial.	out of interest
Herrero SF	2020	Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: an observational study.	letter to the editor
Hassoun A	2020	Utilizing tocilizumab for the treatment of cytokine release syndrome in COVID-19.	letter to the editor
Levi M	2020	Tocilizumab for severe COVID-19: A promising intervention affecting inflammation and coagulation.	letter to the editor
Marfella R	2020	Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients.	out of interest
González-Gay MA	2020	Tocilizumab: from the rheumatology practice to the fight against COVID-19, a virus infection with multiple faces.	review
Buonaguro FM	2020	Anti-IL6R role in treatment of COVID-19-related ARDS.	editorial
Alberici F	2020	A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia.	out of interest
Baker EH	2020	Insights from compassionate use of tocilizumab for COVID-19 to inform appropriate design of randomised controlled trials.	letter to the editor

Supplementary Table S3. Meta-regression for death prevalence in patients treated with Tocilizumab.

	n of studies	Meta-regression coefficient	Adj. R^2	*p*	Residual I^2
Age	23	0.0022	0.00	0.73	84.87
Male gender	22	0.0009	0.00	0.64	85.34
Hypertension	20	0.0017	0.00	0.29	81.66
Diabetes	21	0.0009	0.00	0.68	84.88
Lung diseases	16	0.0001	0.00	0.97	85.91
CVDs	18	0.0048	2.05	0.19	81.64
Patients in ICU	7	0.0046	51.13	**0.02**	71.89
Patients requiring IV	14	0.0037	24.05	**0.035**	87.07
Lymphocytes	8	-0.3727	0.00	0.14	36.56
CRP	19	0.0019	43.19	**0.003**	74.04
IL-6	9	-0.0008	10.51	0.18	84.83
Ferritin	10	0.0002	3.68	0.19	87.55

p: *p*-value; n: number; CVDs: cardiovascular diseases; ICU: intensive care unit; IV: invasive ventilation; IL-6: interleukin-6; CRP: C-reactive protein.



Supplementary Fig. S1. Bubble plots with fitted meta-regression line of the mortality rate in tocilizumab-treated patients.
Bubble plots with fitted meta-regression line of the mortality rate in tocilizumab-treated patients and a) number of participants in ICU, b) number of participants requiring IV, c) CRP sera values. Circles are sized according to the precision of each estimate with larger bubbles for more precise estimates.
ICU: intensive care unit; IV: invasive ventilation; CRP: C-reactive protein.

Supplementary Table S4. Newcastle-Ottawa Assessment Scale for case-control studies.

Study	Selection				Comparability			Exposure		
	Definition of cases	Representativeness of cases	Selection of controls	Definition of controls	On age	On other risk factors	Assessment of exposure	Same methods of ascertainment for cases and controls	Non-response rate	Total score
Capra *et al*. (21)	★	★	★	★	☆	★	★	★	☆	7
Colaneri *et al*. (17)	★	★	☆	☆	★	★	★	★	☆	6
Klopfenstein *et al*. (32)	★	★	★	★	★	★	★	★	★	9
Quartuccio *et al*. (20)	★	☆	☆	☆	★	★	☆	★	☆	5
Price *et al*. (25)	★	★	☆	☆	★	★	★	★	★	7
Campochiaro *et al*. (23)	★	★	★	★	★	★	★	★	★	9
Somers *et al*. (26)	★	★	☆	☆	☆	☆	★	★	★	5
Rojas-Marte *et al*. (27)	★	★	★	★	★	☆	★	★	★	8
Rosotti *et al*. (24)	★	★	★	★	★	★	★	☆	★	8

★, 1; ☆, 0.

Supplementary Table S5. Quality assessment of the included studies without the control group.

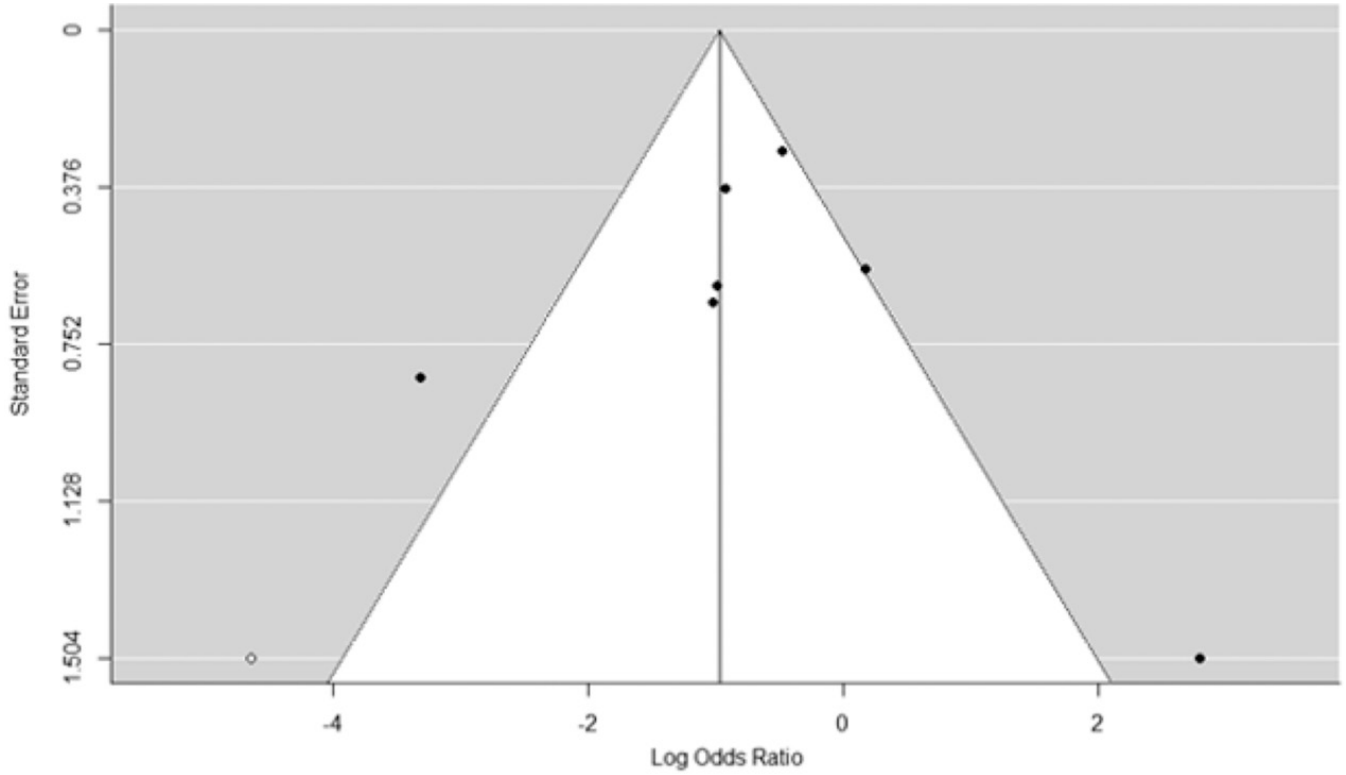
Study	Quality Assessment	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12
Alattar *et al*. 2020 (26)	Poor	No	Yes	No	Yes	Not applicable	Not reported	No	No	Not reported	Yes	No	No
Luo *et al*. 2020 (24)	Poor	No	No	No	Not applicable	Not applicable	No	No	No	Not reported	No	No	No
Xu *et al*. 2020 (23)	Poor	Yes	No	No	Not applicable	Not applicable	No	Yes	No	Not reported	Yes	Yes	No
Sciascia *et al*. 2020 (19)	Fair	Yes	Yes	No	Yes	Not applicable	No	Yes	No	Not reported	Yes	Yes	No
Toniati *et al*. 2020 (18)	Poor	Yes	No	No	Not applicable	Not applicable	No	No	No	Not reported	No	No	No
Morena *et al*.2020 (23)	Fair	No	Yes	No	No	Not applicable	Yes	Yes	No	Not reported	Yes	Yes	No
Borku *et al*. 2020 (29)	Poor	No	No	No	Not applicable	Not applicable	No	No	No	Not reported	Yes	Yes	No
Lohse *et al*. 2020 (33)	Poor	Yes	No	No	Not applicable	Not applicable	Yes	No	No	Not reported	No	No	No
Morrison *et al*. 2020 (28)	Fair	Yes	Yes	No	Yes	Not applicable	No	No	No	Not reported	Yes	Yes	No
Conrozier*et al*. 2020 (34)	Fair	Yes	No	No	Not applicable	Not applicable	Yes	No	No	Not reported	Yes	Yes	No
Knorr *et al*. 2020 (29)	Poor	No	No	No	Not applicable	Not applicable	No	No	No	Not report	Yes	Yes	No
Jordan *et al*. 2020 (30)	Fair	No	Yes	No	Yes	Not applicable	Not reported	Yes	No	Not reported	Yes	Yes	No
Fernández-Ruiz *et al*. 2020 (37)	Fair	Yes	No	No	Not applicable	Not applicable	No	Yes	No	Not reported	Yes	Yes	No
Antony *et al*. 2020 (31)	Fair	Yes	Yes	No	Yes	Not applicable	Yes	No	No	Not reported	Yes	Yes	No

Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group proposed by the National Heart, Lung, and Blood Institute - US Department of Health & Human Services (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after).

Supplementary Table S6. Main outcomes and tocilizumab regimen of included studies.

Author, year, country	Main outcome	Tocilizumab regimen
Capra *et al*. 2020 Italy (21)	Survival rate in patients treated with tocilizumab and controls	Not specified
Price *et al*. 2020 USA (25)	Not specified	8 mg/kg IV, not to exceed 800 mg; a second dose could be given if the patient had a markedly elevat ed BMI
Colaneri *et al*. 2020 Italy (17)	ICU admission and 7-day mortality rate	8 mg/kg IV, not exceed 800 mg, repeated after 12 h if no side effects were reported after the first dose
Campochiaro *et al*. 2020 Italy (23)	Outcome at 28 days in patients treated with tocilizumab and controls	400 mg IV, second dose of 400 mg was given after 24 hours in case of respiratory worsening
Somers *et al*. 2020 USA (26)	Survival probability after intubation	8 mg/kg (maximum 800 mg) x 1; additional doses were discouraged
Rojas-Marte *et al*. 2020 USA (27)	Overall mortality rate	Not specified
Klopfeinstein *et al*. 2020 France (32)	Death and/or ICU admission	Not specified
Quartuccio *et al*. 2020 Italy (20)	Baseline laboratory and immunological features in patients hospitalised for COVID-19 pneumonia and their relationship of standard of care therapy vs. anti-cytokine therapy, mainly tocilizumab	8 mg/kg intravenously as a single infusion
Rosotti *et al*. 2020 Italy (24)	Survival and hospital discharge in patients treated with tocilizumab and controls	8 mg/kg (maximum dose of 800 mg); a second dose would be administered after 12 h in case of fever persistence
Alattar *et al*. 2020 Qatar (26)	Discharge alive from ICU by day 14	Not specified
Lohse *et al*. 2020 France (33)	Number of death and recovery after treatment	2 infusions, at 24 h interval, at a dosing regimen of 8 mg/kg with a maximum dose of 800 mg per infusion
Morrison *et al*. 2020 USA (28)	Characteristics of non-survivors, defined as in-hospital death within 28 days of tocilizumab administration, were compared to survivors	8 mg/kg IV (maximum dose of 800 mg). Doses were rounded to 400 mg, 600 mg, or 800 mg. Patients were eligible for a second dose if persistently febrile despite treatment. Due to medication shortages the dosage was changed to a fixed 400 mg IV dose for all patients on March 30, 2020
Borku *et al*. 2020 Turkey (29)	Not specified	400 mg, a dose of 400 mg was repeated within 24 hours, taking into account the changes in clinical and laboratory findings
Conrozier *et al*. 2020 France (34)	Main biomarker variations the week following the administration of the treatment	2 infusions, ideally at 24 hours interval (in fact 12 to 72 hours), at a dosing regimen of 8 mg/kg (maximum dosage 800 mg)
Knorr *et al*. 2020 USA (29)	Not specified	8 mg/kg with (maximum of 800 mg). The treatment protocol originally allowed for a maximum of three doses if patients had no clinical improvement at least 8 hours after the first dose
Jordan, *et al*. 2020 USA (30)	Not specified	Single dose of 400 mg IV
Luo *et al*. 2020 China (24)	Not specified	Not specified
Fernández-Ruiz *et al*. 2020 Spain (37)	Proportion of patients achieving clinical improvement (defined by hospital discharge and/or a decrease of ≥2 points from baseline on the six-point ordinal scale) by day 7 after the first dose	400 mg IV (if body weight <75 kg) or 600 mg (if body weight ≥75 kg) dose. A second 400 mg dose was administered 12 hours later, whereas a third dose could be given after 24 hours from the first infusion to selected patients that had achieved only a partial response
Morena *et al*. 2020 Italy (23)	Death or hospital discharge	Tocilizumab IV either at fixed dose of 400 mg at T0 followed by 400 mg after 12 hours or 8 mg/kg at T0 followed by 8 mg/kg after 12 hours (in patients with body weight ≥60 kg);
Sciascia *et al*. 2020 Italy (19)	Safety of the medication	Tocilizumab IV (8 mg/kg) or SC (324 mg); a second administration within 24 h was given in 52 out of 63 patients
Antony *et al*. 2020 USA (31)	Not specified	4 mg/kg was given to patients within the first 24 hours of hospitalisation followed by methylprednisolone 60 mg
Toniati*et al*. 2020 Italy (18)	Not specified	8 mg/kg by two consecutive infusions 12 hours apart
Xu *et al*. 2020 China (23)	Changes in body temperature, respiratory function, and CT findings before and after treatment with tocilizumab	4–8 mg/kg IV, the recommended dose was 400 mg drip up to a maximum of 800 mg

IV: intravenously; BMI: body mass index; ICU: intensive care unit; SC: sub-cutaneously.



Supplementary Fig. S2. Funnel plot of the overall analysis of the relationship of mortality with TCZ-treatment.
Funnel plot of the overall analysis of the relationship of mortality with TCZ-treatment. The trim-and-fill analysis identified a putative missing study (white circle) on the left side of the distribution of studies investigating.