Original research

Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19

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ABSTRACT

Background There is accumulating evidence for an overly activated immune response in severe COVID-19, with several studies exploring the therapeutic role of immunomodulation. Through systematic review and meta-analysis, we assess the effectiveness of specific interleukin inhibitors for the treatment of COVID-19.

Methods Electronic databases were searched on 7 January 2021 to identify studies of immunomodulatory agents (anakinra, sarilumab, siltuximab and tocilizumab) for the treatment of COVID-19. The primary outcomes were severity on an Ordinal Scale measured at day 15 from intervention and days to hospital discharge. Key secondary endpoints included overall mortality.

Results 71 studies totalling 22 058 patients were included, 6 were randomised trials. Most studies explored outcomes in patients who received tocilizumab (60/71). In prospective studies, tocilizumab was associated with improved unadjusted survival (risk ratio 0.83, 95% CI 0.72 to 0.96, I^2=0.0%), but conclusive benefit was not demonstrated for other outcomes. In retrospective studies, tocilizumab was associated with less severe outcomes on an Ordinal Scale (generalised OR 1.34, 95% CI 1.10 to 1.64, I^2=98%) and adjusted mortality risk (HR 0.52, 95% CI 0.41 to 0.66, I^2=76.6%). The mean difference in duration of hospitalisation was 0.36 days (95% CI −0.07 to 0.80, I^2=93.8%). There was substantial heterogeneity in retrospective studies, and estimates should be interpreted cautiously. Other immunomodulatory agents showed similar effects to tocilizumab, but insufficient data precluded meta-analysis by agent.

Conclusion Tocilizumab was associated with a lower relative risk of mortality in prospective studies, but effects were inconclusive for other outcomes. Current evidence for the efficacy of anakinra, siltuximab or sarilumab in COVID-19 is insufficient, with further studies urgently needed for conclusive findings.

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Key messages

What is the key question?
► Are specific interleukin inhibitors efficacious and safe for the treatment of COVID-19?

What is the bottom line?
► Immunomodulatory therapies, particularly tocilizumab show promise as therapies for patients with severe COVID-19, but there is an urgent need for further randomised controlled trials to define the role of this treatment.

Why read on?
► Understanding evidence-based treatments for COVID-19 will ensure patients are optimally managed, thereby reducing associated morbidity and mortality.

INTRODUCTION

The novel SARS-CoV-2 was first identified in Wuhan, China, in December 2019.[1] Since then, COVID-19 has been declared a global pandemic by the WHO and continues to spread at an exponential rate with over two million deaths reported worldwide.[2 3]

The clinical manifestations of COVID-19 tend to be heterogenous ranging from asymptomatic infection to acute respiratory disease syndrome, multiorgan failure and death. Mechanisms underlying severe disease are incompletely understood, but accumulating evidence points towards a dysregulated and excessive host immune response referred to as cytokine storm syndrome.[4] During this state of immunological hyperactivation, increased circulating levels of proinflammatory cytokines including interleukin (IL)-1 and IL-6 have been demonstrated and are associated with adverse clinical outcomes.[5–7] Suppression of proinflammatory cytokines in COVID-19 may therefore be a potential therapeutic strategy.[8]

SARS-CoV-2 shares a number of genetic and clinical similarities with other zoonotic coronaviruses, including SARS-CoV and Middle East respiratory syndrome (MERS).[9 10] There are also reports of elevated proinflammatory cytokines in patients with SARS and MERS,[11 12] suggesting overlapping therapeutic targets in the management of SARS, MERS and COVID-19.

Several clinical studies evaluating the role of immunomodulatory agents in COVID-19 have been published recently. Through systematic review and critical appraisal of the literature, we assess the effectiveness and safety of specific IL-1 (anakinra) and IL-6 (tocilizumab, siltuximab, sarilumab) inhibitors for the treatment of COVID-19, drawing on the literature from previous similar coronavirus infections (SARS and MERS) where available. These agents already carry approval for the treatment of other rare non-infectious and autoimmune conditions, with an acceptable safety profile.

METHODS

The systematic review was conducted in accordance with a prespecified protocol and has been reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13]

Search strategy and study selection

Electronic database searches were carried out in MEDLINE (1946 to latest) and EMBASE (1974 to latest) and ongoing clinical trial registries (clinicaltrials.gov and EU Clinical Trials Register), with the last search carried out on 7 January 2021. Search terms were broad and included keywords and controlled vocabulary for patient and treatment-related terms (see online supplemental figure S1 for MEDLINE search strategy). Unpublished and ongoing studies were identified by searching preprint servers including medRxiv and bioRxiv. Searches were carried out independently by two reviewers in a standardised manner, followed by screening through titles and abstracts, before full-text review. Disagreements were resolved by consensus, with unresolved conflicts decided by a third reviewer.

The review included all original studies, evaluating the use of at least one of the following: anakinra, tocilizumab, sarilumab or siltuximab in patients aged over 18 suspected or confirmed with either COVID-19, SARS or MERS. Case reports and retrospective studies without a comparator arm were excluded due to their associated heterogeneity and inherent risk of bias. Language or year of publication restrictions were not applied. No minimal study sample size was specified for inclusion.

The planned primary outcomes were selected based on their clinical usefulness and included time to hospital discharge (days) and severity on an adapted 4-point Ordinal Scale at day 15 following intervention, with the following ratings: (i) death; (ii) requirement for invasive mechanical ventilation (IMV) or extracorporal membrane oxygenation (ECMO); (iii) hospitalised but no requirement of IMV/ECMO and (iv) not hospitalised. Secondary outcomes included overall mortality and treatment-related adverse events. For all outcomes studied, baseline was defined as the day of intervention.

Data extraction and risk of bias assessment

Data were extracted from article's text and figures using a data-extraction proforma and verified by a second reviewer. Information sought included study design, sample size, participant demographics, clinical investigation findings, intervention characteristics (name of agent, dose, route), treatment-related adverse events, requirement and duration of invasive and non-invasive ventilation, use and dosage of oxygen, duration of hospital stay, survival outcome measures and follow-up duration. Where ordinal outcomes were reported at multiple timepoints, those closest to day 15 post intervention were chosen for extraction. For ongoing trial protocols, the registration number, sample size and expected date of completion were recorded.

Risk of bias assessment was carried out independently in duplicate. Due to the heterogeneity of study designs, various quality assessment tools available through the National Institute of Health were applied.[14] The tools assess risk of bias through criterion specific to each study design, before providing an overall quality rating of good, fair or poor. Randomised studies were assessed using the Cochrane risk-of-bias tool for randomised trials (RoB2).[15] As per the review protocol, all studies were included irrespective of their risk of bias rating. Using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, we rated the overall quality of evidence for each outcome as high, moderate, low or very low.[16]

Statistical analysis

All identified studies were included in the narrative summary with summary tables for characteristics. For the primary outcomes, numbers of individuals meeting each outcome on the adapted Ordinal Scale were pooled using rank-based Wilcoxon-Mann-Whitney tests with ties split evenly between positive and negative outcomes, providing a generalised OR (GenOR) with 95% CIs. The GenOR provides a measure of the likelihood that the intervention leads to a better rather than worse outcome when compared with a randomly chosen control.[17] Mean hospital duration and SD were extracted or were estimated from median and range/IQR using the Box-Cox method.[18] Mean difference in hospital stay was calculated where a control arm was reported. Where available, adjusted HRs and unadjusted mortality data were extracted for quantitative synthesis. Where data were not reported in a tabular format, values were extracted from plotted data using a digital plot analyser.[19]

Where sufficient studies were identified for a specific immunomodulator, findings were assessed using random effects meta-analysis and presented as forest plots. Meta-analyses were grouped by retrospective and prospective design and presented on the same plots with no overall estimate. The I^2 statistic was used to evaluate statistical heterogeneity. Although sample sizes were limited, we used pseudo R^2 from meta-regression to explore variability in heterogeneity owing to study design (single centre or multicentre), non-peer-reviewed manuscripts, concomitant use of steroids, route of drug administration (intravenous or

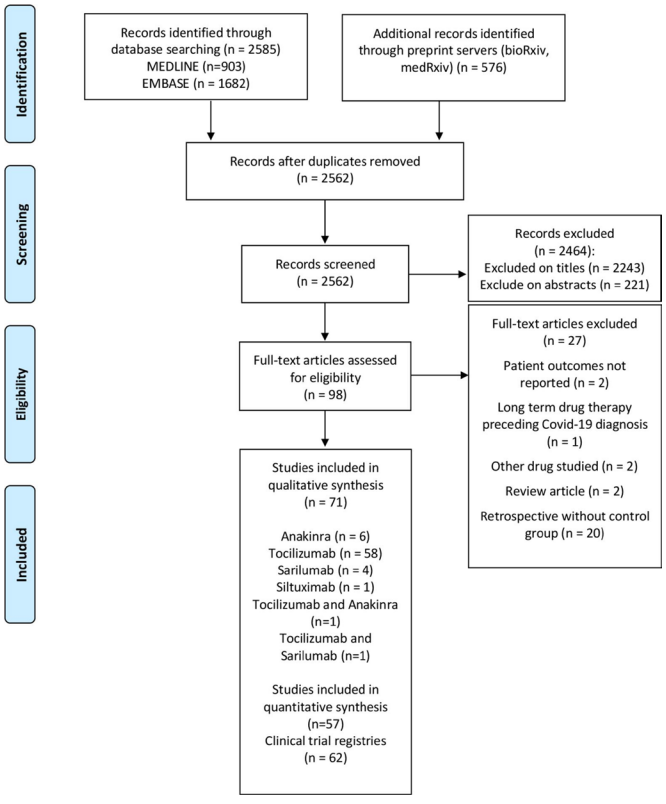

Figure 1 Flow diagram illustrates systematic search and screening strategy, including numbers meeting eligibility criteria and numbers excluded. Last search carried out on 7 January, 2021.

Table 1 Included studies with study characteristics and sample size for treatment (Tx) and control group (control) shown

Author, year	Drug	N, Tx/control	Study country	Centre	Study design	Author, year	Drug	N, Tx/control	Study country	Centre	Study design	Author, year	Drug	N, Tx/ control	Study country	Centre	Study design
Balkhair *et al*, 2020[26]	A	45/24	Oman	Single centre	Prospective with control	Roumier *et al*, 2020[32]	T	49/47	France	Single centre	Prospective with control	Kimmig *et al*, 2020[33]	T	54/57	USA	Single centre	Retrospective
Huet *et al*, 2020[29]	A	52/44	France	Single centre	Prospective with control	Salama *et al*, 2020[22]	T	249/ 128	USA	Multicentre	Double-blind RCT	Klopfenstein *et al*, 2020[34]	T	20/25	France	Single centre	Retrospective
Kooistra *et al*, 2020[35]	A	21/39	Netherlands	Multicentre	Prospective with control	Salvarani *et al*, 2020[36]	T	60/63	Italy	Multicentre	Open-label RCT	Lewis *et al*, 2020[37]	T	497/497	USA	Multicentre	Retrospective
*Kyriazopoulou *et al*, 2020[28]	A	130/130	Greece	Multicentre	Prospective	*Sanchez-Montalva *et al*, 2020[38]	T	82/0	Spain	Single centre	Prospective	Martinez-Sanz *et al*, 2020[39]	T	260/969	Spain	Multicentre	Retrospective
Cauchois *et al*, 2020[24]	A	12/10	France	Multicentre	Retrospective	Sciascia *et al*, 2020[40]	T	63/0	Italy	Multicentre	Prospective	Narain *et al*, 2020[27]	T	73/3076	USA	Multicentre	Retrospective
Cavalli *et al*, 2020[25]	A	29/16	Italy	Single centre	Retrospective	Stone *et al*, 2020[21]	T	161/ 82	USA	Multicentre	Double-blind RCT	Nasa *et al*, 2020[41]	T	22/63	India	Multicentre	Retrospective
Narain *et al*, 2020[27]	A	57/3076	USA	Multicentre	Retrospective	Strohbehn *et al*, 2020[42]	T	32/41	USA	Single centre	Phase II open label	Patel *et al*, 2020[43]	T	60/1505	USA	Single centre	Retrospective
Benucci *et al*, 2020[44]	Sa	8/0	Italy	Single centre	Prospective	Toniati *et al*, 2020[45]	T	100/0	Italy	Single centre	Prospective	*Petrak *et al*, 2020[46]	T	81/37	USA	Multicentre	Retrospective
Della-Torre *et al*, 2020[30]	Sa	28/28	Italy	Single centre	Prospective with control	Biran *et al*, 2020[47]	T	210/ 420	USA	Multicentre	Retrospective	Pettit *et al*, 2020[48]	T	42/41	USA	Single centre	Retrospective
*Gordon *et al*, 2021[20]	Sa	45/397	UK	Multicentre	Adaptive RCT	Canziani *et al*, 2020[49]	T	64/64	Italy	Multicentre	Retrospective	Potere *et al*, 2020[50]	T	74/74	Italy	Single centre	Retrospective
Gremese *et al*, 2020[51]	Sa	53/0	Italy	Single centre	Prospective	Capra *et al*, 2020[52]	T	62/23	Italy	Single centre	Retrospective	*Ramaswamy *et al*, 2020[53]	T	10/10	USA	Multicentre	Retrospective
Sinha *et al*, 2020[54]	Sa	255/0	USA	Single centre	Prospective	Chilimuri *et al*, 2020[55]	T	83/ 685	USA	Single centre	Retrospective	Rodríguez-Baño *et al*, 2020[56]	T	21/65	Spain	Multicentre	Retrospective
*Gritti *et al*, 2020[31]	Si	30/30	Italy	Single centre	Prospective with control	De Rossi *et al*, 2020[57]	T	90/68	Italy	Single centre	Retrospective	Rojas-Marte *et al*, 2020[58]	T	88/344	USA	Single centre	Retrospective
Albertini *et al*, 2020[59]	T	22/22	France	Single centre	Prospective with control	Eimer *et al*, 2020[60]	T	22/22	Sweden	Single centre	Retrospective	Roomi *et al*, 2020[61]	T	96/97	USA	Single centre	Retrospective
Antony *et al*, 2020[62]	T	80/0	USA	Multicentre	Prospective	Fisher *et al*, 2020[63]	T	45/70	USA	Single centre	Retrospective	Rosas *et al*, 2020[64]	T	20/17	Spain	Single centre	Retrospective
Campins *et al*, 2020[65]	T	58/0	Spain	Single centre	Prospective	Galván-Román *et al*, 2020[66]	T	58/88	Spain	Single centre	Retrospective	Rossi *et al*, 2020[67]	T	84/84	France	Single centre	Retrospective
*Carvalho *et al*, 2020[68]	T	29/24	Brazil	Single centre	Prospective with control	*Moreno Garcia *et al*, 2020[69]	T	77/94	Spain	Single centre	Retrospective	Rossotti *et al*, 2020[70]	T	74/148	Italy	Single centre	Retrospective
Dastan *et al*, 2020[71]	T	42/0	Iran	Single centre	Prospective	Gokhale *et al*, 2020[72]	T	70/91	India	Single centre	Retrospective	Ruiz-Antorán *et al*, 2020[73]	T	268/238	Spain	Multicentre	Retrospective
*Gordon *et al*, 2021[20]	T	350/397	UK	Multicentre	Adaptive RCT	Guaraldi *et al*, 2020[74]	T	179/ 365	Italy	Multicentre	Retrospective	Somers *et al*, 2020[75]	T	78/76	USA	Single centre	Retrospective
Hermine *et al*, 2020[23]	T	63/67	France	Multicentre	Open-label RCT	Guisado-Vasco *et al*, 2020[76]	T	132/ 475	Spain	Single centre	Retrospective	Tian *et al*, 2020[77]	T	65/130	China	Multicentre	Retrospective
Malekzadeh *et al*, 2020[78]	T	126/0	Iran	Multicentre	Prospective	Gupta *et al*, 2020[79]	T	433/ 3492	USA	Multicentre	Retrospective	Tsai *et al*, 2020[80]	T	66/66	USA	Single centre	Retrospective
Mikulska *et al*, 2020[81]	T	29/66	Italy	Single centre	Prospective with control	Hill *et al*, 2020[82]	T	43/45	USA	Single centre	Retrospective	*Wadud *et al*, 2020[83]	T	84/84	USA	Single centre	Retrospective
Morena *et al*, 2020[84]	T	51/0	Italy	Single centre	Prospective	Holt *et al*, 2020[85]	T	24/30	USA	Single centre	Retrospective	Zheng *et al*, 2020[86]	T	92/89	China	Single centre	Retrospective

Continued

Table 1 Continued

Author, year	Drug	N, Tx/control	Study country	Centre	Study design	Author, year	Drug	N, Tx/control	Study country	Centre	Study design	Author, year	Drug	N, Tx/ control	Study country	Centre	Study design
Perrone *et al*, 2020[87]	T	708/481	Italy	Multicentre	Single-arm open label and validation	Ip *et al*, 2020[88]	T	134/413	USA	Multicentre	Retrospective						
*Rosas *et al*, 2020[89]	T	294/144	USA	Multicentre	Double-blind RCT	Kewan *et al*, 2020[90]	T	28/23	USA	Single centre	Retrospective						

*Non-peer-reviewed preprint study.
A, anakinra; RCT, randomised clinical trial; Sa, sarilumab; Si, siltuximab; T, tocilizumab.

subcutaneous) and day outcome measured. Publication bias was assessed using funnel plot analysis and Egger's test. Prospective studies without a control arm were excluded from meta-analysis and presented either in the narrative summary or in tables. All analyses were performed using Stata V.16 (StataCorp, College Station, Texas, USA).

RESULTS

Search of the electronic databases (MEDLINE and EMBASE) on 7 January 2021 yielded a total of 2585 studies, with further 576 studies identified through preprint servers. Following removal of duplicates, screening and full-text review, 71 articles published worldwide were shortlisted for inclusion (anakinra, n=6; tocilizumab, n=58; anakinra and tocilizumab, n=1; sarilumab and tocilizumab, n=1; sarilumab, n=4; siltuximab, n=1) (figure 1). Sixty-two studies were published in peer-reviewed journals, with the remaining nine identified through preprint servers. All studies were performed in patients with COVID-19, with no suitable studies identified for SARS or MERS. Overall, 29 studies were prospective in design, with 17 studies including a control group for comparison, of which 6 were randomised studies. The remaining 42 studies were retrospective studies with control arms. Included studies provided a total of 22 058 patients, of which 7328 (33%) received one of the therapies under review alongside standard of care (SOC) and 14 730 (67%) received SOC alone. Individual study characteristics for the published studies are presented in tables 1 and 2 and online supplemental tables S1 and S2.

Risk of bias assessment of the retrieved studies identified multiple limitations and highlighted a number of biases (figure 2 and online supplemental table S3). The majority of included studies defined the study population specifically with clear inclusion/exclusion criteria. Where applicable, control participants were selected from the same population. However, many studies provided insufficient detail of the interventions and outcomes being studied or reporting was inconsistent, with key design, and outcome details omitted. Statistical analysis was variably reported, with few studies providing a sample size justification. In nearly all studies, patients were on concomitant therapies, limiting the ability to discern whether a specific intervention was related to the outcome. Following a formal risk of bias assessment, 23 (32%) studies were rated as good, 37 (52%) fair and 11 (15%) poor. Publication bias, assessed by observation of funnel plots and Egger's test, was not present for any of the outcomes assessed (online supplemental figure S2).

Tocilizumab

Overall, 12 prospective studies with a control arm, eight prospective studies without a control arm, and 40 retrospective studies examining the clinical impact of tocilizumab in COVID-19 were identified. Among the prospective studies there were six randomised clinical trials (RCTs). In total, the studies reported outcomes from 20 972 patients, of whom 6563 (31%) were given tocilizumab. Criteria for eligible participants varied across the studies, with many specifying respiratory failure with laboratory evidence of hyperinflammation as a prerequisite. The dose of tocilizumab was not entirely consistent with intravenous 8 mg/kg or 400 mg the most commonly studied route and dose.

Ordinal Scale

A total of 12 studies provided outcomes on an adapted 4-point scale for 1782 patients including cases and controls (online supplemental table S4). The median time for reporting outcomes

Table 2 Treatment-related adverse events

Author, year	Therapy	Adverse effects
Balkhair *et al*, 2020[26]	Anakinra	Treatment: infection (11%), ALT rise (14%). Control: infection (18%), ALT rise (9%)
Huet *et al*, 2020[29]	Anakinra	Treatment: ALT rise (13%). Control: 9% in anakinra
Kooistra *et al*, 2020[35]	Anakinra	Treatment: secondary infection (33%). Control: secondary infection (23%)
*Kyriazopoulou *et al*, 2020[28]	Anakinra	Increased leucopenia in treatment group versus controls (8.5% vs 2.3%; p=0.05)
Cauchois *et al*, 2020[24]	Anakinra	N/R
Cavalli *et al*, 2020[25]	Anakinra	Treatment: *Staphylococcus* epidermis (14%), deranged liver enzymes (10%). Control: bacteraemia (13%), deranged liver enzymes (31%)
Narain *et al*, 2020[27]	Anakinra	N/R
Benucci *et al*, 2020[44]	Sarilumab	Nil
Della-Torre *et al*, 2020[30]	Sarilumab	Treatment: infections (21%), neutropenia (14%), liver enzyme increase (14%), thromboembolism (7%). Control: infections (18%), thromboembolism (7%)
*Gordon *et al*, 2021[20]	Sarilumab	No serious event in sarilumab group and 11 events in control
Gremese *et al*, 2020[51]	Sarilumab	Neutropenia (15%), elevated liver enzymes (11%)
Sinha *et al*, 2020[54]	Sarilumab or tocilizumab	Bacterial infection (13%)
*Gritti *et al*, 2020[31]	Siltuximab	Nil
Albertini *et al*, 2020[59]	Tocilizumab	Elevated liver enzymes (64%)
Antony *et al*, 2020[62]	Tocilizumab	N/R
Campins *et al*, 2020[65]	Tocilizumab	Nil
*Carvalho *et al*, 2020[68]	Tocilizumab	Nil
Chilimuri *et al*, 2020[55]	Tocilizumab	N/R
Dastan *et al*, 2020[71]	Tocilizumab	Transient diplopia (4.8%), Bell's palsy (2.4%)
*Gordon *et al*, 2021[20]	Tocilizumab	9 serious adverse events in tocilizumab group and 11 events in control
Hermine *et al*, 2020[23]	Tocilizumab	Treatment: serious adverse events occurred in 20 (32%). Control: 29 (43%) (p=0.21)
Lewis *et al*, 2020[37]	Tocilizumab	Increased infection rate in treatment group (aOR 4.18; 95% CI 2.72 to 6.52)
Malekzadeh *et al*, 2020[78]	Tocilizumab	Nil
Mikulska *et al*, 2020[81]	Tocilizumab	N/R
Morena *et al*, 2020[84]	Tocilizumab	Elevated liver enzymes (29%), thrombocytopenia (14%), neutropenia (6%), infections (24%)
Nasa *et al*, 2020[41]	Tocilizumab	Two patients (9.1%) developed deranged LFTs and two patients (9.1%) developed secondary sepsis
Perrone *et al*, 2020[87]	Tocilizumab	Allergic reactions (0.4%), deranged liver enzymes (10.5%)
*Petrak *et al*, 2020[46]	Tocilizumab	N/R
*Rosas *et al*, 2020[86]	Tocilizumab	66 serious infections (21%) were reported in the treatment arm and 49 (25.9%) in the placebo arm. Adverse events similar in both arms
Roumier *et al*, 2020[32]	Tocilizumab	Treatment: higher rates of neutropenia (35% vs 0%, p<0.001). Control: trend towards increased bacterial infections (22% vs 38%, p=0.089; including ventilator-acquired pneumonia: 8% vs 26%, p=0.022) and shorter time to infection (mean 18 vs 10 days, p=0.029)
Salama *et al*, 2020[22]	Tocilizumab	Serious adverse events occurred in 38 of 250 patients (15.2%) in the tocilizumab group and 25 of 127 patients (19.7%) in the placebo group
Salvarani *et al*, 2020[36]	Tocilizumab	Nil
*Sanchez-Montalva *et al*, 2020[38]	Tocilizumab	Nil
Sciascia *et al*, 2020[40]	Tocilizumab	Nil
Stone *et al*, 2020[21]	Tocilizumab	Neutropenia developed in 22 patients in the treatment group, as compared with only 1 patient in the placebo group (p=0.002), but serious infections occurred in fewer patients in the tocilizumab group (13 (8.1%)vs 14 (17.3%); p=0.03)
Strohbehn *et al*, 2020[42]	Tocilizumab	Treatment: bacterial infections (15.6%). Control: not reported
Toniati *et al*, 2020[45]	Tocilizumab	Septic shock (2%), gastrointestinal perforation (1%)
Biran *et al*, 2020[47]	Tocilizumab	Treatment: secondary bacterial infection in 17%. Control: secondary bacterial infection in 13%
Canziani *et al*, 2020[49]	Tocilizumab	HR 0.71 (95% CI 0.38 to 1.32) for infection, HR 0.89 (95% CI 0.39 to 2.06) for thrombosis, HR 1.17 (95% CI 0.47 to 2.92) for bleeding
Capra *et al*, 2020[52]	Tocilizumab	Nil
De Rossi *et al*, 2020[57]	Tocilizumab	Significant rise (from 44.3±28.3 to 103±141.3) in ALT in patients taking intravenous dose
Eimer *et al*, 2020[60]	Tocilizumab	Blood stream infection: 4 (18%) in treatment group versus 6 (27%) in control
Fisher *et al*, 2020[63]	Tocilizumab	No increased risk of secondary infection (OR 1.17; 95% CI 0.51 to 2.71)
Galván-Román *et al*, 2020[66]	Tocilizumab	N/R
*Moreno Garcia *et al*, 2020[69]	Tocilizumab	N/R
Gokhale *et al*,2020[72]	Tocilizumab	N/R
Guaraldi *et al*, 2020[74]	Tocilizumab	13% treated diagnosed with new infections versus 4% in control (p<0.0001)
Guisado-Vasco *et al*, 2020[76]	Tocilizumab	N/R
Gupta *et al*, 2020[79]	Tocilizumab	Treated and control patients experienced the following adverse events: secondary infection (140 (32.3%)vs 1085 (31.1%)), AST or ALT level elevation of more than 250 U/L (72 (16.6%)vs 452 (12.9%))
Hill *et al*, 2020[82]	Tocilizumab	In treatment group compared with control group, there was increased sepsis (21%vs16%), ALT rise (9% vs 4%) and thrombocytopenia (12% vs 4%)

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Table 2 Continued

Author, year	Therapy	Adverse effects
Holt *et al*, 2020[85]	Tocilizumab	N/R
Ip *et al*, 2020[88]	Tocilizumab	N/R
Kewan *et al*, 2020[90]	Tocilizumab	Similar rates of hospital-acquired infections occurred in both cohorts (18% in treatment and 22% in control)
Kimmig *et al*, 2020[33]	Tocilizumab	Treatment associated with increased secondary bacterial (aOR 2.76; 95% CI 1.11 to 7.2) and fungal (5.6% vs 0%, p=0.112) infections
Klopfenstein *et al*, 2020[34]	Tocilizumab	N/R
Martinez-Sanz *et al*, 2020[39]	Tocilizumab	N/R
Narain *et al*, 2020[27]	Tocilizumab	N/R
Patel *et al*, 2020[43]	Tocilizumab	N/R
Pettit *et al*, 2020[48]	Tocilizumab	Overall infection rate was similar (16.2% treatment vs 17.5% control), but late onset infections occurred in more treated patients (23% vs 8%; p=0.013). In treated, 26% experienced an increase to >5 times upper limit normal of LFTs
Potere *et al*, 2020[50]	Tocilizumab	Nil
*Ramaswamy *et al*, 2020[53]	Tocilizumab	N/R
Rodríguez-Baño *et al*, 2020[56]	Tocilizumab	Secondary bacterial infection similar in both groups (treated 12.5% vs 10.3% control; p=0.57)
Rojas-Marte *et al*, 2020[58]	Tocilizumab	Bacteraemia was more common in the control group (24% vs 13%, p=0.43), while fungemia was similar for both (3% vs 4%, p=0.72)
Roomi *et al*, 2020[61]	Tocilizumab	N/R
Rosas *et al*, 2020[64]	Tocilizumab	Nil
Rossi *et al*, 2020[67]	Tocilizumab	N/R
Rossotti *et al*, 2020[70]	Tocilizumab	Infectious complication in 32.4%
Ruiz-Antorán *et al*, 2020[73]	Tocilizumab	32.6% in treated versus 30.3% in control had increase in liver enzymes. Bacteraemia in one patient (0.4%)
Somers *et al*, 2020[75]	Tocilizumab	Higher rate of superinfection in treated group (54% vs 26%; p<0.001)
Tian *et al*, 2020[77]	Tocilizumab	Deranged LFTs in 14% of tocilizumab and 14% of control group
Tsai *et al*, 2020[80]	Tocilizumab	N/R
*Wadud *et al*, 2020[83]	Tocilizumab	N/R
Zheng *et al*, 2020[86]	Tocilizumab	N/R

Adverse events for drug under study reported. Adverse events for control population reported where applicable.
*Non-peer-reviewed preprint study.
ALT, alanine transaminase; aOR, adjusted odds ratio; AST, aspartate transaminase; LFTs, liver function tests; N/R, not reported.

after treatment was 14 days (IQR 14–28). The recently available REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) adaptive RCT interim analysis reported a signal that tocilizumab was associated with clinical improvement at day 14 (adjusted OR (aOR) 1.83, 95% CI 1.40 to 2.41),[20] while in a separate RCT, outcomes on an ordinal severity scale did not differ between the treatment groups (HR 1.06, 95% CI 0.80 to 1.41).[21] Distinctions in statistical methodology and clinical endpoints precluded inclusion of this RCT in the specified meta-analysis. Tocilizumab was not associated with better outcomes on the Ordinal Scale in meta-analysis of the remaining prospective studies, including three RCTs (GenOR 1.09, 95% CI 0.99 to 1.19, I^2=84.3%) (figure 3). Variability in reported concomitant steroid administration had a significant contribution on the substantial heterogeneity observed (online supplemental table S5). Tocilizumab was associated with better outcomes in meta-analysis of retrospective studies, indicating a 34% greater chance of less-severe outcomes on the adapted Ordinal Scale when compared with control (GenOR 1.34, 95% CI 1.10 to 1.64, I^2=98%). However, these results should be interpreted with caution as there was severe heterogeneity which could not be explained by variability in the factors assessed.

Duration of hospitalisation

Two RCTs and nine retrospective studies reported the duration of hospitalisation for a total of 1553 survivors who received tocilizumab (figure 4). Individual RCTs comparing the duration of hospitalisation with controls identified associations of tocilizumab with a reduced hospital stay (−0.34 days, 95% CI −0.55 to −0.12)[22] and earlier hospital discharge (aHR 1.41, 95% CI 1.18 to 1.70).[20] Retrospective studies reporting the duration of hospitalisation were combined to give an overall summary estimate (20.98 days, 95% CI 16.19 to 25.78, I^2=97.1%), which was greater than the duration reported by RCTs (14.55 days, 95% CI −0.37 to 29.67, I^2=99.9%). Compared with 943 patients in retrospective studies who received SOC only, tocilizumab was not associated with a difference in the mean duration of hospital stay (0.36 days, 95% CI −0.07 to 0.80, I^2=93.8%), with variability in route of administration (intravenous or subcutaneous) associated with the severe heterogeneity in this estimate (R^2=81.64%, p<0.001).

Overall mortality

Twenty-two studies totalling 13 702 patients reported adjusted HRs for overall mortality, at a follow-up time censored at a median of 28 days (IQR 14–30). Among the studies, two were RCTs and neither reported a difference between tocilizumab and control for mortality.[21 23] When prospective tocilizumab studies were pooled, there was an emerging survival benefit, but the estimate was inconclusive (HR 0.70, 95% CI 0.44 to 1.10, I^2=0%) (figure 5). In the remaining retrospective studies, tocilizumab was associated with a 48% lower risk of adjusted mortality with substantial heterogeneity (HR 0.52, 95% CI 0.41 to 0.66, I^2=76.6%). Meta-regression identified the day of outcome measurement as a significant source of heterogeneity (R^2=99.99, p=0.08).

Risk ratios (RRs) were calculated from 42 studies, including 6 RCTs, reporting unadjusted mortality data for 15 085 patients at a median follow-up of 24 days (IQR 14–28) (figure 6).

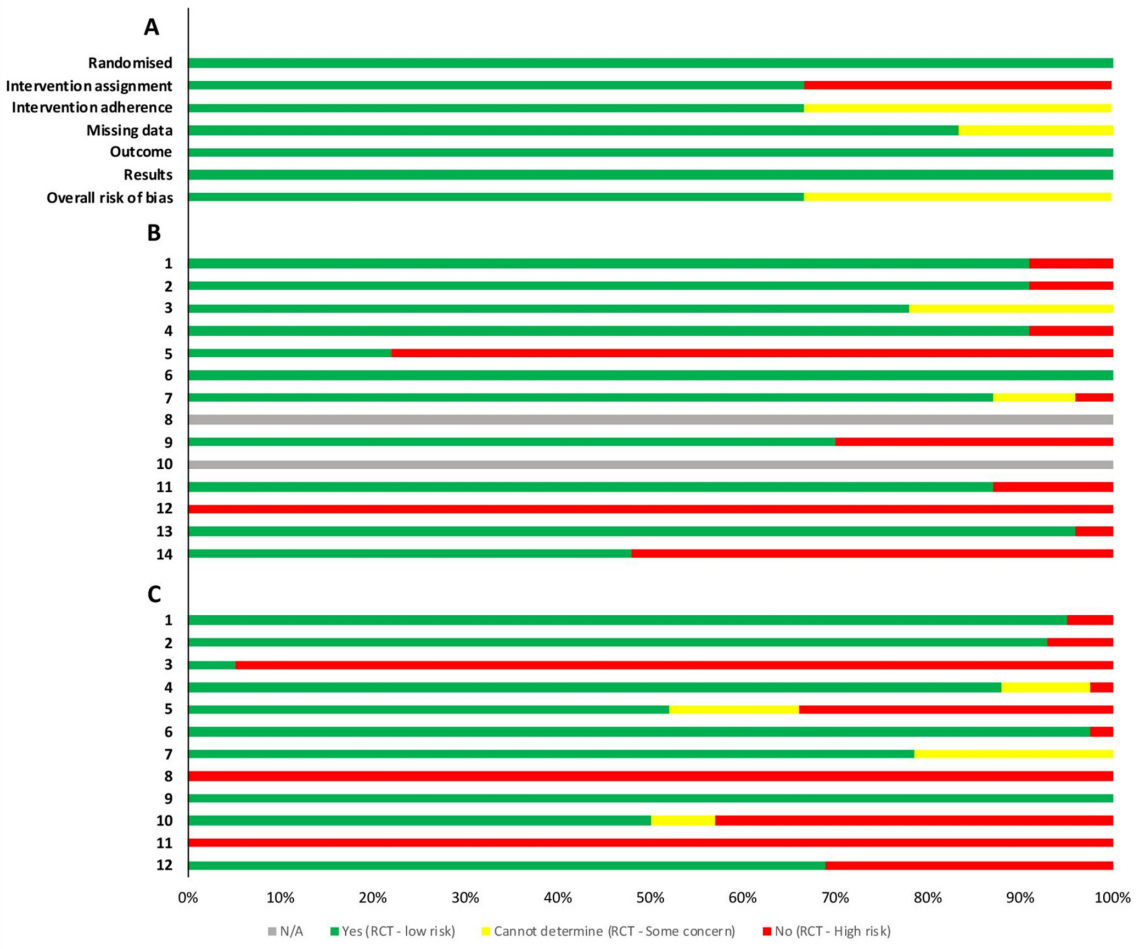

Figure 2 - Summary of risk of bias assessment. (A) Randomised clinical trials assessed using Cochrane risk of bias 2 tool (n=6). Risk of bias was assessed in six categories and scored as either low risk of bias, some concern, or high risk of bias, before an overall risk of bias was given to each study. (B) Non-randomised prospective studies (n=23). Questions numbered in the first column. 1. Was the research question or objective in this paper clearly stated? 2. Was the study population clearly specified and defined? 3. Was the participation rate of eligible persons at least 50%? 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? 5. Was a sample size justification, power description, or variance and effect estimates provided? 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 10. Was the exposure(s) assessed more than once over time? 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 12. Were the outcome assessors blinded to the exposure status of participants? 13. Was loss to follow-up after baseline 20% or less? 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? (C) Summary of risk of bias assessment for retrospective studies (n=42). Questions numbered in first column. 1. Was the research question or objective in this paper clearly stated and appropriate? 2. Was the study population clearly specified and defined? 3. Did the authors include a sample size justification? 4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? 5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? 6. Were the cases clearly defined and differentiated from controls? 7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? 8. Was there use of concurrent controls? 9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? 10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? 11. Were the assessors of exposure/risk blinded to the case or control status of participants? 12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Tocilizumab was associated with a 17% lower unadjusted risk of mortality compared with the control arm in prospective studies (RR 0.83, 95% CI 0.72 to 0.96, I^2=0.0%), which did not reach significance in RCTs alone (RR 0.85, 95% CI 0.71 to 1.01 I^2=0.0%) (online supplemental figure S3). Within retrospective studies, tocilizumab was associated with a 24% lower risk of

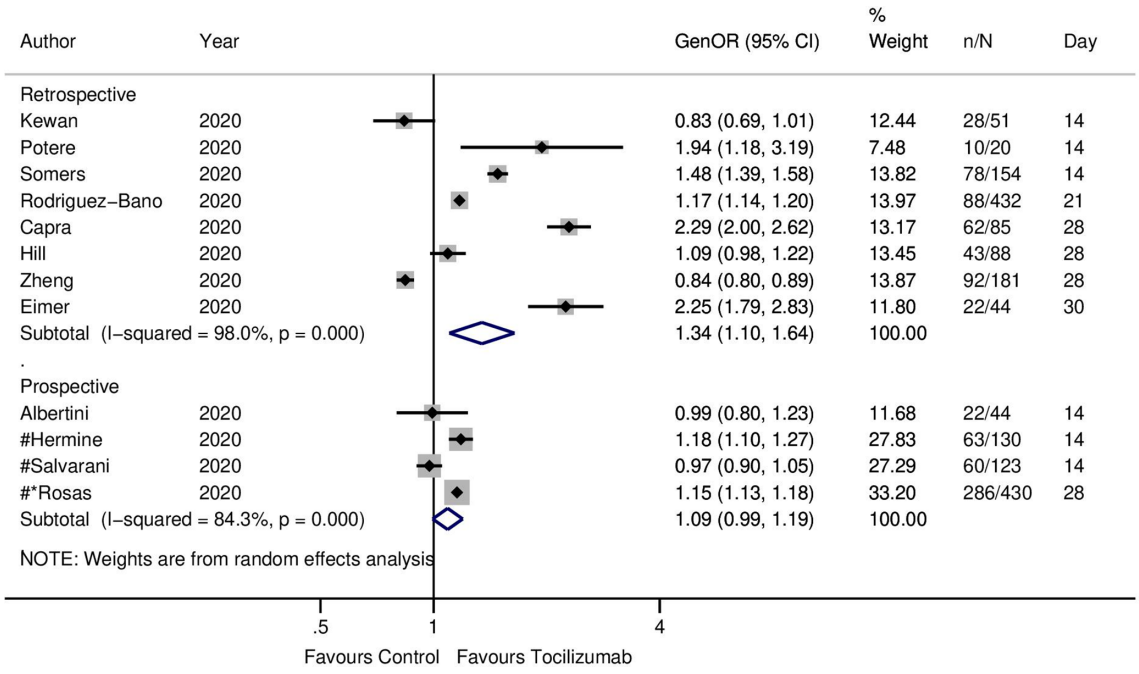

Figure 3 Tocilizumab generalised ORs for ordinal outcome forest plot. GenOR shown for each study with 95% CI and day at which ordinal outcome was recorded. Sample sizes given for patients receiving intervention (n) alongside total patients included (N) in the study. Summary estimates presented separately for prospective and retrospective studies. *Non-peer-reviewed preprint studies. #Randomised controlled trials. GenORs, generalised ORs.

mortality (RR 0.76, 95% CI 0.64 to 0.92, I^2=80.3%), although there was substantial heterogeneity which could not be explained by variability in the factors assessed. The combined case fatality (CFR) across all studies included in the meta-analysis was 21.2% (1118/5284) in the intervention arm and 31.1% (3049/9801) in the control arm. The CFR from single-arm prospective studies unable to be included in meta-analysis was 17.8% (113/634).

Other immunomodulators

Studies exploring outcomes in patients who received anakinra, sarilumab or siltuximab were not quantitatively synthesised for all outcomes, owing to differences in outcomes reported, study design and limited study numbers. Similar to studies in tocilizumab, participant criteria were inconsistent but typically included patients with respiratory failure and signs of hyperinflammation. Doses of therapeutic agents ranged from 200 to 600 mg daily for anakinra and 200–400 mg daily for sarilumab. In all studies, patients received concomitant medications including but not limited to antivirals, hydroxychloroquine and corticosteroids. Meta-analysis inclusive of all immunomodulatory agents without subanalysis is presented in online supplemental figures S4–S7.

Anakinra

Four prospective and three retrospective studies exploring outcomes in 346 patients who received anakinra and 3339 controls were retrieved. Three studies reported ordinal outcome data for both anakinra and control participants, although the outcome day varied. Anakinra was associated with improved clinical outcomes in two retrospective studies of 22 and 45 patients, respectively.[24 25] A similar association with improved clinical outcomes was reported on day 14 in a prospective study of 69 patients (GenOR 1.77, 95% CI 1.52 to 2.06).[26] Two studies reported adjusted HR for mortality with supportive results. A significant association was not observed in a retrospective study of 57 treated patients (aHR 0.79, 95% CI 0.44 to 1.42),[27] while an association was observed in a prospective study of 130 patients (aHR 0.49, 95% CI 0.26 to 0.91).[28] A significant unadjusted association was also observed in a further study of 52 patients treated with anakinra (HR 0.30, 95% CI 0.12 to 0.71).[29] RRs were calculated from four studies totalling 424 participants. In a retrospective study of 29 treated patients, anakinra improved survival (RR 0.24, 95% CI 0.07 to 0.79); associations were inconclusive when prospective studies were pooled (RR 0.70, 95% CI 0.31 to 1.58, I^2=32.8%) (online supplemental figure S8). No studies compared the duration of hospitalisation between recipients and non-recipients of anakinra.

Sarilumab

Five prospective studies exploring outcomes in 389 participants who received sarilumab were included. In the only RCT identified, sarilumab was associated with increased survival (aOR 2.01, 95% CI 1.18 to 4.71), reduced duration of hospitalisation (aHR 1.60, 95% CI 1.17 to 2.40) and improved ordinal outcomes at day 14 (aOR 1.86, 95% CI 1.22 to 2.91).[20] In a further non-randomised study of 28 participants,[30] sarilumab was not significantly associated with mortality (aHR 0.36, 95% CI 0.08 to 1.68) and comparable effects were observed among treated and non-treated patients with respect to ordinal outcomes (GenOR 1.07, 95% CI 0.90 to 1.27) and duration of hospitalisation (mean difference 0.02, 95% CI −0.51 to 0.54). The combined CFR across the five included studies was 11% (43/389) for sarilumab, while in the only study reporting control mortality data the CFR was 35.8% (142/397).

Siltuximab

A single prospective cohort study of siltuximab studying outcomes in 60 patients was identified.[31] Neither ordinal outcome data nor duration of hospitalisation were reported, but the adjusted risk of mortality was reported to be significantly

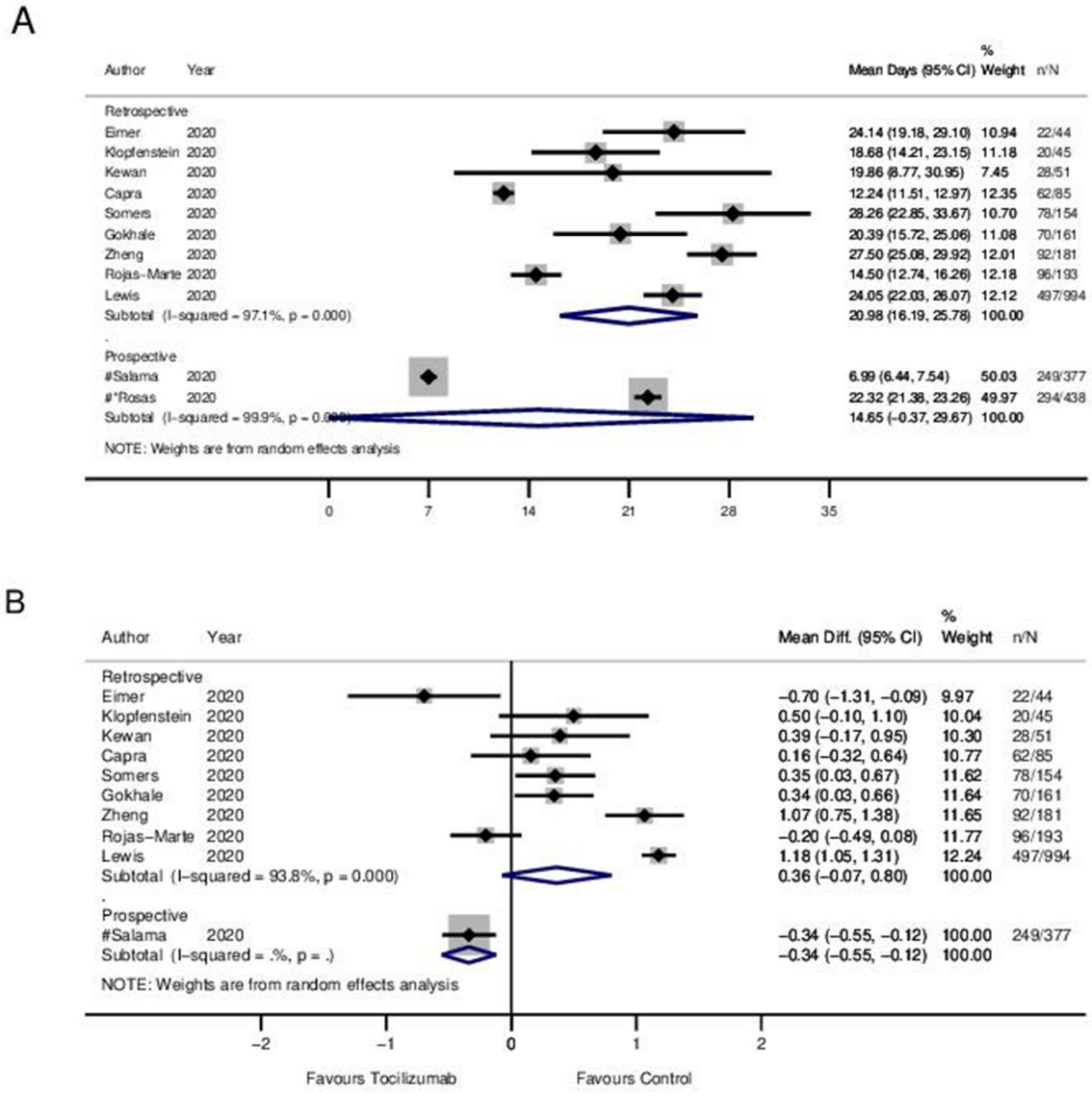

Figure 4 Tocilizumab duration of hospitalisation (days) forest plot. (A) Mean duration of hospital stay. (B) Mean difference compared with controls in duration of hospital stay. Effect sizes and associated 95% CIs presented for each study. Sample sizes given for patients receiving intervention (n) and total patients included in the study (N). Summary estimates presented separately for prospective and retrospective studies.

lower in patients who received siltuximab (aHR 0.46, 95% CI 0.22 to 0.97).

Treatment-related adverse events

Treatment-related adverse events were reported in most studies (70%) and typically included secondary bacterial infections and derangement of liver enzymes (table 2). In studies with a comparator arm exploring outcomes from patients who received anakinra or sarilumab, the frequency of treatment-related adverse events was similar in both treatment and comparator groups. Findings from studies reporting outcomes following tocilizumab administration were inconsistent. In five studies, tocilizumab recipients had an increased prevalence of secondary infections compared with controls. However, in 12 studies, tocilizumab was associated with a lower or similar rate of secondary infections compared with controls.

Clinical trials

Overall, 62 planned or in-process clinical trials (tocilizumab, 44; siltuximab, 4; sarilumab, 9; anakinra, 13) were identified through clinical registry searches, with some clinical trials exploring more than one immunomodulatory agent. Currently registered clinical trials and their estimated dates of completion are provided in online supplemental figure S9.

DISCUSSION

In this systematic review and meta-analysis, we summarised and evaluated the association between immunomodulatory agents and multiple outcomes in COVID-19. Although there was severe heterogeneity across tocilizumab studies exploring outcomes on an adapted 4-point Ordinal Scale, a beneficial effect of tocilizumab was suggested in retrospective studies compared with controls. Prospective studies followed a similar direction of association, though CIs were not conclusive. The certainty of the findings related to the adapted ordinal severity scale are assessed as moderate using GRADE (online supplemental table S6). The mean duration of hospitalisation was not altered by intervention, with low certainty of findings. Tocilizumab was associated with a survival benefit that was consistent across retrospective and prospective studies, with pooled analysis of unadjusted RRs demonstrating a 17% reduced risk of mortality in prospective

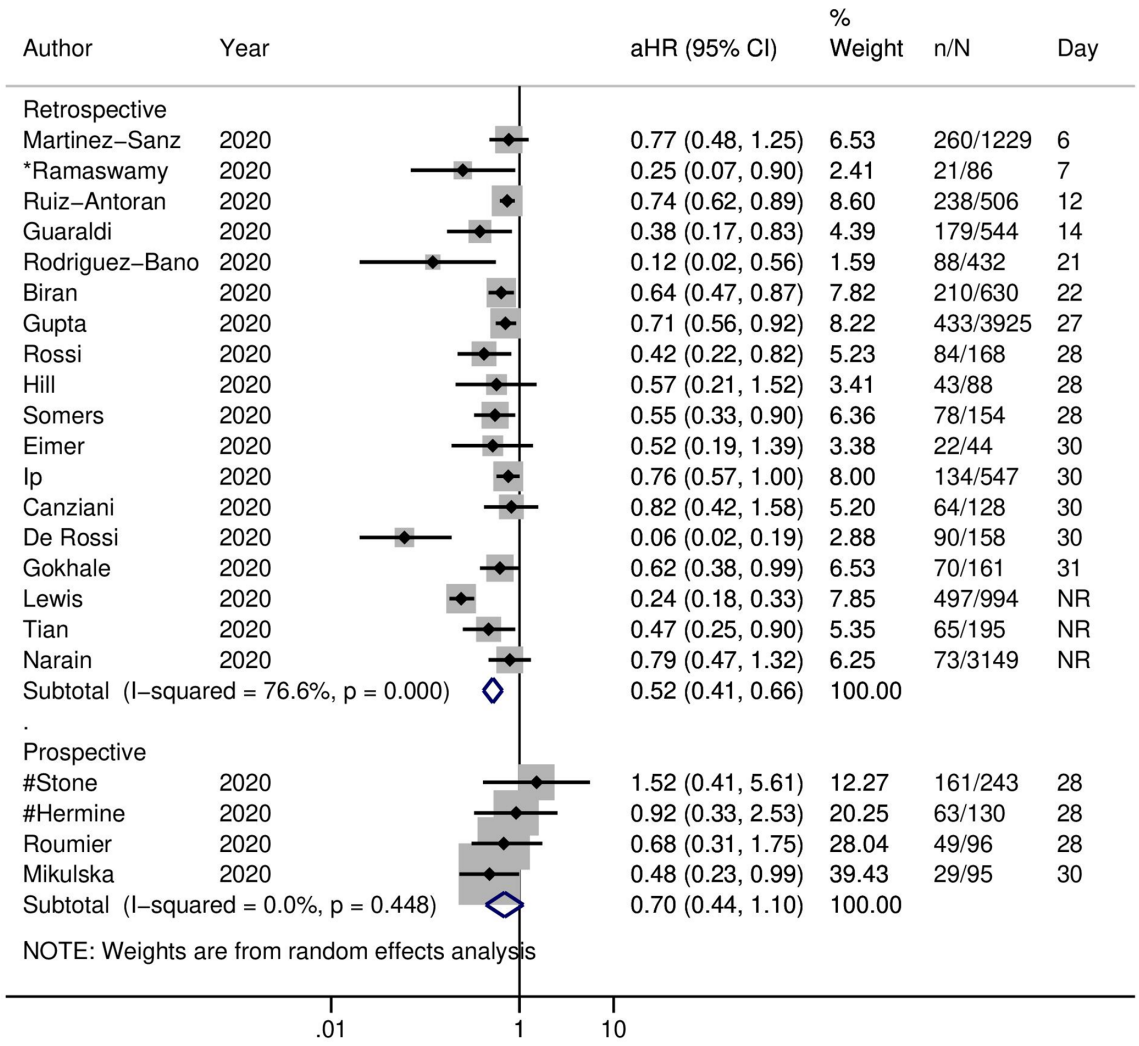

Figure 5 Tocilizumab adjusted HR for overall mortality forest plot. Adjusted HRs with associated 95% CI and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total patients included (N) in the study. Summary estimates presented separately for prospective and retrospective studies. *Non-peer-reviewed preprint studies. #Randomised controlled trials. aHR, adjusted HR; NR, not reported.

studies. We assess the certainty of our findings related to overall mortality as high.

Due to heterogeneity in study designs and reported outcomes, studies in patients receiving immunomodulatory agents other than tocilizumab were not quantitatively synthesised for all outcomes. In the only study reporting adjusted HRs, anakinra was associated with reduced mortality. However, pooled analysis of unadjusted ratios in non-randomised studies did not demonstrate a mortality benefit. A single sarilumab RCT demonstrated that intervention was associated with improved outcomes and reduced hospital stay. No randomised studies were identified for siltuximab. For all agents included in this review, the frequency of adverse events was similar in the treatment and control arms. Sixty-one registered clinical trials exploring immunomodulatory agents in COVID-19 were identified, of which some have been completed and published.

In this review, we highlight multiple limitations and considerable sources of interstudy heterogeneity. The majority of included studies were non-randomised cohorts of relatively modest size. Although most studies necessitated respiratory failure requiring at least basic respiratory support, participant criteria were not entirely consistent across the studies. The dosage and delivery of therapy varied across many of the non-randomised studies, and in nearly all studies patients were on concomitant medications such as antivirals, hydroxychloroquine and steroids with administration at the discretion of the treating physician, precluding causal associations of specific IL inhibitors with outcomes. Study outcomes were heterogeneous and a combination of clinical, laboratory and radiological outcomes was reported, rather than a single consistent endpoint. Furthermore, there was inconsistency in the duration of follow-up and timing of reported outcomes. Individual patient data (IPD) may have mitigated some of these limitations, but in a rapidly progressing area, seeking IPD was deemed to be unrealistic due to the associated delays. We also observed significant statistical heterogeneity as measured by I^2, and therefore the findings of our meta-analysis should be interpreted with caution. We were unable to explain all the residual heterogeneity using the factors we assessed, although concomitant steroid use, route of drug administration and the day the outcome was measured appeared to contribute within specific outcomes.

To maximise value and timeliness of our review of four specific immunomodulators, two primary endpoints and a number of secondary endpoints, we included both retrospective and preprint studies. Risk of bias was minimised by restricting analysis of non-prospective studies to those with a control group,

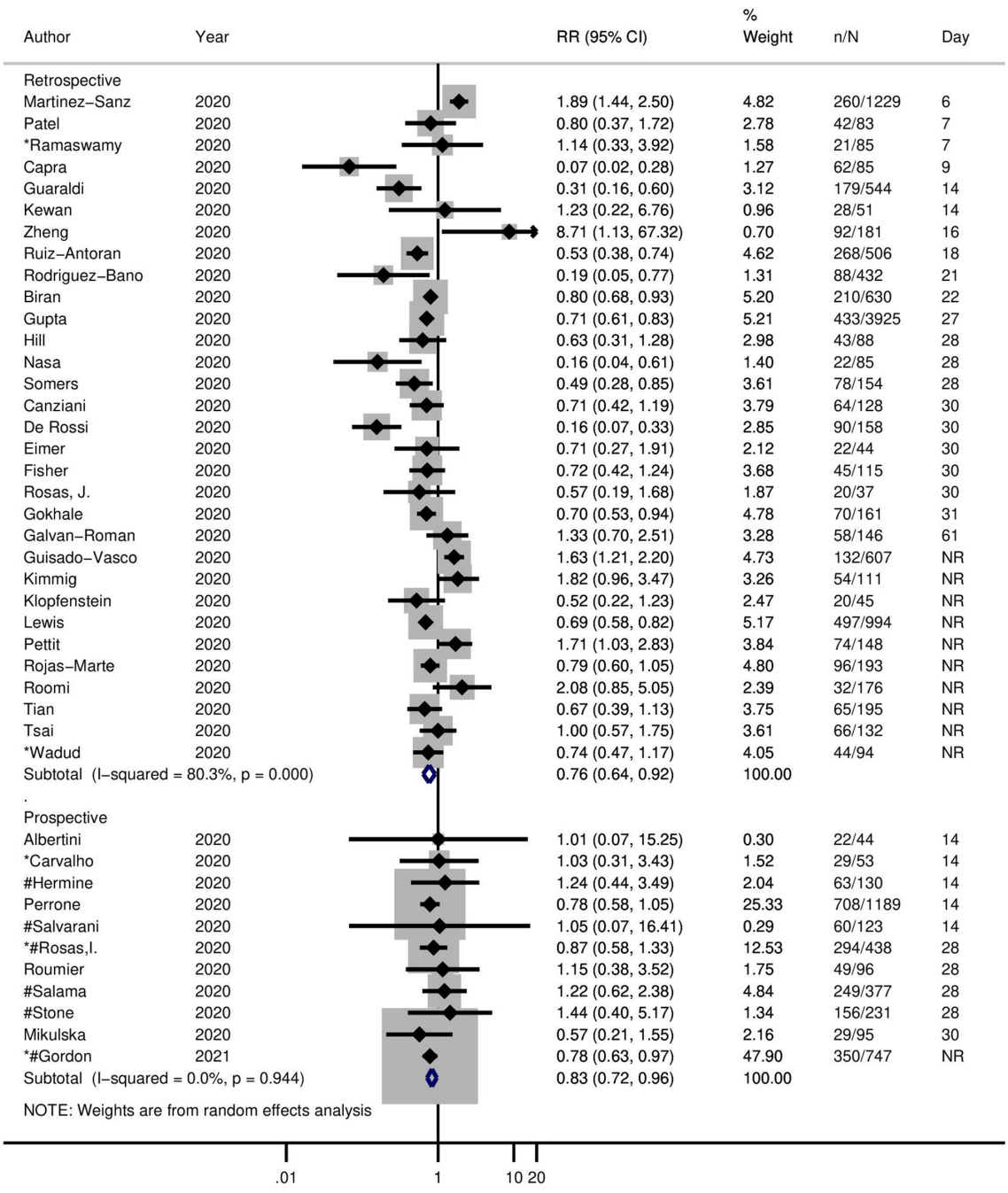

Figure 6 Tocilizumab mortality risk ratios (RRs) forest plot. RRs with associated 95% CI and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total patients included in the study (N). Summary estimates presented separately for prospective and retrospective studies. *Non-peer-reviewed preprint studies. #Randomised controlled trials. NR, not reported.

and caution is used to present summaries separately. We did not detect any significant publication bias in the reporting of effects. Where there was insufficient data for meta-analysis, summary outcomes were presented with qualitative synthesis to ensure the review was comprehensive. The data presented here represent findings from different countries, offering diversity in ethnic background. We were unable to identify suitable studies in SARS or MERS to comment on the generalisability of immunomodulators in other coronavirus outbreaks.

In conclusion, this systematic review provides the most up-to-date and complete evidence for a range of specific immunomodulatory therapies in the management of COVID-19. We have established that evidence for the efficacy of anakinra, siltuximab or sarilumab in COVID-19 is currently insufficient and adequately powered high-quality randomised clinical studies are urgently needed. We demonstrate through quantitative synthesis of retrospective studies that tocilizumab intervention was frequently associated with improved outcomes and reduced mortality. However, data were highly heterogeneous and must be interpreted with caution. Prospective studies demonstrated a 17% lower unadjusted risk of mortality with tocilizumab, with minimal heterogeneity and similar adjusted estimates. Further research should focus on identifying participant and disease characteristics where immunomodulatory therapy is likely to be of maximal effectiveness, while also exploring the relationship with baseline inflammatory biomarkers such as IL-6 and

C reactive protein. In summary, we demonstrate tocilizumab is associated with lower mortality in COVID-19 and other immunomodulatory therapies are worth exploring further.

Contributors FAK, IS and GJ conceived the study. FAK drafted the manuscript, performed the searches and collected the data. LF and SM verified the searches and extracted data. Analysis was performed by FAK and IS. All authors edited and approved the final version before submission.

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REFERENCES

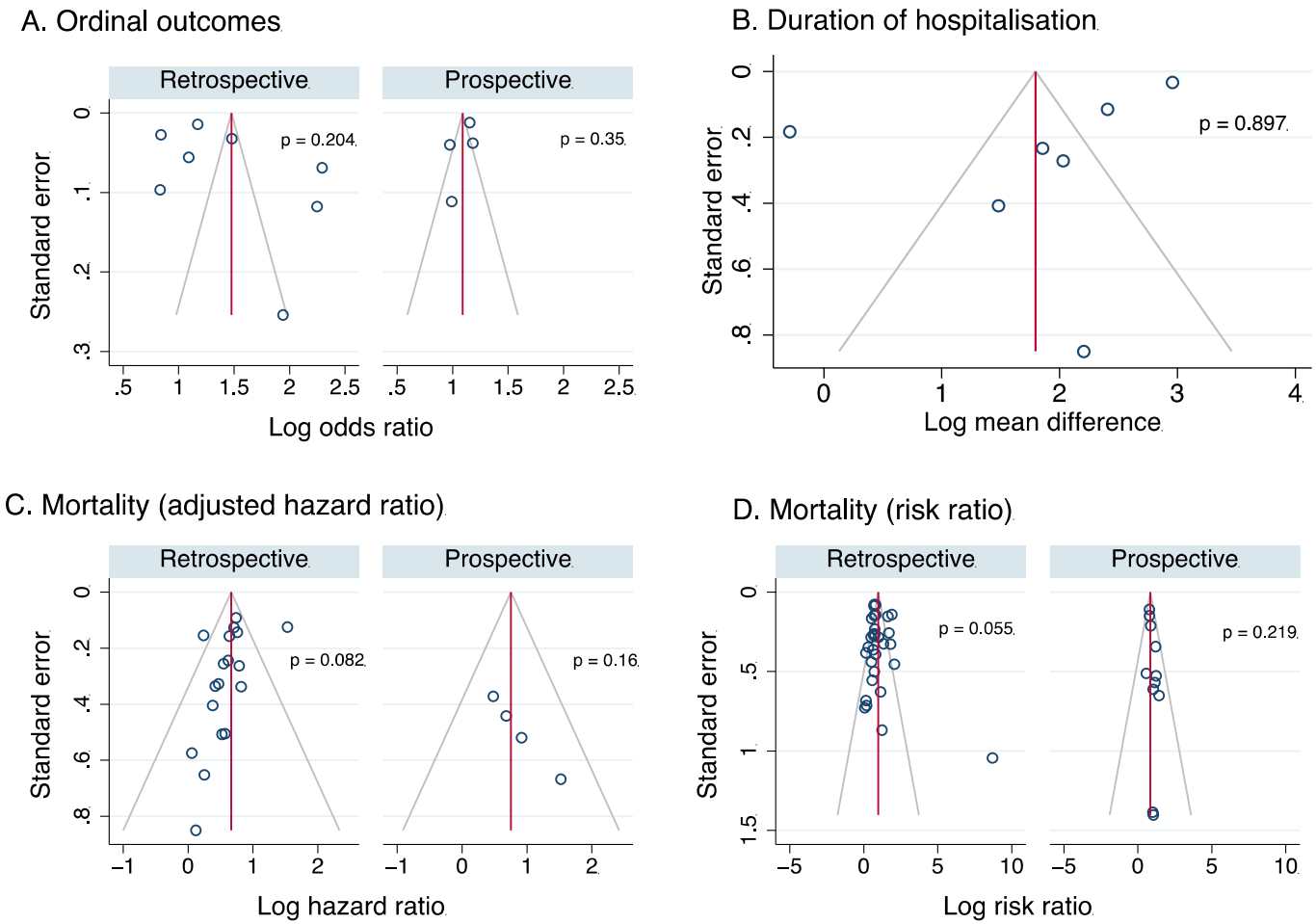
1 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020;395:497–506.
2 WHO Director-General's opening remarks at the media briefing on COVID-19, 2020. Available: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020 [Accessed 11 Mar 2020].
3 Johns Hopkins University (JHU). Johns Hopkins University of medicine COVID-19 dashboard by the center for systems science and engineering (CSSE). Available: https://coronavirusjhuedu/maphtml
4 Mehta P, McAuley DF, Brown M, *et al*. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* 2020;395:1033–4.
5 Qin C, Zhou L, Hu Z, *et al*. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020.
6 Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: a systematic review and meta-analysis. *medRxiv* 2020.
7 Lucas C, Wong P, Klein J, *et al*. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020;584:463–9.
8 Conti P, Ronconi G, Caraffa A, *et al*. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 2020;34:327–31.
9 Cheng ZJ, Shan J. 2019 novel coronavirus: where we are and what we know. *Infection* 2020;48:155–63.
10 Hui DS, I Azhar E, Madani TA, *et al*. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — the latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020;91:264–6.
11 Wong CK, Lam CWK, Wu AKL, *et al*. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 2004;136:95–103.
12 Mahallawi WH, Khabour OF, Zhang Q, *et al*. Mers-Cov infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine* 2018;104:8–13.
13 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
14 National Heart L. National Institute of health. Available: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
15 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;2:l4898.
16 Granholm A, Alhazzani W, Møller MH. Use of the grade approach in systematic reviews and guidelines. *Br J Anaesth* 2019;123:554–9.
17 Churilov L, Arnup S, Johns H, *et al*. An improved method for simple, assumption-free ordinal analysis of the modified Rankin scale using generalized odds ratios. *Int J Stroke* 2014;9:999–1005.
18 McGrath S, Zhao X, Steele R, *et al*. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat Methods Med Res* 2020;29:2520–37.
19 WebPlotDigitizer. Available: https://apps.automeris.io/wpd/
20 Gordon AC. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 - Preliminary report. *medRxiv* 2021.
21 Stone JH, Frigault MJ, Serling-Boyd NJ, *et al*. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med Overseas Ed* 2020;383:2333–44.
22 Salama C, Han J, Yau L. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *New England Journal of Medicine* 2020.
23 Hermine O, Mariette X, Tharaux P-L, *et al*. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Internal Medicine* 2020.
24 Cauchois R, Koubi M, Delarbre D, *et al*. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. *Proc Natl Acad Sci U S A* 2020;117:18951–3.
25 Cavalli G, De Luca G, Campochiaro C, *et al*. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *The Lancet Rheumatology* 2020;2:e325–31.
26 Balkhair A, Al-Zakwani I, Al Busaidi M, *et al*. Anakinra in hospitalized patients with severe COVID-19 pneumonia requiring oxygen therapy: results of a prospective, open-label, interventional study. *Int J Infect Dis* 2021;103:288–96.
27 Narain S, Stefanov DG, Chau AS, *et al*. Comparative survival analysis of immunomodulatory therapy for coronavirus disease 2019 cytokine storm. *Chest* 2020;17:17.
28 Kyriazopoulou E, Panagopoulos P, Metallidis S. Anakinra to prevent respiratory failure in COVID-19. *medRxiv* 2020.
29 Huet T, Beaussier H, Voisin O, *et al*. Anakinra for severe forms of COVID-19: a cohort study. *The Lancet Rheumatology* 2020;2:e393–400.
30 Della-Torre E, Campochiaro C, Cavalli G, *et al*. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. *Ann Rheum Dis* 2020;79:1277–85.
31 Gritti G, Raimondi F, Ripamonti D. Il-6 signalling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study. *medRxiv* 2020.
32 Roumier M, Paule R, Vallée A, *et al*. Tocilizumab for severe worsening COVID-19 pneumonia: a propensity score analysis. *J Clin Immunol* 2020;71:1–12.
33 Kimmig LM, Wu D, Gold M, *et al*. Il-6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. *Front Med* 2020;7:1.
34 Klopfenstein T, Zayet S, Lohse A, *et al*. Impact of tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort of 206 COVID-19 patients. *Int J Infect Dis* 2020;99:491–5.
35 Kooistra EJ, Waalders NJB, Grondman I, *et al*. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care* 2020;24:688.
36 Salvarani C, Dolci G, Massari M, *et al*. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia. *JAMA Intern Med* 2021;181:24.
37 Lewis TC, Adhikari S, Tatapudi V, *et al*. A Propensity-Matched cohort study of tocilizumab in patients with coronavirus disease 2019. *Crit Care Explor* 2020;2:e0283.
38 Sanchez-Montalva A, Selares-Nadal J, Espinosa-Pereiro J. Early outcomes of tocilizumab in adults hospitalized with severe COVID19. An initial report from the Vall dHebron COVID19 prospective cohort study. *medRxiv* 2020.
39 Martínez-Sanz J, Muriel A, Ron R, *et al*. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: a multicentre cohort study. *Clin Microbiol Infect* 2020;323. doi:10.1016/j.cmi.2020.09.021. [Epub ahead of print: 23 Sep 2020].
40 Sciascia S, Aprà F, Baffa A, *et al*. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol* 2020;38:529–32.
41 Nasa P, Singh A, Upadhyay S, *et al*. Tocilizumab use in COVID-19 Cytokine-release syndrome: retrospective study of two centers. *Indian J Crit Care Med* 2020;24:771–6.
42 Strohbehn GW, Heiss BL, Rouhani SJ, *et al*. COVIDOSE: a phase II clinical trial of low-dose tocilizumab in the treatment of Noncritical COVID-19 pneumonia. *Clin Pharmacol Ther* 2020. doi:10.1002/cpt.2117. [Epub ahead of print: 18 Nov 2020].
43 Patel K, Gooley TA, Bailey N, *et al*. Use of the IL-6R antagonist tocilizumab in hospitalized COVID-19 patients. *J Intern Med* 2020. doi:10.1111/joim.13163. [Epub ahead of print: 03 Aug 2020].
44 Benucci M, Giannasi G, Cecchini P, *et al*. COVID-19 pneumonia treated with Sarilumab: a clinical series of eight patients. *J Med Virol* 2020;92:2368–70.
45 Toniati P, Piva S, Cattalini M, *et al*. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* 2020;19:102568.
46 Petrak RM, Van Hise NW, Skorodin NC. Early tocilizumab dosing is associated with improved survival in critically ill patients infected with Sars-CoV-2. *medRxiv* 2020.
47 Biran N, Ip A, Ahn J, *et al*. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol* 2020;2:e603–12.

48 Pettit NN, Nguyen CT, Mutlu GM, *et al*. Late onset infectious complications and safety of tocilizumab in the management of COVID-19. *J Med Virol* 2020.
49 Canziani LM, Trovati S, Brunetta E, *et al*. Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: a retrospective case-control survival analysis of 128 patients. *J Autoimmun* 2020;114:102511.
50 Potere N, Di Nisio M, Rizzo G, *et al*. Low-Dose subcutaneous tocilizumab to prevent disease progression in patients with moderate COVID-19 pneumonia and hyperinflammation. *Int J Infect Dis* 2020;100:421–4.
51 Gremese E, Cingolani A, Bosello SL, *et al*. Sarilumab use in severe SARS-CoV-2 pneumonia. *EClinicalMedicine* 2020;27:100553.
52 Capra R, De Rossi N, Mattioli F, *et al*. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur J Intern Med* 2020;76:31–5.
53 Ramaswamy M, Mannam P, Comer R. Off-Label real world experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community health system: a case-control study. *medRxiv* 2020.
54 Sinha P, Mostaghim A, Bielick CG, *et al*. Early administration of interleukin-6 inhibitors for patients with severe COVID-19 disease is associated with decreased intubation, reduced mortality, and increased discharge. *Int J Infect Dis* 2020;99:28–33.
55 Chilimuri S, Sun H, Alemam A, *et al*. Tocilizumab use in patients with moderate to severe COVID-19: a retrospective cohort study. *J Clin Pharm Ther* 2020;24:24.
56 Rodríguez-Baño J, Pachón J, Carratalà J, *et al*. Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: a multicentre cohort study (SAM-COVID-19). *Clin Microbiol Infect* 2020;395:27.
57 De Rossi N, Scarpazza C, Filippini C, *et al*. Early use of low dose tocilizumab in patients with COVID-19: a retrospective cohort study with a complete follow-up. *EClinicalMedicine* 2020;25:100459.
58 Rojas-Marte G, Khalid M, Mukhtar O, *et al*. Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case–controlled study. *QJM* 2020;113:546–50.
59 Albertini L, Soletchnik M, Razurel A, *et al*. Observational study on off-label use of tocilizumab in patients with severe COVID-19. *Eur J Hosp Pharm* 2021;28:22–7.
60 Eimer J, Vesterbacka J, Svensson A.-K., *et al*. Tocilizumab shortens time on mechanical ventilation and length of hospital stay in patients with severe COVID-19: a retrospective cohort study. *J Intern Med* 2020.
61 Roomi S, Ullah W, Ahmed F, *et al*. Efficacy of hydroxychloroquine and tocilizumab in patients with COVID-19: single-center retrospective chart review. *J Med Internet Res* 2020;22:e21758.
62 Antony SJ, Davis MA, Davis MG, *et al*. Early use of tocilizumab in the prevention of adult respiratory failure in SARS-CoV-2 infections and the utilization of interleukin-6 levels in the management. *J Med Virol* 2021;93:491–8.
63 Fisher MJ, Marcos Raymundo LA, Monteforte M, *et al*. Tocilizumab in the treatment of critical COVID-19 pneumonia: a retrospective cohort study of mechanically ventilated patients. *Int J Infect Dis* 2020;103:14.
64 Rosas J, Liaño FP, Cantó ML, *et al*. Experience with the use of Baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to coronavirus COVID19: a real-world study. *Reumatol Clin* 2020;395:1–3.
65 Campins L, Boixeda R, Perez-Cordon L, *et al*. Early tocilizumab treatment could improve survival among COVID-19 patients. *Clin Exp Rheumatol* 2020;38:578.
66 Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, *et al*. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: an observational study. *J Allergy Clin Immunol* 2020.
67 Rossi B, Nguyen LS, Zimmermann P, *et al*. Effect of tocilizumab in hospitalized patients with severe COVID-19 pneumonia: a case-control cohort study. *Pharmaceuticals* 2020;13:317.
68 Carvalho V, Turon R, Goncalves B. Effects of tocilizumab in critically ill patients with COVID-19: a quasi-experimental study. *medRxiv* 2020.
69 Moreno Garcia E, Caballero R V, Albiach L. Tocilizumab is associated with reduction of the risk of ICU admission and mortality in patients with SARS-CoV-2 infection. *medRxiv* 2020.
70 Rossotti R, Travi G, Ughi N, *et al*. Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: a comparative analysis. *Journal of Infection* 2020;81:08–17.
71 Dastan F, Saffaei A, Haseli S, *et al*. Promising effects of tocilizumab in COVID-19: a non-controlled, prospective clinical trial. *Int Immunopharmacol* 2020;88:106869.
72 Gokhale Y, Mehta R, Karnik N, *et al*. Tocilizumab improves survival in patients with persistent hypoxia in severe COVID-19 pneumonia. *EClinicalMedicine* 2020;24:100467.
73 Ruiz-Antorán B, Sancho-López A, Torres F, *et al*. Combination of tocilizumab and steroids to improve mortality in patients with severe COVID-19 infection: a Spanish, multicenter, cohort study. *Infect Dis Ther* 2020;395:1–3.
74 Guaraldi G, Meschiari M, Cozzi-Lepri A, *et al*. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e474–84.
75 Somers EC, Eschenauer GA, Troost JP. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clin Infect Dis* 2020;11:ciaa954.
76 Guisado-Vasco P, Valderas-Ortega S, Carralón-González MM, *et al*. Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: a retrospective observational study (COQUIMA cohort). *EClinicalMedicine* 2020;28:100591.
77 Tian J, Zhang M, Jin M, *et al*. Repurposed tocilizumab in patients with severe COVID-19. *Journal of immunology* 1950.
78 Malekzadeh R, Abedini A, Mohsenpour B, *et al*. Subcutaneous tocilizumab in adults with severe and critical COVID-19: a prospective open-label uncontrolled multicenter trial. *Int Immunopharmacol* 2020;89:107102.
79 Gupta S, Wang W, Hayek SS, *et al*. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Internal Medicine* 2020.
80 Tsai A, Diawara O, Nahass RG, *et al*. Impact of tocilizumab administration on mortality in severe COVID-19. *Sci Rep* 2020;10:19131.
81 Mikulska M, Nicolini LA, Signori A, *et al*. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. *PLoS One* 2020;15:e0237831.
82 Hill JA, Menon MP, Dhanireddy S, *et al*. Tocilizumab in hospitalized patients with COVID-19: clinical outcomes, inflammatory marker kinetics, and safety. *J Med Virol* 2020. doi:10.1002/jmv.26674. [Epub ahead of print: 17 Nov 2020].
83 Wadud N, Ahmed N, Mannu Shergil M. Improved survival outcome in SARs-CoV-2 (COVID-19) acute respiratory distress syndrome patients with tocilizumab administration. *medRxiv* 2020.
84 Morena V, Milazzo L, Oreni L, *et al*. Off-Label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. *Eur J Intern Med* 2020;76:36–42.
85 Holt GE, Batra M, Murthi M, *et al*. Lack of tocilizumab effect on mortality in COVID19 patients. *Sci Rep* 2020;10:17100.
86 Zheng K-L, Xu Y, Guo Y-F, *et al*. Efficacy and safety of tocilizumab in COVID-19 patients. *Aging* 2020;12:18878–88.
87 Perrone F, Piccirillo MC, Ascierto PA, *et al*. Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. *J Transl Med* 2020;18:405.
88 Ip A, Berry DA, Hansen E, *et al*. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-An observational study. *PLoS One* 2020;15:e0237693.
89 Rosas I, Bräu N, Waters M. Tocilizumab in hospitalized patients with COVID-19 pneumonia. *medRxiv* 2020.
90 Kewan T, Covut F, Al–Jaghbeer MJ, *et al*. Tocilizumab for treatment of patients with severe COVID–19: a retrospective cohort study. *EClinicalMedicine* 2020;24:100418.

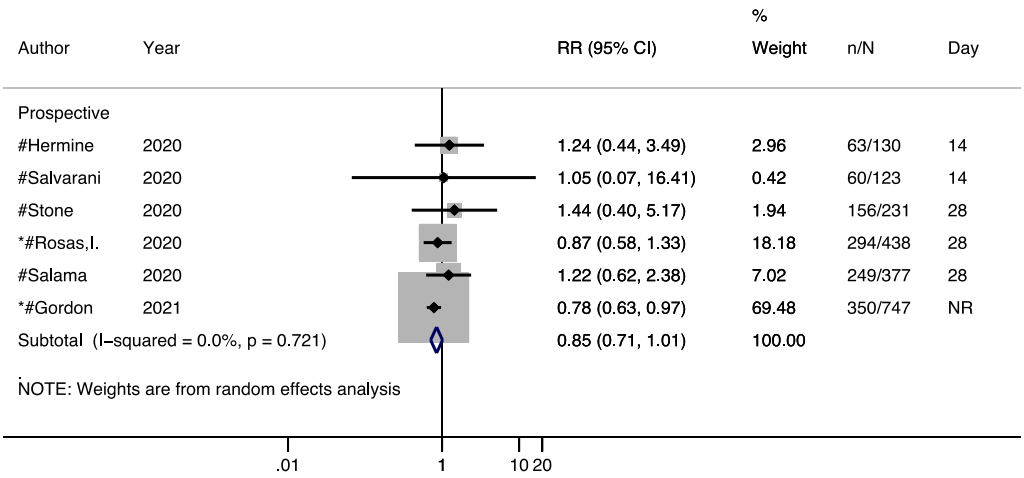
Supplementary material

1. Respiratory Distress Syndrome, Adult/
2. SARS Virus/
3. Severe Acute Respiratory Syndrome/
4. severe acute respiratory distress syndrome*.mp.
5. Coronavirus Infections/
6. Coronavirus/
7. coronav*.mp.
8. covid*.mp.
9. SARS.mp.
10. Middle East Respiratory Syndrome Coronavirus/
11. MERS.mp.
12. anakinra.mp.
13. kineret.mp.
14. tocilizumab.mp.
15. altizumab.mp.
16. actemra.mp.
17. roactemra.mp.
18. sarilumab.mp.
19. kevzara.mp.
20. siltuximab.mp.
21. sylvant.mp.
22. Interleukin 1 Receptor Antagonist Protein/
23. anti-IL6.mp.
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
25. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
26. 24 and 25

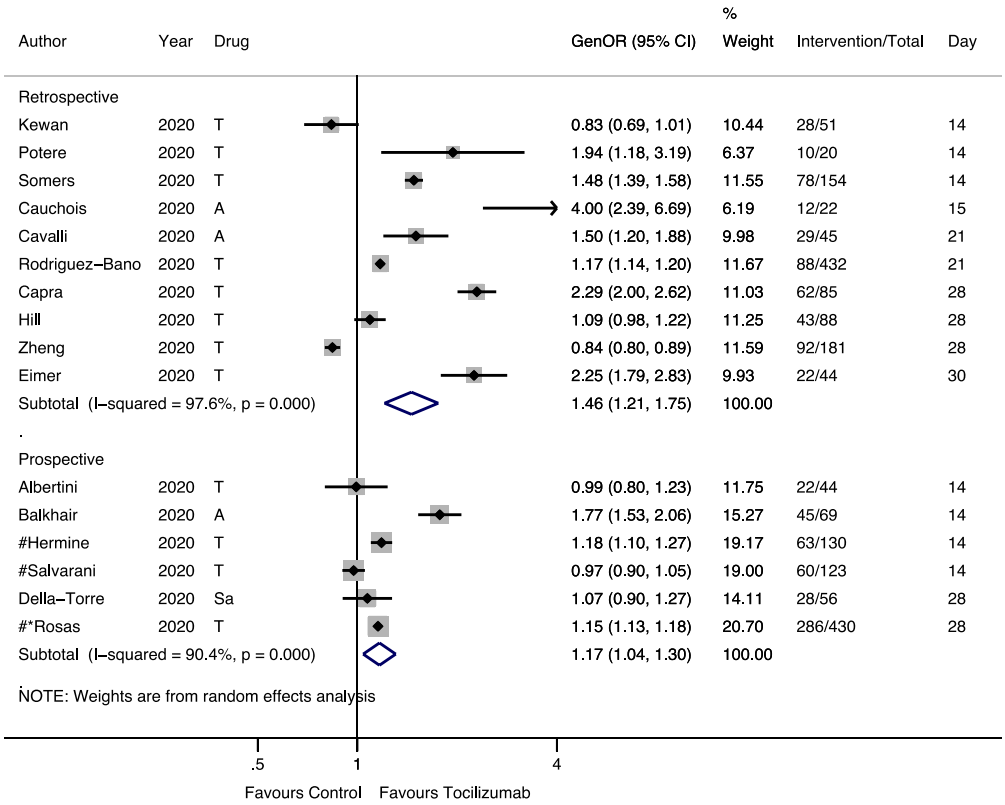
Supplementary Figure 1. MEDLINE search strategy (last carried out on 7th January 2021)


A. Ordinal outcomes
Retrospective
Prospective
p = 0.204
p = 0.35
Standard error
Log odds ratio
B. Duration of hospitalisation
p = 0.897
Standard error
Log mean difference
C. Mortality (adjusted hazard ratio)
Retrospective
Prospective
p = 0.082
p = 0.16
Standard error
Log hazard ratio
D. Mortality (risk ratio)
Retrospective
Prospective
p = 0.055
p = 0.219
Standard error
Log risk ratio

Supplementary Figure 2: Funnel plots for outcomes evaluated in tocilizumab meta-analysis. A: ordinal outcomes, B: duration of hospitalisation, C: mortality (adjusted hazard ratio), D: mortality (risk ratio). Funnel plots presented separately for retrospective and prospective studies were applicable. Publication bias assessed using Egger's test, and p values presented next to funnel plot.



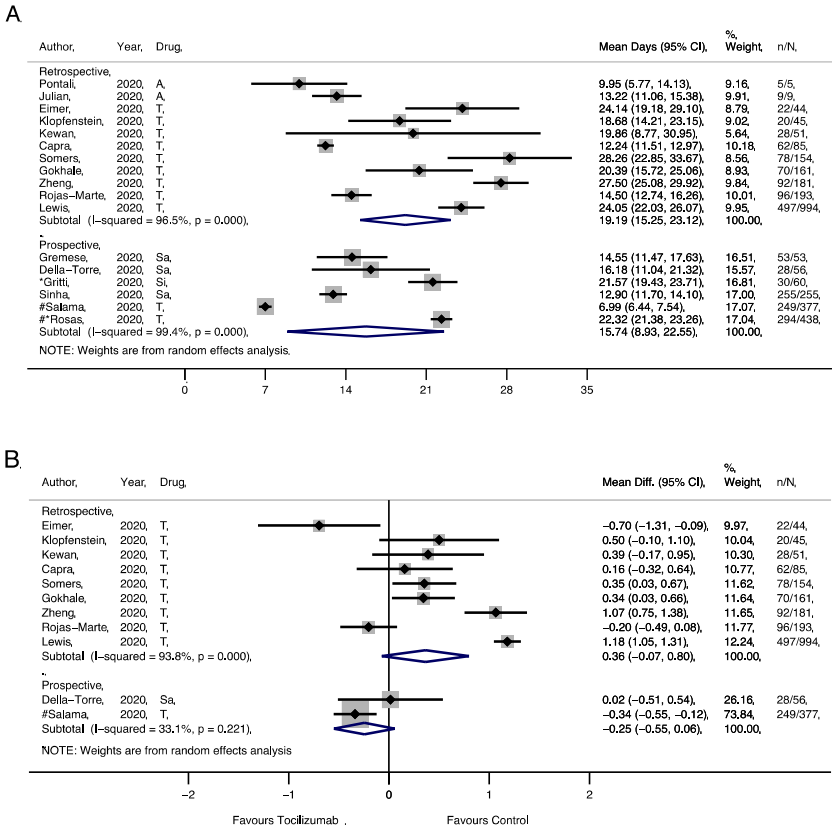
Supplementary Figure 3 – Tocilizumab mortality risk ratios (RR) forest plot for randomised controlled trials only. Risk ratios with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included in study (N).
* non peer-reviewed preprint studies
# randomised controlled trials
NR, not reported



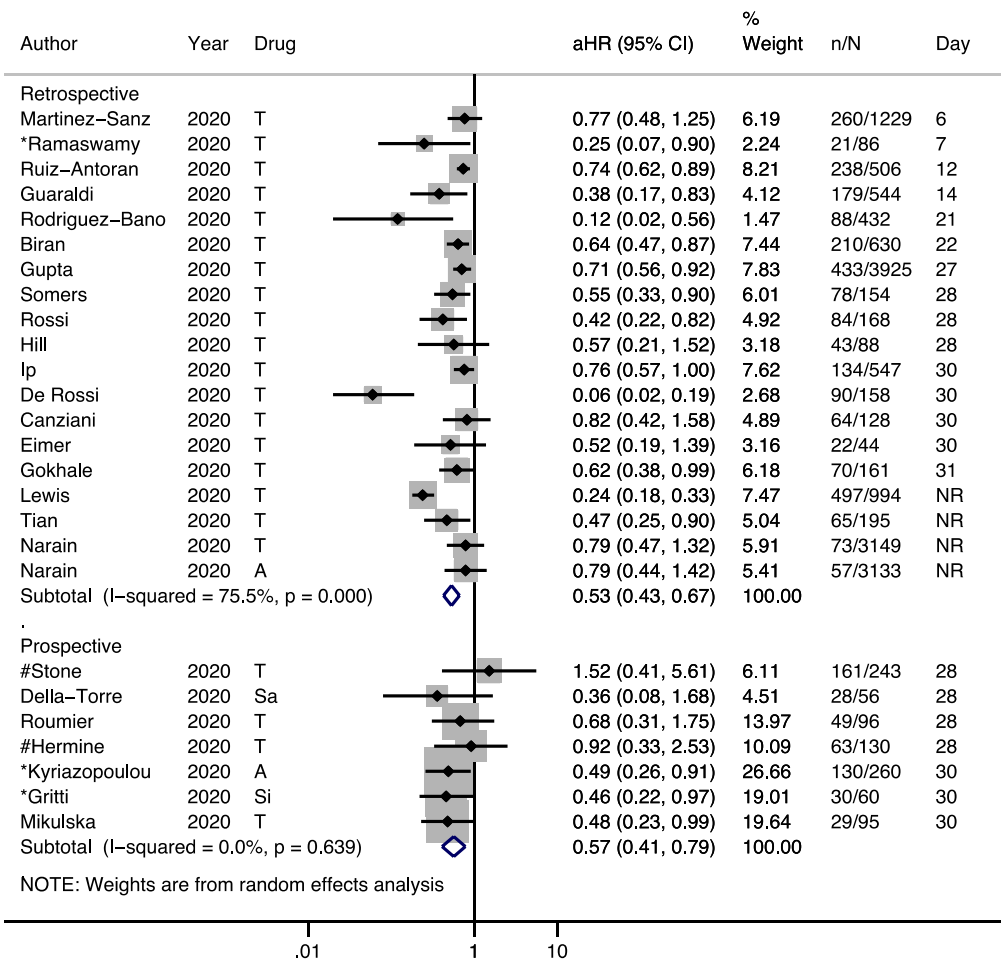
Supplementary Figure 4 – All agents. Generalised odds ratios (OR) for ordinal outcome forest plot. Generalised OR shown for each study with 95% confidence interval and day at which ordinal outcome recorded. Sample sizes given for patients receiving intervention (n) alongside total included (N) in study. Summary estimates presented separately for prospective and retrospective studies. Drugs labelled where T = tocilizumab, A = anakinra, Sa = sarilumab

* non peer-reviewed preprint studies

randomised controlled trials



Supplementary Figure 5 – All studies mean duration of hospitalisation (days) forest plot. **A**: Mean duration of hospital stay. **B**: Mean difference compared with controls in duration of hospital stay. Effect sizes and associated 95% confidence intervals presented for each study. Sample sizes given for patients receiving intervention (n) and total included in study (N). Summary estimates presented separately for prospective and retrospective studies. Drugs labelled where T = tocilizumab, Sa = sarilumab, Si = siltuximab.
* non peer-reviewed preprint studies
# randomised controlled trials

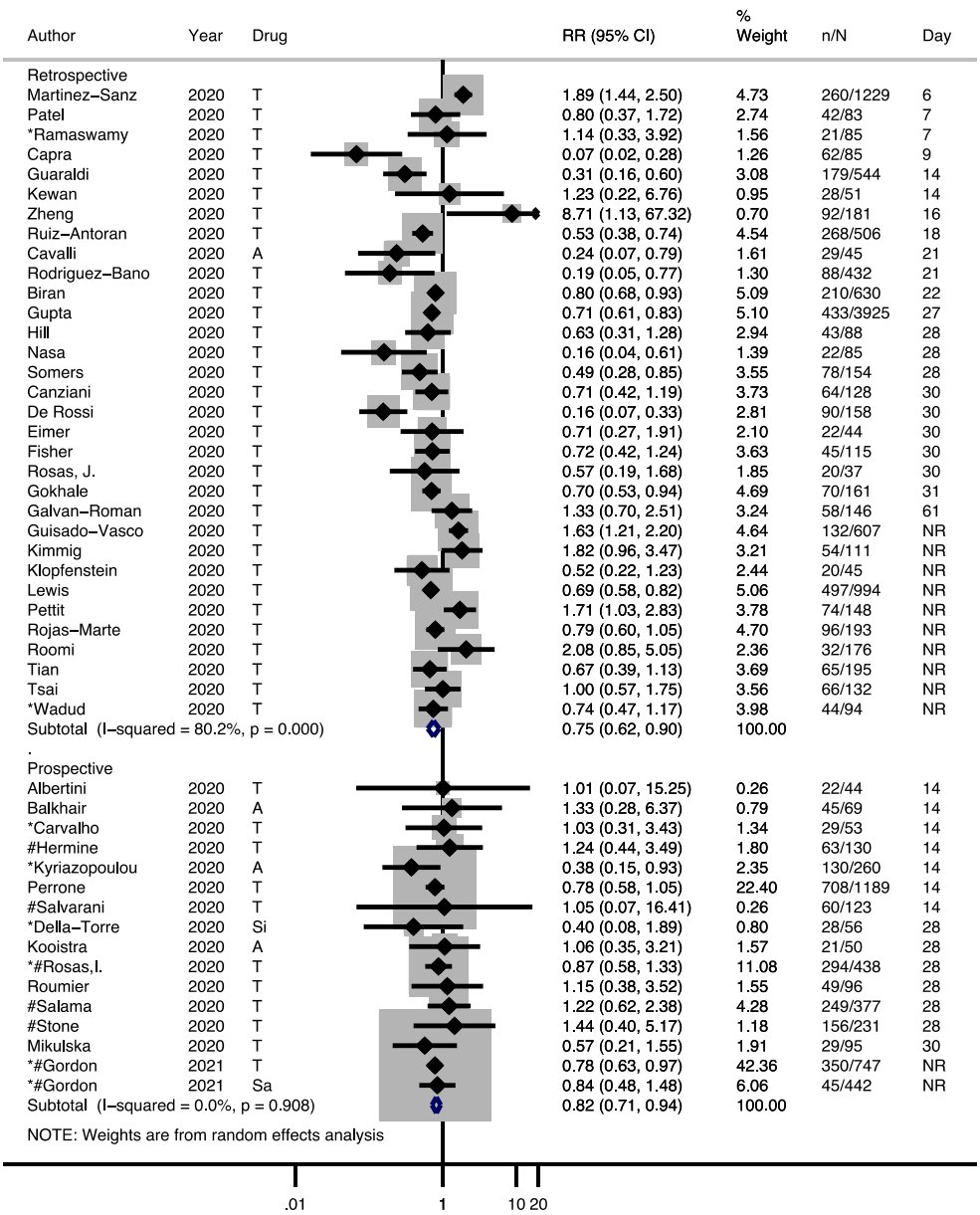


Supplementary Figure 6 – All studies, adjusted hazard ratios (HR) for overall mortality forest plot. Adjusted HRs with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included (N) in study. Summary estimates presented separately for prospective and retrospective studies. Drugs labelled where T = tocilizumab, A = anakinra, Sa = sarilumab, Si = siltuximab.

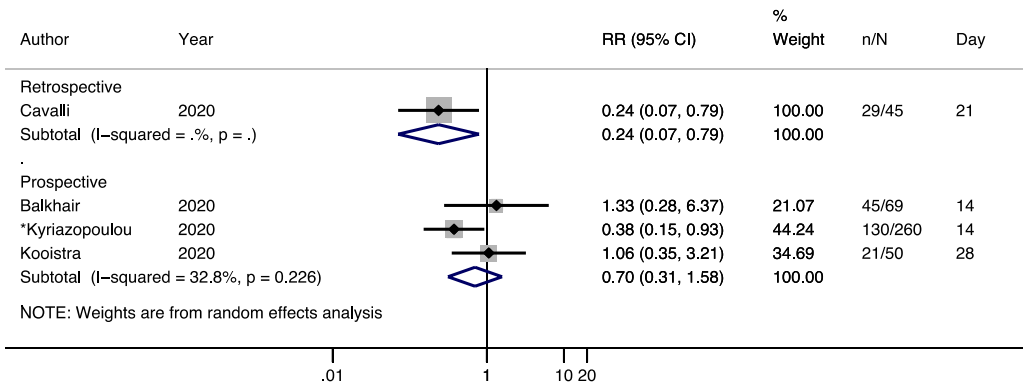
* non peer-reviewed preprint studies

randomised controlled trials

NR, not reported



Supplementary Figure 7 – All agents, mortality risk ratios (RR) forest plot. Risk ratios with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included in study (N). Summary estimates presented separately for prospective and retrospective studies. Drugs labelled where T = tocilizumab, A = anakinra, Si = siltuximab, Sa = sarilumab
* non peer-reviewed preprint studies
# randomised controlled trials
NR, not reported



Supplementary Figure 8 – Anakinra mortality risk ratios (RR) forest plot. Risk ratios with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included in study (N). Summary estimates presented separately for prospective and retrospective studies.
* non peer-reviewed preprint studies

Estimated completion date (quarter)

Clinical Trial No.	Date	Sample size	2020			2021				2022			
			Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
NCT04315480	May-20	38											
NCT04310228	May-20	150											
ChiCTR2000029765	May-20	188											
NCT04322188	May-20	50											
NCT04329650	May-20	100											
NCT04306705	May-20	120											
NCT04346355	May-20	398 ‡											
ChiCTR2000030196	May-20	60											
NCT04359667	Jun-20	30											
NCT04492501	Jul-20	600											
NCT04357860	Jul-20	120											
NCT04335305	Aug-20	24											
NCT04363736	Aug-20	100											
NCT04320615	Aug-20	450 ‡											
NCT04366232	Aug-20	54											
NCT04327388	Aug-20	421											
NCT04519385	Aug-20	69											
NCT04435717	Aug-20	78											
NCT04445272	Aug-20	500											
NCT04315298	Aug-20	1912											
NCT04462757	Sep-20	5											
NCT04364009	Sep-20	240											
NCT04372186	Sep-20	379 ‡											
NCT04335071	Oct-20	100											
NCT04345445	Oct-20	310											
NCT04356937	Oct-20	300 ‡											
NCT04332094	Oct-20	276											
NCT04361032	Oct-20	260											
NCT04560205	Oct-20	50											
NCT04377503	Dec-20	40											
NCT04409262	Dec-20	450											
NCT04386239	Dec-20	40											
NCT04330638	Dec-20	342*											
NCT04324021	Dec-20	54											
NCT04357808	Dec-20	30											
NCT04341584	Dec-20	240											
NCT04412291	Feb-21	120 *											
NCT04331795	Mar-21	332 ‡											
NCT04362111	Mar-21	30											
NCT04332913	Mar-21	30											
NCT04443881	Mar-21	180											
NCT04479358	Mar-21	332											
NCT04377750	May-21	500											
NCT04377659	May-21	40											
NCT04423042	Jun-21	30											
NCT04322773	Jun-21	200*											
NCT04486521	Jul-21	11000 *											
NCT04403685	Jul-21	129 †											
NCT04363853	Aug-21	200											
NCT04364009	Sep-21	240											
NCT04324073	Dec-21	239											
NCT04331808	Dec-21	228 ‡											
NCT04476979	Dec-21	120											
NCT04412772	Dec-21	300											
NCT04339712	Apr-22	40*											
NCT04359901	Apr-22	120											
NCT04357366	Apr-22	100											
NCT04370834	Apr-22	217 †											
NCT04361552	May-22	180 †											
NCT04424056	Nov-22	216 *											
NCT04317092	Dec-22	400 ‡											
NCT02735707	Dec-22	7100 *											

	Tocilizumab
	Siltuximab
	Sarilumab
	Anakinra

Supplementary Figure 9 - Currently registered clinical trials with estimated completion date presented per calendar year quarter. Clinical trials are stratified as per colour key. * same study investigating multiple immunomodulatory agents. † study has been terminated. ‡ results available

(last search 5th Oct)

Author, year	Study country	Centre	Study design	Dose	Participant criteria	Outcomes reported	Concomitant therapies
ANAKINRA							
Bakhair, 2020	Oman	single centre	Prospective with control	100mg S/C twice daily for 72h, then 100mg daily for 7 days	respiratory failure, bilateral lung infiltrates	mortality, ventilatory requirements	antibiotics
Huet, 2020	France	single centre	Prospective with control	100mg S/C twice daily for 72h, then 100mg daily for 7 days	respiratory failure, bilateral lung infiltrates	mortality, ventilatory requirement, laboratory biomarkers	hydroxychloroquine, antibiotics, IV methylprednisolone
Kooistra, 2020	Netherlands	multi-centre	Prospective with control	300mg IV then 100mg 6 hourly	IMV	mortality, ventilatory requirement, laboratory biomarkers	antivirals, hydroxychloroquine, corticosteroids
*Kyriazopoulou	Greece	multi-centre	Prospective	100mg S/C daily for 10 days	lung infiltrates and suPAR level ≥6ug/L	respiratory failure, mortality, SOFA score	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Cauchois, 2020	France	multi-centre	Retrospective	300mg IV daily for 5 days then tapered over 3 days	respiratory failure and CRP > 110mg/L	ventilatory requirement, laboratory biomarkers	hydroxychloroquine, antibiotics
Cavalli, 2020	Italy	single centre	Retrospective	10mg/kg/day IV	moderate-severe ARDS requiring CPAP and hyperinflammation	survival, ventilatory requirement, CRP	CPAP, hydroxychloroquine, lopinavir, ritonavir
Narain, 2020	USA	multi-centre	Retrospective	N/R	hyperinflammation	hospital mortality	hydroxychloroquine
SARILUMAB							
Benucci, 2020	Italy	single centre	Prospective	400mg IV repeated twice at 200mg at 48 hourly intervals	N/R	ventilatory requirement, laboratory biomarkers	hydroxychloroquine, azithromycin, antivirals
Della-Torre, 2020	Italy	single centre	Prospective with control	400mg IV	radiological bilateral lung infiltrates and hyperinflammation	overall survival, ventilatory requirements	hydroxychloroquine, azithromycin, antivirals
* Gordon, 2021	UK	multi-centre	Adaptive RCT	400mg IV	within 24h of ICU admission with respiratory failure	respiratory and cardiovascular organ support-free days up to day 21, mortality, time to discharge	corticosteroids, remdesivir

Gremese, 2020	Italy	single centre	Prospective	400mg IV	respiratory failure and radiological infiltrates	ventilatory requirement, discharge from ICU, mortality	hydroxychloroquine, azithromycin, antivirals
Sinha, 2020	USA	single centre	Prospective	200mg IV	respiratory failure and hyperinflammation	mortality, discharge from hospital, IMV	hydroxychloroquine, azithromycin
SILTUXIMAB							
*Gritti 2020	Italy	single centre	Prospective with control	11mg/kg IV. Second dose 72 hours later (n=6)	respiratory failure requiring IVM or non-IVM support	mortality, time to IVM, laboratory biomarkers	antivirals, hydroxychloroquine, corticosteroids
TOCILIZUMAB							
Albertini, 2020	France	single centre	Prospective with control	8mg/kg IV. Second dose 72 hours later (n=20)	respiratory failure, bilateral radiological infiltrates, elevated CRP	respiratory rate, oxygen requirements, laboratory biomarkers	hydroxychloroquine and azithromycin
Antony, 2020	USA	multi-centre	Prospective	4mg/kg/day IV 12 hourly	supplemental oxygen dose >3L/min, but not mechanically ventilated	mortality, ventilatory requirement, laboratory biomarkers	methylprednisolone
Campins, 2020	Spain	single centre	Prospective	N/R	N/R	mortality	corticosteroids (98%)
*Carvalho, 2020	Brazil	single centre	Prospective with control	400mg IV two doses	respiratory failure, hyperinflammation	in-hospital mortality, need for renal replacement therapy, inflammatory and oxygenation markers, use of antibiotics	hydroxychloroquine, azithromycin
Dastan, 2020	Iran	single centre	Prospective	400mg IV	severe: respiratory failure, or bilateral radiological infiltrates, IL-6>10pg/mL critical: need for ICU or IMV	oxygen requirements, ventilatory requirements, death, laboratory biomarkers	antivirals
* Gordon, 2021	UK	multi-centre	Adaptive RCT	8mg/kg IV repeated after 12-24h	within 24h of ICU admission with respiratory failure	respiratory and cardiovascular organ support-free days up to day 21, mortality, time to discharge	corticosteroids, remdesivir

Hermine, 2020	France	multi-centre	Open label RCT	8mg/kg IV	radiological infiltrates with respiratory failure but not admitted to ICU	dead or ventilatory support on day 4, survival at day 14, laboratory biomarkers	antivirals, corticosteroids
Malekzadeh, 2020	Iran	multi-centre	Prospective	324mg or 486mg SC (weight dependent)	respiratory failure and hyperinflammation	all-cause mortality, change on 6-point ordinal scale, laboratory biomarkers	hydroxychloroquine, antivirals, antibiotics, interferon beta
Mikulska, 2020	Italy	single centre	Prospective with control	8mg/kg IV (62%) or 162mg SC (38%). Second dose in 24%	respiratory failure	IMV, death	hydroxychloroquine, antivirals, antibiotics
Morena, 2020	Italy	single centre	Prospective	8mg/kg IV repeated after 12h	respiratory failure, IL-6 > 40pg/mL	death, hospital discharge	hydroxychloroquine, antivirals, antibiotics
Perrone 2020	Italy	multi-centre	Single arm, open-label & validation	8mg/kg/IV	respiratory failure	mortality rates at 14 and 30 days	hydroxychloroquine, antibiotics, antivirals, steroids
*Rosas, I., 2020	USA	multi-centre	Placebo-controlled, double blind, phase 3 RCT	8mg/kg IV, second dose 8-24h later permitted	respiratory failure with bilateral radiological infiltrates	status on a 7-point ordinal scale, time to hospital/ICU discharge, time to improvement on ordinal scale, incidence of IMV	corticosteroids, antivirals, convalescent plasma
Roumier, 2020	France	single centre	Prospective with control	8mg/kg IV repeated once	respiratory failure, hyperinflammation	mortality, IMV, hospital status	Hydroxychloroquine, azithromycin, corticosteroids
Salvarani, 2020	Italy	multi-centre	Open label RCT	8mg/kg IV, repeated 12h later	respiratory failure and hyperinflammation	ICU admission and need for IMV, death, respiratory failure	hydroxychloroquine, antivirals, antibiotics
*Sanchez-Montalva, 2020	Spain	single centre	Prospective	400-600mg IV	respiratory failure, hyperinflammation	death at 7 days, admission to ICU, ARDS	Hydroxychloroquine, antibiotics, antivirals
Salama, 2020	USA	multi-centre	Double blind RCT	8mg/kg IV	respiratory failure not requiring ventilatory support	mortality, ventilatory requirement, duration of hospitalisation	Antivirals, corticosteroids
Sciascia, 2020	Italy	multi-centre	Prospective	8mg/kg IV or 324mg S/C. Second dose in 83%	respiratory failure, hyperinflammation	medication safety, oxygen requirement, laboratory biomarkers	antivirals

Stone, 2020	USA	multi-centre	Double blind RCT	8mg/kg IV	hyperinflammation with two of: fever, lung infiltrates or respiratory failure	intubation or death,	antiviral, hydroxychloroquine, corticosteroids
Strohbehn, 2020	USA	single centre	Phase 2 open label	40-200mg	bilateral radiological infiltrates, fever, CRP>40mg/L	resolution of fever, CRP reduction, overall survival at 28 days, rate and duration of IMV, duration of supplemental oxygen	hydroxychloroquine, azithromycin, antiviral
Toniati, 2020	Italy	single centre	Prospective	8mg/kg IV, repeated after 12h (87%). Third dose 24h later (13%)	respiratory failure requiring ventilatory support	ventilatory requirements, discharge, death	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Biran, 2020	USA	multi-centre	Retrospective	400mg IV with 12% receiving a second dose	hospitalised requiring ICU stay	mortality, inflammatory biomarkers, oxygenation, infection, use of vasopressors	corticosteroids, hydroxychloroquine, azithromycin
Canziani, 2020	Italy	multi-centre	Retrospective	8mg/kg IV followed by a second dose 24h later (95%)	respiratory failure, elevated CRP, absence of active bacterial infection	mortality, incidence of invasive ventilation, thromboembolic events, haemorrhagic event, infections	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Capra, 2020	Italy	single centre	Retrospective	400mg IV (53%); 324mg SC (44%)	tachypnoea or hypoxia. IMV patients excluded	overall mortality	hydroxychloroquine, antivirals
Chillmuri, 2020	USA	single centre	Retrospective	400mg IV	respiratory failure and hyperinflammation	ventilatory requirement, mortality	hydroxychloroquine, antivirals, corticosteroids
De Rossi, 2020	Italy	single centre	Retrospective	400mg IV (48%); 324mg SC (52%)	respiratory failure, bilateral radiological infiltrates. IMV patients excluded	overall mortality	hydroxychloroquine, antivirals
Eimer, 2020	Sweden	single centre	Retrospective	8mg/kg IV	respiratory failure admitted to intensive care, with hyperinflammation	30-day mortality, time to extubation, ventilator free-days, length of hospital and ICU stay	Nil
Fisher, 2020	USA	single centre	Retrospective	400mg IV, repeated after 24h	respiratory failure	30 day mortality	hydroxychloroquine, steroids

Galvan Roman, 2020	Spain	single centre	Retrospective	8mg/kg/IV, repeated after 12h	respiratory failure, hyperinflammation,	mortality, IL-6 levels, mechanical ventilation,	hydroxychloroquine, antivirals, antibiotics, corticosteroids
*Garcia, 2020	Spain	single centre	Retrospective	400-600mg IV repeated 12h apart with up to 3 doses	radiological infiltrates, respiratory failure and hyperinflammation	ICU admission and need for IMV	hydroxychloroquine, antivirals, azithromycin
Gokhale, 2020	India	single centre	Retrospective	400mg IV	respiratory failure, bilateral radiological infiltrates, hyperinflammation	overall mortality	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Guaraldi, 2020	Italy	multi-centre	Retrospective	8mg/kg IV, repeated after 12h, or 324mg SC single dose	respiratory failure, lung infiltrates >50%	IMV or death	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Guisado-Vasco, 2020	Spain	single centre	Retrospective	8mg/kg/IV	radiological infiltrates and respiratory failure	hospital mortality, length of hospitalisation, admission to ICU, requirement for IMV	hydroxychloroquine, antivirals, corticosteroids
Gupta, 2020	USA	multi-centre	Retrospective	Treated in first 2 days, dose not specified	admitted to ICU	hospital mortality, secondary infections	hydroxychloroquine, azithromycin, corticosteroids
Hill, 2020	USA	single centre	Retrospective	400mg IV, repeated in 3 patients after 24h	fever with either respiratory failure, haemodynamic instability, or serum IL-6 >5 times upper limit of normal	clinical improvement (two-point reduction on six-point scale), mortality within 28 days	hydroxychloroquine, remdesivir
Holt, 2020	USA	single centre	Retrospective	400mg IV	respiratory failure and hyperinflammation	mortality	N/R
Ip, 2020	USA	multi-centre	Retrospective	400mg IV	hospitalised on ICU	overall mortality	hydroxychloroquine, azithromycin, corticosteroids
Kewan, 2020	USA	single centre	Retrospective	8mg/kg IV	respiratory failure, lung infiltrates, hyperinflammation	Time to clinical improvement, duration of IMV, duration of vasopressor support	hydroxychloroquine, azithromycin, corticosteroids
Kimmig, 2020	USA	single centre	Retrospective	400mg IV	clinical deterioration with hyperinflammation	mortality, infection rate	N/R
Klopfenstein, 2020	France	single centre	Retrospective	N/R	respiratory failure, >25% lung infiltrates, hyperinflammation	death and/or ICU admission	hydroxychloroquine, antivirals, antibiotics, corticosteroids

Lewis, 2020	USA	multi-centre	Retrospective	400mg IV	respiratory failure and hyperinflammation	mortality, duration of hospitalisation	azithromycin, corticosteroids
Martinez-Sanz, 2020	Spain	multi-centre	Retrospective	600-800mg	hospitalised	time to death or intensive care unit admission	hydroxychloroquine, antivirals, antibiotics, corticosteroids
# Narain, 2020	USA	multi-centre	Retrospective	N/R	hyperinflammation	hospital mortality	hydroxychloroquine
Nasa, 2020	India	multi-centre	Retrospective	8mg/kg IV, repeated after 12 hours	respiratory failure with hyperinflammation	mortality at day 28	hydroxychloroquine, antivirals, corticosteroids
Patel, 2020	USA	single centre	Retrospective	N/R	severe: respiratory failure critical: requiring IMV	overall mortality, hospital discharge, inflammatory biomarkers	hydroxychloroquine, antivirals, corticosteroids
* Petrak, 2020	USA	multi-centre	Retrospective	N/R	IMV	mortality	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Pettit, 2020	USA	single centre	Retrospective	400mg IV	respiratory failure with hyperinflammation	infection rate	hydroxychloroquine and remdesivir
Potere, 2020	Italy	single centre	Retrospective	324mg SC	hyperinflammation with no hypoxaemia	disease progression, inflammatory biomarkers	hydroxychloroquine, antivirals, corticosteroids
*Ramaswamy, 2020	USA	multi-centre	Retrospective	400mg IV, 8mg/kg	respiratory failure, hyperinflammation	inpatient mortality	hydroxychloroquine, azithromycin, corticosteroids
Rodriguez-Bano, 2020	Spain	multi-centre	Retrospective	N/R	hyperinflammation. IMV patients excluded	intubation, death, secondary bacterial infections, scores on a seven-point ordinal scale	hydroxychloroquine, antivirals, antibiotics, interferon beta
Rojas-Marte, 2020	USA	single centre	Retrospective	N/R	respiratory failure	overall mortality rate	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Roomi, 2020	USA	single centre	Retrospective	N/R	hospitalised	overall mortality, IMV	hydroxychloroquine, corticosteroids
Rosas, J., 2020	Spain	single centre	Retrospective	400/600mg IV	radiological infiltrates and respiratory failure	admission to ICU, hospital discharge, mortality	hydroxychloroquine, antivirals, antibiotics, corticosteroids

Rossi, 2020	France	single centre	Retrospective	400mg IV	respiratory failure. IMV patients excluded	composite of all-cause mortality and invasive ventilation	hydroxychloroquine, antivirals, corticosteroids
Rossotti, 2020	Italy	single centre	Retrospective	8mg/kg IV repeated 12h later if ongoing fever	respiratory failure, bilateral radiological infiltrates, hyperinflammation	overall survival	hydroxychloroquine, antivirals
Ruiz-Antoran, 2020	Spain	multi-centre	Retrospective	400-600mg IV repeated up to three doses	respiratory failure, hyperinflammation	in-hospital mortality	hydroxychloroquine, antivirals, antibiotics, corticosteroids
Somers, 2020	USA	single centre	Retrospective	8mg/kg IV	IMV	survival probability, ordinal scale at day 28	hydroxychloroquine, corticosteroids
Tian, 2020	China	multi-centre	Retrospective	4-8mg/kg IV repeated after 12h if ongoing fever	respiratory failure and hyperinflammation	mortality, time from admission to discharge	antivirals, antibiotics, corticosteroids
Tsai, 2020	USA	single centre	Retrospective	400-800mg IV	respiratory failure and ferritin >300ug/mL	overall mortality	hydroxychloroquine, azithromycin
* Wadud, 2020	USA	single centre	Retrospective	N/R	hospitalised	mortality, discharge, number of days on ventilator, in ICU and in hospital	N/R
Zheng, 2020	China	single centre	Retrospective	400mg IV, repeat after 24h if persistent fever	severe: respiratory failure critical: shock	mortality, discharge, inflammatory biomarkers	Nil

Supplementary Table 1 – Methodological characteristics of included studies. Age in years reported as mean (standard deviation) unless otherwise stated.
ARDS, acute respiratory distress syndrome; CPAP, continuous positive airways pressure; CRP, C reactive protein; ICU, intensive care unit; IL6, interleukin 6; IV, intravenous; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; N/R, not reported; SC, subcutaneous; SOFA, sequential organ failure assessment; suPAR, soluble urokinase plasminogen activator receptor. * non peer-reviewed preprint study; #, study investigating both anakinra and tocilizumab

Author, year	Study design	N Treatment/ Control	Follow up, days	Control Age	Intervention Age	Sex (male control) %	Sex (male) intervention %	Outcomes
				ANAKINRA				
Balkhair, 2020	Prospective with control	45/24	N/R	51.7 (14.8)[a]	49.8 (16)[a]	71	78	IMV occurred in 31% in the anakinra group and 75% in the control (p < 0.001). Death occurred in 29% in the anakinra group and 46% in the control (p = 0.082).
Huet, 2020	Prospective with control	52/44	N/R	71 (15)[a]	71 (13)[a]	57	69	IMV or death in anakinra group vs control HR 0.22; 95% CI 0.1-0.49. For death alone: HR 0·30; 95% CI 0·12–0·71. Decrease in CRP vs control group.
Kooistra, 2020	Prospective with control	21/39	28	67 (59-72)[c]	63 (55-71)[c]	85	67	No difference between anakinra and control group in time on IMV (23 vs 17 days; p=0.79), length of ICU stay (24 days vs 17; p=0.59), 28 day mortality (19% vs 18%; p=087)
*Kyriazopoulou, 2020	Prospective	130/130	30	63.5 (13.7)	63.2 (14.1)	65	62	severe respiratory failure lower in anakinra treated group (22.3% vs 59.2%), and lower 30-day mortality (aHR 0.49, 95%CI 0.25-0.97).
Cauchois, 2020	Retrospective	12/10	N/R	N/R	N/R	N/R	N/R	Fewer no. days with oxygen < 3L/min in anakinra group vs control at day 20 (p<0.05). No. of days without IMV similar. Rapid reduction of CRP with anakinra vs. controls (p<0.001)
Cavalli, 2020	Retrospective	29/16	21	70 (64-78)[c]	63 (51-73)[c]	88	83	Control: Survival at 21 days of 56%. Mechanical ventilation-free survival 50%. Tocilizumab high dose: Survival of 90% at 21 day (p=0.009 vs control group). IMV-free survival 72% (p=0.15 vs control group)
# Narain, 2020	Retrospective	57/3076	N/R	65 (54-77)[c]	67 (58-75)[c]	62	67	No effect on mortality (aHR 0.79; 95% CI 0.44-1.42)
				SARILUMAB				
Benucci, 2020	Prospective	8/0	14	-	62	-	75	87% discharged within 14 days.

Della-Torre, 2020	Prospective with control	28/28	28	57 (52-60) [c]	56 (49-60) [c]	71	85	Survival similar in both groups (HR 0.36; 95% CI 0.08-1.68). In treatment group, median time to death higher (19 vs. 4 days; p=0.006), median time to CRP normalisation lower (6 vs. 12 days; p<0.0001). Median time to clinical improvement, discharge and IMV free survival similar. Median time to clinical improvement shorter in patients with a baseline PaO2/FiO2 >100mgHg (7 vs 28 days; HR 0.18; 95% CI 0.02-0.26)
* Gordon, 2021	Adaptive RCT	45/397	NR	61.1 (12.8) [a]	63.4 (13.4) [a]	70	81	Mean adjusted odds ratio for survival was 2.01 (95%CI 1.18-2.71). Compared with control, median adjusted odds ratios for organ support-free days was 1.76 (95%CI 1.17-2.91). Sarilumab associated with improved time to ICU discharge (aHR 1.64; 95%CI 1.21-2.45), improved time to hospital discharge (aHR 1.6; 95%CI 1.17-2.40), improved ordinal scale outcomes at day 14 (aOR 1.86; 95%CI 1.22-2.91).
Gremese, 2020	Prospective	53/0	16 (14-24) [b]	-	66 (40-95) [c]	-	89	83% (89.7% in medical wards and 64.3% in ICU) improved on therapy. Overall mortality of 5.7%
Sinha, 2020	Prospective	255/0	N/R	-	59 (47-70) [c]	-	63	10.9% of patients died. Mortality was lower in patients with FiO2 < 0.45 (HR 0.24; 95% CI 0.08-0.74)
				SILTUXIMAB				
* Gritti 2020	Prospective with control	30/30	33.3 (7-58) [b]	65 (56-70) [b]	64 (57-66) [b]	80	77	30-day mortality lower in treatment arm (HR 0.46; 95% CI 0.22-0.97). 53% recovered and were discharged.
				TOCILIZUMAB				
Albertini, 2020	Prospective with control	22/22	14	65 (41-82) [b]	64 (41-80) [b]	68	73	average respiratory rate at d14 lower in treated (21.5 vs 25.5 breaths/min; 95% CI -7.5 to -0.4). No difference in requirement for intubation. Significant fall in CRP in treated patients on d7 (p=0.04)
Antony, 2020	Prospective	80/0	N/R	-	63 (51-72) [b]	-	57	8.8% of patients died and 11.3% required mechanical ventilation. CRP levels reduced post therapy, whereas IL-6 increased

Campins, 2020	Prospective	58/0	N/R	-	60.6	-	72	32.4% of patients were admitted to intensive care, 13.8% died. No difference in median CRP and IL-6 between survivors and dead
* Carvalho, 2020	Prospective with control	29/24	14	59 (51-72) [c]	55 (44-65) [c]	75	62	Tocilizumab not associated with mortality (HR 3.97; 95% CI 0.28-5.72), or positive cultures (OR 1.73; 95% CI 0.22-13.82)
Dastan, 2020	Prospective	42/0	28	-	56 (44-61) [c]	-	64	14% required IMV, remaining patients showed clinical improvement. By d28, 16.7% of patients died
* Gordon, 2021	Adaptive RCT	350/397	NR	61.1 (12.8) [a]	61.5 (12.5) [a]	70	74	Mean adjusted odds ratio for survival was 1.64 (95%CI 1.14-2.35). Compared with control, median adjusted odds ratios for organ support-free days was 1.64 (95%CI 1.25-2.14). Tocilizumab associated with improved time to ICU discharge (aHR 1.42; 95%CI 1.18-1.70), improved time to hospital discharge (aHR 1.41; 95%CI 1.18-1.70), improved ordinal scale outcomes at day 14 (aOR 1.83; 95%CI 1.40-2.41).
Hermine, 2020	Open label RCT	64/67	90	63 (57-72) [c]	64 (57-74) [c]	66	70	At day 14, fewer patients died or needed ventilation compared with controls (aHR 0.58; 90% CI 0.30-1.09). At day 28, mortality was similar in both groups (aHR 0.92; 95%CI 0.33-2.53)
Malekzadeh, 2020	Prospective	126/0	14	-	54 (13) [a]	-	64	By day 14, 4.7% (4/86) of severe patients and 50% (20/40) of critical patients died. By the end, 7% (6/86) of severe patients and 60% (24/40) of critical patients died.
Mikulska, 2020	Prospective with control	29/66	53 (4-70) [b]	68 (13) [a]	66 (10) [a]	67	83	14-day mortality was 13.8% vs. 21.8% in control group. Mortality at study end lower in treatment group (HR 0.48; 95% CI 0.23-0.99)
Morena, 2020	Prospective	51/0	30	N/A	60 (50-70) [c]	N/A	78	Over a median follow up of 34 days, 67% of patients showed an improvement in clinical severity. Overall mortality rate was 27%
Perrone, 2020	Single-arm, open-label phase 2 trial	180/121	30	≤60: 36% 61-70: 33% ≥71: 31%	≤60: 44% 61-70: 37% ≥71: 19%	77	83	Pre-specified expected lethality rates defined as 20% and 35% at 14 and 30 days respectively. Lethality rates were 18.4% (95% CI 13.6-24.0, p=0.52) and 22.4% (95% CI 17.2-28.3, p<0.001) at 14 and 30 days. In tocilizumab group alone, lethality rates were 15.6% and 20%.
Perrone, 2020	Prospective with control	528/360	30	≤60: 43% 61-70: 30% ≥71: 27%	≤60: 40% 61-70: 28% ≥71: 32%	77	83	In the validation cohort, lethality rates were consistently lower than the predefined null hypothesis both at 14 and 30 days in the overall cohort (11.4% and 18.4%) and in the tocilizumab only group (10.9% and 20.0%)

* Rosas, I., 2020	Placebo-controlled, double phase 3 RCT	294/144	60	61 (14) [a]	61	70	70	No improvement in clinical status at day 28 (p=0.36), or mortality. Ordinal scale values similar (OR 1.19; 95% CI 0.81-1.76). Median time to hospital discharge shorter with tocilizumab than placebo (20 and 28 days; HR 1.35 95% CI 1.02-1.79). Median duration of ICU stay shorter with tocilizumab (9.8 and 15.5 respectively, p=0.045). Median time to improvement from baseline in 2 or more categories on ordinal scale was 14 days (12-17) in tocilizumab arm and 18 (15-28) days in placebo (p=0.08). Incidence of IMV was 27.9% in tocilizumab arm and 36.7% in placebo (p=0.14)
Roumier, 2020	Prospective with control	49/47	28	62 (13) [a]	58 (12) [a]	81	82	Tocilizumab reduced requirement for IMV (aHR 0.58; 95% CI 0.36-0.94). No difference in mortality (aHR 0.68; 95% CI 0.31-1.75)
Salama, 2020	Double-blind RCT	249/128	60	55.6 (14.9)[a]	56 (14.3) [a]	57	60	IMV or death at day 28 was lower in tocilizumab group (aHR 0.56; 95% CI 0.33 - 0.97). Mortality similar in both groups (10.4% vs 8.6%).
Salvarani, 2020	Open label RCT	60/63	30	60 (54-69) [c]	62 (52-74) [c]	56	67	28% in the tocilizumab arm and 27% in SOC group showed clinical worsening within 14 days (RR, 1.05; 95% CI, 0.59-1.86). Mortality at 14 days and at 30 days (was comparable in the 2 groups
* Sanchez-Montalva, 2020	Prospective	82/0	N/R	-	59 (20) [a]	-	63	Mortality at 7 days was 26.8%. ARDS developed in 54.9%
Sciascia, 2020	Prospective	63/0	14	-	63 (13) [a]	-	88	Tocilizumab associated with increased survival (HR 2.2; 95% CI 1.3-6.7). Overall mortality was 11%
Stone, 2020	Double blind RCT	161/82	28	57 (45-70) [c]	62 (46-70) [c]	55	60	HR for intubation or death compared with placebo was 0.83;95% CI, 0.38 to 1.81. At 14 days, 18.0% in tocilizumab and 14.9% in of placebo had disease progression. At 14 days, 24.6% of tocilizumab group and 21.2% of placebo were receiving supplemental oxygen.
Strohbehn, 2020	Phase 2 open label trial with control	32/41	28	68 (58-78) [c]	69 (41-73) [c]	59	50	At 24 hours, 75% of tocilizumab vs 34.1% of control were afebrile (p=0.001). 86.2% of tocilizumab vs. 14.3% control achieved CRP decrease of at least 25% (p<0.001). Median time to recovery was 3 days (IQR 2-5)

Toniati, 2020	Prospective	100/0	10	-	62 (57-71) [c]	-	88	Overall at 10 days 77% of patients improved or stabilised and 23% worsened. Mortality was 20%
Biran, 2020	Retrospective	210/420	22 (11-53) [c]	65 (56-74) [c]	62 (53-71) [c]	67	74	Exposure to tocilizumab was associated with lower hospital mortality (HR 0.64; 95% CI 0.47-0.87). In subgroup analyses, tocilizumab associated with decreased hospital mortality in those with a CRP≥150mg/L (HR 0.48;95% CI 0.3-0.77), but not in those with CRP>150mg/L (HR 0.92;95% CI 0.57-1.48).
Canziani, 2020	Retrospective	64/64	N/R	64 (8) [a]	63 (12) [a]	73	73	30-day mortality unaffected (aHR 0.82; 95% CI 0.42-1.58). Between days 6 and 30, HR 0.41 (95% CI 0.17-0.96) for tocilizumab vs controls. Tocilizumab associated with lower risk of IMV (HR 0.36; 95% CI 0.16-0.83). No effect on thrombotic events, bleeding, infection
Capra, 2020	Retrospective	62/23	28	70 (55-80) [c]	63 (54-73) [c]	83	73	Tocilizumab associated with reduced risk of mortality (HR 0.035; 95% CI 0.004-0.347)
Chillmuri, 2020	Retrospective	83/685	N/R	63 (54-73) [c]	60 (50-70) [c]	61	74	Tocilizumab associated with lower composite endpoint of IMV or death (aHR 0.29; 95% CI 0.16-0.54)
De Rossi, 2020	Retrospective	90/68	N/R	71 (15) [a]	63 (13) [a]	72	71	Tocilizumab group associated with reduced risk of mortality (aHR 0.057; 95% CI 0.017-0.187). Survival rate or mean time to discharge did not differ between two administration (IV and SC) routes.
Eimer, 2020	Retrospective	22/22	30	60 (54-67) [c]	61 (49-64) [c]	77	96	No difference in all-cause mortality at 30 days (HR 0.52; 95% CI 0.19-1.39).Median time to death was 8 days in treated (IQR 5-12.5) and 14 days (IQR 10-19, p = 0.15) in control. In tocilizumab group, significantly more ventilator free days. Freedom from IMV was achieved earlier and in a higher proportion of patients (HR 2.83; 95% CI 1.48-5.4). Length of hospital stay shorter in tocilizumab group
Fisher, 2020	Retrospective	45/70	30	60.6 (13.4)[a]	56.2 (14.7) [a]	73	64	No difference in mortality associated with tocilizumab (OR 1.04, 95% C.I. 0.27 – 3.75)
Galvan Roman, 2020	Retrospective	58/88	61 (58-64) [c]	64 (54-72) [b]	61 (54-70) [c]	65	69	patients with high IL-6 not treated with TCZ showed high 139 mortality (HR: 4.6; p=0.003), as well as those with low IL-6 treated with tocilizumab (HR: 3.6; p=0.016).

* Garcia, 2020	Retrospective	77/94	14.7 (10.6) [a]	61 (16) [a]	62 (12) [a]	63	69	Tocilizumab associated with fewer ICU admissions (10.3% vs. 27.6%; p=0.005) and need for IMV (0 vs 13.8%, OR 0.03, 95% CI 0.007-0.1)
Gokhale, 2020	Retrospective	70/91	31 (12-48) [c]	55 (48-65) [c]	52 (44-57) [c]	58	67	Tocilizumab associated with reduced mortality (HR 0.616;95% CI 0.38-0.99)
Guaraldi, 2020	Retrospective	179/365	12 (6-17) [c]	69 (57-78) [c]	64 (54-72) [c]	64	71	Tocilizumab use associated with reduced risk of death (7% vs. 20%; aHR 0.38; 95% CI 0.17-0.83) and composite outcome of IMV or death (aHR 0.61;95% CI 0.4-0.92).
Guisado-Vasco, 2020	Retrospective	132/475	N/R	N/R	69 (22) [c]	N/R	65	Increased mortality with tocilizumab (aOR 2·4, 95% CI, 1·13 - 5·11)
Gupta, 2020	Retrospective	433/3492	26 (15-38) [c]	63 (52-72) [c]	58 (48-65) [c]	62	69	Patients treated with tocilizumab had a lower risk of death compared with those not treated with tocilizumab (HR, 0.71; 95% CI, 0.56-0.92)
Hill, 2020	Retrospective	43/45	28	N/R	N/R	69	70	Tocilizumab not associated with lower risk of mortality (aHR 0.57; 95% CI 0.21-1.52) or a difference in clinical improvement (aHR 0.92; 95% CI 0.38-2.22)
Holt, 2020	Retrospective	24/30	N/R	N/R	N/R	N/R	N/R	In multivariate analysis, tocilizumab administration had no effect on mortality (OR 0.32; 95% CI 0.02-3.69)
Ip, 2020	Retrospective	134/413	N/R	69 (58-77) [c]	62 (533-70) [c]	62	74	Tocilizumab associated with reduced mortality within the ICU setting (aHR 0.76; 95% CI 0.57-1.00)
Kewan, 2020	Retrospective	28/23	10 (6-17) [c]	70 (55-75) [c]	62 (53-71) [c]	48	71	Median time to clinical improvement in tocilizumab vs. no tocilizumab was 6.5 days (IQR 4-9) vs. 7 days (IQR 5-10) among all patients (HR 1.14; 95% CI 0.55-2.38). Shorter median length of hospital stay with tocilizumab. The median duration of vasopressor support and IMV were 2 days (IQR: 1·75 – 4·25 days) vs. 5 days (IQR: 4 – 8 days), p = 0.039, and 7 days (IQR: 4 – 14 days) vs. 10 days (IQR: 5 – 15 days) in tocilizumab vs. no tocilizumab cohorts, p = 0.11
Kimmig, 2020	Retrospective	54/57	N/R	62 (17) [a]	65 (14) [a]	44	69	Tocilizumab was associated with higher risk of mortality (35.2% vs 19.3%, p=0.02)

Klopfenstein, 2020	Retrospective	20/25	N/R	71 (15) [a]	77 (11) [a]	N/R	N/R	Death and/or ICU admissions higher in tocilizumab cohort vs control (72% vs 25%; p=0.002). No difference in death alone (25% vs 48%; p=0.0066)
Lewis, 2020	Retrospective	497/497	N/R	64 (52-76) [c]	61 (52-69) [c]	58	71	Tocilizumab associated with improved survival (aHR 0.24; 95% CI 0.18-0.33). Similar time to hospital discharge (aHR 0.86; 95% CI 0.78-1.17)
Martinez-Sanz, 2020	Retrospective	260/969	6 (3-9) [c]	68 (57-80) [c]	65 (55-76) [c]	59	73	In patients with CRP>150mg/L, tocilizumab associated with decreased risk of death (aHR 0.34; 95% CI 0.16-0.72) and ICU admission or death (aHR 0.38; 95% CI 0.19-0.81), but not in those with CRP <150mg/L. For all patients, tocilizumab not associated with risk of death (HR 0.77; 95% CI 0.48-1.22)
# Narain, 2020	Retrospective	73/3076	N/R	65 (54-77) [c]	62 (55-69) [c]	65	71	No effect on mortality (aHR 0.79; 95% CI 0.47-1.32)
Nasa, 2020	Retrospective	22/63	N/R	52 [a]	51 [a]	95	100	mortality at day 7 and 28 was significantly lower in the tocilizumab group (p = 0.007 and p = 0.001 respectively).
Patel, 2020	Retrospective	42/41	19 (5.5) [c]	67 (20-91) [b]	68 (25-96) [b]	49	50	CRP improved in all tocilizumab patients. No difference in mortality with tocilizumab but more patients discharged compared with controls (55% vs 24%)
* Petrak, 2020	Retrospective	81/37	N/R	62.3 (12.9)[a]	56.3 (12.7) [a]	57	67	No difference between tocilizumab and mortality (aOR 0.83; 95%CI 0.34-1.98). However early therapy was associated with reduced mortality (aOR 0.15; 95%CI 0.04-0.5)
Pettit, 2020	Retrospective	74/74	58	65 (16) [a]	66 (14) [a]	45	58	Mortality rate higher in tocilizumab cohort (39% vs 23%; p=0.03).
Potere, 2020	Retrospective	10/10	N/R	56 (49-60) [c]	55 (54-60) [c]	60	60	Tocilizumab associated with reduction in CRP over three days. None of the tocilizumab patients had disease progression (requirement of oxygen or mechanical ventilation) whereas progression occurred in 50% of control group
*Ramaswamy, 2020	Retrospective	21/65	N/R	64 (16) [a]	63 (16) [a]	55	62	Mortality lower in tocilizumab group (HR 0.25; 95% CI 0.07-0.9)

Rodriguez-Bano, 2020	Retrospective	88/344	21	69 (59-76) [c]	66 (56-72) [c]	69	72	Tocilizumab associated with reduced risk of death (aHR 0.12; 95% CI 0.02-0.56) and reduced risk of composite outcome of intubation or death (aHR 0.32; 95% CI 0.15-0.67)
Rojas-Marte, 2020	Retrospective	96/97	14.5 (8.8) [a]	62 (14) [a]	58 (14) [a]	[a]65	77	Similar mortality in both groups (52% vs 61%; p=0.09)
Roomi, 2020	Retrospective	32/144	N/R	66	58	45	64	No difference in hospital mortality (aOR 0.28; 95% CI 0.05-1.4), IMV (aOR 1.2;95% CI 0.49-2.9) and hospital discharge (aOR 0.78;95% CI 0.28-2.1). Reduction in CRP levels on day 7 compared with control (21% vs 56%; OR 0.21; 95% CI 0.08-0.55
Rosas, J., 2020	Retrospective	20/17	30	73.8 (14.8)[a]	59.4 (14.5) [a]	65	75	Mortality was 20% in tocilizumab group and 35% in control group. Admission to ICU was 65% in tocilizumab and 0% in control
Rossi, 2020	Retrospective	84/84	28	64 (17) [a]	65 (13) [a]	58	66	Tocilizumab associated with reduced mortality (aHR 0.42; 95% CI 0.22-0.82), and reduced composite of mortality or IMV (aHR 0.34; 95% CI 0.22-0.52)
Rossotti, 2020	Retrospective	74/148	N/R	59 (52-70) [c]	59 (51-71) [c]	81	82	Tocilizumab associated with reduced mortality (unadjusted HR 0.49; 95% CI 0.26-0.95), but longer hospital stay (HR 1.66; 95% CI 1.09-2.52)
Ruiz-Antoran, 2020	Retrospective	268/238	12 (7-18) [b]	71 14) [a]	65 (12) [a]	59	69	Mortality lower in patients treated with tocilizumab than controls (16.8% vs. 31.5%, aHR 0.74; 95%CI 0.62-0.89)
Somers, 2020	Retrospective	78/76	N/R	60 (15) [a]	55 (15) [a]	64	68	Tocilizumab associated with lower risk of death (aHR 0.55; 95% CI 0.33-0.9)
Tian, 2020	Retrospective	65/130	NR	67.5 (61-75) [c]	71(63-75) [c]	63	74	Mortality lower in tocilizumab group (aHR 0.47; 95%CI 0.25-0.9)
Tsai, 2020	Retrospective	66/66	N/R	61 (16) [a]	62 (14) [a]	76	70	No difference in mortality between two groups (OR 1.0;95% CI 0.465-2.151)
* Wadud, 2020	Retrospective	44/50	N/R	66 [b]	56 [b]	70	84	Lower mortality in tocilizumab group (38.6% vs. 52%; p<0.001)

Zheng, 2020	Retrospective	92/89	28 (6-62) [b]	67 (25-85) [b]	69 (25-87) [b]	53	62	Increased mortality in tocilizumab group, but significant reduction in CRP level at 1 week

Supplementary Table 2 – Patient characteristics and outcomes of included studies. Absolute numbers reported for follow up days unless otherwise statement. Number of males in control and intervention group reported as percentage (%)

[a], mean and standard deviation; [b], median and range; [c], median and interquartile range; aHR, adjusted hazard ratio; CI, confidence interval; CRP, C-reactive protein; ICU, intensive care unit; IL6, interleukin-6; IMV, invasive mechanical ventilation; IV, intravenous; N/R, not reported; OR, odds ratio; SC, subcutaneous; -, not available; * non peer-reviewed preprint study #, study investigating both anakinra and tocilizumab

Randomised controlled trials						
	Tocilizumab					
	Gordon 2021 *	Hermine 2020	Rosas, I. 2020 *	Salama 2020	Salvarani 2020	Stone 2020
Randomisation	Low	Low	Low	Low	Low	Low
Intervention assignment	Low	High	Low	Low	High	Low
Intervention adherence	Low	Some concern	Low	Low	Some concern	Low
Missing data	Some concern	Low	Low	Low	Low	Low
Outcome	Low	Low	Low	Low	Low	Low
Results	Low	Low	Low	Low	Low	Low
Overall risk of bias	Low	Some concern	Low	Low	Some concern	Low

Supplementary Table 3(a) – Risk of bias assessment for randomised clinical trials using Cochrane risk of bias 2 tool. Risk of bias was assessed in six categories and scored as either low risk of bias, some concern, or high risk of bias, before an overall risk of bias was given to each study.

* non peer-reviewed preprint study

Prospective studies														
	Tocilizumab													
	Albertini 2020	Antony 2020	Campins 2020	Carvalho 2020 *	Dastan 2020	Malekzadeh, 2020	Mikulsa 2020	Morena 2020	Perrone 2020	Roumier, 2020	Sanchez-Motalva 2020 *	Sciascia 2020	Strohbehn 2020	Toniati 2020
1	+	+	-	+	+	+	+	+	+	+	+	-	+	+
2	+	+	-	+	+	+	+	+	+	+	+	+	+	+
3	+	+	CD	CD	+	CD	+	+	+	+	+	CD	+	+
4	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5	-	-	-	-	-	-	-	-	+	+	-	-	-	-
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	-	CD	+	+	+	+	+	+	+	+	+	+	+
8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
9	-	+	-	-	+	+	-	+	+	+	-	-	+	-
10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11	+	-	-	+	+	+	+	+	+	+	+	+	+	-
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	+	+	CD	+	+	+	+	+	+	+	+	+	+	+
14	-	-	-	+	-	-	+	+	-	+	+	-	+	-
Total	8	7	2	8	9	8	9	10	10	11	9	6	10	7
Rating	**Fair**	**Fair**	**Poor**	**Fair**	**Fair**	**Fair**	**Fair**	**Good**	**Good**	**Good**	**Fair**	**Poor**	**Good**	**Fair**

Prospective studies									
	Anakinra				Sarilumab				Siltuximab
	Balkhair, 2020	Huet 2020	Kooistra, 2020	Kyriazopoulou, 2020 *	Benucci 2020	Della-Torre 2020	Sinha 2020	Gremese 2020	Gritti 2020 *
1	+	+	+	+	+	+	+	+	+
2	+	+	+	+	-	+	+	+	+
3	+	+	+	+	CD	+	+	+	+
4	+	+	-	+	-	+	+	+	+
5	+	+	-	+	-	-	-	-	-
6	+	+	+	+	+	+	+	+	+
7	+	CD	+	+	+	+	+	+	+
8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
9	+	+	+	+	+	+	+	+	+
10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11	+	+	+	+	+	+	+	+	+
12	-	-	-	-	-	-	-	-	-
13	+	+	+	+	+	+	+	+	+
14	-	+	-	+	-	+	+	-	+
Total	10	10	8	10	6	10	10	9	10
Rating	**Good**	**Good**	**Fair**	**Good**	**Poor**	**Good**	**Good**	**Fair**	**Good**

Supplementary Table 3(b). Risk of bias assessment for prospective studies. Questions numbered in the first column. 1. Was the research question or objective in this paper clearly stated? 2. Was the study population clearly specified and defined? 3. Was the participation rate of eligible persons at least 50%? 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? 5. Was a sample size justification, power description, or variance and effect estimates provided? 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 10. Was the exposure(s) assessed more than once over time? 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 12. Were the outcome assessors blinded to the exposure status of participants? 13. Was loss to follow-up after baseline 20% or less? 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

+, criteria satisfied; - , not satisfied; N/A, not applicable; CD, cannot determine; * non peer-reviewed preprint study

Retrospective studies																		
	Tocilizumab																	
	Biran 2020	Canziani 2020	Capra 2020	Chillmuri, 2020	De Rossi 2020	Eimer 2020	Fisher, 2020	Galvan-Roman 2020	Garcia 2020 *	Gokhale 2020	Guaraldi 2020	Guisado-Vasco 2020	Gupta 2020	Hill 2020	Holt 2020	Ip 2020	Kewan 2020	Kimmig 2020
1	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
2	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
3	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	CD	+	+	+
5	+	+	+	-	+	-	+	CD	-	+	-	+	+	-	CD	+	-	CD
6	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
7	+	+	+	+	+	+	CD	CD	+	+	+	+	+	+	CD	+	+	+
8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10	-	-	-	-	-	+	+	+	+	+	-	-	+	-	+	+	+	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+
Total	8	8	9	7	9	7	8	6	7	8	7	7	9	7	6	9	8	7
Rating	**Fair**	**Fair**	**Good**	**Fair**	**Good**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Good**	**Fair**	**Fair**	**Good**	**Fair**	**Fair**

Retrospective studies																		
	Tocilizumab																	
	Klopfenstein 2020	Lewis, 2020	Martinez-Sanz 2020	Narain 2020	Nasa 2020	Patel 2020	Petrak 2020 *	Pettit 2020	Potere 2020	Ramaswamy 2020 *	Rodriguez-Bano 2020	Rojas-Marte 2020	Roomi 2020	Rosas, J.2000	Rossi 2020	Rossotti 2020	Ruiz-Antoran 2020	Somers 2020
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	+	+	+	+	-	+	+	+	+	+	+	+	CD	CD	+	+	+	+
5	-	+	-	+	-	-	+	+	+	+	+	CD	-	-	+	+	CD	CD
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+	+	CD	CD	CD	+	+	+	CD
8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10	-	+	-	-	-	CD	-	-	+	+	CD	CD	-	+	+	+	-	+
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	+	+	+	-	-	+	-	-	+	+	-	+	-	+	+	+	+
Total	6	9	7	8	5	5	8	7	8	9	8	4	4	5	9	9	7	7
Rating	**Poor**	**Good**	**Fair**	**Fair**	**Poor**	**Poor**	**Fair**	**Fair**	**Fair**	**Good**	**Fair**	**Poor**	**Poor**	**Poor**	**Good**	**Good**	**Fair**	**Fair**

Retrospective studies							
	Tocilizumab				Anakinra		
	Tian 2020	Tsai 2020	Wadud 2020 *	Zheng 2020	Cauchois 2020	Cavalli 2020	Narain 2020
1	+	+	-	+	+	+	+
2	+	+	-	+	+	+	+
3	-	-	-	-	-	-	-
4	+	+	+	CD	+	+	+
5	+	+	-	-	+	+	+
6	+	+	+	+	+	+	+
7	+	+	CD	CD	+	+	+
8	-	-	-	-	-	-	-
9	+	+	+	+	+	+	+
10	+	+	-	+	+	+	-
11	-	-	-	-	-	-	-
12	+	+	-	-	-	-	+
Total	9	9	3	5	8	8	8
Rating	**Good**	**Good**	**Poor**	**Poor**	**Fair**	**Fair**	**Fair**

Supplementary Table 3(c). Risk of bias assessment for Retrospective studies. 1. Was the research question or objective in this paper clearly stated and appropriate? 2. Was the study population clearly specified and defined? 3. Did the authors include a sample size justification? 4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? 5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? 6. Were the cases clearly defined and differentiated from controls? 7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? 8. Was there use of concurrent controls? 9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? 10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? 11. Were the assessors of exposure/risk blinded to the case or control status of participants? 12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

+, criteria satisfied; - , not satisfied; N/A, not applicable; CD, cannot determine; * non peer-reviewed preprint study

Author, year	Study design	N Treatment/ Control	Outcome recorded (day)	Control				Intervention			
				Dead	Ventilated	Hospitalised	Discharged	Dead	Ventilated	Hospitalised	Discharged
ANAKINRA											
Balkhair, 2020	Prospective with control	45/24	14	2	11	5	6	5	9	6	25
Huet, 2020	Prospective with control	52/44	-	32 #	-	-	-	13 #	-	-	-
Kooistra, 2020	Prospective with control	21/39	28	7	-	-	-	4	-	-	-
*Kyriazopoulou, 2020	Prospective with control	130/130	30	16	-	-	-	6	-	-	-
Cauchois, 2020	Retrospective	12/10	15	1	1	6	2	0	0	3	9
Cavalli, 2020	Retrospective	29/16	21	7	1	1	7	3	5	8	13
Narain, 2020	Retrospective	57/3076	-	-	-	-	-	-	-	-	-
SARILUMAB											
Benucci, 2020	Prospective	8/0	14	-	-	-	-	1	0	0	7
Della-Torre, 2020	Prospective with control	28/28	28	5	2	4	17	2	4	5	17
* Gordon, 2021	Adaptive RCT	45/397	14	Adjusted OR for improvement – 1.86 (95%CI 1.22-2.91)							
Gremese, 2020	Prospective	53/0	15	-	-	-	-	2	7	25	19
Sinha, 2020	Prospective	255/0	25	-	-	-	-	28	1	9	218
SILTUXIMAB											
* Gritti, 2020	Prospective with cohort	30/30	15	-	-	-	-	6	11	8	5
TOCILIZUMAB											
Albertini, 2020	Prospective with control	22/22	14	0	6	14	2	1	4	16	1
Antony, 2020	Prospective	80/0	N/R	-	-	-	-	7	9	-	-
Campins, 2020	Prospective	58/0	N/R	-	-	-	-	8	-	-	-

* Carvalho, 2020	Prospective with control	29/24	14	4	-	-	-	5	-	-	-
Dastan, 2020	Prospective	42/0	15	-	-	-	-	6	6	11	19
* Gordon, 2021	Adaptive RCT	350/397	14	Adjusted OR for improvement – 1.83 (95%CI 1.40-2.41)							
Hermine, 2020	Open label RCT	63/67	14	6	11	20	30	7	3	21	32
Malekzadeh, 2020	Prospective	126/0	14	-	-	-	-	24	9	7	86
Mikulska, 2020	Prospective with control	29/66	14	16	-	-	-	4	2	-	-
Morena, 2020	Prospective	51/0	15	-	-	-	-	14	2	35	0
Perrone, 2020	open-label phase 2 trial	180/121	14	27	-	-	-	27	-	-	-
Perrone, 2020	Prospective with control	528/360	14	45	-	-	-	56	-	-	-
* Rosas, I., 2020	phase 3 RCT	294/144	28	28	23	22	71	50	44	26	166
Roumier, 2020	Prospective with control	49/47	28	5	-	-	33	6	-	-	23
Salama, 2020	Double-blind RCT	249/128	28	11	-	-	-	26	-	-	-
Salvarani, 2020	Open label RCT	60/63	14	1	5	21	36	1	6	19	34
* Sanchez-Montalva, 2020	Prospective	82/0	7	-	-	-	-	22	14	12	34
Sciascia, 2020	Prospective	63/0	14	-	-	-	-	7	2	-	-
Stone, 2020	Double blind RCT	161/82	28	3	-	-	72	9	-	-	147
Strohbehn, 2020	Phase 2 open label	32/41	28	-	-	-	-	5	-	-	-
Toniati, 2020	Prospective	100/0	10	-	-	-	-	20	-	-	15
Biran, 2020	Retrospective	210/420	N/R	-	-	-	-	102	-	-	135
Canziani, 2020	Retrospective	64/64	N/R	24	-	-	-	17	-	-	-
Capra, 2020	Retrospective	62/23	9	11	4	0	8	2	5	32	23
Chillmuri, 2020	Retrospective	83/685	N/R	-	-	-	-	-	-	-	-
De Rossi, 2020	Retrospective	90/68	N/R	34	6	-	-	7	13	-	-
Eimer, 2020	Retrospective	22/22	30	7	5	7	3	5	1	4	12

Fisher, 2020	Retrospective	45/70	30	28	-	-	-	13	-	-	-
Galvan Roman, 2020	Retrospective	58/88	61	16	-	-	-	14	-	-	-
* Garcia, 2020	Retrospective	77/94	14	-	-	-	71	-	-	-	65
Gokhale, 2020	Retrospective	70/91	N/R	61	-	-	30	33	2	9	26
Guaraldi, 2020	Retrospective	179/365	14	60	117	-	-	9	42	-	-
Guisado-Vasco, 2020	Retrospective	132/475	N/R	97	-	-	-	44	-	-	-
Gupta, 2020	Retrospective	433/3492	27	1419	-	-	-	125	-	-	-
Hill, 2020	Retrospective	43/45	28	15	0	3	27	9	6	2	26
Holt, 2020	Retrospective	24/30	N/R	-	-	-	-	-	-	-	-
Ip, 2020	Retrospective	134/413	30	231	-	-	-	62	-	-	-
Kewan, 2020	Retrospective	28/23	14	2	7	4	10	3	10	5	10
Kimmig, 2020	Retrospective	54/57	N/R	11	-	-	34	19	-	-	18
Klopfenstein, 2020	Retrospective	20/25	N/R	12	-	-	11	5	-	-	11
Lewis, 2020	Retrospective	497/497	N/R	211	-	-	283	145	-	-	332
Martinez-Sanz, 2020	Retrospective	260/969	N/R	120	-	-	-	61	-	-	-
Narain, 2020	Retrospective	73/3076	N/R	-	-	-	-	-	-	-	-
Nasa, 2020	Retrospective	22/63	28	36	-	-	-	2	-	-	-
Patel, 2020	Retrospective	42/41	7	11	-	7	7	9	-		7
* Petrak, 2020	Retrospective	81/37	N/R	-	-	-	-	-	-	-	-
Pettit, 2020	Retrospective	74/74	N/R	17	-	-	-	29	-	-	-
Potere, 2020	Retrospective	10/10	14	0	1	4	5	0	0	2	8
* Ramaswamy, 2020	Retrospective	21/65	N/R	8	-	-	-	3	-	-	-
Rodriguez-Bano, 2020	Retrospective	88/344	21	41	20	30	253	2	6	10	70
Rojas-Marte, 2020	Retrospective	96/97	N/R	55	-	-	-	43	-	-	
Roomi, 2020	Retrospective	32/144	N/R	13	-	-	38	6	-	-	25
Rosas,J., 2020	Retrospective	20/17	30	6	-	-	-	4	-	-	-
Rossi, 2020	Retrospective	84/84	N/R	-	-	-	-	-	-	-	-
Rossotti, 2020	Retrospective	74/148	NR	-	-	-	-	8	18	45	14
Ruiz-Antoran, 2020	Retrospective	268/238	N/R	75	-	-	-	45	-	-	-
Somers, 2020	Retrospective	78/76	14	28	15	11	22	14	21	12	31
Tian, 2020	Retrospective	65/130	N/R	42	-	-	-	14	-	-	-
Tsai, 2020	Retrospective	66/66	N/R	18	-	-	-	18	-	-	-

* Wadud, 2020	Retrospective	44/50	N/R	26	-	-	-	17	-	-	-
Zheng, 2020	Retrospective	92/89	27.5	1	0	0	88	9	0	0	83

Supplementary Table 4 – Primary clinical outcome. Outcome scores presenting using absolute scores with number of individuals in each category, using adapted ordinal outcome scores 1 indicates death, 2 described hospitalised patients requiring invasive ventilatory support, 3 describes patients not requiring invasive ventilatory support but still hospitalised, 4 describes discharged patients. Day outcomes reported shown where applicable.
* non peer-reviewed preprint study, CI, confidence interval
# death or ventilation

Retrospective studies								
Variables	Generalised odds ratios for ordinal outcomes (N=10)		Difference in duration of hospitalisation (N=9)		Adjusted hazard ratios for mortality (N=18)		Risk ratios for mortality (N=31)	
	R^2	P value	R^2	P value	R^2	P value	R^2	P value
Steroid use	0.00	0.7921	7.17	0.2305	0.00	0.9710	0.00	0.5252
Peer review	N/A	N/A	N/A	N/A	0.9	0.5638	0.00	0.4137
Route of administration	4.75	0.3526	81.64	<0.001	0.00	0.3921	2.68	0.2053
Single centre	0.00	0.6028	11.03	0.2013	2.96	0.4103	0.00	0.2154
Outcome day	0.00	0.7921	N/A	N/A	99.99	0.0818	9.54	0.4141
Prospective studies								
Variables	Generalised odds ratios for ordinal outcomes (N=5)		Difference in duration of hospitalisation (N=1)		Adjusted hazard ratios for mortality (N=4)		Risk ratios for mortality (N=11)	
	R^2	P value	R^2	P value	R^2	P value	R^2	P value
Steroid use	99.99	<0.0001	N/A	N/A	45.29	0.3464	0.00	0.9050
Peer review	0.00	0.4890	N/A	N/A	N/A	N/A	0.00	0.5764
Route of administration	N/A	N/A	N/A	N/A	45.29	0.3464	69.89	0.5922
Single centre	0.00	0.5332	N/A	N/A	0.00	0.2425	0.00	0.8638
Outcome day	0.00	0.5351	N/A	N/A	0.00	0.7187	0.00	0.6115

Supplementary Table 5 - Results of meta-regression for variables assessed separated by study design (retrospective and prospective) and study outcomes. Study numbers for each outcome shown (N). R^2 and p values from meta-regression shown were applicable.
N/A, not applicable.

Outcome	The GRADE domains	Ratings for quality of evidence
Ordinal scale (12 studies; 4 prospective and 8 retrospective. Total of 1782 patients)	Risk of bias	Of the 4 prospective included, 3 RCTs of low/moderate risk of bias included. Retrospective studies generally of fair quality, although cannot exclude failure to control confounding factors.
	Imprecision	No serious imprecision, with appropriately narrow 95% confidence intervals. Outcome based on 1782 patients.
	Inconsistency	High inconsistency with significant heterogeneity in both prospective and retrospective studies.
	Indirectness	No serious indirectness. All studies included a control arm from the same population. All study subjects had Covid-19, although severity and participation criteria were inconsistent.
	Publication bias	No publication bias as indicated by funnel plots and Egger's tests
	Certainty of evidence	Moderate certainty of evidence.
Difference in duration of hospitalisation (9 retrospective studies, 1 RCT. Total of 2285 patients)	Risk of bias	All included retrospective studies with moderate/high risk of bias. Confounding factors were poorly controlled for.
	Imprecision	Serious imprecision, with studies showing shorter and longer duration of hospitalisation with tocilizumab. Appropriately narrow 95% confidence intervals.
	Inconsistency	High inconsistency with significant heterogeneity (I^2 = 93.8%).
	Indirectness	No serious indirectness. All studies included a control arm from the same population. All study subjects had Covid-19, although severity and participation criteria were inconsistent.
	Publication bias	No publication bias as indicated by funnel plots and Egger's tests

	Certainty of evidence	Low certainty of evidence.
Overall mortality (aHR - 22 studies. Total of 13,702 patients. RR - 42 studies, 15,085 patients)	Risk of bias	RCTs of low/moderate risk of bias included.
	Imprecision	No imprecision present
	Inconsistency	High inconsistency in retrospective studies, but not in prospective studies.
	Indirectness	No serious indirectness. All studies included a control arm from the same population. All study subjects had Covid-19, although severity and participation criteria were inconsistent
	Publication bias	No publication bias as indicated by funnel plots and Egger's tests
	Certainty of evidence	High certainty of evidence.

Supplementary Table 6 – GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to rate the quality of evidence on the effects of tocilizumab