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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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

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.

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
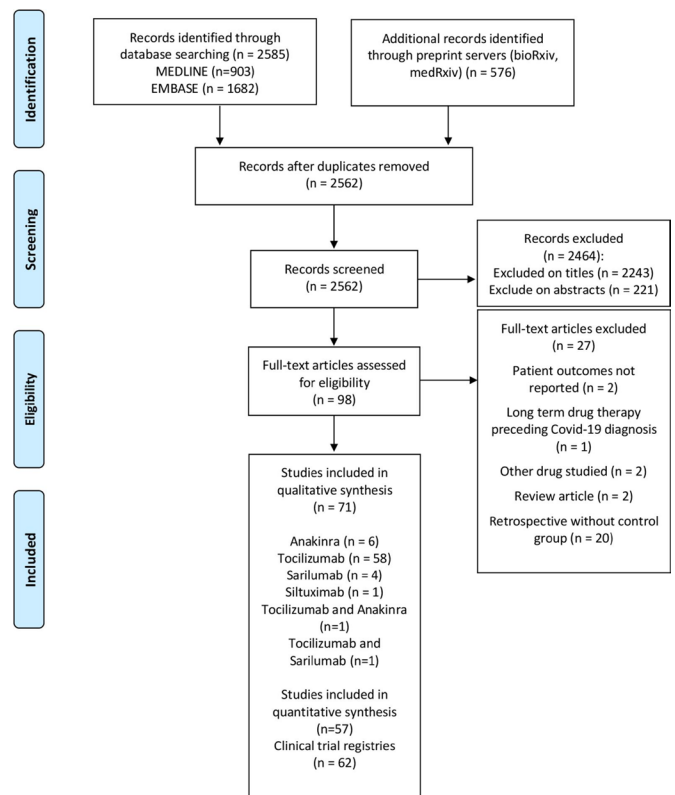

Figure 1 Flow diagram illustrates systematic search and screening strategy, including numbers meeting eligibility criteria and numbers excluded. Last search carried out on 7 January, 2021.

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

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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).
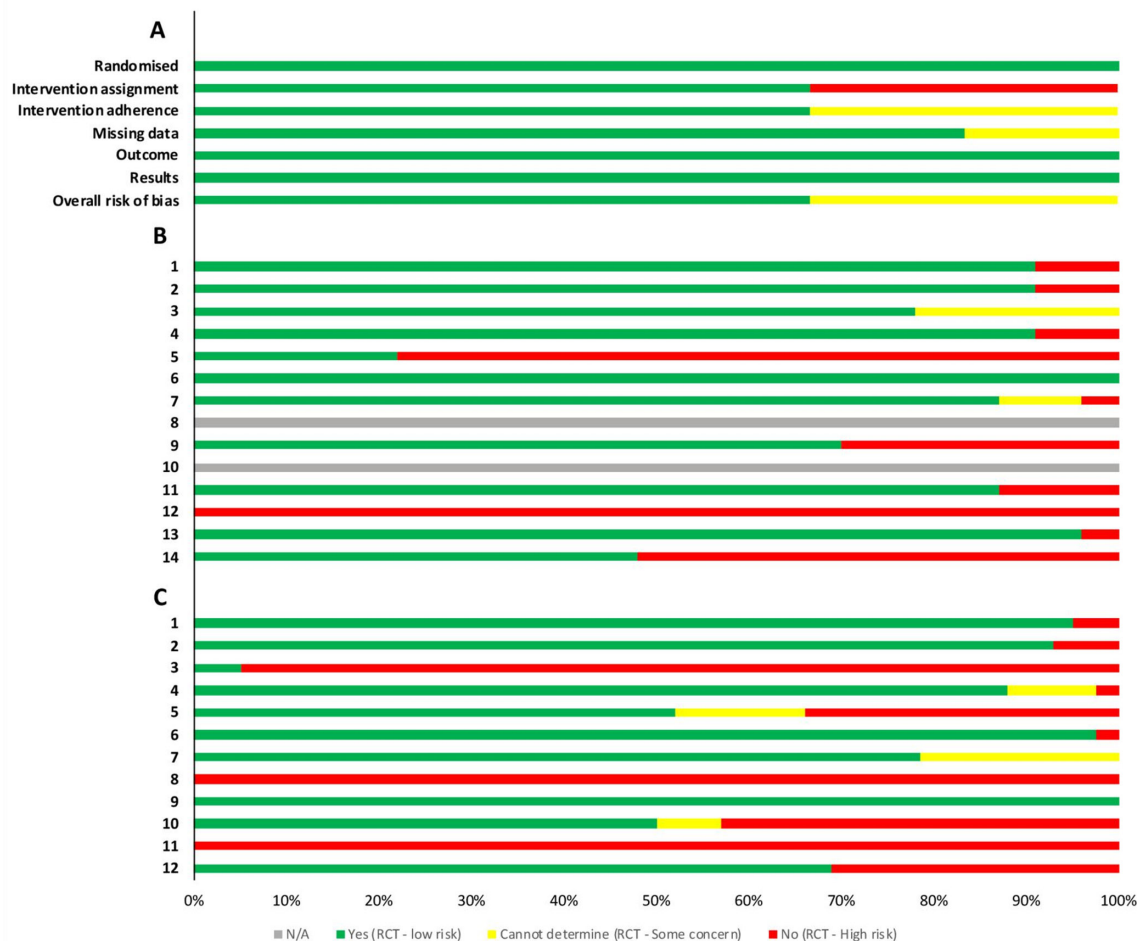
Figure 2 - Summary of risk of bias assessment. (A) Randomised clinical trials assessed using Cochrane risk of bias 2 tool (n=6). Risk of bias was assessed in six categories and scored as either low risk of bias, some concern, or high risk of bias, before an overall risk of bias was given to each study. (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
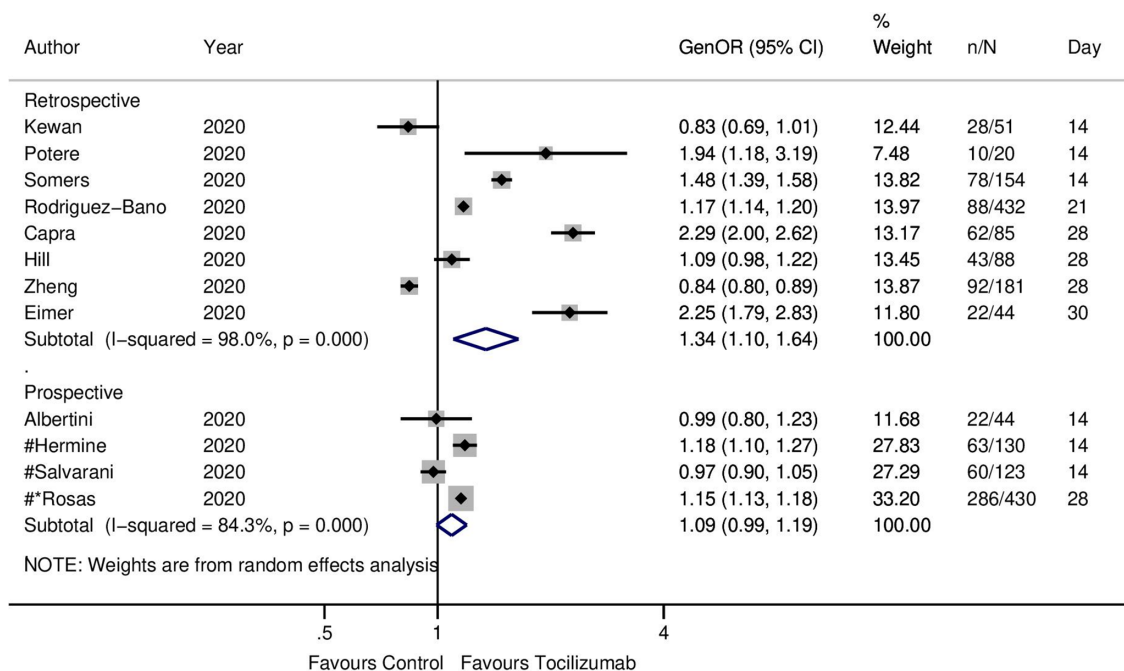
Figure 3 Tocilizumab generalised ORs for ordinal outcome forest plot. GenOR shown for each study with 95% CI and day at which ordinal outcome was recorded. Sample sizes given for patients receiving intervention (n) alongside total patients included (N) in the study. Summary estimates presented separately 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
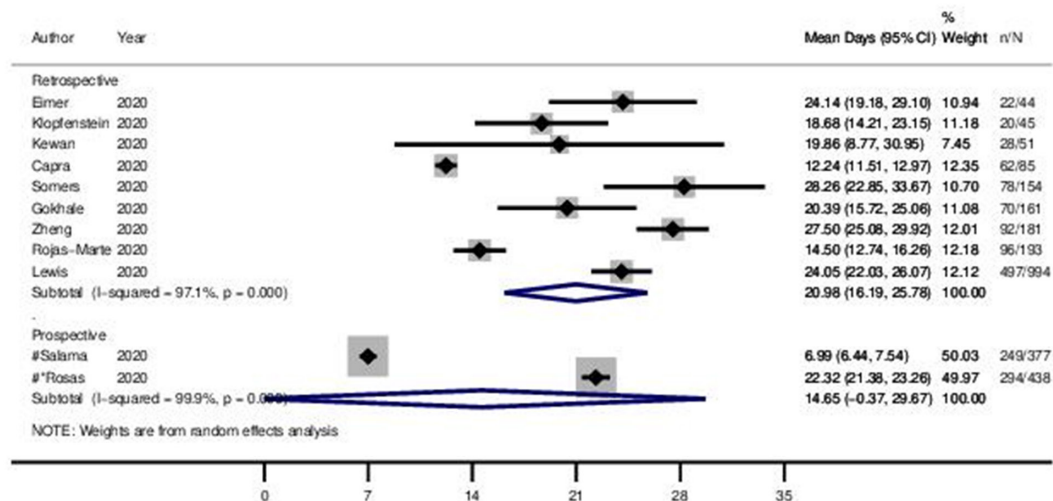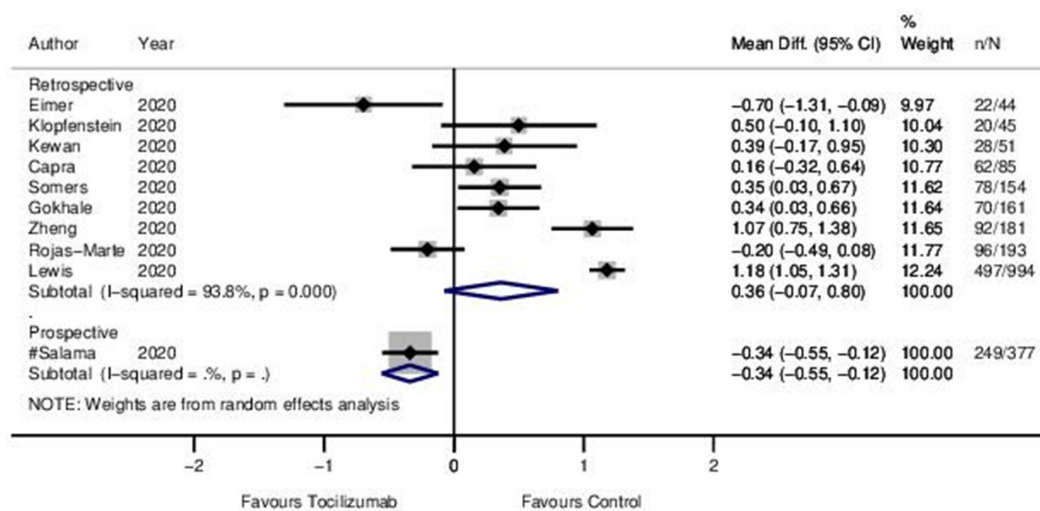
Figure 4 Tocilizumab duration of hospitalisation (days) forest plot. (A) Mean duration of hospital stay. (B) Mean difference compared with controls in duration of hospital stay. Effect sizes and associated 95% CIs presented for each study. Sample sizes given for patients receiving intervention (n) and 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
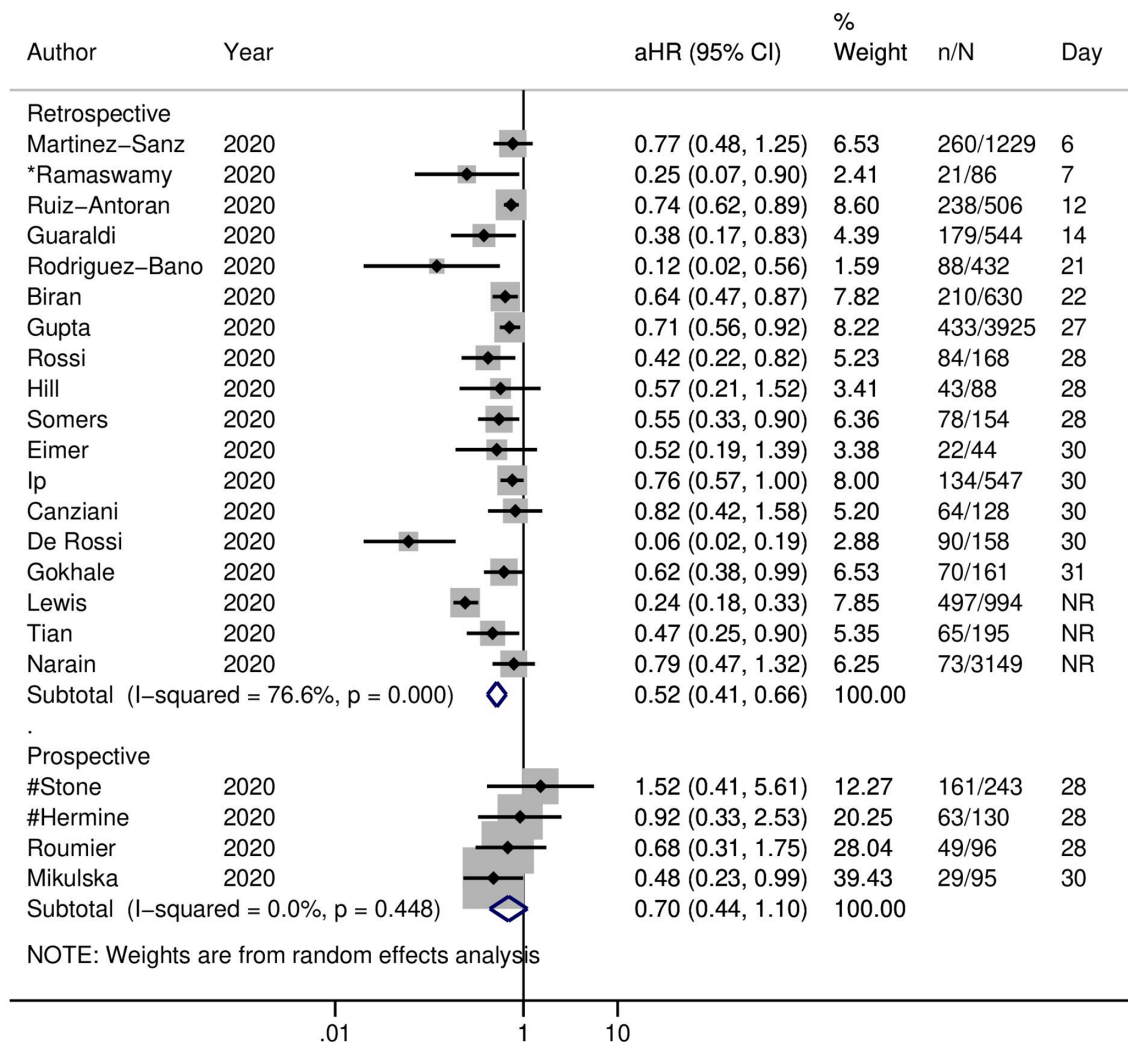
Author	Year		aHR (95% CI)	% Weight	n/N	Day
Retrospective						
Martinez–Sanz	2020		0.77 (0.48, 1.25)	6.53	260/1229	6
*Ramaswamy	2020		0.25 (0.07, 0.90)	2.41	21/86	7
Ruiz–Antoran	2020		0.74 (0.62, 0.89)	8.60	238/506	12
Guaraldi	2020		0.38 (0.17, 0.83)	4.39	179/544	14
Rodriguez–Bano	2020		0.12 (0.02, 0.56)	1.59	88/432	21
Biran	2020		0.64 (0.47, 0.87)	7.82	210/630	22
Gupta	2020		0.71 (0.56, 0.92)	8.22	433/3925	27
Rossi	2020		0.42 (0.22, 0.82)	5.23	84/168	28
Hill	2020		0.57 (0.21, 1.52)	3.41	43/88	28
Somers	2020		0.55 (0.33, 0.90)	6.36	78/154	28
Eimer	2020		0.52 (0.19, 1.39)	3.38	22/44	30
Ip	2020		0.76 (0.57, 1.00)	8.00	134/547	30
Canziani	2020		0.82 (0.42, 1.58)	5.20	64/128	30
De Rossi	2020		0.06 (0.02, 0.19)	2.88	90/158	30
Gokhale	2020		0.62 (0.38, 0.99)	6.53	70/161	31
Lewis	2020		0.24 (0.18, 0.33)	7.85	497/994	NR
Tian	2020		0.47 (0.25, 0.90)	5.35	65/195	NR
Narain	2020		0.79 (0.47, 1.32)	6.25	73/3149	NR
Subtotal (I–squared = 76.6%, p = 0.000)			0.52 (0.41, 0.66)	100.00		
.						
Prospective						
#Stone	2020		1.52 (0.41, 5.61)	12.27	161/243	28
#Hermine	2020		0.92 (0.33, 2.53)	20.25	63/130	28
Roumier	2020		0.68 (0.31, 1.75)	28.04	49/96	28
Mikulska	2020		0.48 (0.23, 0.99)	39.43	29/95	30
Subtotal (I–squared = 0.0%, p = 0.448)			0.70 (0.44, 1.10)	100.00		

NOTE: Weights are from random effects analysis

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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,
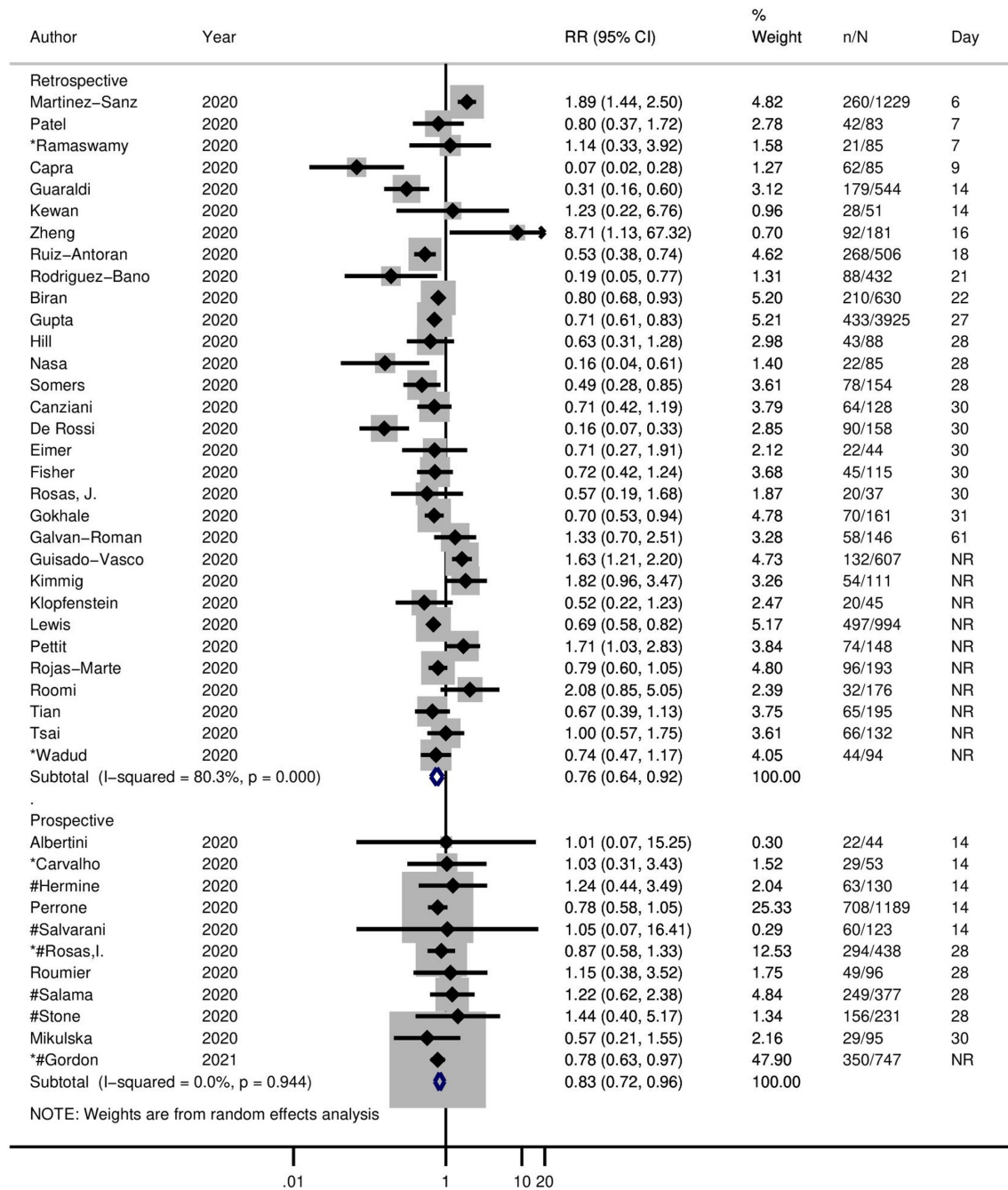
Figure 6 Tocilizumab mortality risk ratios (RRs) forest plot. RRs with associated 95% CI and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total patients included in the study (N). Summary estimates presented separately for prospective and 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.

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