# A 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 published 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 7th 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, six were randomised controlled studies. Most explored outcomes in patients who received tocilizumab (59/71). In prospective studies, tocilizumab was associated with improved survival (RR 0.83 95%CI 0.72;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 odds ratio 1.34 95%CI 1.10;1.64, $I^2$=98%) and reduced mortality (HR 0.54 95%CI 0.40;0.72, $I^2$ =86.6%). The mean difference in duration of hospitalisation was 0.36 days (95%CI -0.07;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**

Meta-analysis revealed tocilizumab was associated with reduced mortality in prospective studies, with an inconclusive effect for other outcomes. Current evidence for the efficacy of anakinra, siltuximab or sarilumab in Covid-19 is insufficient. Adequately powered, high-quality studies are urgently needed for conclusive findings.

## INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China in December 2019(1). Since then, coronavirus disease 2019 (Covid-19) has been declared a global pandemic by the World Health Organisation (WHO) and continues to spread at an exponential rate with almost 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 (ARDS), multi-organ 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 (CSS)(4). During this state of immunological hyperactivation, increased circulating levels of pro-inflammatory cytokines including interleukin (IL)-1 and IL-6 have been demonstrated, and are associated with adverse clinical outcomes (5-7). Suppression of pro-inflammatory 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 severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome (MERS)(9, 10). There are also reports of elevated pro-inflammatory 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, whilst concurrently drawing on literature from previous similar coronavirus infections (SARS and MERS). 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 pre-specified protocol (PROSPERO registration number: CRD42020176375), and has been reported in accordance with PRISMA (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, EU Clinical Trials Register and the Chinese Clinical Trial Registry), with the last search carried out on 7th January 2021. Search terms were kept broad and included keywords and controlled vocabulary for patient and treatment-related terms (see supplementary appendix for MEDLINE search strategy). Unpublished and ongoing studies were identified by searching pre-print 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 excluding case reports, evaluating the use of at least one of anakinra, tocilizumab, sarilumab or siltuximab in patients aged over 18 with either suspected or confirmed Covid-19, SARS or MERS. 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 four-point ordinal scale at day 15 following intervention, with the following ratings: i) death; ii) requirement for invasive mechanical ventilation (IMV) or ECMO; iii) hospitalised but no requirement for IMV/ECMO; iv) not hospitalised. Secondary outcomes included time to clinical improvement (days), duration of mechanical ventilation (days), overall mortality, mortality at 28 days 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 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 included in the review, 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 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 odds ratio (GenOR) with 95% confidence intervals (CI). The GenOR provides a measure of the likelihood

that the intervention leads to a better rather than worse outcome when compared to a randomly chosen control (17). Mean hospital duration and standard deviation (SD) were extracted or were estimates from median and range/interquartile range (IQR) using the Box-Cox method (18). Mean difference in hospital stay was calculated where a control arm was reported. Where available, adjusted hazard ratios (HR) 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, use of concomitant steroids, route of drug administration (intravenous or subcutaneous) and day outcome measured. Publication bias was assessed using funnel plot analysis and Egger's test. 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, TX, USA).

## RESULTS

Search of the electronic databases (MEDLINE and EMBASE) on 7th January 2021 yielded a total of 2585 studies, with a 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). 62 studies were published in peer-reviewed journals, with the remaining 9 identified through preprint servers. All studies were performed in patients with Covid-19, with no suitable studies identified for SARS or MERS. Twenty-nine studies were prospective in design, with seventeen studies including a control group for comparison, of which six 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 14730 (67%) received SOC alone. Individual study characteristics for the published studies are presented in Tables 1 and 2.

Risk of bias assessment of the retrieved studies identified multiple limitations and highlighted a number of biases (Figure 2). 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 (Supplementary Appendix)

**Tocilizumab**

Twelve 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. Amongst 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 administration was not entirely consistent with intravenous 8mg/kg or 400mg 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. The median time for reporting outcomes after treatment was 14 days (IQR 14-28). The recently published, REMAP-CAP trial suggested tocilizumab was associated with clinical improvement at day 14 (aOR 1.83 95%CI 1.40;2.41)(20), but in another RCT, outcomes on an ordinal scale did not differ between the treatment groups (HR 1.06 95%CI 0.80;1.41)(21). Neither of these RCTs were included in the meta-analysis as there was significant heterogeneity in methods of reporting ordinal outcomes. The remaining prospective studies, including three RCTs, were combined in meta-analysis (Figure 3), and estimated tocilizumab was not associated with better outcomes (GenOR 1.09 95% CI 0.99;1.19, $I^2$ = 84.3%). Variability in reported concomitant steroid administration had a

significant contribution upon the substantial heterogeneity observed (Supplementary Appendix). When retrospective studies were included in meta-analysis, tocilizumab was associated with better outcomes, indicating a 34% greater chance of less-severe outcomes on the adapted ordinal scale when compared to control (GenOR 1.34 95% CI 1.10;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

Nine retrospective studies and two RCTs reported the duration of hospitalisation for a total of 1553 survivors who received tocilizumab (Figure 4). Retrospective studies reporting the duration of hospitalisation were combined to give an overall summary estimate (20.98 days 95%CI 16.19;25.78, $I^2$ = 97.1%), which was greater than the duration reported by combining the RCTs (14.55 days 95%CI -0.37;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;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). In an RCT comparing the duration of hospitalisation with controls, tocilizumab was associated with a reduced hospital stay (-0.34 days 95%CI -0.55;-0.12)(22). Similarly, another RCT found the time to hospital discharge was shorter with tocilizumab (aHR 1.41 95%CI 1.18;1.70)(20).

Overall mortality

Twenty-two studies totalling 13,702 patients reported adjusted hazard ratios for overall mortality, at a follow up time censored at a median of 28 days (IQR 14-30). Amongst 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;1.10, $I^2$ = 0%) (Figure 5). In the remaining retrospective studies, tocilizumab was associated with a 47% lower risk of adjusted mortality with substantial heterogeneity (HR 0.54 95%CI 0.41;0.71, $I^2$ = 85.9%). Meta-regression identified non-peer reviewed manuscripts as a significant source of heterogeneity ($R^2$ = 88.58, p<0.001).

Rate ratios (RR) were calculated from 42 studies, including six RCTs, reporting unadjusted mortality data for 15,085 patients at a median follow up of 24 days (IQR 14-28) (Figure 6). Tocilizumab was associated with a 17% reduced risk of mortality compared with the control arm in prospective studies (RR 0.83 95%CI 0.72;0.96, $I^2$ = 0.0%). In further subgroup analysis restricted to RCTs, summary estimates for mortality were inconclusive (RR 0.85 95%CI 0.71;1.01 $I^2$ = 0.0%) (Figure 7). Within retrospective studies, tocilizumab was associated with a 25% reduced risk of mortality (RR 0.76 95%CI 0.64;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).

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**Other immunomodulators**

Studies exploring outcomes in patients who received anakinra, sarilumab or siltuximab were not quantitively 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 200-600mg daily for anakinra, and 200-400mg 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 sub analysis are presented in Supplementary Figures 5-8.

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;2.06)(26). Two studies reported adjusted HRs for mortality with contrasting results. No association was observed in a retrospective study of 57 treated patients (aHR 0.79 95%CI 0.44;1.42)(27), whereas an association was observed in a prospective study of 130 patients (aHR 0.49 95%CI 0.26;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 0.12-0.71)(29). Risk ratios 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;0.79), but when prospective studies were pooled, there was no association of anakinra with mortality (RR 0.70 95%CI 0.31;1.58, $I^2$ = 32.8%) (Figure 8). 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, sarilumab was associated with increased survival (aOR 2.01 95%CI 1.18;4.71), reduced duration of hospitalisation (aHR 1.60 95%CI 1.17;2.40) and improved ordinal outcomes at day 14 (aOR 1.86 95%CI 1.22;2.91)(20). In a further non-randomised study of 28 participants (30), sarilumab did not influence mortality (aHR 0.36 95%CI 0.08;1.68) nor was intervention associated with improved ordinal outcomes on day 28 (GenOR 1.07 95%CI 0.90;1.27) whilst the duration of hospitalisation was comparable amongst treated and non-treated patients (mean difference 0.02 95%CI -0.51;0.54). The combined CFR across the five included studies was 11% (43/389) compared with 35.8% (142/397) in the only study reporting control mortality data.

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 lower in patients who received siltuximab (aHR 0.46 95%CI 0.22;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 twelve studies, tocilizumab was associated with a lower or similar rate of secondary infections compared with controls.

**Clinical trials**

Sixty-two 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 the supplementary appendix.

## DISCUSSION

In this systematic review and meta-analysis, we summarise and evaluate the association between immunomodulatory agents and multiple outcomes in Covid-19. Although there was severe heterogeneity across tocilizumab studies exploring outcomes on an adapted four-point ordinal scale, a beneficial effect of tocilizumab compared with controls was suggested in retrospective studies, and whilst prospective studies followed a similar direction of association, findings were not conclusive. The certainty of the findings related to the adapted ordinal severity scale are assessed as moderate using GRADE (Supplementary appendix). 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 risk ratios demonstrating a 17% reduced risk of mortality in prospective studies. We assess the certainty of our findings related to overall mortality as high.

~~a survival benefit was noted in retrospective studies, although substantial heterogeneity was observed. Amongst prospective studies, there was less heterogeneity, and although a clear association was not observed, the estimates were inconclusive with wide confidence intervals, suggesting further studies are needed to better inform this question. Consequently, we assess the certainty of our findings related to overall mortality as moderate.~~Due to heterogeneity in study designs and reported outcomes, studies in patients receiving non-tocilizumab immunomodulatory agents 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 promise, with intervention 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 completed and been published.

In this review we highlight multiple limitations and considerable sources of inter-study 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 interleukin inhibitors with outcomes. Study outcomes were heterogeneous and a combination of clinical, laboratory and radiological outcomes were 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 non-peer reviewed manuscript 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, 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 in tocilizumab that intervention was frequently associated with improved outcomes and reduced mortality. However, data were highly heterogeneous and must be interpreted with caution. In contrast, prospective studies demonstrated a 17% reduction in the risk of mortality. Further research should focus on identifying participant and disease characteristics where immunomodulatory therapy is likely to be of maximal effectiveness, whilst also

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exploring the relationship with baseline inflammatory biomarkers such as interleukin-6 and C reactive protein. In summary, we demonstrate tocilizumab is associated with reduced mortality in Covid-19, and other immunomodulatory therapies are worth exploring further.

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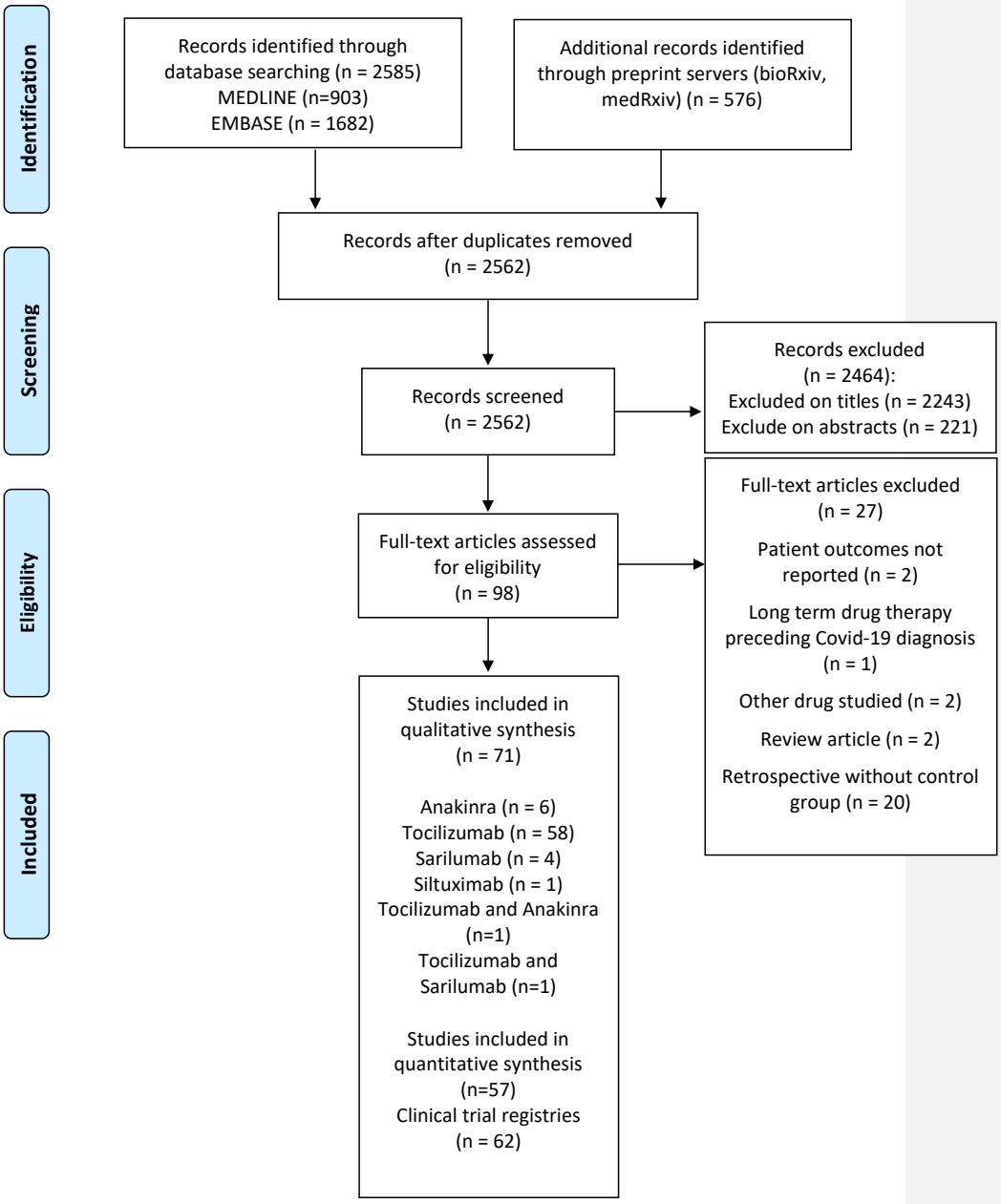
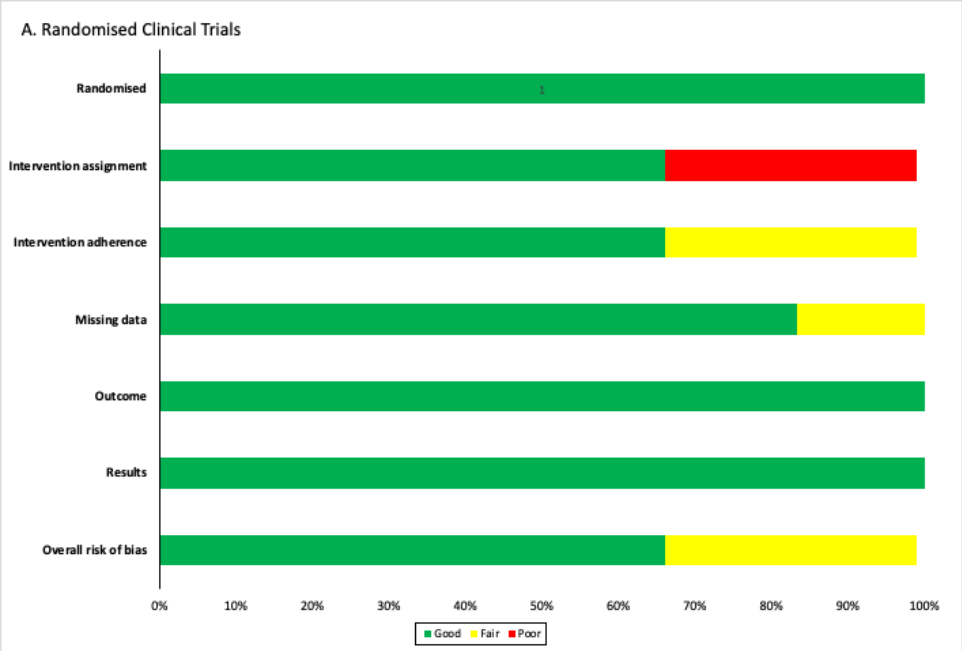
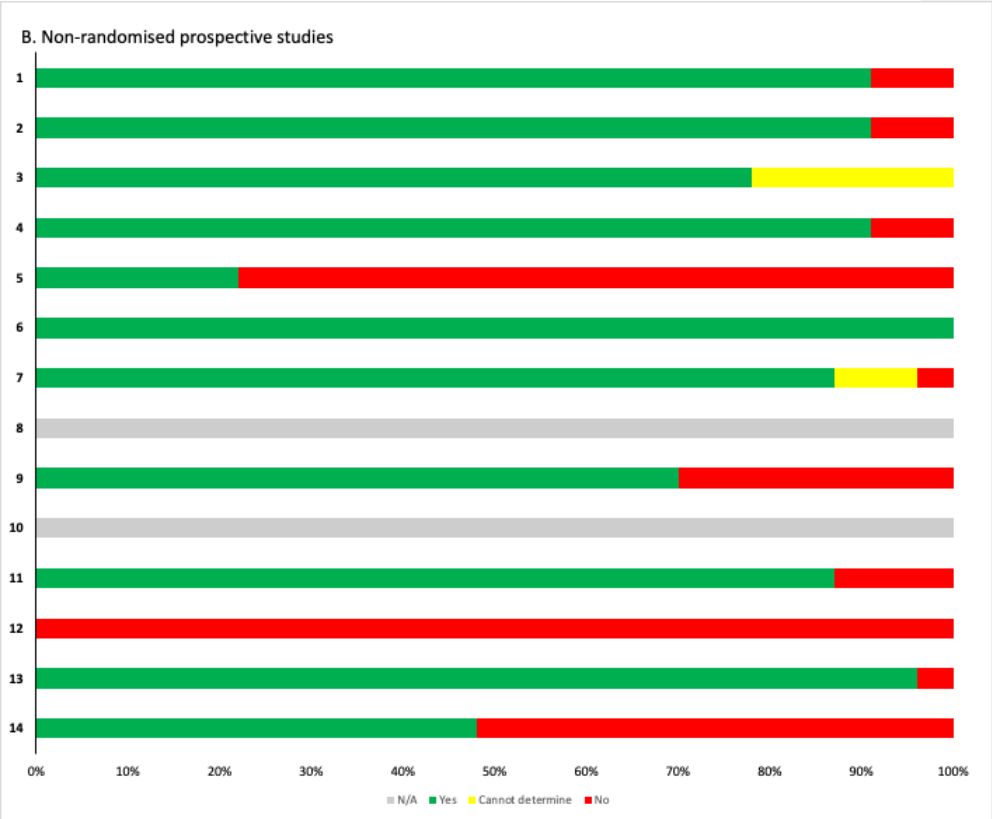

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2585)
MEDLINE (n=903)
EMBASE (n = 1682)
Additional records identified through preprint servers (bioRxiv, medRxiv) (n = 576)
Records after duplicates removed (n = 2562)
Records screened (n = 2562)
Records excluded (n = 2464):
Excluded on titles (n = 2243)
Exclude on abstracts (n = 221)
Full-text articles assessed for eligibility (n = 98)
Full-text articles excluded (n = 27)
Patient outcomes not reported (n = 2)
Long term drug therapy preceding Covid-19 diagnosis (n = 1)
Other drug studied (n = 2)
Review article (n = 2)
Retrospective without control group (n = 20)
Studies included in qualitative synthesis (n = 71)
Anakinra (n = 6)
Tocilizumab (n = 58)
Sarilumab (n = 4)
Siltuximab (n = 1)
Tocilizumab and Anakinra (n=1)
Tocilizumab and Sarilumab (n=1)
Studies included in quantitative synthesis (n=57)
Clinical trial registries (n = 62)

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




B. Non-randomised prospective studies
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70%
80%
90%
100%
N/A
Yes
Cannot determine
No

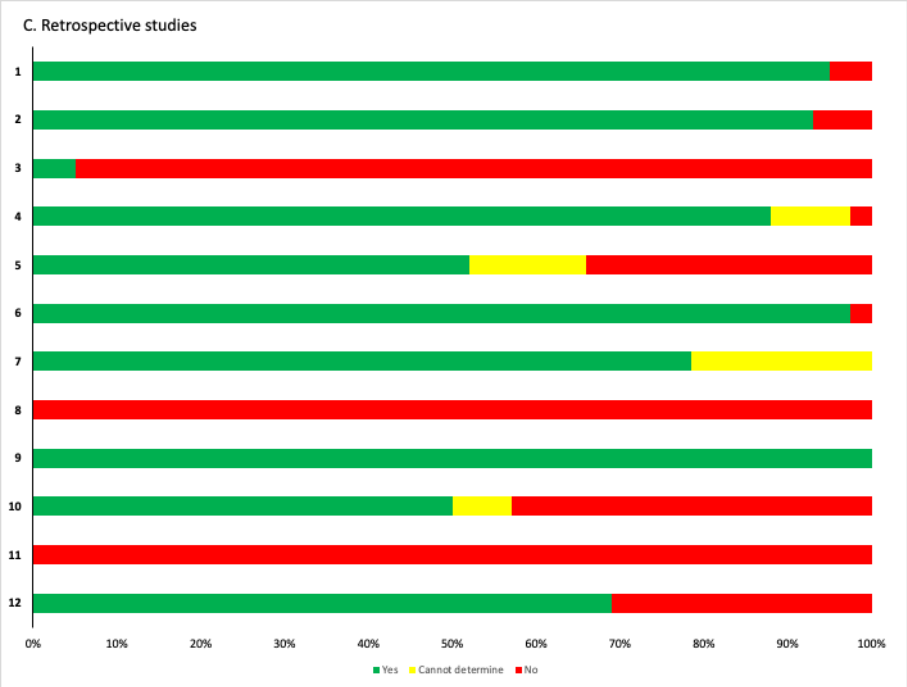



**Figure 2 –** Summary of risk of bias assessment

**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?

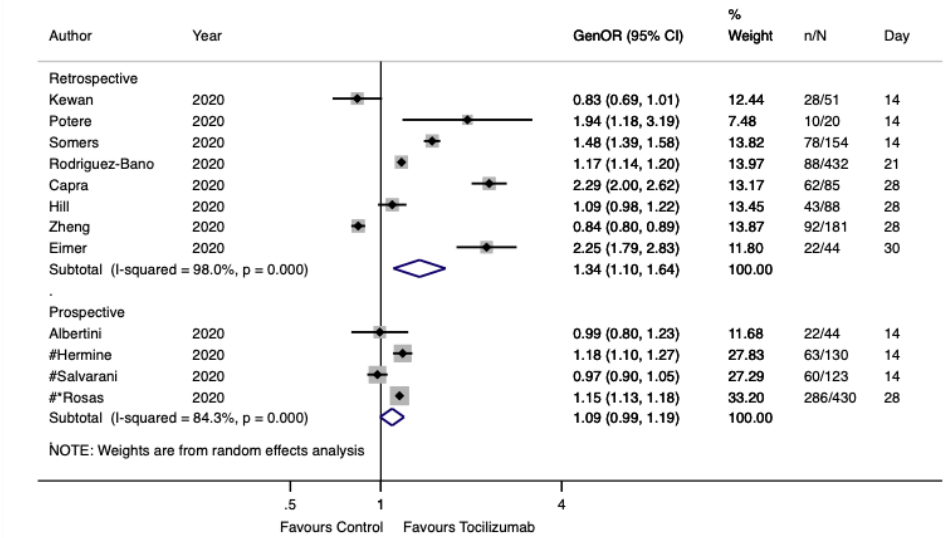



**Figure 3** – Tocilizumab generalised odds ratios (OR) for ordinal outcome forest plot. Generalised OR shown for each study with 95% confidence interval and day at which ordinal outcome recorded. Sample sizes given for patients receiving intervention (n) alongside total included (N) in study. Summary estimates presented separately for prospective and retrospective studies.
* non peer-reviewed preprint studies
# randomised controlled trials

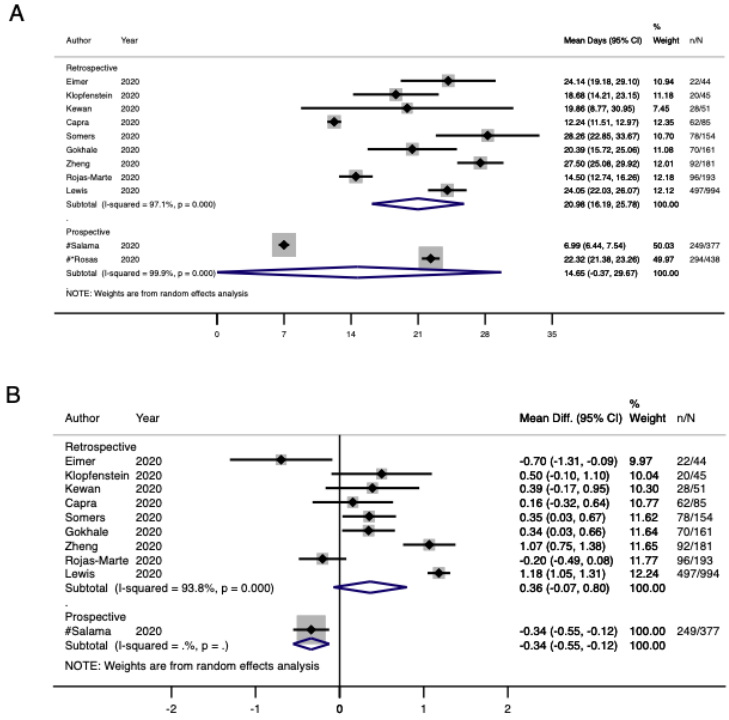



**Figure 4** – Tocilizumab duration of hospitalisation (days) forest plot. **A**: Mean duration of hospital stay. **B**: Mean difference compared with controls in duration of hospital stay. Effect sizes and associated 95% confidence intervals presented for each study. Sample sizes given for patients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

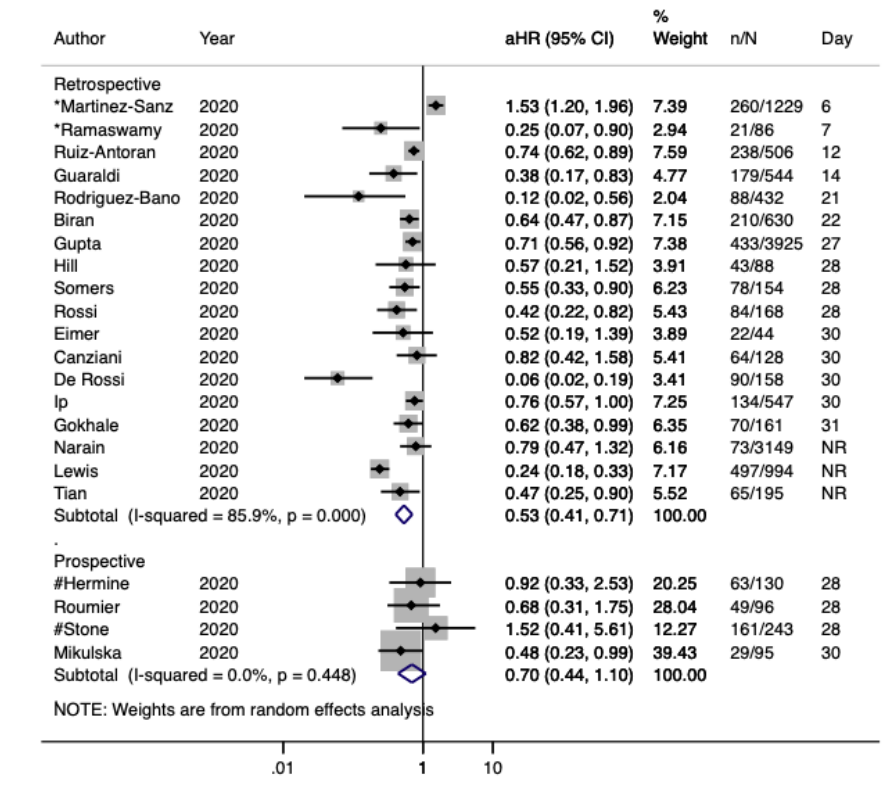



**Figure 5** – Tocilizumab adjusted hazard ratios (HR) for overall mortality forest plot. Adjusted HRs with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included (N) in study. Summary estimates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

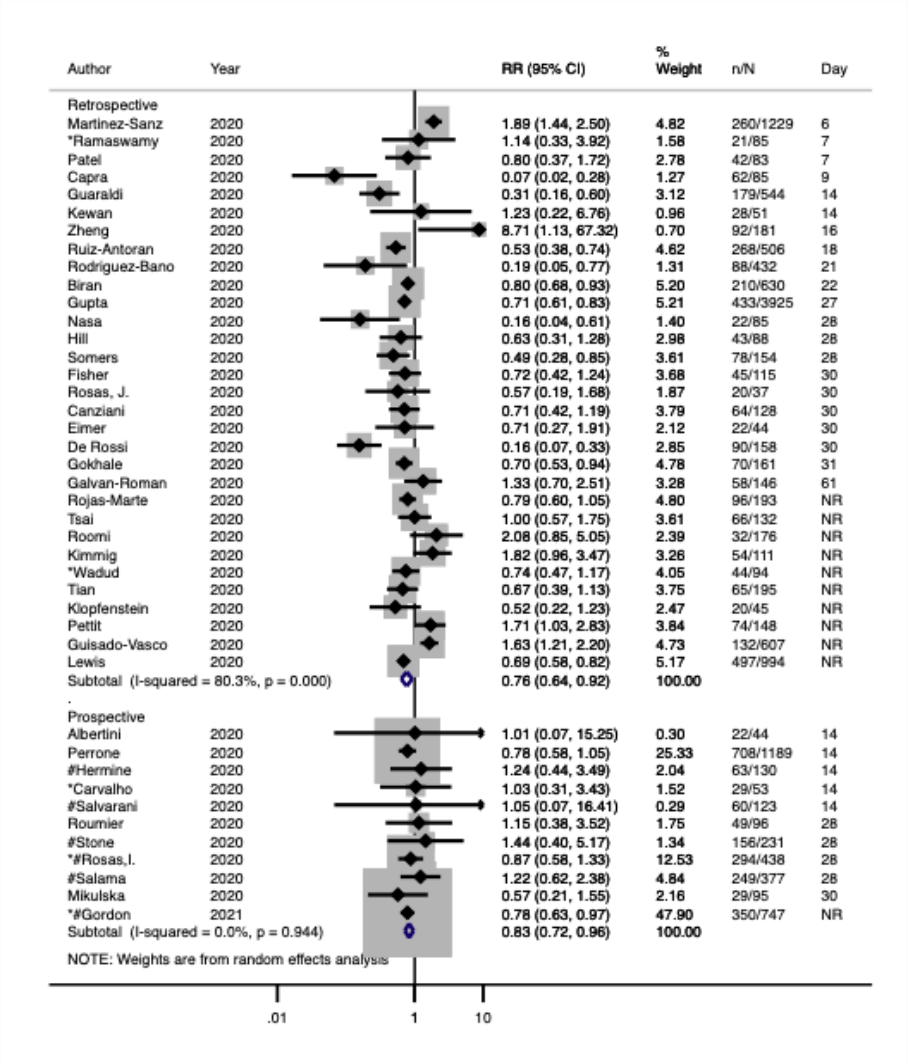



**Figure 6** – Tocilizumab mortality risk ratios (RR) forest plot. Risk ratios with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included in study (N). Summary estimates presented separately for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

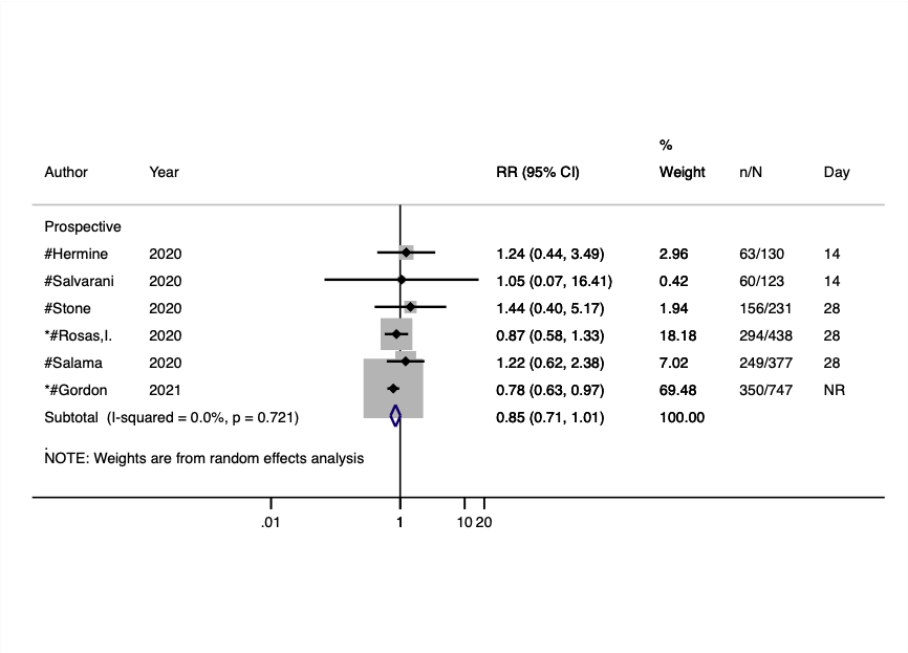



**Figure 7** – Tocilizumab mortality risk ratios (RR) forest plot for randomised controlled trials only. Risk ratios with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included in study (N).
* non peer-reviewed preprint studies
# randomised controlled trials
NR, not reported

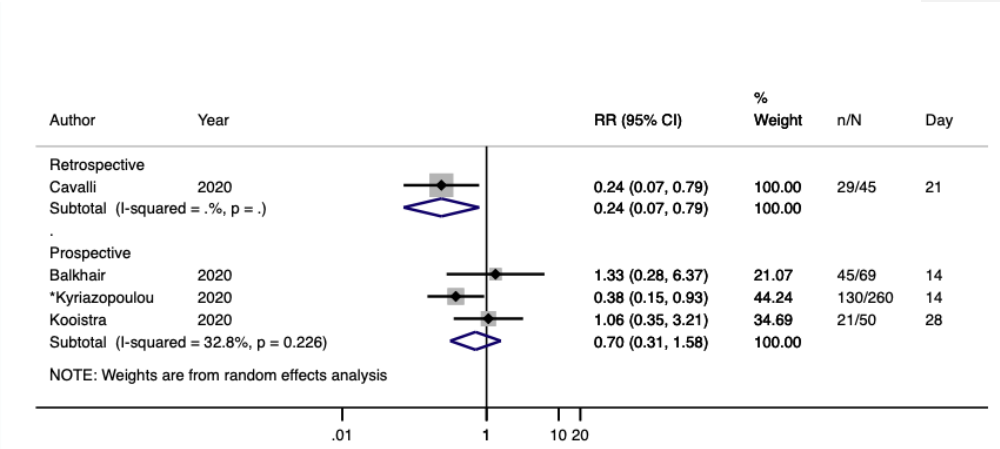



**Figure 8** – Anakinra mortality risk ratios (RR) forest plot. Risk ratios with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included in study (N). Summary estimates presented separately for prospective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

| 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, 2020(26) | A | 45/24 | Oman | single centre | Prospective with control | Roumier, 2020(32) | T | 49/47 | France | single centre | Prospective with control | Kimmig, 2020(33) | T | 54/57 | USA | single centre | Retrospective |
| Huet, 2020(29) | A | 52/44 | France | single centre | Prospective with control | Salama, 2020(22) | T | 249/ 128 | USA | multi-centre | Double blind RCT | Klopfenstein, 2020(34) | T | 20/25 | France | single centre | Retrospective |
| Kooistra, 2020(35) | A | 21/39 | Netherlands | multi-centre | Prospective with control | Salvarani, 2020(36) | T | 60/63 | Italy | multi-centre | Open label RCT | Lewis, 2020(37) | T | 497/497 | USA | multi-centre | Retrospective |
| *Kyriazopoulou, 2020(28) | A | 130/130 | Greece | multi-centre | Prospective | *Sanchez-Montalva, 2020(38) | T | 82/0 | Spain | single centre | Prospective | Martinez-Sanz, 2020(39) | T | 260/969 | Spain | multi-centre | Retrospective |
| Cauchois, 2020(24) | A | 12/10 | France | multi-centre | Retrospective | Sciascia, 2020(40) | T | 63/0 | Italy | multi-centre | Prospective | Narain, 2020(27) | T | 73/3076 | USA | multi-centre | Retrospective |
| Cavalli, 2020(25) | A | 29/16 | Italy | single centre | Retrospective | Stone, 2020(21) | T | 161/ 82 | USA | multi-centre | Double blind RCT | Nasa, 2020(41) | T | 22/63 | India | multi-centre | Retrospective |
| Narain, 2020(27) | A | 57/3076 | USA | multi-centre | Retrospective | Strohbehn, 2020(42) | T | 32/41 | USA | single centre | Phase 2 open label | Patel, 2020(43) | T | 60/1505 | USA | single centre | Retrospective |
| Benucci, 2020(44) | Sa | 8/0 | Italy | single centre | Prospective | Toniati, 2020(45) | T | 100/0 | Italy | single centre | Prospective | * Petrak, 2020 (46) | T | 81/37 | USA | multi-centre | Retrospective |
| Della-Torre, 2020(30) | Sa | 28/28 | Italy | single centre | Prospective with control | Biran, 2020(47) | T | 210/ 420 | USA | multi-centre | Retrospective | Pettit, 2020(48) | T | 42/41 | USA | single centre | Retrospective |
| * Gordon, 2021 (20) | Sa | 45/397 | UK | multi-centre | Adaptive RCT | Canziani, 2020(49) | T | 64/64 | Italy | multi-centre | Retrospective | Potere, 2020(50) | T | 74/74 | Italy | single centre | Retrospective |
| Gremese, 2020(51) | Sa | 53/0 | Italy | single centre | Prospective | Capra, 2020 (52) | T | 62/23 | Italy | single centre | Retrospective | *Ramaswamy, 2020(53) | T | 10/10 | USA | multi-centre | Retrospective |
| Sinha, 2020(54) | Sa | 255/0 | USA | single centre | Prospective | Chillmuri, 2020 (55) | T | 83/ 685 | USA | single centre | Retrospective | Rodriguez-Bano, 2020(56) | T | 21/65 | Spain | multi-centre | Retrospective |
| *Gritti 2020(31) | Si | 30/30 | Italy | single centre | Prospective with control | De Rossi, 2020(57) | T | 90/68 | Italy | single centre | Retrospective | Rojas-Marte, 2020(58) | T | 88/344 | USA | single centre | Retrospective |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Albertini, 2020(59) | T | 22/22 | France | single centre | Prospective with control | Eimer, 2020(60) | T | 22/22 | Sweden | single centre | Retrospective | Roomi, 2020(61) | T | 96/97 | USA | single centre | Retrospective |
| Antony, 2020(62) | T | 80/0 | USA | multi-centre | Prospective | Fisher, 2020(63) | T | 45/70 | USA | single centre | Retrospective | Rosas, J.(64) | T | 20/17 | Spain | single centre | Retrospective |
| Campins, 2020(65) | T | 58/0 | Spain | single centre | Prospective | Galvan Roman, 2020(66) | T | 58/88 | Spain | single centre | Retrospective | Rossi, 2020(67) | T | 84/84 | France | single centre | Retrospective |
| *Carvalho, 2020(68) | T | 29/24 | Brazil | single centre | Prospective with control | *Garcia, 2020(69) | T | 77/94 | Spain | single centre | Retrospective | Rossotti, 2020(70) | T | 74/148 | Italy | single centre | Retrospective |
| Dastan, 2020(71) | T | 42/0 | Iran | single centre | Prospective | Gokhale, 2020(72) | T | 70/91 | India | single centre | Retrospective | Ruiz-Antoran, 2020(73) | T | 268/238 | Spain | multi-centre | Retrospective |
| * Gordon, 2021(20) | T | 350/397 | UK | multi-centre | Adaptive RCT | Guaraldi, 2020(74) | T | 179/ 365 | Italy | multi-centre | Retrospective | Somers, 2020(75) | T | 78/76 | USA | single centre | Retrospective |
| Hermine, 2020(23) | T | 63/67 | France | multi-centre | Open-label RCT | Guisado-Vasco, 2020(76) | T | 132/ 475 | Spain | single centre | Retrospective | Tian, 2020(77) | T | 65/130 | China | multi-centre | Retrospective |
| Malekzadeh, 2020(78) | T | 126/0 | Iran | multi-centre | Prospective | Gupta, 2020(79) | T | 433/ 3492 | USA | multi-centre | Retrospective | Tsai, 2020(80) | T | 66/66 | USA | single centre | Retrospective |
| Mikulska, 2020(81) | T | 29/66 | Italy | single centre | Prospective with control | Hill, 2020(82) | T | 43/45 | USA | single centre | Retrospective | * Wadud, 2020(83) | T | 84/84 | USA | single centre | Retrospective |
| Morena, 2020(84) | T | 51/0 | Italy | single centre | Prospective | Holt, 2020(85) | T | 24/30 | USA | single centre | Retrospective | Zheng, 2020(86) | T | 92/89 | China | single centre | Retrospective |
| Perrone 2020(87) | T | 708/481 | Italy | multi-centre | Single arm open label & Validation | Ip, 2020(88) | T | 134/413 | USA | multi-centre | Retrospective | | | | | | |
| *Rosas, 2020(89) | T | 294/144 | USA | multi-centre | Double blind RCT | Kewan, 2020(90) | T | 28/23 | USA | single centre | Retrospective | | | | | | |

**Table 1 –** Included studies with study characteristics and sample size for treatment (Tx) and control group (control) shown.
* non peer-reviewed preprint study; #, study investigating both anakinra and tocilizumab; A, anakinra; Sa, sarilumab; Si, siltuximab; T, tocilizumab

| Author, year | Therapy | Adverse effects |
|---|---|---|
| Balkhair, 2020 | Anakinra | Treatment: infection (11%), ALT rise (14%). Control: infection (18%), ALT rise (9%) |
| Huet, 2020 | Anakinra | Treatment: ALT rise (13%). Control: 9% in anakinra |
| Kooistra, 2020 | Anakinra | Treatment: secondary infection (33%). Control: secondary infection (23%) |
| * Kyriazopoulou, 2020 | Anakinra | Increased leukopenia in treatment group vs. controls (8.5% vs 2.3%; p=0.05) |
| Cauchois, 2020 | Anakinra | N/R |
| Cavalli, 2020 | Anakinra | Treatment: staphylococcus epidermis (14%); deranged liver enzymes (10%). Control: bacteraemia (13%); deranged liver enzymes (31%). |
| Narain, 2020 | Anakinra | N/R |
| | | |
| Benucci, 2020 | Sarilumab | Nil |
| Della-Torre, 2020 | Sarilumab | Treatment: Infections (21%); neutropenia (14%); liver enzyme increase (14%); thromboembolism (7%). Control: Infections (18%); thromboembolism (7%) |
| * Gordon, 2021 | Sarilumab | No serious event in sarilumab group, and 11 events in control |
| Gremese, 2020 | Sarilumab | neutropenia (15%); elevated liver enzymes (11%) |
| Sinha, 2020 | Sarilumab or Tocilizumab | bacterial infection (13%) |
| | | |
| * Gritti 2020 | Siltuximab | Nil |
| | | |
| Albertini, 2020 | Tocilizumab | elevated liver enzymes (64%) |
| Antony, 2020 | Tocilizumab | N/R |
| Campins, 2020 | Tocilizumab | Nil |
| * Carvalho, 2020 | Tocilizumab | Nil |
| Chillmuri, 2020 | Tocilizumab | N/R |
| Dastan, 2020 | Tocilizumab | transient diplopia (4.8%); Bell's palsy (2.4%) |
| * Gordon, 2021 | Tocilizumab | 9 serious adverse events in Tocilizumab group and 11 events in control |
| Hermine, 2020 | Tocilizumab | Treatment: Serious adverse events occurred in 20 (32%). Control: 29 (43%) (P = .21) |
| Lewis, 2020 | Tocilizumab | Increased infection rate in treatment group (aOR 4.18; 95% CI 2.72-6.52) |
| Malekzadeh, 2020 | Tocilizumab | Nil |
| Mikulska, 2020 | Tocilizumab | N/R |
| Morena, 2020 | Tocilizumab | elevated liver enzymes (29%), thrombocytopenia (14%), neutropenia (6%), infections (24%) |
| Nasa, 2020 | Tocilizumab | two patients (9.1%) developed deranged LFTs and two patients (9.1%) developed secondary sepsis. |
| Perrone, 2020 | Tocilizumab | allergic reactions (0.4%), deranged liver enzymes (10.5%) |
| * Petrak, 2020 | Tocilizumab | N/R |
| * Rosas,I., 2020 | 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, 2020 | 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, 2020 | 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, 2020 | Tocilizumab | Nil |
| * Sanchez-Montalva, 2020 | Tocilizumab | Nil |
| Sciascia, 2020 | Tocilizumab | Nil |
| Stone, 2020 | 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, 2020 | Tocilizumab | Treatment: bacterial infections (15.6%). Control: not reported |
| Toniati, 2020 | Tocilizumab | septic shock (2%), gastrointestinal perforation (1%) |
| Biran, 2020 | Tocilizumab | Treatment: secondary bacterial infection in 17%. Control: secondary bacterial infection in 13% |
| Canziani, 2020 | Tocilizumab | HR 0.71 (95% CI 0.38-1.32) for infection; HR 0.89 (95% CI 0.39-2.06) for thrombosis; HR 1.17 (95% CI 0.47-2.92) for bleeding |
| Capra, 2020 | Tocilizumab | Nil |
| De Rossi, 2020 | Tocilizumab | Significant rise (from 44.3 +/- 28.3 to 103 +/- 141.3) in ALT in patients taking IV dose |
| Eimer, 2020 | Tocilizumab | Blood stream infection: 4 (18%) in treatment group vs. 6 (27%) in control |
| Fisher, 2020 | Tocilizumab | No increased risk of secondary infection (OR 1.17; 95%CI 0.51-2.71) |
| Galvan Roman, 2020 | Tocilizumab | N/R |
| * Garcia, 2020 | Tocilizumab | N/R |
| Gokhale, 2020 | Tocilizumab | N/R |
| Guaraldi, 2020 | Tocilizumab | 13% treated diagnosed with new infections vs 4% in control (p<0.0001) |
| Guisado-Vasco, 2020 | Tocilizumab | N/R |
| Gupta, 2020 | 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, 2020 | Tocilizumab | In treatment vs control group, there was increased sepsis (21% and 16%), ALT rise (9% vs 4%) and thrombocytopenia (12% vs 4%) |
| Holt, 2020 | Tocilizumab | N/R |
| Ip, 2020 | Tocilizumab | N/R |
| Kewan, 2020 | Tocilizumab | Similar rates of hospital–acquired infections occurred in both cohorts (18% in treatment and 22% in control). |
| Kimmig, 2020 | Tocilizumab | Treatment associated with increased secondary bacterial (aOR 2.76; 95% CI 1.11-7.2) and fungal (5.6% vs. 0%, p=0.112) infections |
| Klopfenstein, 2020 | Tocilizumab | N/R |
| Martinez-Sanz, 2020 | Tocilizumab | N/R |
| Narain, 2020 | Tocilizumab | N/R |
| Patel, 2020 | Tocilizumab | N/R |
| Pettit, 2020 | Tocilizumab | Overall infection rate was similar (16.2% treatment vs. 17.5% control), but late on-set 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, 2020 | Tocilizumab | Nil |
| * Ramaswamy, 2020 | Tocilizumab | N/R |
| Rodriguez-Bano, 2020 | Tocilizumab | secondary bacterial infection similar in both groups (treated 12.5% vs. 10.3% control; p=0.57) |
| Rojas-Marte, 2020 | 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, 2020 | Tocilizumab | N/R |

| | | |
|---|---|---|
| Rosas, J. 2020 | Tocilizumab | Nil |
| Rossi, 2020 | Tocilizumab | N/R |
| Rossotti, 2020 | Tocilizumab | infectious complication in 32.4% |
| Ruiz-Antoran, 2020 | Tocilizumab | 32.6% in treated vs. 30.3% in control had increase in liver enzymes. Bacteraemia in 1 patient (0.4%) |
| Somers, 2020 | Tocilizumab | higher rate of superinfection in treated group (54% vs 26%; p<0.001) |
| Tian, 2020 | Tocilizumab | Deranged LFTs in 14% of tocilizumab and 14% of control group |
| Tsai, 2020 | Tocilizumab | N/R |
| * Wadud, 2020 | Tocilizumab | N/R |
| Zheng, 2020 | Tocilizumab | N/R |

**Table 2 –** Treatment related adverse events. Adverse events for drug under study reported. Adverse events for control population reported where applicable. * non peer-reviewed preprint study

## Supplementary material

**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 * | | | | | | | | | | | |

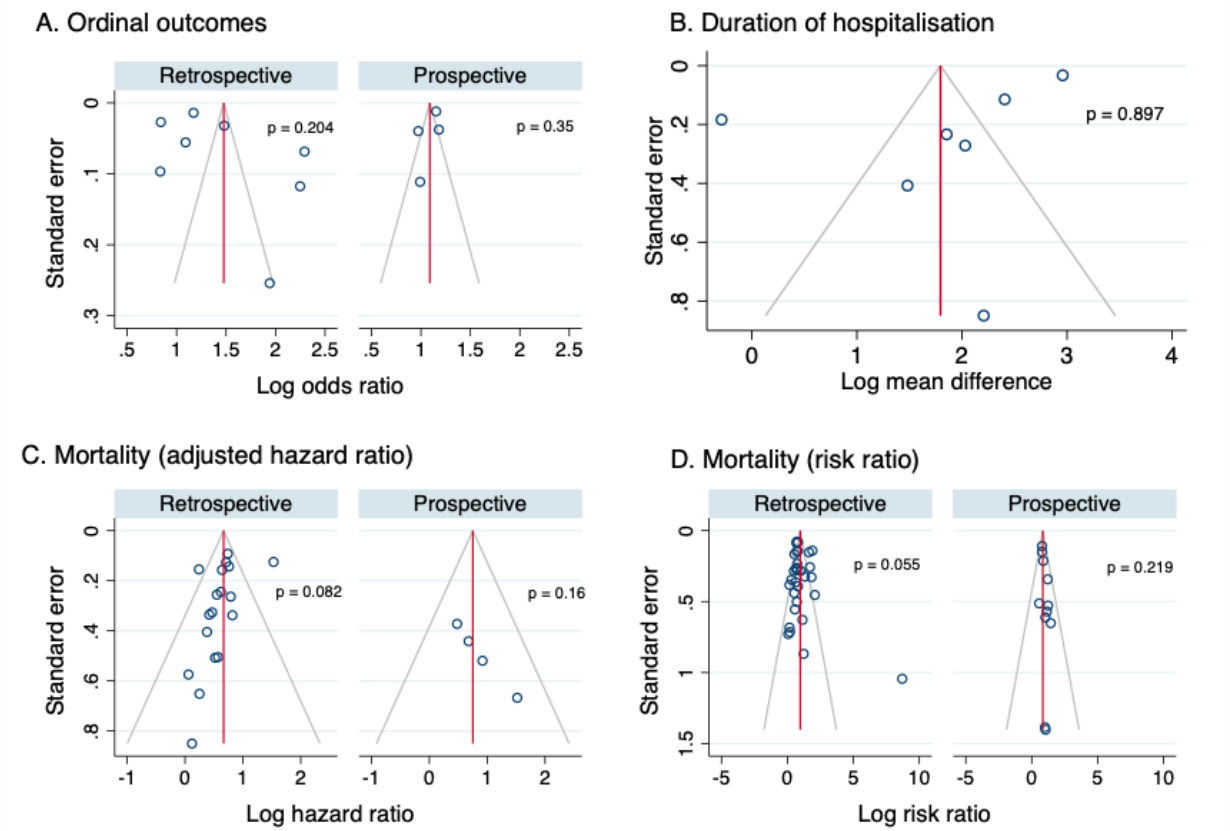
| | |
|---|---|
| | Tocilizumab |
| | Siltuximab |
| | Sarilumab |
| | Anakinra |

**Supplementary Figure 1.** 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

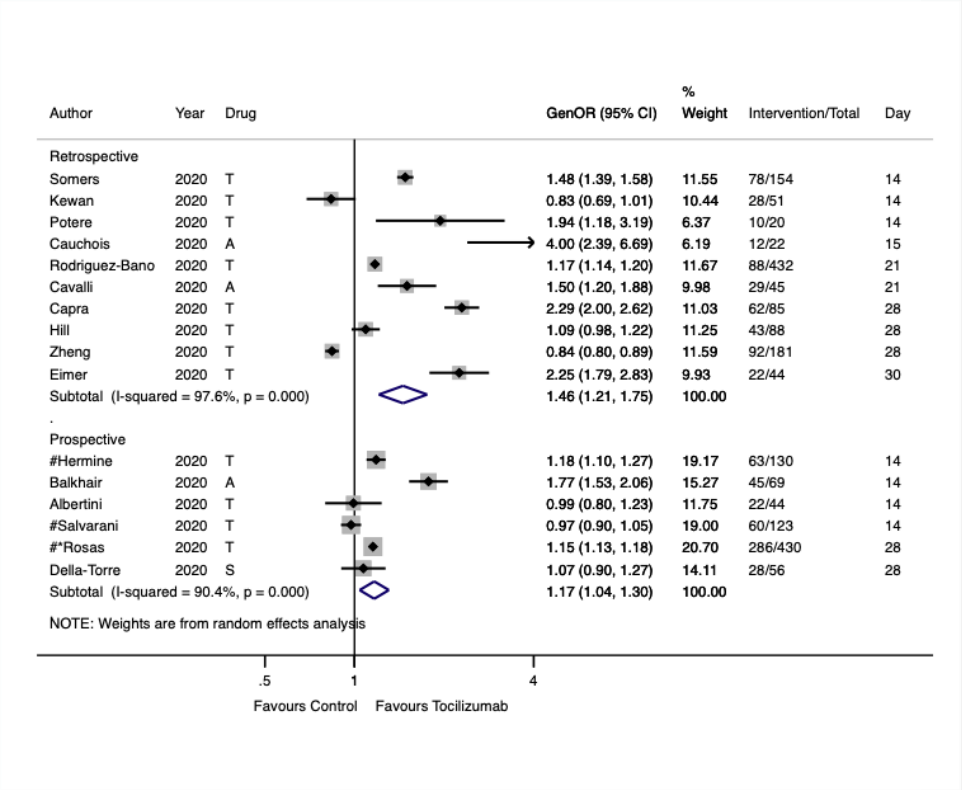
(last search 5th Oct)

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

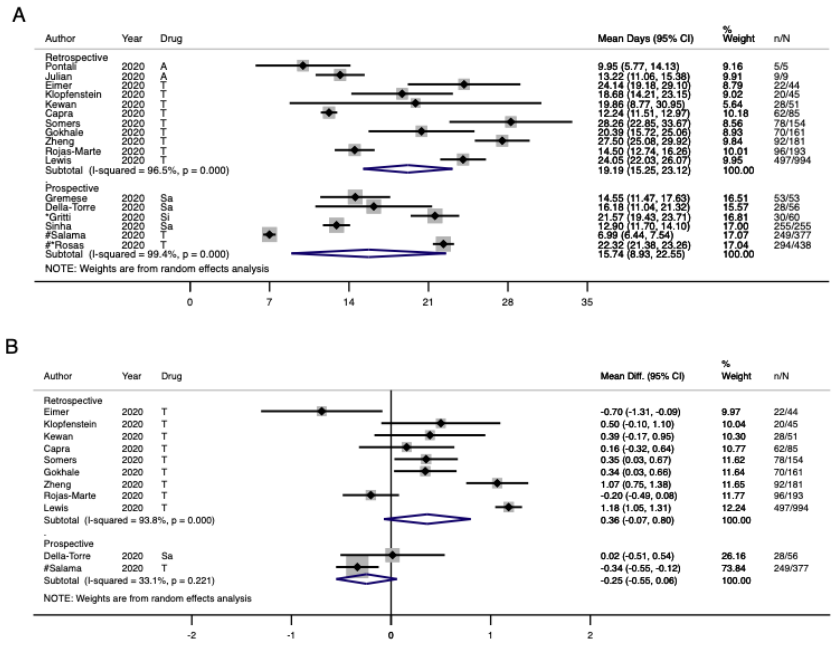
**Supplementary Figure 2.** MEDLINE search strategy (last carried out on 7th January 2021)



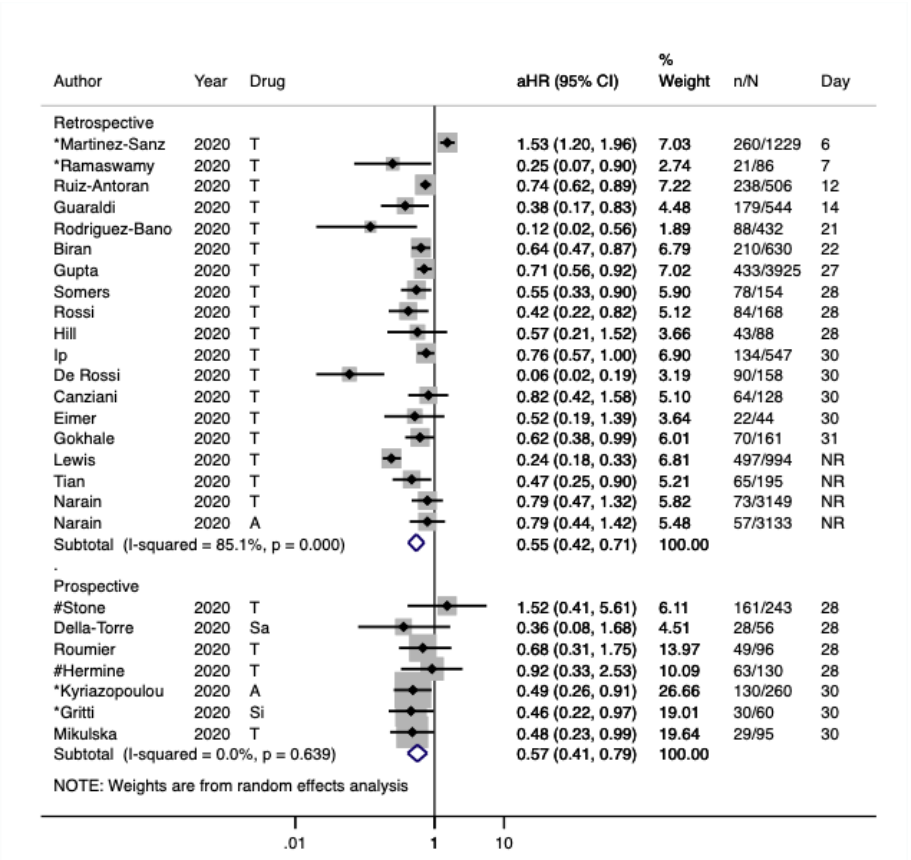

**Supplementary Figure 3:** Funnel plots for outcomes evaluated in tocilizumab meta-analysis. A: ordinal outcomes, B: duration of hospitalisation, C: mortality (adjusted hazard ratio), D: mortality (risk ratio). Funnel plots presented separately for retrospective and prospective studies were applicable. Publication bias assessed using Egger's test, and p values presented next to funnel plot.




**Supplementary Figure 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, S = 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, S = sarilumab, Si = siltuximab.
* non peer-reviewed preprint studies
# randomised controlled trials

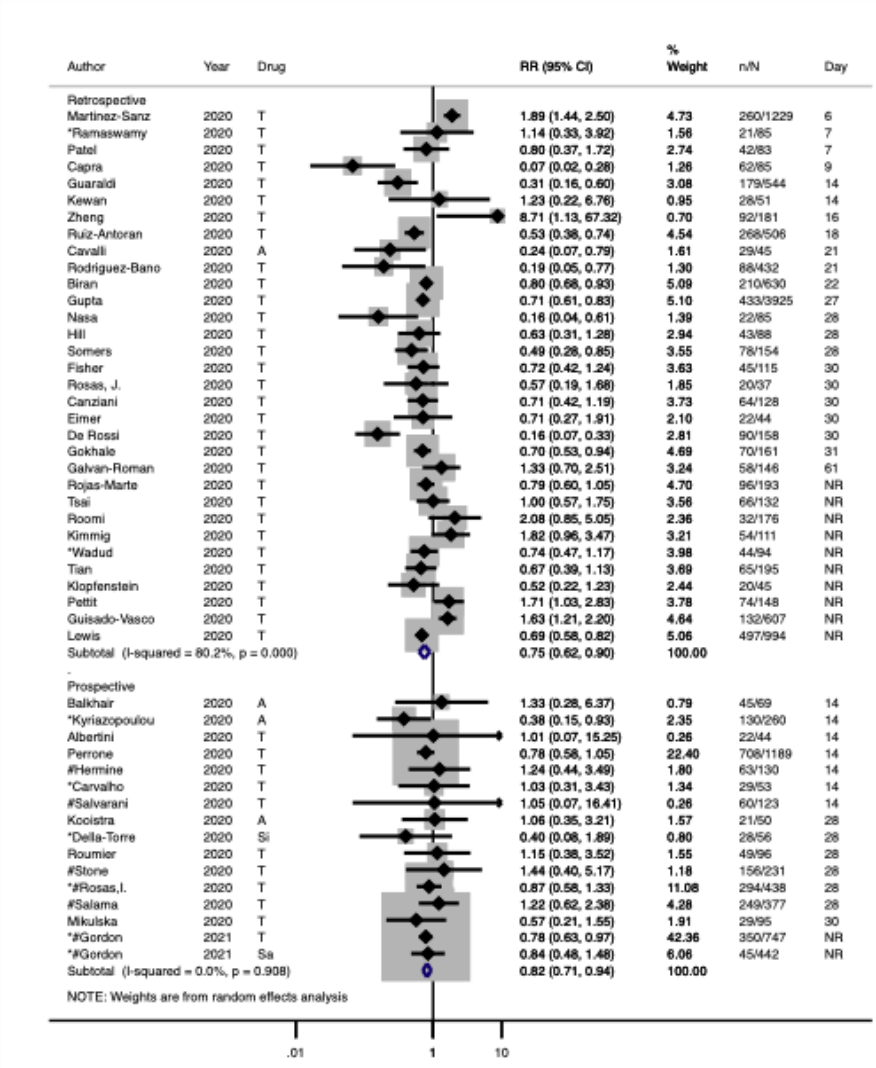



**Supplementary Figure 6** – All studies, adjusted hazard ratios (HR) for overall mortality forest plot. Adjusted HRs with associated 95% confidence interval and day of censorship presented for each study. Sample sizes given for patients receiving intervention (n) and total included (N) in study. Summary estimates presented separately for prospective and retrospective studies. Drugs labelled where T = tocilizumab, A = anakinra, S = 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.
* non peer-reviewed preprint studies
# randomised controlled trials
NR, not reported

| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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. |

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| 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 |

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| 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%<br>61-70: 33%<br>≥71: 31% | ≤60: 44%<br>61-70: 37%<br>≥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%<br>61-70: 30%<br>≥71: 27% | ≤60: 40%<br>61-70: 28%<br>≥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%) |

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| * 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) |

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| 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). |

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| * 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 1.53; 95% CI 1.2-1.96) or ICU/death (HR 1.77l; 95% CI 1.41-2.22) |
| # 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

| 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 3** – 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

| 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 4 –** GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to rate the quality of evidence on the effects of tocilizumab

| 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 | 0.7444 | 0.00 | 0.5252 |
| Peer review | N/A | N/A | N/A | N/A | 88.84 | <0.001 | 0.00 | 0.4137 |
| Route of administration | 4.75 | 0.3526 | 81.64 | <0.001 | 36.89 | 0.0373 | 2.68 | 0.2053 |
| Single centre | 0.00 | 0.6028 | 11.03 | 0.2013 | 1.89 | 0.3127 | 0.00 | 0.2154 |
| Outcome day | 0.00 | 0.7921 | N/A | N/A | 33.62 | 0.0959 | 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.

| 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 6(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 6(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 6(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