The Effectiveness of Tocilizumab in the Treatment of COVID-19 in Adults: A Meta-Analysis of Randomized Controlled Trials.

Chun Chen
University of Chinese Academy of Sciences, Chongqing General Hospital
ZeMei Zhou
University of Chinese Academy of Sciences, Chongqing General Hospital
Jing Zhang (799138261@qq.com)
University of Chinese Academic of Sciences, Chongqing General Hospital

Research

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Abstract

Background: Since December 2019, COVID-19 has spread to the world which leads to a global health threat. We aimed to investigate the effectiveness of tocilizumab on COVID-19 patients.

Methods: We systematically searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and WHO international Clinical Trials Registry Platform (ICTRP) from their inception to March 10, 2021 for randomized controlled trials (RCTs) on tocilizumab supplementation in adults with COVID-19 disease. The primary outcomes were mortality at 28-30 day and 60-day, incidence of mechanical ventilation (MV), composite outcome of death or MV, time to hospital discharge, and intensive care unit (ICU) admissions. A random-effects meta-analysis model was used to pool studies.

Results: Eleven studies with a total of 6,579 patients were included in our meta-analysis, of which 3,406 and 3,173 were respectively assigned to the tocilizumab and control groups. Tocilizumab could significantly reduce 28-30 day mortality (RR = 0.89, 95% *CI* 0.80-0.99, *P* = 0.04), incidence of MV (RR= 0.79, 95% *CI* 0.71-0.89, *P* = 0.0001), composition outcome of MV or death (RR = 0.81, 95% *CI* 0.72-0.90, *P* = 0.0002), time to hospital discharge (HR = 1.30, 95% *CI* 1.16-1.45, *P* 0.00001), ICU admissions (RR = 0.64, 95% *CI* 0.47-0.88, *P* = 0.006), serious infection (RR = 0.61, 95% *CI* 0.40-0.94, *P* = 0.02) and events of serious adverse advents (RR = 0.64, 95% *CI* 0.47-0.86, *P* = 0.004). There was no significant difference between tocilizumab and control groups in 60-day mortality and adverse events (AEs).

Conclusions: Tocilizumab could reduce the short-term mortality, incidence of MV, composite outcome of death or MV, ICU admissions, serious infection and events of serious adverse advents, and shorten the time to hospital discharge in hospitalized patients with COVID-19. The optimal effective dose needs to be confirmed by further studies.

Introduction

In December 2019, there had been more and more confirmed cases of novel coronavirus pneumonia in Wuhan, China, which then quickly spread to the world leading to a global health threat [1]. The World Health Organization (WHO) officially named this pneumonia coronavirus disease 2019 (COVID-19) on February 11, 2020. [2] COVID-19 can be mild or progressive to dyspnea and/or hypoxemia, and severe cases often progress to respiratory failure, acute respiratory distress syndrome (ARDS) and septic shock, which can further lead to multiple organ dysfunction syndrome (MODS) or death [3, 4]. Although most COVID-19 patients are self-limited, it still causes serious loss of life worldwide [3]. As of April 26, 2021, more than 14.6 million people have been infected and more than 3 million people have died around the world [5]. All parts of the world are striving to find effective treatments to control the ongoing COVID-19 pandemic [6].

Recently, many studies have shown that cytokine release syndrome (CRS) is an important cause of death in COVID-19 patients, and IL-6 plays an important role [7–9]. Tocilizumab is a recombinant humanized

monoclonal antibody against human interleukin 6 (IL-6) receptor, which has been confirmed that it could reduce the biomarkers of COVID-19 infection and increase the level of lymphocyte count [10].

There are several meta-analyses of observational studies which have showed that tocilizumab could reduce the mortality of COVID-19 [11–15]. Considering the low levels of evidence in observational studies may confound the findings, the benefits of tocilizumab on mortality of COVID-19 must be cautiously interpreted. Several newly published randomized controlled trials (RCTs) [6, 16–25] and meta-analyses [26–28] of RCTs have investigated the effects of tocilizumab as adjunctive therapy in COVID-19 patients, but reported inconsistent results. Moreover, due to daily update of studies regarding tocilizumab anti-COVID-19, it is mandatory to conduct an updated study on this field. Hence, we conducted an updated meta-analysis to synthesize the evidence of well-conducted RCTs to evaluate the effects of tocilizumab in COIVD-19 treatment.

Methods

Literature search

We systematically searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and WHO international Clinical Trials Registry Platform (ICTRP) from their inception to March 10, 2021 for RCTs, by using a combination of Medical Subject Headings (MeSH) or Emtree and related key words in all fields. The keywords used were “tocilizumab” or “atlizumab” or “Actemra” or “Roactemra” or “lusinex” or “anti-interleukin 6 antibody”, and “COVID-19” or “coronavirus 2019” or “2019-nCoV Infection” or “SARS CoV 2 Infection” or “2019 Novel Coronavirus Disease”. We also scanned the reference lists from relevant studies and key review articles to locate relevant studies.

Inclusion Criteria

Studies meeting the following criteria were included: (1) participants: patients aged ≥ 18 years with confirmed SARS-coV-2 infection by a positive polymerase-chain -reaction test for SARS-CoV-2 in any body fluid and/or bilateral chest infiltrates on chest x-ray or computed tomography; (2) intervention: tocilizumab administered intravenously (IV), with dosages ranging from 400 to 800 mg; (3) comparison: standard care; (4) outcomes: the primary outcomes were mortality at 28–30 day and 60-day, incidence of mechanical ventilation (MV), composite outcome of death or MV, intensive care unit (ICU) admissions, and time to hospital discharge. The secondary outcomes were time to oxygen supply independency, non-serious adverse events, serious adverse events, serious infection, events of serious adverse advents; (5) study design: RCTs. The language was restricted to English. Two of the authors (JZ and CC) independently evaluated the eligibility of all studies obtained from the databases according to the above selection criteria. Discrepancies regarding study inclusion between reviewers were resolved through discussion.

Data Extraction And Risk Of Bias Assessment

Two of the authors (JZ and CC) independently extracted data. The following data were extracted from the studies: study name (name of the first author with publication year), country and design, participants (sample size, sex and age), intervention arms and controls (intervention drug, dose, and duration of follow-up) and outcomes (primary and secondary outcomes). The Cochrane Collaboration's tool for assessing risk of bias was used to appraise the quality of each RCT, which includes the following criteria: adequacy of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other biases [29]. JZ and CC reviewed all the included studies and rated them "low risk", "unclear risk" or "high risk" based on the Cochrane risk-of -bias tool.

Statistical analysis

To evaluate the effect of tocilizumab on COVID-19, we calculated relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes. As for continuous outcomes, mean differences or standard mean differences between the tocilizumab and placebo groups were used for meta-analysis. Time-to-event outcomes were analyzed by using hazard ratios (HRs). Heterogeneity in results across studies was examined by using Cochran's Q and I^2 statistics [30]. The null hypothesis that the studies are homogeneous was rejected if the P value for heterogeneity was < 0.10 or I^2 was > 50%. Studies with an I^2 statistic of > 50% were considered to have significant heterogeneity. A random-effects model was used to pool the study estimates for each outcome.

A sensitivity analysis was conducted to assess the influence of individual studies on the pooled result when P was < 0.10 or I^2 was > 50%, by excluding each study one by one and recalculating the combined results on the remaining studies [30]. All analyses of data were performed with Review Manager 5.4 (Cochrane Informatics and Knowledge Management Department), available from http://tech.cochrane.org/.

Results

Fig 1 shows a flow diagram of the study selection process. A total of 1,074 records were initially identified from the database search. Of these, 382 records were excluded for duplicates, and 653 records were excluded after screening the titles and abstracts. After full-text screening, a total of 11 studies [6, 16-25] were included in the meta-analysis.

Characteristics of included studies

The characteristics of studies included in our meta-analysis were summarized in Table 1. All 11 RCTs were multicenter studies. Three [16, 18, 19] studies were conducted in multi-countries, while the remaining eight trials were each from France [17], Itay [20], USA [21], Brazil [22], China [6, 23], UK [25], India [24].

Overall, a total of 6,579 patients were enrolled in our meta-analysis, 4,906 of them were male (74.6%), and the average age ranged from 54 to 75 years old. A total of 3,406 were administrated with tocilizumab in addition to standard care or placebo, 14 of which were administrated with tocilizumab and favipiravir, and 3,173 were administrated with standard care or placebo, 7 of which were administrated with favipiravir. Except two [21, 22] RCTs used only a single dose of tocilizumab, other nine [6, 16-20, 23-25] RCTs allowed additional dose if needed. The tocilizumab doses vary from 400 mg to 800 mg and were all administrated intravenously infusion for more than one hour. The maximum dose was 480 mg/d in one study [24], 800 mg/d in eight studies [16-22, 25], 400 mg/d in two [6, 23] studies.

Assessment of risk of bias

There was a high risk of bias in blinding of participants and personnel and blinding of outcome assessment because of open-labelled design in eight studies [6, 16, 17, 20, 22-25], there was an unclear risk of bias in allocation concealment because of no mentioned of allocation in one study [23], shown in Fig 2.

Primary outcomes

Mortality

Nine studies [16-22, 24, 25] with 6,493 patients were included in the meta-analysis. Overall, there was a significant difference between tocilizumab and control groups at 28–30day mortality (RR = 0.89, 95% *CI* 0.80-0.99, *P* = 0.04). Two trials with 507 patients contributed to the 60-day mortality, and no statistically difference was found (RR = 0.88, 95% *CI* 0.54-1.43, *P* = 0.60), shown in Fig 3.

Incidence of mechanical ventilation

Eight trials [16-19, 21, 22, 24, 25] examined the incidence of MV between tocilizumab and control groups. The pooled analysis including 5,369 participants showed that tocilizumab could significantly decrease the incidence of MV (RR = 0.79, 95% *CI* 0.71-0.89, *P* = 0.0001), shown in Fig 4.

Composite outcome of death or MV

Eight RCTs [16-19, 21-23, 25] including 5,241 adults examined the composite outcome of death or MV. The pooled analysis showed that there was a significant difference between tocilizumab and control groups (RR = 0.81, 95% *CI* 0.72-0.90, *P* = 0.0002) (supplemental Fig 5).

Time to hospital discharge

Pooled analysis of five trials [16-19, 21] with 1,943 cases showed that there was a statistically significant difference in time to hospital discharge between tocilizumab and control groups (HR = 1.30, 95% *CI* 1.16-1.45, *P*□ 0.00001) (supplemental Fig 6).

ICU admissions

Four trials [17, 18, 20, 24] with 499 cases were included in the meta-analysis. Overall, there was statistically significant difference between tocilizumab and control groups in ICU admissions (RR= 0.64, 95% *CI* 0.47-0.88, *P* = 0.006) (supplemental Fig 7).

Secondary outcomes

Time to oxygen supply independency

Our meta-analysis including three RCTs [17, 21, 22] with 502 cases showed that there was no significant difference in time to oxygen supply independency between tocilizumab and control groups (HR = 1.21, 95% *CI* 0.94-1.57, *P* = 0.14) (supplemental Fig 8).

Serious infection

Five RCTs [17-21] including 1,311 cases were included in the meta-analysis. Overall, there was statistically significant difference between tocilizumab and control groups in serious infection (RR = 0.61, 95% *CI* 0.40-0.94, *P* = 0.02) (supplemental Fig 9).

Non-serious adverse events and serious adverse events

Eight studies [6, 17-20, 22-24] including 1463 patients showed that there was no difference between tocilizumab and control groups in non-SAE (RR = 1.19, 95% *CI* 0.94-1.50, *P* = 0.14) (supplemental Fig 10). Nine trials [6, 16-22, 24] with 2,440 participants showed that there was no significant difference between tocilizumab and control groups in SAE (RR = 0.91, 95% *CI* 0.76-1.08, *P* = 0.28) (supplemental Fig 11).

Events of serious adverse advents

Our meta-analysis including four trials [17, 18, 21, 24] with 991 cases showed that there was a significant difference between tocilizumab and control groups in events of serious adverse advents (RR = 0.64, 95% *CI* 0.47-0.86, *P* = 0.004) (supplemental Fig 12).

Discussion

Our meta-analysis investigated the effect of adjunctive tocilizumab on COVID-19 patients in hospital and found that tocilizumab supplementation could reduce 28–30 days mortality, the incidence of mechanical ventilation, composite outcome of death or mechanical ventilation, ICU admissions, serious infection and events of SAE, and shorten the time to discharge. There was no evidence that tocilizumab could increase the adverse advents and reduce 60-day mortality and time to oxygen supply independency.

The results of our meta-analysis are not completely consistent with recently published meta-analyses [26, 28, 31, 32], which showed that tocilizumab had no effect on 28–30 days mortality in COVID-19 patients. There are several strengths in our meta-analysis. Firstly, with the updating of the literature, our meta-analysis was able to include the most recently published RCTs. Secondly, given the clinical heterogeneity

across included studies, we used the random-effects model to pool the results, which is generally a plausible match to the underlying population effect distribution [33].

All published meta-analyses have different degrees of benefit from tocilizumab. Tleyjeh et al [32] showed that tocilizumab could reduce the risk of MV and the composition outcome of MV or death. Lin et al [26] found that COVID-19 patients receiving tocilizumab had a lower rate of MV, ICU admission, composite outcome of MV or death compared with control group. Sophie et al [28] showed evidence of a beneficial effect of tocilizumab compared with control on MV. Chia et al [31] found that COVID-19 patients with use of tocilizumab could benefit in the composite endpoint of MV and/or death. Moreover, Ghosn et al [27] including 8 RCTs had the same result that tocilizumab could reduce all-cause mortality at 28-day in hospitalized COVID-19 patients. Rezaei et al [34] including forty-five studies with 13,189 patients showed that tocilizumab can reduce mortality rates in severe to critical COVID-19 patients. Researches [35, 36] have shown that interleukin-6 is an important cytokine associated with mortality and severity of COVID-19. One genomic analysis [37] showed that genetic variants in interleukin-6 inflammatory pathway are associated with life-threatening in COVID-19. All of the studies support the therapeutic strategy of inhibiting interleukin-6 in severe COVID-19 patients. Tocilizumab is an anti-IL-6 receptor-a monoclonal antibody, which has been identified to specifically bind soluble and membranal IL-6R and inhibit signal transduction [6]. Combined with our meta-analysis, we conclude that tocilizumab could reduce the short-term mortality, the composition outcome of MV or death, risk of MV, ICU admission in moderate to critical COVID-19 patients.

Our study analyzed time to discharge and found that tocilizumab could significantly shorten time to hospital discharge. We also analyzed time to oxygen supply independency, and found that there was no significant difference between tocilizumab and control group. A retrospective study [38] found that patients had lowered their oxygen intake after using tocilizumab compared with control group in severe COVID-19 patients. Considering the data that could be analyzed was limited, we only included three RCTs [17, 21, 22] in this meta-analysis. Considering the limited studies and patients, we could not conclude that tocilizumab has no effect on time to oxygen supply independency. There are need more effective and larger RCTs to confirm this issue.

As for safety, all published meta-analyses [26–28, 31, 32] got the similar conclusions that tocilizumab was safe and did not increase adverse events and serious adverse events compared with control group in COVID-19 patients which were consistent with our results. We also found that tocilizumab could reduce the serious infection and events of SAEs. Lin et al [26] and Ghosn et al [27] also separately found that tocilizumab could reduce serious infection and SAEs, which were consistent with our results.

Although a major strength of this meta-analysis was that we included the largest number of RCTs in currently, this study also had limitations. First, there are many ongoing RCTs, also indicate that follow-up of ongoing trials is needed and meta-analyses need to be updated when necessary. Second, the dose of tocilizumab varied from 400–800 mg/d in included studies, the optimal effective dose of tocilizumab is

still uncertain. Thirdly, given the limited data on oxygen supply independency and 60-day mortality, further studies are warranted.

Conclusions

Tocilizumab could reduce the short-term mortality, the incidence of mechanical ventilation, the composite outcome of death or MV, ICU admissions, serious infection and events of SAE, and shorten the time to discharge, and could not increase the adverse advents of the hospitalized patients with COVID-19. But the optimal effective dose needs to be confirmed by further studies.

Abbreviations

CENTRAL
Cochrane Central Register of Controlled Trials
ICTRP
international Clinical Trials Registry Platform
RCTs
randomized controlled trials
MV
mechanical ventilation
ICU
intensive care unit
WHO
World Health Organization
ARDS
acute respiratory distress syndrome
MODS
multiple organ dysfunction syndrome
CRS
cytokine release syndrome
IL-6
interleukin 6
MeSH
Medical Subject Headings
AE
adverse events
SAE
serious adverse events
RR
relative risks

CI
confidence interval
HR
hazard ratio
d
day

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing of interest

The authors declare that they have no competing interests.

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Authors' contributions

Chun Chen and Jing Zhang initiated and coordinated the study. Chun Chen, Jing Zhang and ZeMei Zhou were responsible for the literature research, data extraction, statistical analysis, and Chun Chen wrote the first draft. Studies reviewed by Jing Zhang. All authors read and approved the final manuscript.

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References

1. Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. Jama. 2020;323(8):709–10.

2. Cheng AC, Williamson DA. An outbreak of COVID-19 caused by a new coronavirus: what we know so far. Med J Aust. 2020;212(9):393-4.e1.
3. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239–42.
4. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med. 2020;35(5):1545–9.
5. http://2019ncov.chinacdc.cn/2019-nCoV/global.html. Accessed 26, April 2021.
6. Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. Front Med. 2021:1–9.
7. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:25–32.
8. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5):105954.
9. An PJ, Zhu YZ, Yang LP. Biochemical indicators of coronavirus disease 2019 exacerbation and the clinical implications. Pharmacol Res. 2020;159:104946.
10. Ivan Hariyanto T, Kurniawan A. Tocilizumab administration is associated with the reduction in biomarkers of coronavirus disease 2019 infection. J Med Virol. 2021;93(3):1832–6.
11. Aziz M, Haghbin H, Abu Sitta E, Nawras Y, Fatima R, Sharma S, et al. Efficacy of tocilizumab in COVID-19: A systematic review and meta-analysis. J Med Virol. 2021;93(3):1620–30.
12. Berardicurti O, Ruscitti P, Ursini F, D'Andrea S, Ciaffi J, Meliconi R, et al. Mortality in tocilizumab-treated patients with COVID-19: a systematic review and meta-analysis. Clin Exp Rheumatol. 2020;38(6):1247–54.
13. Boregowda U, Perisetti A, Nanjappa A, Gajendran M, Kutti Sridharan G, Goyal H. Addition of Tocilizumab to the Standard of Care Reduces Mortality in Severe COVID-19: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2020;7:586221.
14. Hariyanto TI, Hardyson W, Kurniawan A. Efficacy and Safety of Tocilizumab for Coronavirus Disease 2019 (Covid-19) Patients: A Systematic Review and Meta-analysis. Drug Res (Stuttg). 2021.
15. Kotak S, Khatri M, Malik M, Malik M, Hassan W, Amjad A, et al. Use of Tocilizumab in COVID-19: A Systematic Review and Meta-Analysis of Current Evidence. Cureus. 2020;12(10):e10869.
16. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491–502.
17. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021;181(1):32–40.

18. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021;384(16):1503–16.
19. Salama C, Mohan SV. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. Reply. N Engl J Med. 2021;384(15):1473–4.
20. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: a Randomized Clinical Trial. JAMA internal medicine. 2021;181(1):24–31.
21. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020;383(24):2333–44.
22. Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021;372:n84.
23. Zhao H, Zhu Q, Zhang C, Li J, Wei M, Qin Y, et al. Tocilizumab combined with favipiravir in the treatment of COVID-19: a multicenter trial in a small sample size. Biomedicine and pharmacotherapy. 2021;133.
24. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021.
25. Horby PWLMJ. Tocilizumab in patients hospitalized with Covid-19 pneumonia. New England journal of medicine. 2021;384(1):20–30.
26. Lin WT, Hung SH, Lai CC, Wang CY, Chen CH. The effect of tocilizumab on COVID-19 patient mortality: A systematic review and meta-analysis of randomized controlled trials. Int Immunopharmacol. 2021;96:107602.
27. Ghosn L, Chaimani A, Evrenoglou T, Davidson M, Graña C, Schmucker C, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;3:CD013881.
28. Juul S, Nielsen EE, Feinberg J, Siddiqui F, Jørgensen CK, Barot E, et al. Interventions for treatment of COVID-19: Second edition of a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project). PLoS One. 2021;16(3):e0248132.
29. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.
30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557–60.
31. Kow CS, Hasan SS. The effect of tocilizumab on mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2021:1–6.
32. Tleyjeh IM, Kashour Z, Damlaj M, Riaz M, Tlayjeh H, Altannir M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin Microbiol Infect.

2021;27(2):215–27.
33. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97–111.
34. Rezaei S, Fatemi B, Karimi Majd Z, Minaei H, Peikanpour M, Anjidani N, et al. Efficacy and safety of Tocilizumab in severe and critical COVID-19: A Systematic Review and Meta-Analysis. Expert Rev Clin Immunol. 2021:1–13.
35. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
36. Zhu J, Pang J, Ji P, Zhong Z, Li H, Li B, et al. Elevated interleukin-6 is associated with severity of COVID-19: A meta-analysis. J Med Virol. 2021;93(1):35–7.
37. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, et al. Genetic mechanisms of critical illness in COVID-19. Nature. 2021;591(7848):92–8.
38. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970–5.

Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

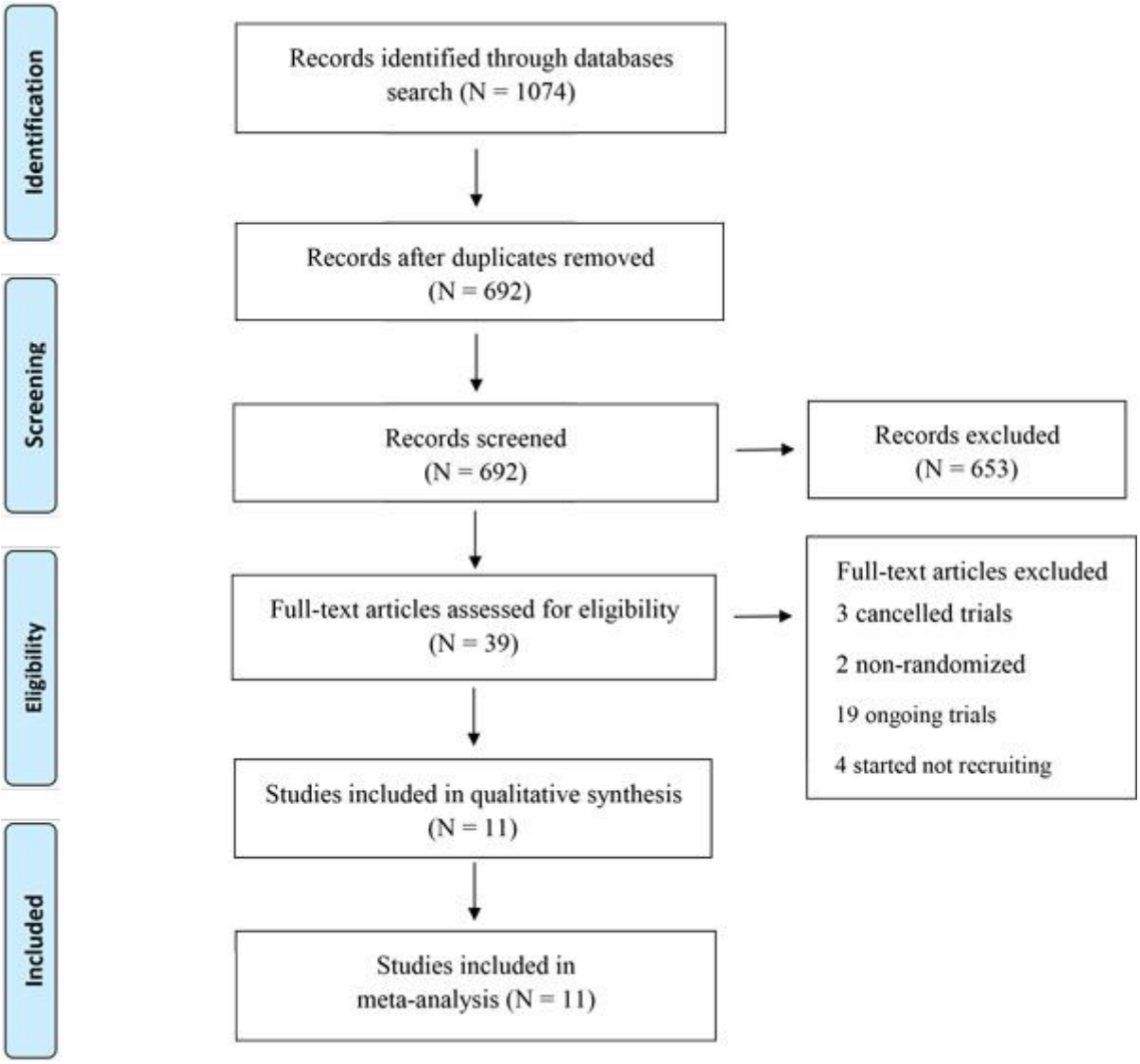

Figure 1

Study flow diagram. All studies were randomized controlled trials.

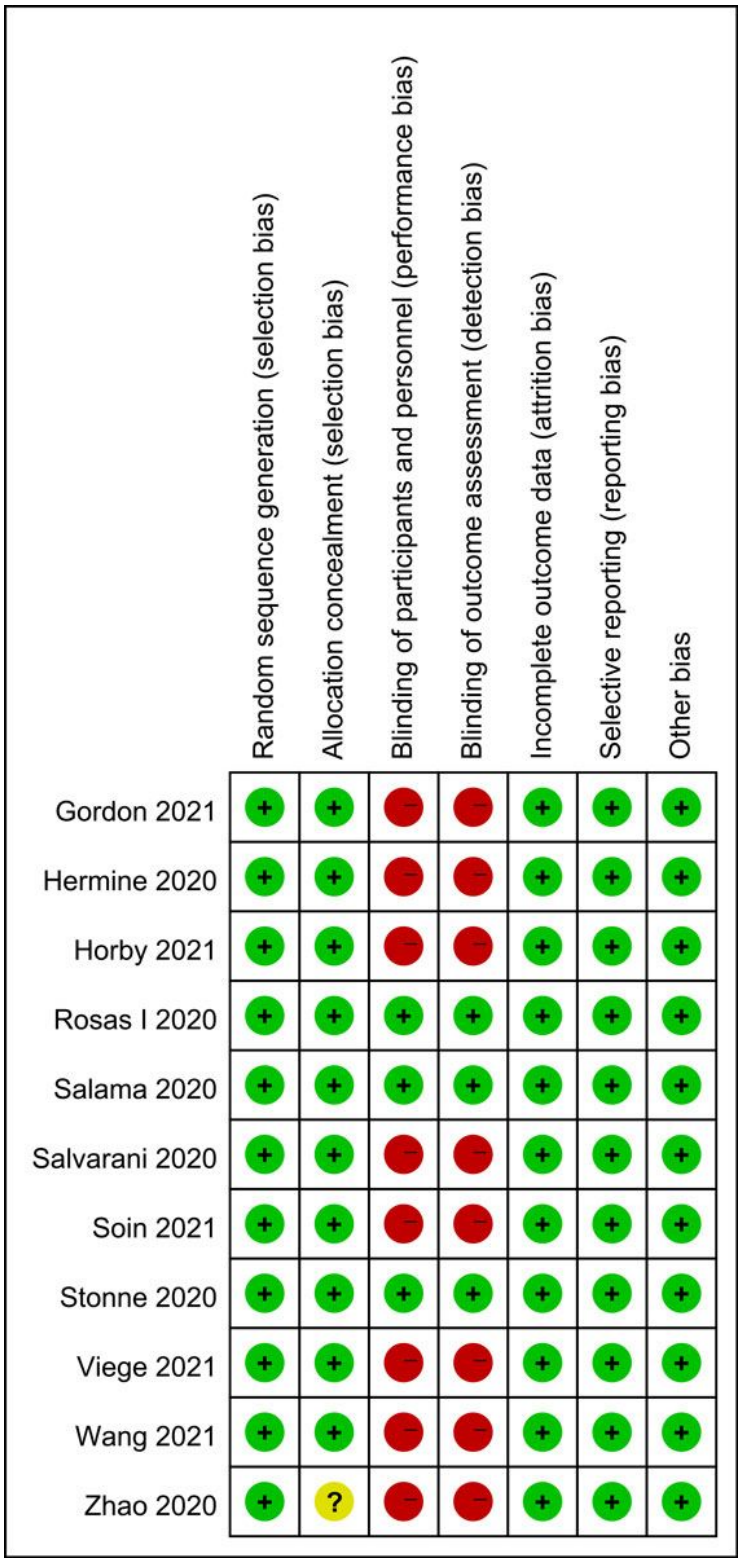

Figure 2

Risk of bias summary of the included studies.

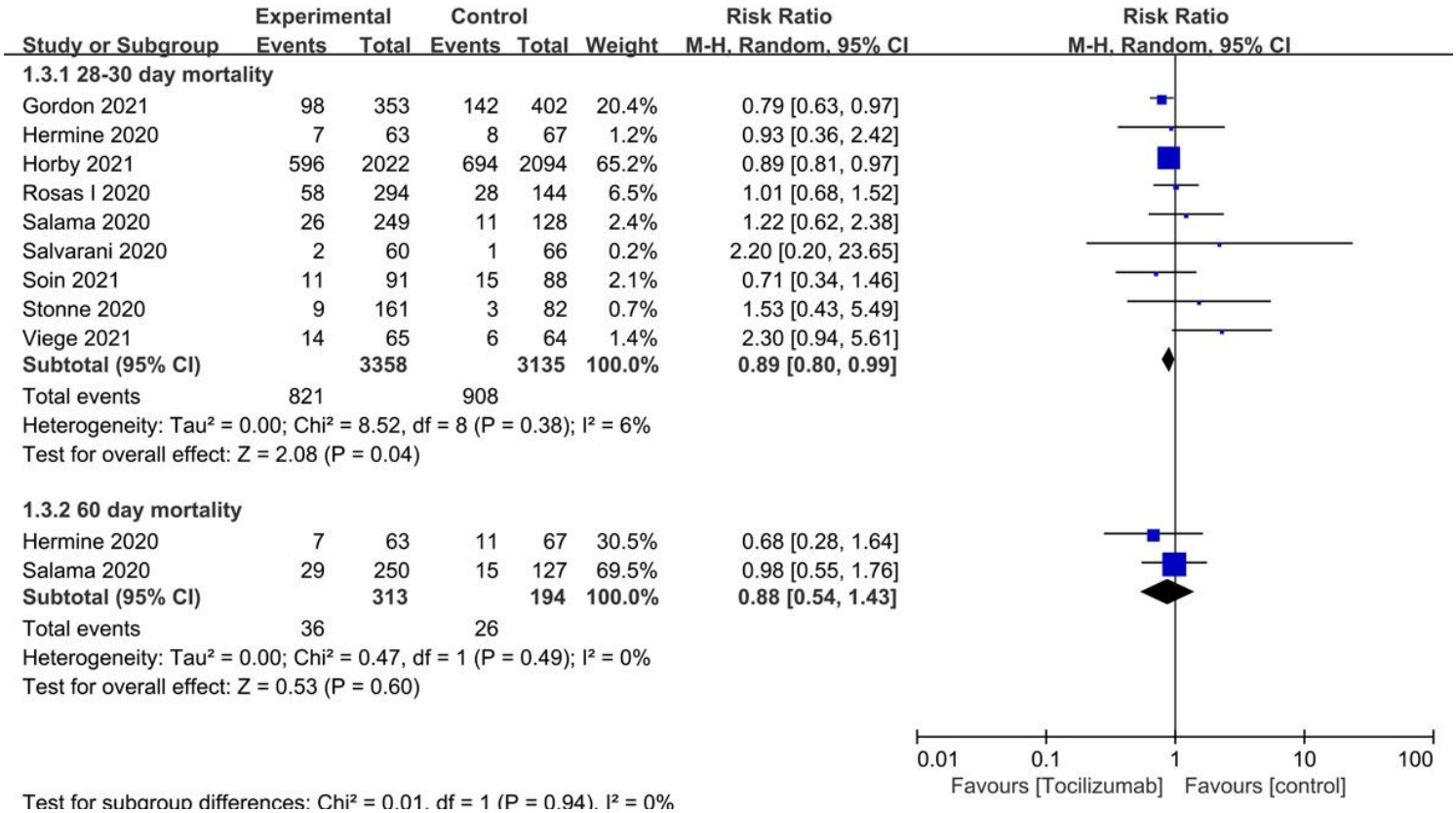

Figure 3

The forest plot of mortality at 28-30 day and 60 day between the tocilizumab and control groups.

Figure 4

The forest plot of incidence of mechanical ventilation between the tocilizumab and control groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- PRISMA2020checklist.docx
- Fig5.jpg
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