Systematic Review and Meta-Analysis

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Effectiveness of tocilizumab in the treatment of hospitalized adults COVID-19

A systematic review and meta-analysis

Jing Zhang, MD[a], Chun Chen, MD[b], Yi Yang, MD[a], Jin Yang, MD[a,*]

Abstract

Background: Since December 2019, the coronavirus disease (COVID-19) has spread worldwide, leading to a global health threat. This study aimed to investigate the effectiveness of tocilizumab in COVID-19 patients.

Methods: We systematically searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and World Health Organization International Clinical Trials Registry Platform to March 10, 2021 for randomized controlled trials in which patients were randomly assigned to receive tocilizumab plus usual care or usual care alone in hospitalized adults with COVID-19. A random-effects meta-analysis model was used to pool studies. All data analyses were performed using Review Manager version 5.4.

Results: Eleven studies with 6579 patients were included in our meta-analysis, of which 3406 and 3173 were assigned to tocilizumab and control groups, respectively. Tocilizumab significantly reduced the 28 to 30-day mortality (relative risk [RR] = 0.89, 95% confidence interval [CI] 0.80-0.99, $P = .04$), incidence of mechanical ventilation (MV) (RR = 0.79, 95% *CI* 0.71-0.89, $P < .001$), composite outcome of MV or death (RR = 0.81, 95% *CI* 0.72-0.90, $P < .001$), time-to-hospital discharge (hazard ratio = 1.30, 95% *CI* 1.16-1.45, $P < .001$), intensive care unit admission (RR = 0.64, 95% *CI* 0.47-0.88, $P = .006$), serious infection (RR = 0.61, 95% *CI* 0.40-0.94, $P = .02$), and number of serious adverse events (RR = 0.64, 95% *CI* 0.47-0.86, $P = .004$).

Conclusion: Tocilizumab reduced short-term mortality, incidence of MV, composite outcome of death or MV, intensive care unit admission, serious infection, serious adverse events, and time-to-hospital discharge in hospitalized COVID-19 patients. Further studies are required to determine the optimal dose.

Abbreviations: AE = adverse event, CI = confidence interval, COVID-19 = coronavirus disease, HR = hazard ratio, ICU = intensive care unit, IL-6 = interleukin 6, MV = mechanical ventilation, RCT = randomized controlled trial, RR = relative risk, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SMD = standardized mean difference.

Keywords: COVID-19, meta-analysis, mortality, tocilizumab

1. Introduction

In December 2019, there were an increasing number of confirmed cases of a novel coronavirus in Wuhan, China, which quickly spread to other countries, leading to a global health threat.[1] The World Health Organization named this coronavirus disease (COVID-19) on February 11, 2020.[2] COVID-19 can be mild, progress to dyspnea and/or hypoxemia, or in severe cases, progress to respiratory failure, acute respiratory distress syndrome, and septic shock, which in turn may lead to multiple organ dysfunction syndrome or death.[3,4] Although most patients with COVID-19 have a self-limiting illness, COVID-19 has caused significant loss of life worldwide.[3] As of April 26, 2021, more than 14.6 million people have been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and more than 3 million people have died.[5] Scientists are striving to identify effective treatments to control the ongoing COVID-19 pandemic.[6]

Many studies have shown that cytokine release syndrome is an important cause of death in patients with COVID-19, and that interleukin 6 (IL-6) plays an important role.[7–9] Tocilizumab is a recombinant humanized monoclonal antibody against the human IL-6 receptor, which reduces the biomarkers of SARS-CoV-2 infection and increases lymphocyte count.[10]

Several meta-analyses of observational studies have shown that tocilizumab can reduce COVID-19 mortality.[11–15] Considering that low levels of evidence from observational studies may confound these findings, the benefits of tocilizumab on COVID-19 mortality must be interpreted cautiously. Several newly published randomized controlled trials (RCTs)[6,16–25] and meta-analyses[26–28] of RCTs have investigated the effects of tocilizumab as an adjunctive therapy in patients with COVID-19

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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but have reported inconsistent results. Moreover, there is an increasing number of newly available studies regarding tocilizumab treatment for COVID-19. Hence, we conducted an updated meta-analysis to synthesize evidence from well-conducted RCTs to evaluate the effects of tocilizumab in hospitalized COVID-19 patients.

2. Methods

2.1. Literature search

We systematically searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform from their inception to March 10, 2021, for RCTs using a combination of Medical Subject Headings, Emtree, and related keywords 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 of the identified studies and key review articles to identify additional studies. All analyses were based on previously published studies, thus no ethical approval or patient consent was required.

2.2. Inclusion criteria

Studies meeting the following criteria were included: participants: hospitalized patients aged ≥18 years with confirmed COVID-19 by a positive polymerase chain reaction test for SARS-CoV-2 in any body fluid and/or bilateral chest infiltrates on chest radiography or computed tomography; intervention: tocilizumab administered intravenously, with dosages ranging from 400 to 800 mg; comparison: standard care; outcomes: the primary outcomes were mortality on day 28 to 30 and day 60, incidence of mechanical ventilation (MV), composite outcome of death or MV, intensive care unit (ICU) admission, and time to hospital discharge. The secondary outcomes were time-to-oxygen independence, organ failure-free days, mean ventilator-free days, length of ICU stay, nonserious adverse events (AEs), serious AEs, serious infection, and number of serious AEs; and study design: RCTs. The language used in this study is restricted to English. Two authors (JZ and CC) independently evaluated the eligibility of all studies obtained from the databases, according to the above selection criteria. Discrepancies in study inclusion between reviewers were resolved through discussions.

2.3. Data extraction and risk-of-bias assessment

Two authors (JZ and CC) independently extracted data. The following data were included: 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 the risk of bias was used to appraise the quality of each RCT, which included 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 included studies and rated them as "low risk", "unclear risk" or "high risk" based on the Cochrane risk-of-bias tool. All relevant data are within the paper.

2.4. Statistical analysis

To evaluate the effect of tocilizumab on COVID-19, we calculated relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes. For continuous outcomes, mean differences or standard mean differences (SMDs) between tocilizumab and placebo groups were used for the meta-analysis. Time-to-event outcomes were analyzed using hazard ratios (HRs). Heterogeneity in the results across the studies was examined using Cochran's Q and I^2 statistics.[30] The null hypothesis that the studies were homogeneous was rejected if the *P value* for heterogeneity was $<.10$, or I^2 was $>50\%$. A random-effects model was used to pool study estimates for each outcome.

A sensitivity analysis was conducted to assess the influence of individual studies on the pooled results when P was $<.10$, or I^2 was $>50\%$, by excluding each study individually and recalculating the combined results from the remaining studies.[30] All data analyses were performed using Review Manager 5.4 (Cochrane Informatics and Knowledge Management Department; London, England), available at http://tech.cochrane.org/.

3. Results

Figure 1 shows the flow diagram for the study selection process. A total of 1074 records were initially identified in the database search. Of these, 382 records were excluded as duplicates and 653 records were excluded after screening the titles and abstracts. After full-text screening, 11 studies[6,16–25] were included in the meta-analysis.

3.1. Characteristics of included studies

The characteristics of the studies included in this meta-analysis are summarized in Table 1. All 11 RCTs were multi-center studies. Three[16,18,19] studies were conducted in multiple countries, while the remaining 8 trials were from France,[17] Italy,[20] the USA,[21] Brazil,[22] China,[6,23] the UK,[25] and India.[24] Overall, 6579 patients were enrolled in our meta-analysis; 4906 were men (74.6%), and the average age ranged from 54 to 75 years. A total of 3406 patients were administered tocilizumab in addition to standard care or placebo, 14 of whom were administered tocilizumab and favipiravir, and 3173 were administered standard care or placebo, 7 of whom were administered favipiravir. Except for 2[21,22] RCTs that used only a single dose of tocilizumab, the other 9[6,16–20,23–25] RCTs allowed additional doses if needed. The tocilizumab doses varied from 400 mg to 800 mg and were administered intravenously for more than 1 hour. The maximum dose was 480 mg/d in 1 study,[24] 800 mg/d in 8 studies,[16–22,25] and 400 mg/d in 2 studies.[6,23]

3.2. Assessment of risk of bias

There was a high risk of bias in the blinding of participants, personnel, and outcome assessments because of the open-label design in 8 studies,[6,16,17,20,22–25] and there was an unclear risk of bias in allocation concealment because of the failure to mention it in 1 study.[23] See Figure 2.

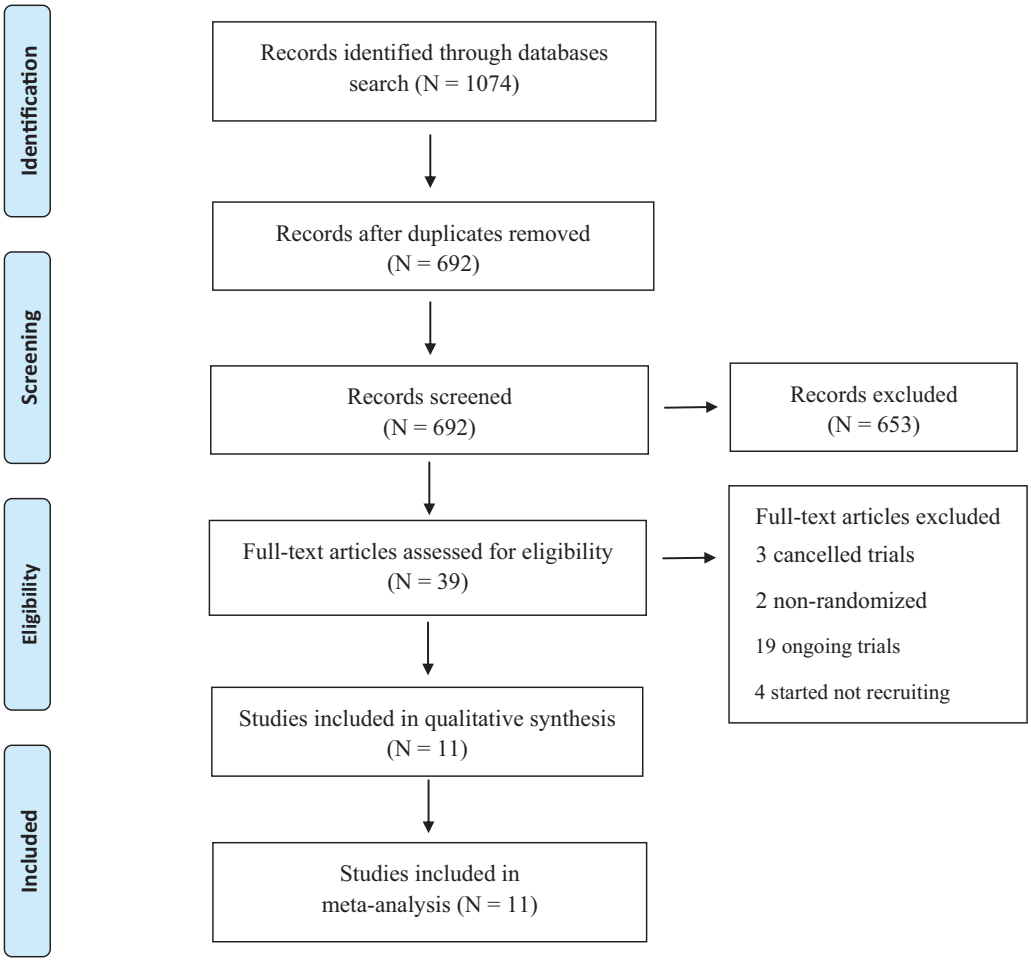

Figure 1. Study flow diagram. All studies were randomized controlled trials.

3.3. Primary outcomes

3.3.1. Mortality. Nine studies[16–22,24,25] with 6493 patients were included in the meta-analysis. Overall, there was a significant difference between the tocilizumab and control groups in 28 to 30-day mortality (RR = 0.89, 95% *CI* 0.80-0.99, *P* = .04). Two trials[17,19] with 507 patients contributed to the 60-day mortality, and no statistically significant difference was found between the tocilizumab and control groups (RR = 0.88, 95% *CI* 0.54-1.43, *P* = .60) (Fig. 3).

3.3.2. 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 5369 participants showed that tocilizumab significantly decreased the incidence of MV compared to the control group (RR = 0.79, 95% *CI* 0.71-0.89, *P* < .001) (Fig. 4).

3.3.3. Composite outcome of death or MV. Eight RCTs,[16–19,21–23,25] including 5241 adults, examined the composite outcomes of death or MV. The pooled analysis showed that there was a significant difference between the tocilizumab and control groups in this composite outcome (RR = 0.81, 95% *CI* 0.72-0.90, *P* < .001) (Fig. 5).

3.3.4. Time-to-hospital discharge. A pooled analysis of 5 trials[16–19,21] with 1943 cases showed that there was a statistically significant difference in the time-to-hospital discharge between the tocilizumab and control groups (HR = 1.30, 95% *CI* 1.16-1.45, *P* < .001) (Fig. 6).

3.3.5. ICU admissions. Four trials[17,18,20,24] with 499 cases were included in the meta-analysis. Overall, there was a statistically significant difference in the risk of ICU admission between the tocilizumab and control groups (RR = 0.64, 95% *CI* 0.47-0.88, *P* = .006) (Fig. 7).

3.4. Secondary outcomes

3.4.1. Time-to-oxygen independence. Our meta-analysis, including 3 RCTs[17,21,22] with 502 cases, showed that there was no significant difference in time-to-oxygen independence between the tocilizumab and control groups (HR = 1.21, 95% *CI* 0.94-1.57, *P* = .14) (Fig. 8).

3.4.2. Organ failure-free days. Two trials[16,24] with 934 patients were included in the meta-analysis. Overall, there was no significant difference between the tocilizumab and control groups in organ failure-free days (SMD = 0.49, 95% *CI* -0.17-1.16, *P* = .15) (Fig. 9).

3.4.3. Mean ventilator-free days. Our meta-analysis, which included 4 RCTs[16,18,22,24] with 1501 cases, showed that there was no significant difference in mean ventilator-free days between

Table 1

Characteristics of studies included in the meta-analysis.

Authors	Study design	Country	Age (mean ± SD)	Comparisons	No. of patients (male/total)	Intervention/tocilizumab	Follow-up (d)	Outcomes
Hermine et al 2020	Open-label RCT	France	64.0 (12.7) 63.3 (11.3)	Tocilizumab Control	44/63 44/67	8 mg/kg on day 1 and on day 3 400 mg was recommended if clinically indicated	90	1.2.3.4.5. 6.7.8.9.10
Rosas I et al 2020	double-blinded RCT	Canada, Denmark, France, Germany, Italy Netherland, UK, United States, Spain	60.9 (14.6) 60.6 (13.7)	Tocilizumab Control	205/294 101/144	8 mg/kg (maximum 800 mg) followed by a second dose after 8-24 h	60	1.2.3.4.5.6.7. 9.10.12.13
Salvarani et al 2020	Open-label RCT	Italy	61.5 (16.3) 60.0 (11.10)	Tocilizumab Control	40/60 37/66	8 mg/kg (maximum 800 mg) followed by a second dose after 12 h	30	1.5.6.7.10
Salama et al 2020	Double-blinded RCT	United States, Mexico, Kenya, South Africa, Peru, or Brazil	56.0 (14.3) 55.6 (14.9)	Tocilizumab Control	150/249 73/128	8 mg/kg (maximum 800 mg) and followed by a second dose after 8-24 h	60	1.2.3.6.7.10
Stonne et al 2020	Double-blinded RCT	USA	61.6 (17.3) 56.5 (17.1)	Tocilizumab Control	96/161 45/82	A single dose of 8 mg/kg (maximum 800 mg)	28	1.2.3.6.7.9
Veiga et al 2021	Open-label RCT	Brazil	57.4 (15.7) 57.5 (13.5)	Tocilizumab Control	44/65 44/64	A single dose of 8 mg/kg (maximum 800 mg)	29	1.2.3.6.8.10.12
Zhao et al 2020	Multicenter RCT	China	75 (11.8) 70 (11)	Combination Favipiravir	6/14 5/7	400 mg followed by a second dose after 24 h	60	3.6.10
Wang et al 2021	Open-label RCT	China	63.5 (9.6) 63 (11.1)	Tocilizumab Control	18/34 15/31	400 mg followed by a second dose after 24 h	14	6.10
Horby et al 2021	Platform trial, RCT	UK	63.3 (13.7) 63.9 (13.6)	Tocilizumab Control	1335/2022 1437/2094	6-8 mg/kg (maximum 800 mg) followed by a second dose after 12-24 h	28	1.2.3
Gordon et al 2021	Platform trial, RCT	UK, Netherland, Australia, New Zealand Ireland, Saudi Arabia	61.5 (12.5) 61.1 (12.8)	Tocilizumab Control	261/353 283/402	8 mg/kg (maximum 800 mg) followed by a second dose after 12-24 h	90	1.2.3.4.6.11.12
Soin et al 2021	Open-label RCT	India	56 (11.85) 54 (14.81)	Tocilizumab Control	76/91 76/88	6 mg/kg (maximum 480 mg) followed by a second same dose between 12 h to 7 d	30	1.2.5.6.10. 11.12.13

Outcomes: 1. Mortality at 28 to 30 d; 2. Incidence of mechanical ventilation; 3. Composite outcome of mechanical ventilation or death; 4. Time to discharge; 5. Incidence of ICU transfer; 6. Serious adverse advents; 7. Serious infection; 8. Time to oxygen supply independence; 9. Numbers of serious adverse advents; 10. Nonserious adverse events; 11. Organ failure-free days; 12.Mean ventilator-free days; 13. Length of ICU stay.

h = hour, ICU = intensive care unit, RCT = randomized controlled trial.

the tocilizumab and control groups (SMD = 0.38, 95% *CI* –0.00-0.77, *P* = .05) (Fig. 10).

3.4.4. Length of ICU stay. Two trials[18,24] with 617 patients were included in this meta-analysis. Overall, there was no significant difference in the length of ICU stay between the tocilizumab and control groups (SMD = –0.35, 95% *CI* –0.94-0.25, *P* = .26) (Fig. 11).

3.4.5. Serious infection. Five RCTs[17–21] with 1311 cases were included in the meta-analysis. Overall, there was a statistically significant difference between the tocilizumab and control groups in the risk of serious infection (RR = 0.61, 95% *CI* 0.40-0.94, *P* = .02) (Fig. 12).

3.4.6. Nonserious AEs and serious AEs. Eight studies[6,17–20,22–24] including 1463 patients showed that there was no difference between tocilizumab and control groups in the risk of nonserious AEs (RR = 1.19, 95% *CI* 0.94-1.50, *P* = .14) (Fig. 13). Nine trials[6,16–22,24] with 2440 participants showed that there was no significant difference between tocilizumab and control groups in the risk of serious AEs (RR = 0.91, 95% *CI* 0.76-1.08, *P* = .28) (Fig. 14).

3.4.7. Numbers of serious AEs. Our meta-analysis included 4 trials[17,18,21,24] with 991 cases and showed that there was a significant difference between the tocilizumab and control groups

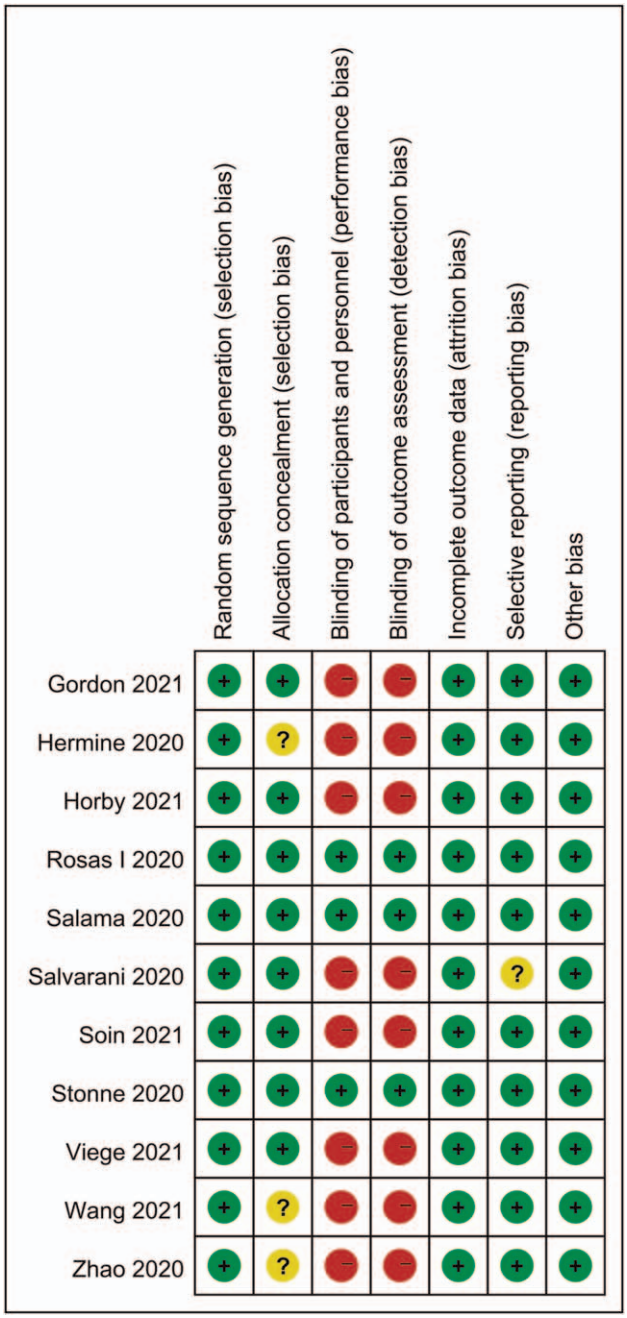

Figure 2. Risk-of-bias summary of the included studies.

in the number of serious AEs (RR = 0.64, 95% *CI* 0.47-0.86, *P* = .004) (Fig. 15).

4. Discussion

Our meta-analysis investigated the effects of adjunctive tocilizumab in hospitalized patients with COVID-19 and found that tocilizumab supplementation could reduce 28 to 30-day mortality, the incidence of MV, the composite outcome of death or MV, ICU admission, serious infection, number of serious AEs, and shortened the time to discharge. There was no evidence that tocilizumab could increase the number of AEs and reduce the 60-day mortality or time-to-oxygen independence.

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 to 30-day mortality in patients with COVID-19. Our meta-analysis has several strengths. First, this meta-analysis included the most recently published randomized controlled trials (RCTs). Second, given the clinical heterogeneity across the included studies, we used a random-effects model to pool the results, which is a plausible match to the underlying population effect distribution.[33]

All published meta-analyses have reported different degrees of benefits from tocilizumab. Tleyjeh et al[32] showed that tocilizumab could reduce the risk of MV and composite outcome of MV or death. Lin et al[26] found that patients with COVID-19 receiving tocilizumab had lower rates of MV, ICU admission, and the composite outcome of MV or death than the control group. Sophie et al[28] showed evidence of a beneficial effect of tocilizumab compared with the control on MV. Chia et al[31] found that patients with COVID-19 who were treated with tocilizumab showed improvements in the composite endpoint of MV and/or death. Moreover, Ghosn et al,[27] including 8 RCTs, also showed that tocilizumab reduced 28-day all-cause mortality in hospitalized patients with COVID-19. Rezaei et al[34] including 45 studies with 13,189 patients, showed that tocilizumab reduces mortality in patients with severe to critical COVID-19. Research[35,36] has shown that IL-6 is an important cytokine associated with mortality and severity of COVID-19. Genomic analysis[37] has shown that genetic variations in the IL-6 inflammatory pathway are associated with life-threatening COVID-19. These studies support the therapeutic strategy for inhibiting IL-6 expression in severe COVID-19. Tocilizumab is an anti-IL-6 receptor monoclonal antibody that specifically binds to soluble and membrane-bound IL-6 receptors and inhibits signal transduction.[6] We conclude that tocilizumab can reduce short-term mortality, the composition outcome of MV or death, risk of MV, and ICU admission in patients with moderate to critical COVID-19.

Our study found that tocilizumab significantly reduced the time-to-hospital discharge. We also analyzed the time-to-oxygen independence, and found that there was no significant difference between the tocilizumab and control groups. A retrospective study[38] found that patients had lowered oxygen intake after using tocilizumab compared with the control group in patients with severe COVID-19. Considering that the data were limited, we included only 3 RCTs[17,21,22] in this meta-analysis; therefore, we could not conclude that tocilizumab had no effect on time-to-oxygen independence. More effective and larger RCTs are required to confirm these findings.

There were no significant differences in organ failure-free days, mean ventilator-free days, or length of ICU stay between the tocilizumab and control groups. Considering that the study heterogeneity was very high, by excluding each study one by one and recalculating the combined results of the remaining studies, we found that the results became significant after excluding the study by Soin et al.[24] There are a few reasons for this finding. First, most patients received concomitant corticosteroids, and about half received antiviral therapy with remdesivir, which could have reduced any beneficial effects that tocilizumab might have had. Second, the dose of tocilizumab used in Soin et al's study[24] was lower than that used in other studies. Third, the number of participants who were initially considered by the researchers but not screened was unknown during the pandemic, which may have influenced the results. Thus, further studies are

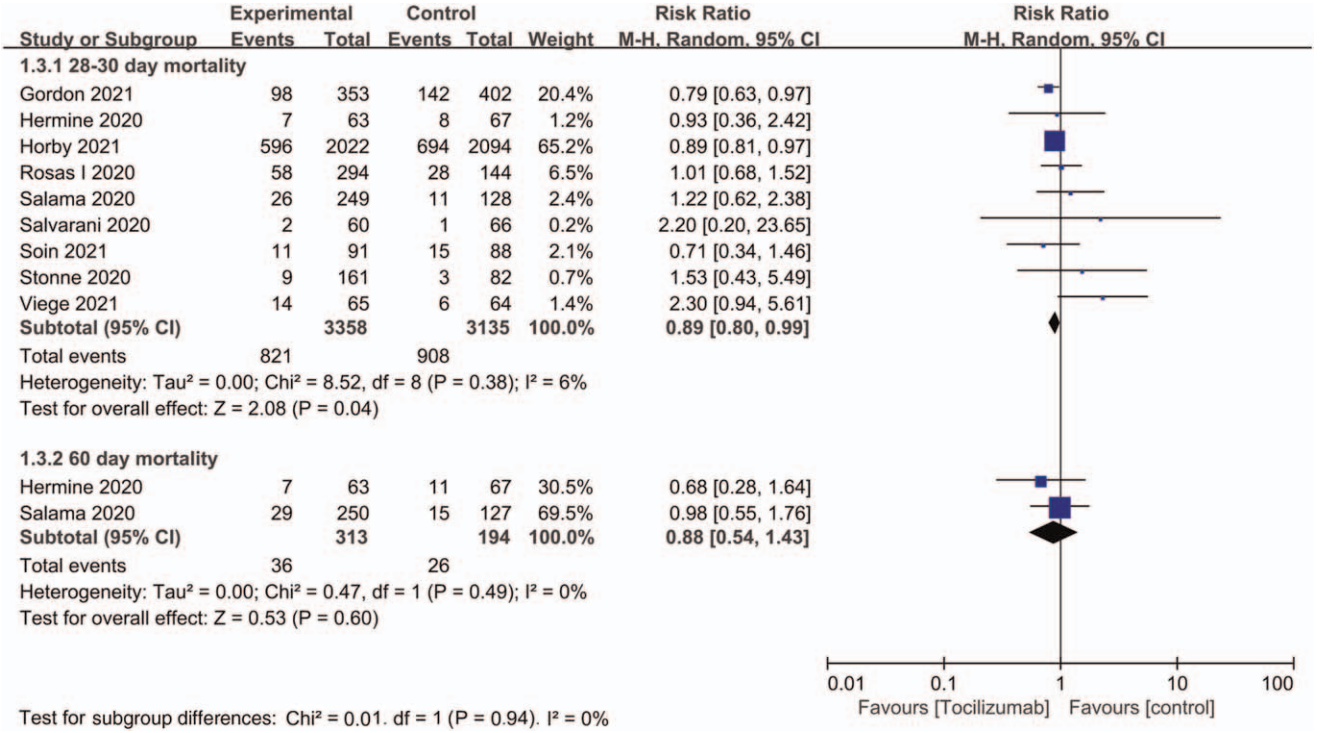

Figure 3. The forest plot of mortality at 28 to 30 and 60 d between the tocilizumab and control groups.

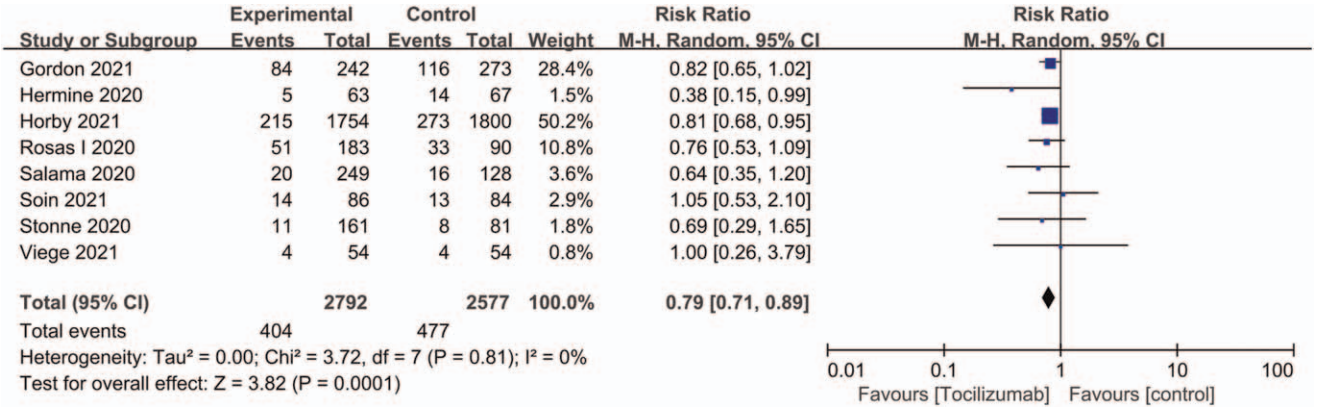

Figure 4. The forest plot of incidence of mechanical ventilation between the tocilizumab and control groups.

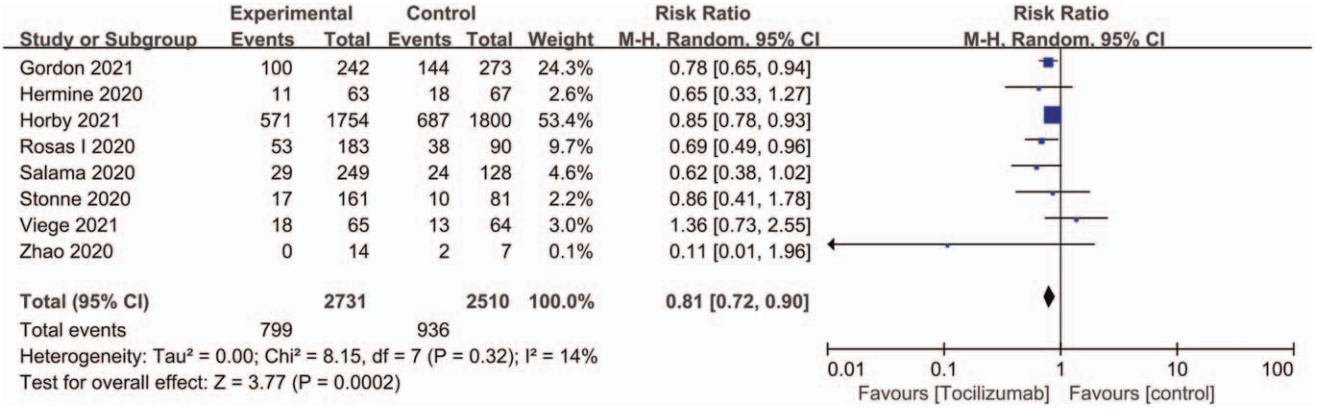

Figure 5. The forest plot of the composite outcome of death or MV between the tocilizumab and control groups.

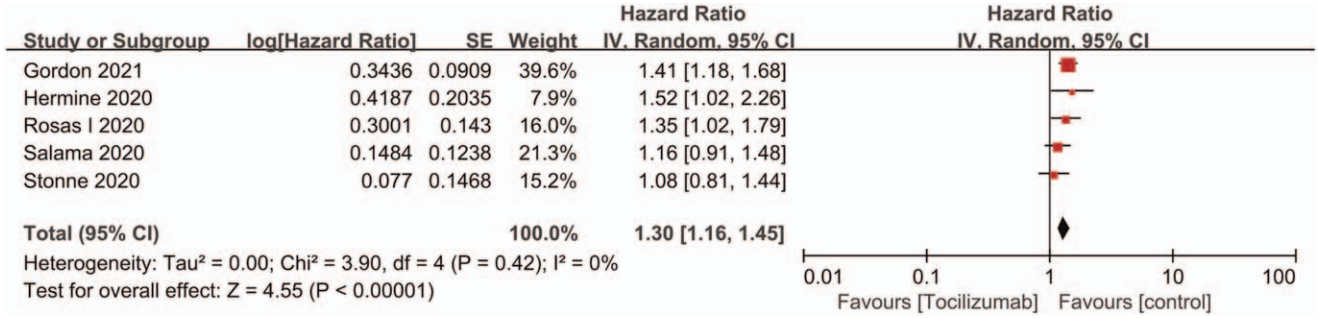

Figure 6. Hazard ratios for time-to-hospital discharge from 5 included studies. CI = confidence interval, IV = inverse variance, SE = standard error.

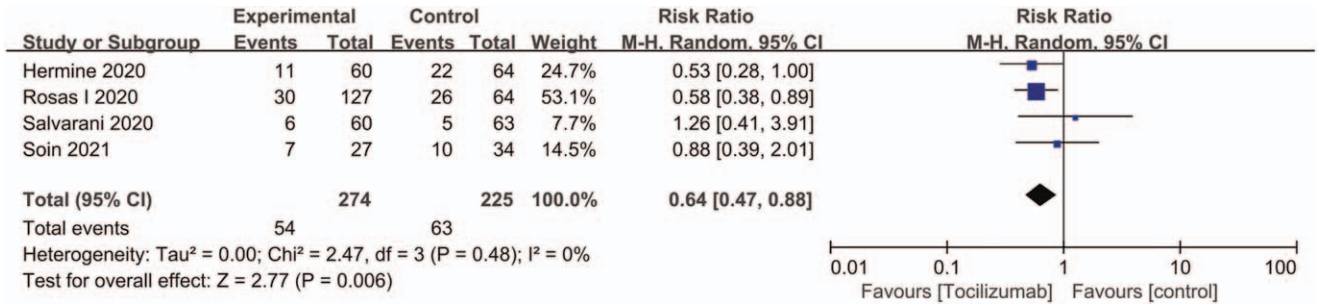

Figure 7. The forest plot of ICU admissions between the tocilizumab and control groups.

needed to confirm the results of organ failure-free days, mean ventilator-free days, and length of ICU stay.

All published meta-analyses[26–28,31,32] concluded that tocilizumab was safe and did not increase nonserious or serious AEs compared with the control group in patients with COVID-19, which was consistent with our results. We also found that tocilizumab reduced the number of serious infections and AEs. Lin et al[26] and Ghosn et al[27] also found that tocilizumab reduced the incidence of serious infections and AEs.

Although a major strength of this meta-analysis is that we incorporated the largest number of RCTs, this study also has limitations. First, there are many ongoing RCTs, whose results will require addition to this meta-analysis when available. Second, the dose of tocilizumab varied from 400 to 800 mg/d in the included studies, and the optimal effective dose of tocilizumab remains uncertain. Third, given the limited data on oxygen independence, 60-day mortality, organ failure-free days, mean ventilator-free days, and length of ICU stay, further studies are warranted.

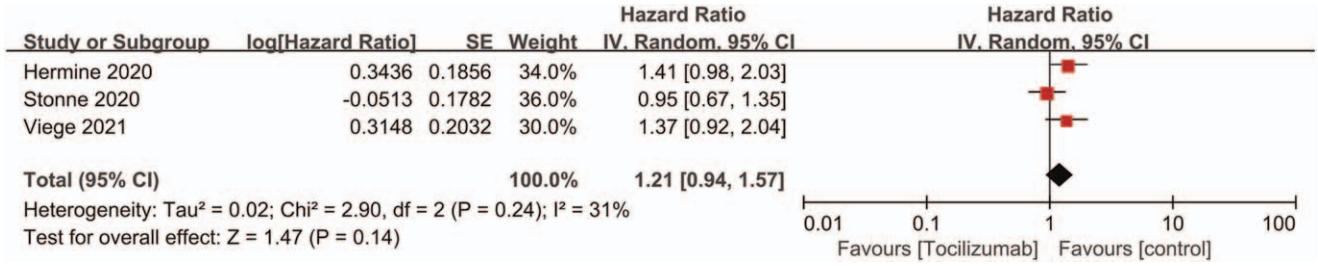

Figure 8. Hazard ratios for time-to-oxygen independence from 3 included studies. CI = confidence interval, IV = inverse variance, SE = standard error.

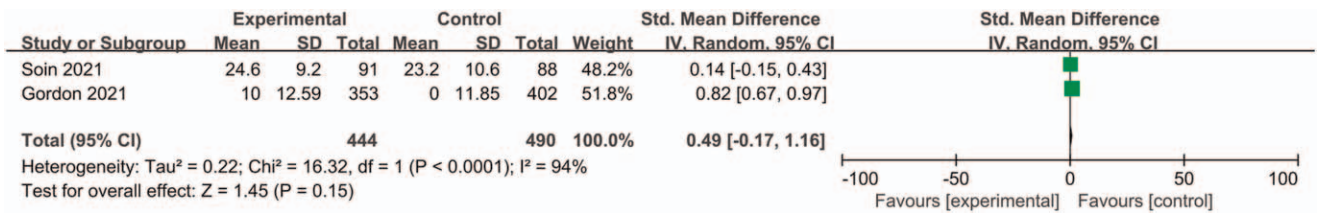

Figure 9. The forest plot of organ failure-free days between the tocilizumab and control groups.

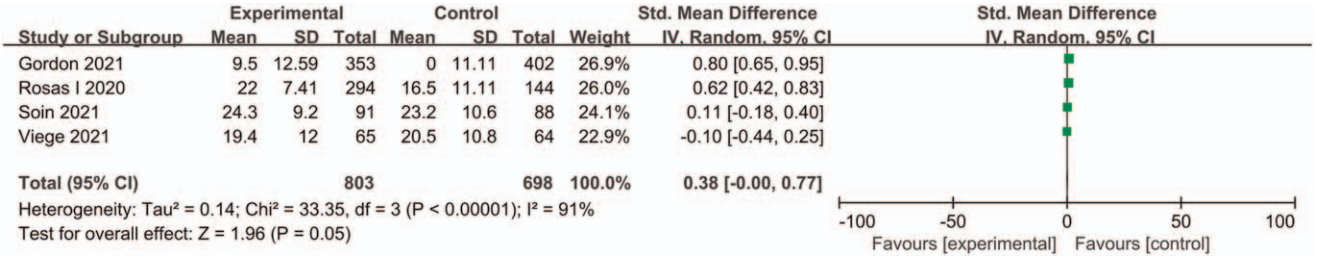

Figure 10. The forest plot of mean ventilator-free days between the tocilizumab and control groups.

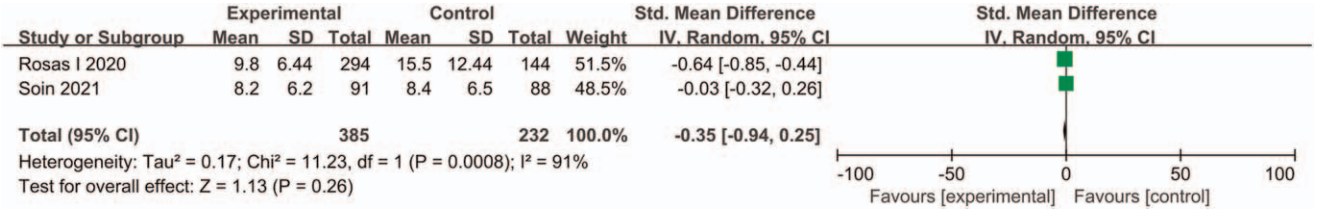

Figure 11. The forest plot of length of ICU stay between the tocilizumab and control groups.

5. Conclusion

Tocilizumab reduced short-term mortality, the incidence of MV, the composite outcome of death or MV, ICU admissions, serious infection, number of serious AEs, and time to discharge in adult patients hospitalized with COVID-19, but it did not increase the risk of AEs. However, tocilizumab did not decrease organ failure-free days, mean ventilator-free days, or length of ICU stay in critically ill patients with COVID-19. The optimal effective dose needs to be confirmed by further studies.

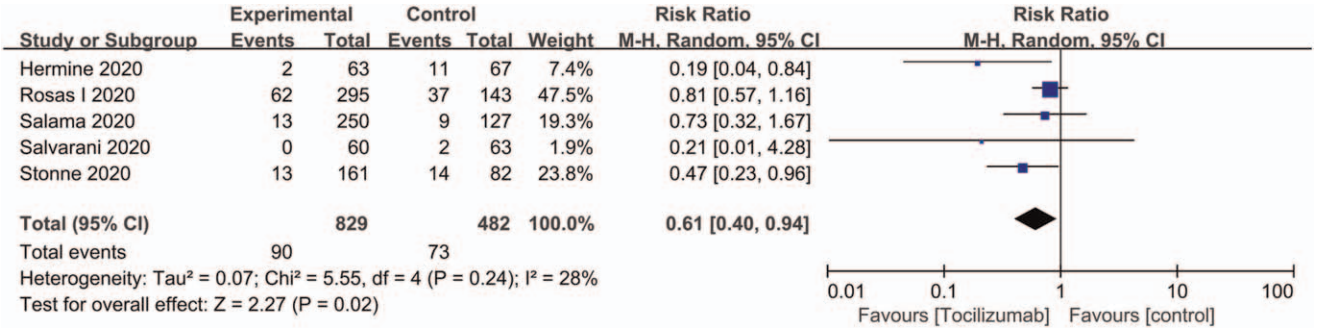

Figure 12. The forest plot of serious infection between the tocilizumab and control groups.

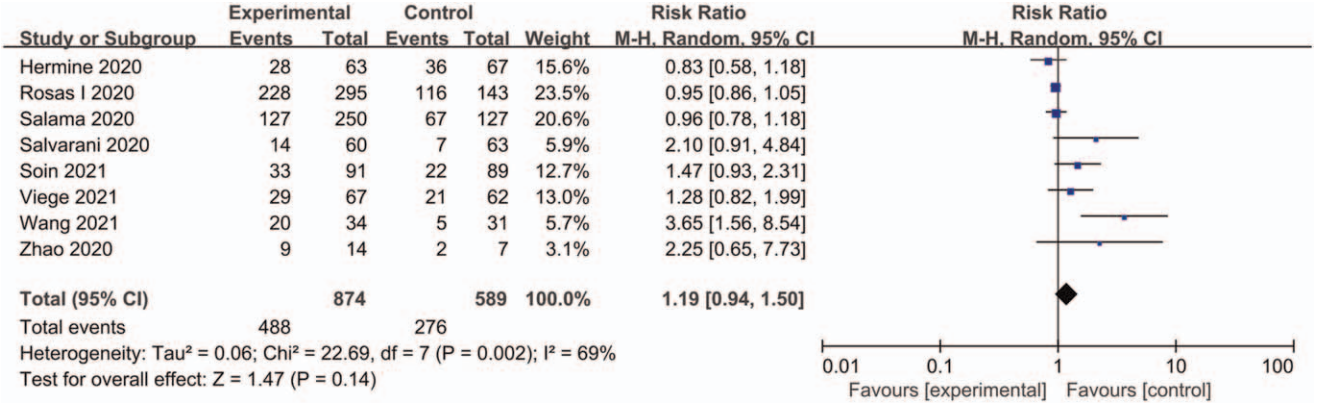

Figure 13. The forest plot of nonserious adverse events between the tocilizumab and control groups.

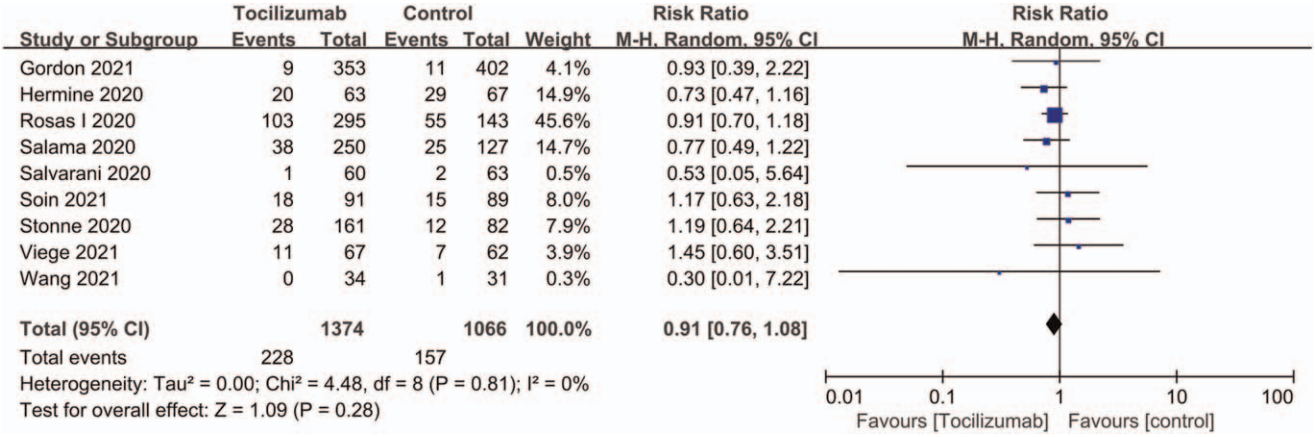

Figure 14. The forest plot of serious adverse events between the tocilizumab and control groups.

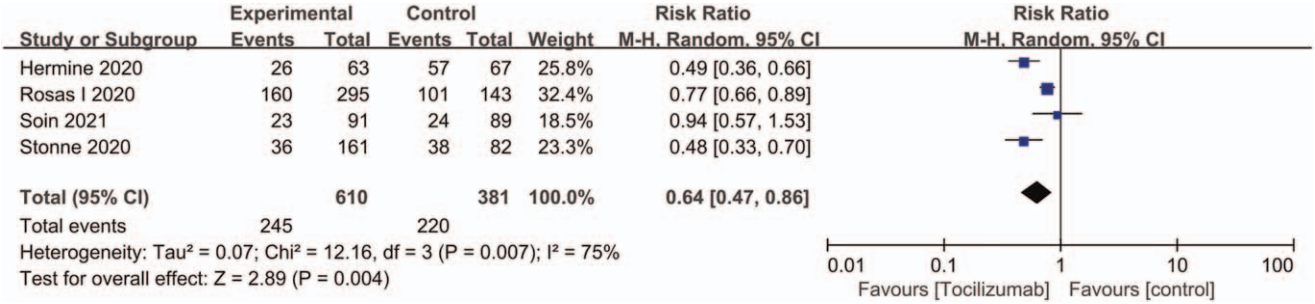

Figure 15. The forest plot of numbers of serious adverse advents between the tocilizumab and control groups.

Author contributions

Chen and Zhang initiated and coordinated this study. Chun Chen, Jing Zhang, and Jin Yang were responsible for the literature research, data extraction, and statistical analysis. Yi Yang participated in the data extraction, and Jing Zhang wrote the first draft. These studies were reviewed by Jin Yang. All authors have read and approved the final manuscript.

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