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The effect of tocilizumab on COVID-19 patient mortality: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: This systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to investigate the clinical efficacy and safety of tocilizumab for treating patients with COVID-19.

Methods: The PubMed, Embase, Cochrane Library, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform and the preprint server of medRxiv.org were searched from their inception to February 20, 2021. Only RCTs that compared the treatment efficacy and safety of tocilizumab with the placebo or the standard of care for adult patients with COVID-19 were included in this meta-analysis. The primary outcome was 28-day mortality.

Results: This meta-analysis included eight RCTs which enrolled a total of 6314 patients for randomization, in which 3267 and 3047 patients were assigned to the tocilizumab and control groups, respectively. The mortality at day 28 was 24.4% and 29.9% in patients in the tocilizumab and control groups, respectively, meaning there was no significant difference observed between these two groups (OR, 0.92; 95% CI, 0.66–1.28; I² = 62). This finding did not change in the subgroup analysis according to the initial use of MV or steroid while enrollment. The patients receiving tocilizumab had a lower rate of mechanical ventilation (MV) and intensive care unit (ICU) admission at day 28 compared with the control group (MV use: OR, 0.75; 95% CI, 0.62–0.90; I² = 11; ICU admission: OR, 0.51; 95% CI, 0.28–0.92; I² = 30). There were no significant differences between these two treatment groups in terms of the risk of treatment-emergent adverse events (AEs) (OR, 1.03; 95% CI, 0.71–1.49; I² = 43), serious AEs (OR, 0.86; 95% CI, 0.67–1.12; I² = 0) or infection (OR, 0.87; 95% CI, 0.63–1.20; I² = 0).

Conclusions: Tocilizumab does not provide a survival benefit for patients with COVID-19, but it may help reduce the risk of MV and ICU admission. In addition, tocilizumab is a safe agent to use for the treatment of COVID-19.

1. Introduction

From the end of 2019 until now, coronavirus disease 2019 (COVID-19) has had a terrible impact on global public health [1]. As of November 19th 2020 more than 56 million patients had been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 has caused more than 1.3 million deaths [2]. Although patients infected with SARS-CoV-2 can present as either asymptomatic or with acute respiratory diseases which have favorable outcomes, patients with severe COVID-19 may develop acute respiratory distress syndrome, cytokine release syndrome (CRS) or even death [3–5]. However, effective treatment options in this fight against COVID-19 are limited.

In severe COVID-19 disease, increased levels of cytokines, especially interleukin-6 (IL-6) have been found to be a key factor associated with inflammation [6]. As tocilizumab is widely used in the treatment of IL-6-induced CRS, it has been proposed as a promising agent for the treatment of patients with moderate to severe COVID-19 disease and its usefulness has been demonstrated in many studies and associated meta-analyses [7–11]. A retrospective observational study of 96 COVID-19 admitted to ICU showed that fewer deaths were observed among tocilizumab-treated patients than control group (15% vs. 37%; p = 0.02) [12]. Another matched retrospective cohort analysis showed the similar...
findings – tocilizumab was associated with a lower mortality rate (27.8% vs 34.4%) and reduced hazards of death (aHR, 0.47; 95% CI, 0.25 to 0.88) [13]. Although these studies showed that the addition of tocilizumab could help reduce COVID-19 patient mortality, their conclusions were based on the meta-analysis of observational studies with low levels of evidence [7–10]. Recently, the results of several randomized controlled trials (RCTs) investigating the effect of tocilizumab for COVID-19 patients have been published [14–21]. However, their findings regarding the mortality benefit of tocilizumab were not consistent. Therefore, we conducted this systematic review and meta-analysis of the RCTs to provide updated information based on strong evidence.

2. Methods

2.1. Data sources and search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines when searching for articles, selecting studies, evaluating article quality, and analyzing data [22]. The protocol was registered at PROSPERO with the reference number: CRD42020220003.

We searched for eligible articles and studies in PubMed, Embase, Cochrane Library, Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) from their inception to February 20, 2021. The search terms used were “COVID-19”, “tocilizumab” and “RCT”. Detailed information on key words and the search strategy are described in supplemental Table 1. The reference lists of the relevant articles, Google Scholar, and the preprint server of medRxiv.org were also searched manually for additional eligible articles. No publication year or language limitations were considered during the literature review.

Two investigators (WTL and SHH) independently screened and reviewed each study. Studies were included if they met the following criteria: (1) studied patients with COVID-19 infection; (2) patients were aged ≥ 18 years; (3) included intervention with tocilizumab; (4) compared tocilizumab with a placebo, or standard of care; (5) RCT, either blinded or open labelled; (6) study outcomes of clinical efficacy, including mortality or clinical improvement. Studies including additional treatments which were received in both the intervention and comparison arms were not excluded. If there were any disagreements between the investigators, the third investigator (CHC) was consulted and made the final decision.

Three investigators reviewed the full texts of the candidate articles to finalize the experimental and control groups for the meta-analysis. The investigators reviewed the study methods, sites, durations, populations, and treatment regimens reported in the articles. Two investigators

Table 1 Characteristics of the included studies.

| Study, published year | Study design | Study sites | Study populations | No of patients | Regimen of TCZ |
|-----------------------|-------------|-------------|-------------------|----------------|----------------|
| Stone et al, 2020     | Randomized, double-blind, placebo-controlled trial | 7 hospitals in US | Patients with confirmed SARS-CoV-2 infection, hyperinflammatory states and at least two of the following signs: fever (body temperature >38 °C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. | 161 | 1 TCZ at 8 mg/kg but not to exceed 800 mg |
| Hermine et al, 2020   | Cohort-embedded, investigator-initiated, open-label, randomized clinical trial | 9 hospitals in France | Patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min oxygen but without ventilation or admission to the ICU | 63 | TCZ 8 mg/kg D1 and if no response (no decrease of oxygen requirement) a second injection of 400 mg at D3. |
| Salvareni et al, 2020 | Prospective, open-label, randomized clinical trial | 24 hospitals in Italy | Hospitalized patients with COVID-19 pneumonia, PaO<sub>2</sub>/FiO<sub>2</sub> between 200 and 300 mmHg, and an inflammatory phenotype defined by fever and elevated CRP | 60 | TCZ within 8 h from randomization (8 mg/kg up to a maximum of 800 mg), followed by a second dose after 12 h |
| Salama et al, 2020    | Randomized, double-blind, placebo-controlled, phase III study | 61 hospital in 6 countries | Nonventilated patients hospitalized with COVID-19 pneumonia | 249 | 1 TCZ at 8 mg/kg (but not exceeding 800 mg), but up to one additional dose may be given. |
| Rosas et al, 2020     | Randomized, double-blind, placebo-controlled trial | 67 hospital in 9 countries | Hospitalized patients with severe COVID-19 pneumonia and a blood oxygen saturation ≤93% or PaO<sub>2</sub>/FiO<sub>2</sub> ≤300 mmHg | 294 | 1 IV infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose may be given if clinical symptoms worsen or show no improvement. |
| REMAP-CAP Investigator, 2021 | Randomized, adaptive platform trial | 113 sites in 6 countries | Critically ill patients, 18 years of age or older, with either clinically suspected or microbiologically confirmed COVID-19 who were admitted to ICU and receiving respiratory or cardiovascular organ support | 353 | 1 TCZ at 8 mg/kg (but not exceeding 800 mg), but up to 1 additional dose may be given after 12 to 24 h |
| RECOVERY Collaborative Group, 2021 | Randomized, controlled, open-label, platform trial | 131 sites in UK | Hospitalized patients with clinical suspected or laboratory confirmed SARS-CoV-2 infection and with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP >75 mg/L) | 2022 | 1 IV infusion of TCZ, dose up to a maximum dose 800 mg. Up to 1 additional dose may be given after 12 – 24 h |
| Viega et al, 2021     | Randomized, open label trial | 9 hospitals in Brazil | Adults with confirmed COVID-19 who were receiving supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (C reactive protein, D dimer, lactate dehydrogenase, or ferritin) | 65 | 1 TCZ at 8 mg/kg |

PaO<sub>2</sub>/FiO<sub>2</sub>: partial pressure of arterial oxygen to fraction of inspired oxygenation; CRP, C-reactive protein; TCZ, tocilizumab.
initially independently examined the publications to avoid bias, and the third investigator resolved any disagreements. Data including the author name, year of publication, study design, site and duration, demographic characteristics of the study subjects, intervention regimens, comparative therapy types, outcomes and adverse events were extracted from each included study.

2.2. Definitions and outcomes

The primary outcome was all-cause mortality at 28–30 days. Secondary outcomes included the use of mechanical ventilation (MV), intensive care unit (ICU) admission, survival to discharge and risk of adverse events.

2.3. Quality assessment and data analysis

The Cochrane risk-of-bias tool was used to assess the quality and associated risk of bias for the enrolled RCTs [23]. Two reviewers subjectively reviewed all the included studies and rated them “low risk,” “high risk,” or “unclear” based on the following items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and inclusion of intention-to-treat analyses. A random-effects model in Review Manager version 5.3 was used for the statistical analyses. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for outcome analyses.

3. Results

3.1. Literature search and study evaluation

A total of 697 articles were identified from the search of PubMed (n = 131), Embase (n = 258), Cochrane CENTRAL (n = 129), the Cochrane Database of Systematic Reviews (CDSR) (n = 5), Clinicaltrials.gov (n = 75) and WHO ICTRP (n = 99). Fifty-seven articles remained after the removal of duplicates (n = 248) and ineligible articles as determined by a review of the titles and abstracts (n = 392). A total of eight studies [14–21] were included after 49 articles were removed following a full-text review process (Fig. 1).

3.2. Study characteristics

All eight RCTs [14–21] were multicenter studies. Three [14,17,18] were multinational studies, while the other five trials were conducted solely in the US [20], France [15], Brazil [21], UK [16] and Italy [19]. Overall, a total of 6314 patients were included in this meta-analysis, in which 3267 and 3047 patients were assigned to the tocilizumab and control groups, respectively. Except one RCT [20] used only a single dose of tocilizumab, other 7 RCTs [14–19,21] allowed one additional dose if needed. The characteristics of the study populations varied and are summarized in Tables 1 and 2. Their mean or medium age ranged from 56 to 64 years and men comprised more than 60% of patients. Diabetes, hypertension and cardiovascular disease were the most common underlying diseases, followed by chronic obstructive pulmonary diseases, asthma, chronic kidney disease and malignancy.

3.3. Quality assessment

There was a risk of performance and detection bias due to the open labelled design in five of the studies [14–16,19,21]. Risk of bias for the included studies is depicted in Fig. 2.

3.4. Clinical outcomes

The pooled analysis of the eight RCTs [14–21] showed that the mortality rate at day 28 was 24.4% and 29.9% among patients in the tocilizumab and control groups, respectively, and therefore no significant difference was observed between these two groups (OR, 0.92; 95% CI, 0.66–1.28; I² = 62, Fig. 3). The leave-one-out sensitivity analysis showed that the magnitude of association for tocilizumab with mortality

Fig. 1. PRISMA flow diagram for the selection of RCTs. CDSR: Cochrane database of systematic reviews, ICTRP: international clinical trials registry platform.
Table 2
Demographic features of the study populations between tocilizumab (TCZ) and control group in each study.

| Study, publish year | Age, year * | Male sex, no (%) | BMI * | Underlying disease, no (%) | Time from symptom onset to randomization, day * |
|---------------------|-------------|------------------|-------|----------------------------|-----------------------------------------------|
| TCZ                 | Control     | TCZ              | Control | TCZ                          | Control                                      |
| Stone et al, 2020   | 61.6        | 56.5             | 96     | 45 (55)                     | 29.9 (26.0–34.2); 30.2 (25.7–33.8)            |
|                     | (46.4–69.7) | (44.7–67.8)      | (60)   |                             |                                               |
| Hermine et al, 2020 | 64.0        | 63.3             | 44     | 44 (66)                     | 27.9 (23.3–30.8); 27.4 (24.5–31.3)            |
|                     | (57.1–74.3) | (57.1–72.3)      | (70)   |                             |                                               |
| Salvarani et al, 2020 | 61.5      | 60.0             | 40     | 37 (56.1)                   | 32.0 (7.9); BMI ≥ 30: 16 (28.1); 30.0 (26.4)  |
|                     | (51.5–73.5) | (54.0–69.0)      | (66.7) |                             |                                               |
| Salama et al, 2020  | 56.0        | 55.6             | 150    | 73 (57)                     | 31.3 (7.2)                                   |
|                     | (14.3)      | (14.9)           | (60)   |                             |                                               |
| Rosas et al, 2020   | 60.9        | 60.6             | 205    | 101 (70)                    | 30.5 (26.9–34.9); 30.9 (27.1–34.9)            |
|                     | (14.6)      | (13.7)           | (70)   |                             |                                               |
| REMAP-CAP Investigator, 2021 | 61.5 | 63.4             | 261    | 283 (70)                    | 30.5 (26.9–34.9); 30.9 (27.1–34.9)            |
|                     | (12.5)      | (13.4)           | (74)   |                             |                                               |
| RECOVERY Collaborative Group, 2021 | 63.3   | 63.9             | 1335   | 1437 (69)                   |                                               |
|                     | (13.7)      | (13.6)           | (66)   |                             |                                               |
| Viega et al, 2021   | 57.4        | 57.5             | 44     | 44 (69)                     |                                               |
|                     | (15.7)      | (13.5)           | (68)   |                             |                                               |

**Study, publish year**

| Other treatments, n (%) | Use of corticosteroid, n (%) | Use of NIV or high flow and MV, n (%) | CRP, mg/L * | IL-6, pg/mL * |
|-------------------------|------------------------------|--------------------------------------|--------------|---------------|
| TCZ                     | Control                      | TCZ                                  | Control      | TCZ            | Control        |
| Stone et al, 2020       | Remdesivir: 55 (33); HCQ: 6 (4) | Remdesivir: 24 (29); HCQ: 3 (4)      | 18 (11); 5 (6) | NIV or high flow oxygen: 5 (3); MV: 0 (0) | 116.0 (67.1–190.6) |
|                         |                              |                                      |              | NIV or high flow oxygen: 5 (6); MV: 1 (0) | 94.3 (58.4–142.0) |
|                         |                              |                                      |              | 23.6 (14.0–49.9) | 25.4 (14.6–40.3) |
| Hermine et al, 2020     | Antiviral drug: 7 (11)       | Antiviral drug: 16 (24)              | 21 (33); 41 (61) | NIV: 0 (0); MV: 0 (0) | 119.5 (74.5–219.5) |
|                         |                              |                                      |              | NIV: 0 (0); MV: 0 (0) | 127.0 (84.0–171.0) |
|                         |                              |                                      |              | NA (NA–NA) | NA (NA) |
| Salvarani et al, 2020   | Antiviral drug: 21 (35)      | Antiviral drug: 31 (47)              | NA (NA–NA) | NIV: 0 (0); MV: 0 (0) | 82 (37–135) |
|                         |                              |                                      |              | NIV: 0 (0); MV: 0 (0) | 105 (50–146) |
| Salama et al, 2020      | Antiviral drug: 196 (79)     | Antiviral drug: 101 (79)             | 200 (80.3); 112 (87.5) | NIV or high flow oxygen: 64 (25.7); MV: 0 (0) | 151.9 (177.2) |
|                         |                              |                                      |              | NIV or high flow oxygen: 36 (28.1); MV: 0 (0) | 202.8 (404.9) |
| Rosas et al, 2020       | Antiviral drug: 71 (24.1); convalescent plasma: 5 (1.7) | Antiviral drug: 42 (29.2); convalescent plasma: 1 (0.7) | 57 (19.4); 41 (28.5) | NIV or high flow oxygen: 94 (32); MV: 111 (37.8) | 168.4 (101.4) |
|                         |                              |                                      |              | NIV or high flow oxygen: 39 (27.1); MV: 54 (37.5) | 172.6 (114.0) |
|                         |                              |                                      |              | 160.9 (85–221) | 201.9 (418.4) |
| REMAP-CAP Investigator, 2021 | Antiviral drug: 169 (48) | Anti-virus: 217 (54)            | 50 (14.2); 52 (12.9) | High flow oxygen: 101 (29); MV: 147 (42); MV: 104 (29) | 150 (85–221) |
|                         |                              |                                      |              | NIV: 121 (30); MV: 867 (41); MV: 294 (14) | 137 (71–208) |
| RECOVERY Collaborative Group, 2021 | Lopinavir/ritonavir: 51 (3); HCQ: 37 (2); azithromycin: 197 (10) | Lopinavir/ritonavir: 64 (3); HCQ: 38 (2); azithromycin: 177 (8) | 166 (82); 172 (82) | High flow oxygen: 101 (29); MV: 147 (42); MV: 104 (29) | 143 (107–203) |
|                         |                              |                                      |              | NIV: 819 (41); MV: 268 (13) | 144 (106–205) |
| Viega et al, 2021       | HCQ: 11 (17); azithromycin: 41 (63) | HCQ: 9 (14); azithromycin: 31 (48) | 45 (69); 47 (73) | NIV or high flow oxygen: 15 (23); MV: 11 (17) | 160 (104) |
|                         |                              |                                      |              | NIV or high flow oxygen: 26 (41); MV: 10 (16) | 193 (283) |

*TCS, tocilizumab; HTN, hypertension; DM, diabetes; COPD, chronic obstructive pulmonary disease; NIV: non-invasive ventilation; MV: mechanical ventilation; HCQ: hydroxychloroquine; NA, not applicable; CRP, C-reactive protein; IL-6, interleukin-6.

* Presented as the median (IQR) or mean (SD).
was not influenced by any individual study. In addition, this finding did not change according to the initial use of MV or steroid use while enrollment. The pooled analysis of 4 RCTs, which did not include MV patients showed mortality rate at day 28 was 7.7% and 6.5% among patients in the tocilizumab and control groups, respectively (OR, 1.21; 95% CI, 0.69–2.11; I² = 0) [15,18,19,24]. The pooled analysis of another 4 RCTs [14,16,17,21], which also included MV patients showed mortality rate at day 28 was 27.6% and 32.8% among patients in the tocilizumab and control groups, respectively (OR, 0.86; 95% CI, 0.56–1.31; I² = 81). The pooled analysis of 4 RCTs [14,16,18,21], in which more than 50% of patients using steroid showed mortality rate at day 28 was 26.9% and 32.4% among patients in the tocilizumab and control groups, respectively (OR, 0.89; 95% CI, 0.56–1.43; I² = 81). The pooled analysis of 4 RCTs [15,17,19,20], in which less than 50% of

| Study                | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Intention-to-treat analyses |
|----------------------|--------------------------------------------|----------------------------------------|---------------------------------------------------------|---------------------------------------------|----------------------------------------|-----------------------------------|--------------------------|
| Gordon, et al, 2021  | +                                          | +                                      | -                                                       | +                                          | +                                      | +                                 | +                        |
| Hermine, et al, 2020 | +                                          | +                                      | -                                                       | +                                          | +                                      | +                                 | +                        |
| Horby, et al, 2021   | +                                          |                                        | -                                                       | +                                          | +                                      | +                                 | +                        |
| Rosas, et al, 2021   | +                                          |                                        | -                                                       | +                                          | +                                      | +                                 | +                        |
| Salama, et al, 2020  | +                                          |                                        | -                                                       | +                                          | +                                      | +                                 | +                        |
| Salvarani, et al, 2020 | +                                      |                                        | -                                                       | +                                          | +                                      | +                                 | +                        |
| Stone, et al, 2020   | +                                          |                                        | -                                                       | +                                          | +                                      | +                                 | +                        |
| Veiga, et al, 2021   | +                                          |                                        | -                                                       | +                                          | +                                      | +                                 | +                        |

Fig. 2. Summary of the risks of bias in each domain in each study. High risk of bias (−); low risk of bias: green color (+).
patients using steroid showed mortality rate at day 28 was 12.6% and
11.0% among patients in the tocilizumab and control groups, re-
spectively (OR, 1.06; 95% CI, 0.69–1.63; I² = 0).
Moreover, the rate of death at day 14 was 11.3% and 13.1% in the
tocilizumab and control groups, respectively and no significant differ-
ence was observed (OR, 1.15; 95% CI, 0.63–3.92; I² = 59) in the pooled
analysis of five RCTs [14,15,19–21]. In addition, the rate of survival to
discharge at day 14 remained similar between the tocilizumab and
control groups (48.2% vs 38.6%; OR, 1.38; 95% CI, 1.12–1.70; I² = 0) in
the pooled analysis of six RCTs [14,15,17,19–21]. However, patients
receiving tocilizumab had a lower rate of MV and ICU admission at day
28 compared with the control group (MV use: OR, 0.75; 95% CI, 0.62–0.90; I² = 11; ICU admission: OR, 0.51; 95% CI, 0.28–0.92; I² =
30). Three RCTs [16,18,20] reported the composite outcome of MV or
death at day 28, and lower rate of this composite outcome was observed
in the tocilizumab group than the control group (28.6% vs 35.6%; OR,
0.78; 95% CI, 0.68–0.89; I² = 0).

3.5. Risk of adverse events (AEs)

Fig. 4 shows a comparison of the risk of AEs between the tocilizumab
and control groups. There was no significant difference between these
two groups in terms of the risk of treatment-emergent AEs (OR, 1.03;
95% CI, 0.71–1.49; I² = 43), serious AEs (OR, 0.86; 95% CI, 0.67–1.12;
I² = 0) or infection (OR, 0.87; 95% CI, 0.63–1.20; I² = 0). However, the
tocilizumab group was associated with a lower rate of serious infection
compared with the control group (OR, 0.57; 95% CI, 0.36–0.89; I² = 21).

4. Discussion

In this meta-analysis, eight RCTs [14–21] were reviewed to compare
the use of tocilizumab with a control group to determine its efficacy and
safety for the treatment of hospitalized patients with COVID-19. From
the pooled analysis of these 8 RCTs, we could not find an additional
survival benefit of tocilizumab, compared with the control group and
this finding was supported by the following evidence. First, the overall
28-day mortality of the hospitalized patients with COVID-19 was not
significantly different between the tocilizumab and control groups in
this study. Second, the similarities between the two groups remained
unchanged following the leave-one-out sensitivity analysis. Third, the
findings of the subgroup analysis according to the use of MV or steroid
while enrollment remained the same. Finally, no significant difference
was observed between the tocilizumab and control groups in terms of
14-day mortality. All these findings were consistent with previous meta-
analyses [25,26] which included 5 and 6 RCTs, respectively and indicate
that tocilizumab does not improve the mortality rate of hospitalized
patients with COVID-19, compared with the control group.

Although several previous meta-analyses [7,8,27] showed that
tocilizumab could help reduce mortality among critically ill COVID-19
patients, their level of evidence was lower than the present study as
most of them only included observation studies in their analysis. By
contrast, our study was based on the analysis of RCTs. Therefore, our
findings provide more solid evidence regarding this issue than previous
studies [7–11,27], and suggests that tocilizumab does not reduce the
short-term mortality of hospitalized patients with COVID-19.

Despite the fact that our findings showed that tocilizumab did not
have a positive impact on COVID-19 patient mortality, we found that
tocilizumab was associated with a lower rate of MV and ICU admission
compared with the control group. This is consistent with the findings of
previous studies [9,27]. A previous meta-analysis of seven case-
controlled studies, which included 766 patients (351 in the tocilizu-
marb arm and 414 in the control arm), demonstrated that the need for
artificial invasive ventilation was significantly lower in the tocilizumab
group (risk ratio, 0.34; 95% CI: 0.12–0.99; I² = 0%) compared with the
control group [27]. Zhao et al reported similar findings as a lower risk of
admission to the ICU (OR: 0.53; 95% CI: 0.26–1.09), and use of venti-
lation (OR: 0.66; 95% CI, 0.46–0.94) were found in the tocilizumab
treatment group compared with the control group [9]. Overall, the findings
of this study and previous meta-analyses suggest that tocilizumab may help
to reduce the rate of MV and ICU admission.

Finally, this meta-analysis also assessed the risk of AEs associated
with tocilizumab. We found that tocilizumab was not associated with a
higher risk of treatment emergent AEs, serious AEs or infection
compared with the control group. In fact, a lower rate of serious in-
festions was found in patients receiving tocilizumab compared with
those in the control group. These findings are consistent with the results
of previous meta-analyses of observational studies [9,11,27]. Therefore,
together these findings indicate that tocilizumab is a tolerable agent for
the treatment of COVID-19 patients.

Although a major strength of this meta-analysis was that only RCTs
were included, this study also had several limitations. First, the number
of included studies and the total number of patients was limited. Second,
the design of each study and the patient populations were varied. Some
findings were associated with high heterogeneity. However, we did
leave-one-out sensitivity analysis and subgroup analysis, and found that
the results did not change. Finally, we could not assess the effect of
tocilizumab on the time to clinical improvement, length of hospital stays
or MV duration due to the associated data was limited. More large-scale
RCTs are needed to clarify these issues. However, many RCTs investi-
gating the usefulness of tocilizumab are still ongoing or being prepared
(Appendix Table 2). In the near future, we will be able to obtain more
data to validate our findings and to perform more subgroup analyses to
determine if there are some types of COVID-19 cases which respond well
to tocilizumab.

In conclusion, tocilizumab does not appear to provide a survival
benefit for hospitalized patients with COVID-19, but it may help reduce
the risk of MV and ICU admission. In addition, tocilizumab is a safe agent
to use in the treatment of COVID-19.

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**Authors’ contributions**

Study concept and design: WTL, SHH, CCL, CYW, and CHC. Acquisition of data: WTL, SHH, CCL, and CHC. Analysis and interpretation of data: All. Drafting of the manuscript: WTL, SHH, CCL, and CHC. Critical revision of the manuscript for important intellectual content: All. Statistical analysis: CYW, and CHC. Guarantor: CHC. Approval of final manuscript: All.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2021.107602.

**Fig. 4.** The risk of adverse events between the tocilizumab and control groups.

**References**

[1] C.C. Lai, C.Y. Wang, Y.H. Wang, S.C. Hsueh, W.C. Ko, P.R. Hsueh, Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status, Int. J. Antimicrob. Agents 55 (4) (2020) 105946.

[2] WHO, https://www.who.int/emergencies/diseases/novel-coronavirus-2019 Accessed on November , 2020.

[3] C.C. Lai, Y.H. Liu, C.Y. Wang, Y.H. Wang, S.C. Hsueh, M.Y. Ven, W.C. Ko, P.R. Hsueh, Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths, J. Microbiol. Immunol. Infect. 53 (3) (2020) 404–412.

[4] C.C. Lai, W.C. Ko, P.I. Lee, S.S. Jean, P.R. Hsueh, Extra-respiratory manifestations of COVID-19, Int. J. Antimicrob. Agents 56 (2) (2020) 106024.

[5] R. de la Rica, M. Borges, M. Gonzalez-Freire, COVID-19: in the eye of the cytokine storm, Front. Immunol. 11 (2020) 558898.

[6] J. Wang, M. Jiang, X. Chen, L.J. Montaner, Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts, J. Leukoc. Biol. 108 (1) (2020) 17–41.

[7] U. Borgowda, A. Perisetti, A. Nanjappa, M. Gajendran, G. Kutti Sridharan, H. Goyal, Addition of tocilizumab to the standard of care reduces mortality in severe COVID-19. A systematic review and meta-analysis, Front. Med. (Lausanne) 7 (2020) 586221.

[8] J. Malgie, J.W. Schoones, B.G. Pijls, Decreased mortality in COVID-19 patients treated with Tocilizumab: a rapid systematic review and meta-analysis of observational studies, Clin. Infect. Dis. (2020).
[9] M. Zhao, J. Lu, Y. Tang, Y. Dai, J. Zhou, Y. Wu, Tocilizumab for treating COVID-19: a systemic review and meta-analysis of retrospective studies, Eur. J. Clin. Pharmacol. (2020) 1–9.

[10] M. Aziz, H. Haghibin, E. Abu Sitta, Y. Nawras, R. Fatima, S. Sharma, W. Lee-Smith, J. Duggan, A.A. Kamnney, J. Hanrahan, R. Assaly, Efficacy of tocilizumab in COVID-19: a systematic review and meta-analysis, J. Med. Virol. (2020).

[11] S.H. Lan, C.C. Lai, H.T. Huang, S.P. Chang, L.C. Lu, P.B. Houch, Tocilizumab for severe COVID-19: a systematic review and meta-analysis, Int. J. Antimicrob. Agents 56 (3) (2020) 106103.

[12] E. Huang, S. Isonaka, H. Yang, E. Salce, E. Rosales, S.C. Jordan, Tocilizumab for the treatment of COVID-19 among hospitalized patients: a matched retrospective cohort analysis, Open Forum Infect. Dis. 8 (1) (2021) oof598.

[13] A.C. Gordon, P.R. Mouncey, F. Al-Beidh, K.M. Rowan, A.D. Nichol, Y.M. Arabi, E.H. Ignatius, K. Wang, A. Karaba, M. Robinson, R.K. Avery, P. Blair, N. Chida, E. Huang, S. Isonaka, H. Yang, E. Salce, Effect of tocilizumab on mortality among critically ill patients with COVID-19: a meta-analysis of randomized controlled trials, Eur. J. Clin. Pharmacol. (2021) 1–9.

[14] J. Freedman, S.V. Mohan, Tocilizumab in patients hospitalized with Covid-19: a systemic review and meta-analysis, Ann. Intern. Med. 172 (8) (2020) 540–548.

[15] I.O. Rosas, N. Braggia, P.F. Ballerini, R. Sciascia, L. Zammarchi, O. Para, P.F. Ballerini, R. Sciascia, L. Zammarchi, O. Para, P. McGuinness, B.J. McVerry, S.K. Montgomery, A. Mumford, K. Rowan, G. Thwaites, J. Estcourt, M. Fitzgerald, H. Goossens, R. Haniffa, Tocilizumab in patients with severe Covid-19 pneumonia, N. Engl. J. Med. (2020) .

[16] C. Salama, J. Han, L. Vau, W.G. Reiss, B. Kramer, J.D. Neidhart, G.J. Criner, C. Salvarani, G. Dolci, M. Massari, D.F. Merlo, S. Cavuto, L. Savoldi, P. Bruzzi, F. Boni, L. Bagliva, C. Turra, P.P. Ballerini, R. Sciascia, L. Zammarchi, O. Para, P. G. Scotton, W.O. Inojosa, V. Ravagnani, N.D. Salerno, P.P. Spinaghi, A. Brignone, M. Codeluppi, E. Teopompi, M. Milesi, P. Bertomoro, N. Claudio, M. Salio, M. Falcone, G. Cenderello, L. Donghi, V. Del Bono, P.L. Colombelli, A. Anhebge, A. Pausaro, G. Secondo, R. Pancale, I. Fazzio, N. Paccincio, M. Costantini, Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial, JAMA Intern. Med. (2020).

[17] J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Hernandez, L. Harvey, A. S. Foulkes, N.K. Horick, B.C. Heady, R. Shah, A.M. Bennaci, A.E. Woolley, S. Nikiiforow, N. Lin, M. Sagar, H. Schragger, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.D. Halvorsen, T.K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugini, S.H. Unizney, D.S. Collier, M.A. Matza, J.M. Yin, K.A. Bowman, E. Meyrowitz, A. Zafar, Z.D. Drobin, M.B. Bolster, M. Kohler, K. M. D’Souza, J. Dau, M.M. Lockwood, C. Cubbinson, B.N. Weber, M.K. Mansour, Efficacy of tocilizumab in patients hospitalized with Covid-19, N. Engl. J. Med. (2020).

[18] V.C. Veiga, J. Prats, D.L.C. Farias, R.G. Rosa, L.K. Dourado, P.G. Zapfneri, R. Machado, R.D. Lopes, O. Berwanger, L.C.P. Azevedo, A. Aveuzem, T.C. Lisboa, S.O. Rojas, J.C. Coelho, R.T. Leite, J.C. Carvalho, I.E.C. Andrade, A.F. Sandes, M.C. M. Pinto, C.G. Castro Jr., S.V. Santos, T.M.L. de Almeida, A.N. Costa, O.C. G. Gebara, F.G.R. de Freitas, E.S. Pacheco, D.J.R. Machado, J. Martin, F. G. Conceição, S.R.R. Siqueira, L.P. Damiano, I.M. Ishihara, D. Schneider, D. de Souza, A.B. Cavalcanti, P. Scheleberg, Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial, BMJ 372 (2021) e864.

[19] L. Shameer, D. Moher, M. Clarke, D. Gheri, A. Liberati, M. Petticrew, P. Shokele, L.A. Stewart, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation, BMJ 350 (2015) i67467.

[20] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Juni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.

[21] J.A.C. Sterne, S. Murray, J.V. Díaz, A.S. Slusky, J. Villar, D.C. Angus, D. Annane, L.C.P. Azevedo, O. Berwanger, A.B. Cavalcanti, P.F. Dequin, B. Du, J. Emerson, D. Fisher, B. Girauduea, A.C. Gordon, A. Granholm, C. Green, R. Haynes, N. Heming, J.P.T. Higgins, P. Horby, P. Juni, M.I. Landray, A. Le Gouge, M. Leclerc, W.S. Lim, F.R. Machado, C. McArthur, F. Meziani, M.H. Müller, A. Nøst, M.W. Petersen, J. Savovic, B. Tomini, V.C. Veiga, S. Webb, J. C. Marshall, Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis, JAMA 324 (15) (2020) 1330–1341.

[22] I.M. Tleyjeh, Z. Kashour, M. Damlaj, M. Riaz, H. Tlayjeh, M. Altannir, Y. Altannir, Tocilizumab protocols (PRISMA-P) 2015: elaboration and explanation, BMJ 350 (2015) i67467.