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MAJOR ARTICLE

# Decreased Mortality in Coronavirus Disease 2019 Patients Treated With Tocilizumab: A Rapid Systematic Review and Meta-analysis of Observational Studies

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**(See the Editorial Commentary by Moehring and Holland on pages e750–2.)**

***Background.*** We systematically reviewed the literature to answer the following research questions: (1) Does interleukin 6 (IL-6) (receptor) antagonist therapy reduce mortality in coronavirus disease 2019 (COVID-19) patients compared to patients not treated with IL-6 (receptor) antagonists; and (2) is there an increased risk of side effects in COVID-19 patients treated with IL-6 (receptor) antagonists compared to patients not treated with IL-6 (receptor) antagonists?

***Methods.*** We systematically searched PubMed, PMC PubMed Central, Medline, World Health Organization COVID-19 Database, Embase, Web of Science, Cochrane Library, Emcare, and Academic Search Premier (through 30 June 2020). Random effects meta-analysis was used to pool the risk ratios and risk differences of individual studies. Risk of bias was appraised using the Methodological Index for Non-randomized Studies (MINORS) checklist.

***Results.*** The search strategy retrieved 743 unique titles, of which 10 studies (all on tocilizumab [TCZ]) comprising 1358 patients were included. Nine of 10 studies were considered to be of high quality. Meta-analysis showed that the TCZ group had lower mortality than the control group. The risk ratio was 0.27 (95% confidence interval [CI], .12–.59) and the risk difference was 12% (95% CI, 4.6%–20%) in favor of the TCZ group. With only a few studies available, there were no differences observed regarding side effects.

***Conclusions.*** Our results showed that mortality was 12% lower for COVID-19 patients treated with TCZ compared with those not treated with TCZ. The number needed to treat was 11, suggesting that for every 11 (severe) COVID-19 patients treated with TCZ, 1 death is prevented. These results require confirmation by randomized controlled trials.

**Keywords.** COVID-19; mortality; IL-6 receptor antagonists; tocilizumab.

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a pandemic with serious medical and economic consequences around the world. As of 5 October 2020, >35 million patients have been diagnosed with COVID-19 and > 1 million of them have died [1]. It is therefore paramount that treatments are discovered and become available to reduce disease severity and mortality caused by COVID-19.

Some reports have shown that immune response (inflammation) markers such as interleukin 6 (IL-6) are associated with disease severity and mortality in COVID-19 patients [2, 3]. Importantly, IL-6 can be antagonized by IL-6 receptor antagonists such as tocilizumab (TCZ) and sarilumab, or by IL-6 antagonists such as siltuximab. These compounds may therefore be considered as possible candidates for treatment of COVID-19 patients, and early case series are cautiously optimistic [4, 5]. Improvement of clinical and biochemical signs of hyperinflammation and cytokine storm has been observed after treatment with TCZ, resulting in a significant improvement in the levels of ferritin, C-reactive protein, and D-dimer [5]. Given this proposed pathophysiological mechanism and early observations, a systematic review on the treatment effect and its possible side effects is required to establish the evidence-base for IL-6 (receptor) antagonists. We therefore systematically reviewed the literature to answer the following research questions: (1) Does IL-6 (receptor) antagonist therapy reduce mortality in COVID-19 patients compared to those not treated with IL-6 (receptor) antagonists; and (2) is there an increased risk of side effects in COVID-19 patients treated with IL-6 (receptor) antagonists compared to patients not treated with IL-6 (receptor) antagonists?

## METHODS

The reporting of this meta-analysis is in accordance with the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses (PRISMA) statement [6]. We produced a short working protocol before the start of the study. However, due to the rapid review design, this protocol was not registered at, eg, the Prospero registry. We initially set out to search the literature on studies comparing either IL-6 receptor antagonists (TCZ, sarilumab), or IL-6 antagonists (siltuximab) to a control group, but only studies on TCZ were identified. Hence, this review will focus on TCZ.

The population of interest consisted of COVID-19 patients treated with TCZ (intervention group) and patients not treated with TCZ as the control group. The primary outcome was mortality, expressed as the number of patients who died within the study period. The secondary outcomes were mortality after intensive care unit (ICU) admission, mortality after mechanical ventilation, days to recovery, days in ICU, days on mechanical ventilator support, and possible side effect of the TCZ treatment such as secondary infection, neutropenia, intestinal perforation, and impaired liver function.

#### Data Sources and Searches

The search strategy was composed in collaboration with a librarian (J. W. S.). The following databases were searched from their inception up to 30 June 2020: PubMed, PMC PubMed Central, Medline, World Health Organization COVID-19 Database, Embase, Web of Science, Cochrane Library, Emcare, and Academic Search Premier. The search strategy consisted of the following components, each defined by a combination of controlled vocabulary and free text terms: (1) anti-IL-6 treatment; (2) COVID-19. The full search strategy is provided in the Supplementary Appendix.

#### Study Selection

Studies identified by the search strategy were screened by title and abstract. This screening was performed by 2 reviewers (J. M. and B. G. P.) independently. Both reviewers recorded their findings in a predesigned electronic database. Both databases were then compared and any disagreements were resolved by consensus. When the information in the abstract did not suffice, or if any doubt remained, the studies remained eligible.

The full text articles of eligible studies were independently evaluated by 2 reviewers (J. M. and B. G. P.). Both recorded their findings in a predesigned electronic database. Any disagreements were resolved by consensus. All bibliographic records identified through the electronic searches were collected in an electronic reference database and subjected to inclusion and exclusion criteria. Inclusion criteria were (1) COVID-19 clinical patient study and (2) anti-IL-6 therapy vs non–anti-IL-6 therapy, with a minimum of 5 patients in each treatment arm. Exclusion criteria were (1) no data on primary or secondary outcomes comparing anti-IL-6 therapy to non–anti-IL-6 therapy; (2) anti-IL-6 therapy reserved for patients with severe disease or cytokine storm (severe and apparent confounding by indication), whereas mild patients get standard therapy; and (3) language not spoken by the review team.

#### Data Extraction and Quality Assessment

Two reviewers (J. M. and B. G. P.) independently extracted data and appraised the risk of bias from included studies regarding the primary and secondary outcomes, patient demographics, and study characteristics in a predefined electronic data sheet. The data sheet was designed during the extraction of trial data on a random sample of eligible studies. Any disagreements were resolved by consensus.

Risk of bias was appraised using the Methodological Index for Non-randomized Studies (MINORS) checklist [7]. MINORS is specifically designed to assess the methodological quality of nonrandomized studies, as we did not expect to find any randomized controlled trials (RCTs) during the rapid review period [7]. A MINORS item scored 0 if not reported, 1 if reported but not adequate, and 2 if reported and adequate. With 12 items, this gives a maximum possible score of 24 points. We considered a study of high quality if the total MINORS score was ≥17 and low quality if the total score was <17 [8].

#### Data Synthesis and Analysis

For the meta-analysis, we used a random-effects model to pool the risk ratio (RR) and risk difference (RD) of individual studies in order to estimate an overall RR and RD (absolute RD) along with their associated confidence intervals (CIs) [9]. The RD was included because it is an appropriate solution for the empty cell problem and it allows calculation of the number needed to treat (NNT) [10, 11]. The amount of statistical heterogeneity was assessed through visual inspection of the forest plots and by calculating $I^2$ statistics [12]. The $I^2$ statistic estimates how much of the total variability in the effect size estimates is due to heterogeneity among the true effects. In the presence of heterogeneity, and if the data allowed, we performed a random-effects meta-regression on predefined factors (study-level covariates). All analyses were performed using the metafor package in R statistics [13].

We constructed a funnel plot for studies reporting the primary outcome to assess the amount of publication bias. In case the funnel plot was asymmetric, we used trim-and-fill to explore the magnitude and direction of the publication bias.

## RESULTS

#### Study Selection and Study Characteristics

The search strategy retrieved 1686 hits, of which 743 were unique (no double entries for different databases). After selection, 10 studies were included with a total of 554 patients (95 deaths) who received TCZ and 804 patients (222 deaths) in the control group who did not receive TCZ [14–23]. Details of the study selection and the flowchart of the review are shown in Figure 1.

From the included studies, 4 were from Italy, 3 from the United States, 2 from Spain, and 1 from France. Details of

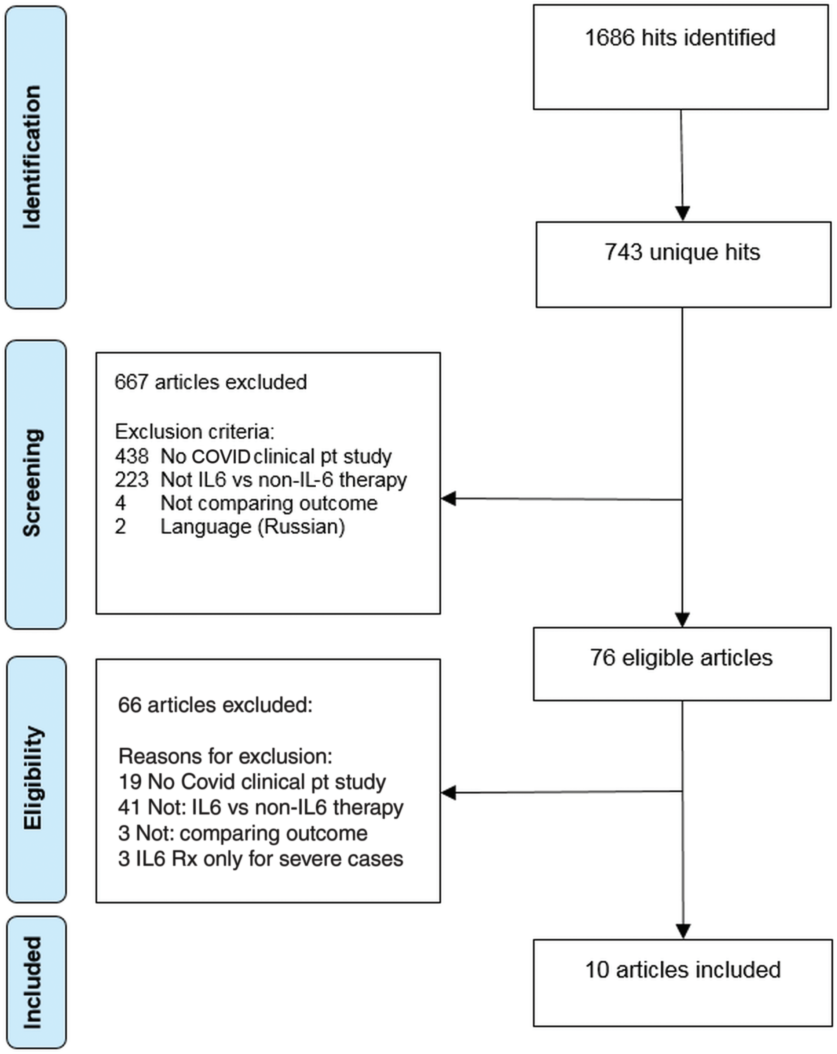


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flowchart. Abbreviations: COVID, coronavirus disease 2019; IL-6, interleukin 6; pt, patient; Rx, prescription.

included studies are shown in Table 1. On a study level, there were baseline differences between the TCZ group and control group regarding age, percentage of men, and percentage of comorbidities. However, a systematic difference between the TCZ and control groups regarding these baseline characteristics was not apparent. Based on the higher C-reactive protein (CRP) and the lower ratio of arterial oxygen partial pressure to fraction of inspired oxygen ($PaO_2/FiO_2$) for the TCZ group, the TCZ group appeared to be more severely affected by COVID-19 at baseline than the control group (Table 1).

#### Risk of Bias

Details on the risk of bias are presented in Table 2. The mean MINORS score was 18.7 (range, 13–21) out of 24 points. Nine studies were considered to be of high quality with a MINORS score of 17 or higher and 1 study was considered of low quality, which was mostly due to nonreporting.

#### Synthesis of the Results and Sensitivity Analyses

##### *Primary Outcome*

A summary of the data synthesis is presented in Table 3. The TCZ group had lower mortality than the control group based on 10 studies with 1358 patients: the RR was 0.27 (95% CI, .12–.59) and the RD was 12% (95% CI, 4.6%–20%) in favor of the TCZ group (Figure 2). This RD for mortality translates into an NNT of 8 (95% CI, 5–22). There was substantial heterogeneity $I^2$ of 61%. Upon inspection of the forest plot, this heterogeneity appeared to be caused by a single study [16], so a sensitivity (outlier) analysis was necessary. Leaving out this outlier gave low heterogeneity ($I^2$ = 19%) and gave similar results to the full analyses: RR, 0.34 (95% CI, .18–.66) compared to 0.27 and RD, 9.9% (95% CI, 4.7%–15%) compared to 12%. The outlier study did not use glucocorticoids, whereas most other studies did use them (see Table 4 for details on comedication use for each study).

**Table 1. Baseline Study Characteristics**

| Study, First Author | Group | No. | Age, y | % Men | % With DM | % With HT | % With CVD | CRP, mg/L | $PaO_2/FiO_2$ |
|---|---|---|---|---|---|---|---|---|---|
| Callejas Rubio [14] | TCZ | 32 | … | … | … | … | … | … | … |
| | Control | 60 | … | … | … | … | … | … | … |
| Campochiaro [15] | TCZ | 32 | 64 | 91 | 13 | 38 | 13 | 156 | 107 |
| | Control | 33 | 60 | 82 | 18 | 48 | 18 | 169 | 124 |
| Capra [16] | TCZ | 62 | 63 | 73 | 13 | 45 | 13 | … | … |
| | Control | 23 | 70 | 83 | 22 | 48 | 26 | … | … |
| Colaneri [17] | TCZ | 21 | 62 | 90 | 10 | 38 | 10 | 214 | … |
| | Control | 91 | 64 | 69 | 8.8 | 22 | 7.6 | 149 | … |
| Guaraldi [18] | TCZ | 179 | 64 | 71 | 13[a] | 45[a] | 11[a] | … | 169 |
| | Control | 365 | 69 | 64 | 3[a] | 14[a] | 5[a] | … | 277 |
| Kewan [19] | TCZ | 28 | 63 | 71 | 39 | 68 | 7.1 | 161 | 148 |
| | Control | 23 | 70 | 47 | 35 | 74 | 30 | 51 | 207 |
| Klopfenstein [20] | TCZ | 20 | 77 | … | 25 | 40 | 70 | 158 | … |
| | Control | 25 | 71 | … | 32 | 44 | 68 | 105 | … |
| Martín-Moro [21] | TCZ | 6 | 62 | 100 | … | … | … | … | … |
| | Control | 11 | 83 | 45 | … | … | … | … | … |
| Rojas-Marte [22] | TCZ | 96 | 59 | 77 | 30 | 55 | … | 171 | … |
| | Control | 97 | 62 | 65 | 39 | 53 | … | 146 | … |
| Somers [23] | TCZ | 78 | 55 | 68 | 13 | 67 | 21 | 185 | 154 |
| | Control | 76 | 60 | 64 | 20 | 68 | 26 | 231 | 196 |

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HT, hypertension; $PaO_2/FiO_2$, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; TCZ, tocilizumab.

[a]Values are from the Modena subcohort, not the entire study population.

The sensitivity analyses revealed that glucocorticoids and lopinavir/ritonavir (LPV/r) were effect modifiers for risk of mortality between the TCZ and control groups. In studies that used glucocorticoids, the treatment effect of TCZ on mortality was smaller compared with studies that did not use glucocorticoids ($I^2$ = 33%): the RD was 9.1% (95% CI, 2.8%–15%) in favor of the TCZ group compared with an RD of 31% (95% CI, 15%–47%) in favor of the TCZ group. In studies that used LPV/r, the treatment effect of TCZ on mortality was larger compared to studies that did not use LPV/r ($I^2$ = 46%): the RD was 19% (95% CI, 9.2%–28%) in favor of the TCZ group compared to an RD of 4.5% (95% CI, 5.9%–15%) in favor of the TCZ group. Since there was overlap in the use of glucocorticoids and LPV/r (Table 4), we created 3 comedication groups. The results of this subgroup analysis are presented in Figure 3 ($I^2$ = 17%). For studies that used glucocorticoids without LPV/r, there was no longer a difference in mortality between the TCZ and control group. For studies that used LPV/r either with or without glucocorticoids, the TCZ group had lower mortality than the control

**Table 2. Risk of Bias Assessment With Methodological Index for Non-randomized Studies (MINORS) Score**

| | Checklist Item[a] and Score[b] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study, First Author | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Total Score[c] |
| Callejas Rubio [14] | 2 | 1 | 1 | 2 | 2 | 1 | 0 | 0 | 2 | 0 | 0 | 2 | 13 |
| Campochiaro [15] | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 20 |
| Capra [16] | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 20 |
| Colaneri [17] | 2 | 2 | 1 | 2 | 2 | 1 | 0 | 0 | 2 | 2 | 1 | 2 | 17 |
| Guaraldi [18] | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 20 |
| Kewan [19] | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 20 |
| Klopfenstein [20] | 2 | 2 | 1 | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 1 | 2 | 18 |
| Martín-Moro [21] | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 18 |
| Rojas-Marte [22] | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 20 |
| Somers [23] | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 21 |

[a]Checklist items: 1, a stated aim of the study; 2, inclusion of consecutive patients; 3, prospective collection of data; 4, endpoints appropriate to study aim; 5, unbiased assessment of study endpoint; 6, follow-up period appropriate to the major endpoint; 7, <5% lost to follow-up; 8, adequate control group; 9, contemporary groups; 10, baseline equivalence of groups; 11, prospective calculation of study size; 12, adequate statistical analyses.

[b]Items are scored as 0 (not reported); 1 (reported but inadequate); or 2 (reported and adequate).

[c]The maximum possible score is 24 points.

**Table 3. Summary of Data Synthesis**

| | Outcome | No. of Studies | No. of Patients | Pooled Estimates | | Heterogeneity, $I^2$ |
|---|---|---|---|---|---|---|
| | | | | RR[a] (95% CI) | RD[b], % (95% CI) | |
| Treatment outcome | Mortality | 10 | 1358 | 0.27 (.12–.59) | −12 (−20 to −4.6) | 61% |
| | Mortality after MV | 4 | 942 | 0.28 (.21–1.32) | −4.1 (−11 to 3.1) | 46% |
| | MV | 7 | 889 | 1.7 (.21–1.32) | 1.8 (−15 to 11) | 81% |
| | ICU admission | 5 | 290 | 1.6 (.81–3.12) | 1.0 (−24 to 22) | 85% |
| Side effect | Secondary infection | 6 | 1092 | 1.9 (.42–8.9) | 3.8 (−6.4 to 14) | 83% |
| | Neutropenia | 2 | 609 | NA[c] | 6.4 (−7.5 to 20) | 77% |
| | Impaired liver function | 2 | 609 | 1.7 (.1–55) | 0.7 (−.7 to 2.1) | 0% |

Abbreviations: CI, confidence interval; ICU, intensive care unit; MV, mechanical ventilation; NA, not estimable; RD, risk difference; RR, risk ratio.

[a]RR defined as risk in the tocilizumab group/risk in the control group.

[b]RD defined as risk in the tocilizumab group – risk in the control group.

[c]Not estimable due to empty cells (both studies had no cases of neutropenia in the control group).

group. Remdesivir, azithromycin, anticoagulation medication, and hydroxychloroquine were not effect modifiers.

The funnel plot showed some asymmetry, so a trim-and-fill analysis was warranted, which revealed a minor influence of possible publication bias: RR, 0.33 (95% CI, .17–.63) compared to 0.34 and RD, 9.4% (95% CI, 4.2%–15%) compared to 9.9%. When restricting the analyses to high-quality studies with a MINORS score of ≥20 points (6 studies), the RD was 15.7% (95% CI, 5.7%–25.7%) in favor of TCZ and the risk ratio was 0.17 (95% CI, .05–.58) in favor of TCZ.

Three studies presented adjusted analyses for baseline imbalances regarding demographics and disease severity to account for differences at baseline. These analyses confirmed the lower mortality for the TCZ group: hazard ratio (HR), 0.38 [18]; HR, 0.58 [23]; and odds ratio (OR), 0.78 [17].

Meta-regression on demographic variables showed that differences in age and sex did not influence the observed difference in treatment effects of TCZ on mortality for the included studies.

***Secondary Outcomes***

A summary of the data synthesis is presented in Table 3. There were no differences observed regarding mechanical ventilation, mortality after mechanical ventilation, ICU admission, secondary infection, neutropenia, or impaired liver function.

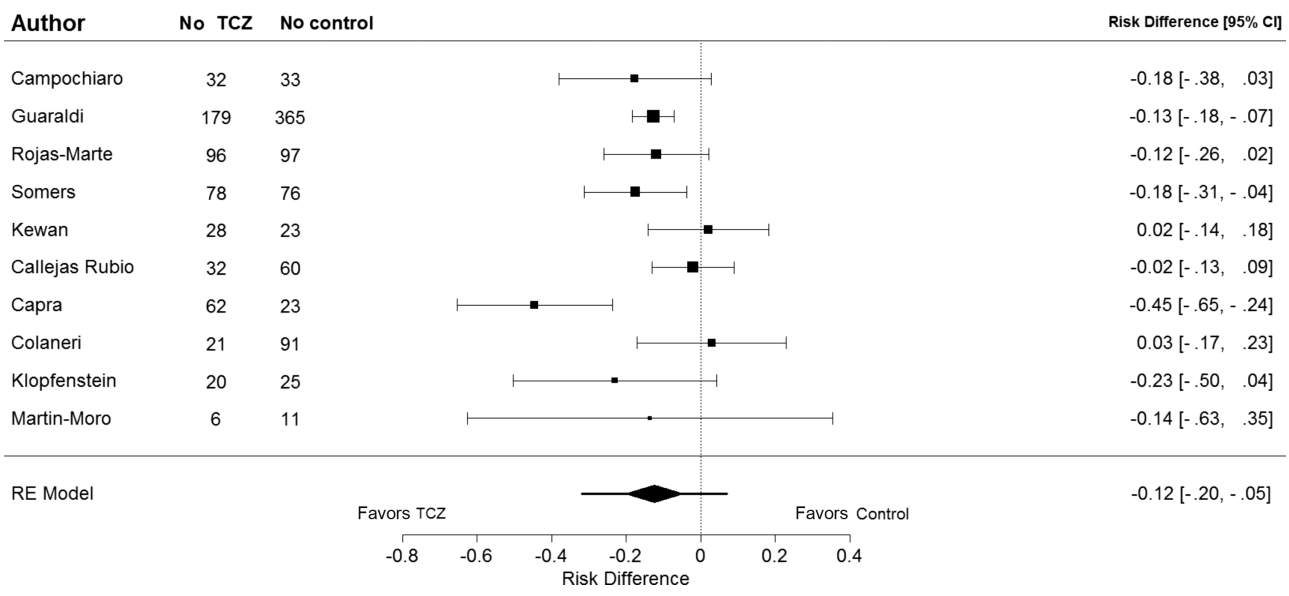


**Figure 2.** Forest plot showing the risk difference in mortality between patients treated with tocilizumab (TCZ) and patients not treated with TCZ. Meta-analysis on 10 observational studies comprising 1358 patients showed that mortality was 12% lower for patients with coronavirus disease 2019 (COVID-19) treated with TCZ compared to those not treated with TCZ. Abbreviations: CI, confidence interval; RE, Random Effects; TCZ, tocilizumab.

**Table 4. Comedication Use on Study Level**

| Study | Glucocorticoids | LPV/r | Remdesivir | AZM | Anticoagulation | HCQ |
|---|---|---|---|---|---|---|
| Callejas Rubio [14] | Yes | No | No | No | No | |
| Campochiaro [15] | No | Yes | No | Yes | Yes | Yes |
| Capra [16] | No | Yes | No | No | No | Yes |
| Colaneri [17] | Yes | No | No | Yes | Yes | Yes |
| Guaraldi [18] | Yes | Yes | No | Yes | Yes | Yes |
| Kewan [19] | Yes | No | No | Yes | No | Yes |
| Klopfenstein [20] | Yes | Yes | No | No | No | Yes |
| Martín-Moro [21] | Yes | Yes | No | Yes | No | Yes |
| Rojas-Marte [22] | Yes | Yes | Yes | Yes | Yes | Yes |
| Somers [23] | Yes | No | Yes | No | Yes | Yes |

Abbreviations: AZM, azithromycin; HCQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir.

However, there were only a few studies (2–7) that reported these outcomes and there was considerable heterogeneity (Table 3). Due to the low number of studies, this heterogeneity could not be adequately explored. The following outcomes could not be assessed, because either no included studies reported them or the data presentation in the article did not allow for pooling of these outcomes: days to recovery, days on ICU, days on mechanical ventilator support, and intestinal perforation.

## DISCUSSION

### Summary of Evidence

In this systematic review and meta-analysis, we evaluated the treatment effect of TCZ on mortality and possible side effects in COVID-19 patients compared with COVID-19 patients who did not receive TCZ. Our results showed that TCZ was associated with a 12% reduction in mortality for COVID-19 patients compared to the control group. After rigorous sensitivity analyses—outlier analyses and taking into account the effect of possible publication bias—the most conservative estimate was 9.4% risk reduction, which translates to an NNT of 11. This analysis therefore suggests that for every 11 (severe) COVID-19 patients treated with TCZ, 1 death is prevented. We are not aware of other meta-analyses on this topic. Results of high-quality RCTs are needed to prove or refute our results regarding the positive effect of TCZ on mortality in COVID-19 patients.

Our analyses also suggested that use of comedication is an important source of between-study variation. In studies that

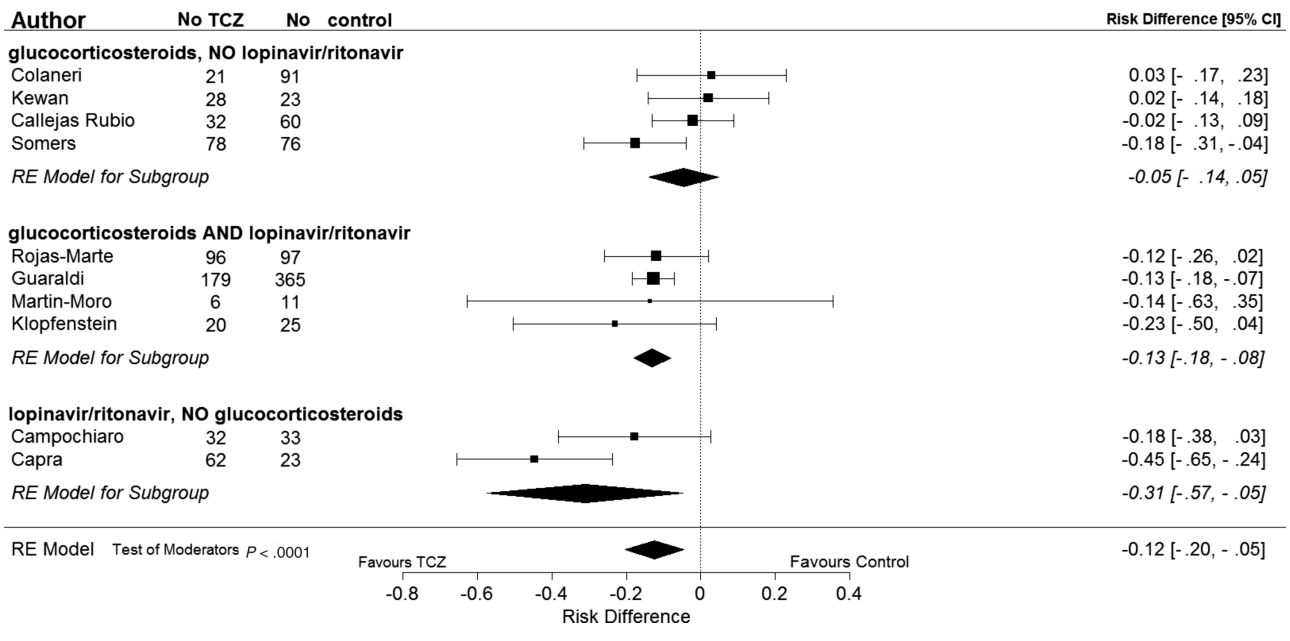


**Figure 3.** Forest plot showing the risk difference in mortality between patients treated with tocilizumab (TCZ) and patients not treated with TCZ according to comedication group. Abbreviations: CI, confidence interval; RE, Random Effects; TCZ, tocilizumab.

used glucocorticoids, the treatment effect of TCZ on mortality was smaller compared with those that did not use glucocorticoids. This finding implies that the treatment effect of TCZ is smaller when other immunosuppressive medications, such as glucocorticoids, are used. Importantly, for studies that used glucocorticoids without LPV/r, there was no longer a difference in mortality between the TCZ and control group. However, a recent study by Ramiro et al has shown that a treatment strategy of high-dose methylprednisolone, followed by TCZ if needed, may accelerate respiratory recovery, lower hospital mortality, and reduce the likelihood of invasive mechanical ventilation in COVID-19–associated cytokine storm syndrome [24]. Furthermore, Martínez-Urbistondo et al have shown that timing of this combination is very important [25].

For studies that used LPV/r either with or without glucocorticoids, the TCZ group had lower mortality than the control group. Remdesivir, azithromycin, anticoagulation medication, and hydroxychloroquine were not effect modifiers.

Regarding the secondary outcomes, there were no differences observed for mechanical ventilation, mortality after mechanical ventilation, ICU admission, secondary infection, neutropenia, or impaired liver function. However, there were only a few studies (2–7) in the analyses, and there was considerable heterogeneity, meaning that a possible effect for these outcomes could not reliably be determined (wide 95% CIs). Therefore, further research is necessary. Regarding secondary infections, concomitant treatments such as (prophylactic) antibiotics and corticosteroids could be contributing to the observed heterogeneity. Although we found no difference in neutropenia between the groups, it should be noted that in the 2 studies reporting neutropenia, there were zero cases in the control group compared with 5 and 6 cases in the TCZ group, which raises concerns for this side effect. There were no intestinal perforations reported in the 10 included studies totaling 554 patients who received TCZ and 804 patients in the control group. In the field of rheumatology, there is ample experience with TCZ in patients suffering from rheumatoid arthritis, who often use concomitant immunosuppressive medications [26]. A review on TCZ in treatment of patients with rheumatoid arthritis reported that the overall rate of serious infections with TCZ was approximately 5 events per 100 person-years of exposure and that the overall rate of intestinal perforation was 0.28 events per 100 person-years of exposure [26]. However, it is unknown whether these adverse event rates are similar in COVID-19 patients.

### Limitations and Strengths

We should also consider some limitations. The most important one is the fact that all included studies were observational. Presently there are no published results of RCTs of TCZ vs controls on mortality in COVID-19 patients. In theory, observational studies overestimate the treatment effect of the interventions. However, this theory conflicts with empirical evidence, especially when the methodological quality of included observational studies is high [8, 27]. Moreover, the patients who received TCZ in the included studies were more severely affected by COVID-19 given their higher CRP values and lower $PaO_2/FiO_2$ ratio. This potential bias underestimates the observed effect of TCZ on mortality and may (partially) neutralize the overestimating effect of the observational study design. High-quality RCTs are thus needed. When results from RCTs become available, it is paramount to explore potential sources of heterogeneity when they are included in meta-analyses: Differences between studies may arise not only from study design (eg, RCT or observational) but also from other study-level factors such as comedication use [28]. RCTs may help in achieving balanced groups at baseline, but they do not guarantee balanced comedication use after randomization. Our results suggest that use of comedication is particularly important as the effect of TCZ was no longer significant when glucocorticoids were used (without LPV/r).

The fact that we used crude risks for the calculation of RRs and RDs can be considered a limitation, as this does not allow control of baseline imbalances by treatment group. However, there were 3 studies that reported adjusted analyses for baseline imbalances, and these analyses confirmed the lower mortality for the TCZ group (HR, 0.38 [18]; HR, 0.58 [23]; and OR, 0.78 [17]).

Another limitation is the small number of studies for the secondary outcomes. These outcomes could be addressed when more studies become available.

Our review has the following strengths: All phases of the review were performed independently by 2 reviewers. The methodological quality as reflected by the MINORS score was high in 9 of 10 included articles, and rigorous sensitivity analyses could not refute the conclusions. Restricting the analyses to studies with the highest methodological quality (MINORS score $\geq$20), the results remained the same. The influence of publication bias was negligible as determined by funnel plots and trim-and-fill analyses. Sensitivity analyses on comedication explained almost all heterogeneity.

## CONCLUSIONS

Meta-analysis on 10 observational studies comprising 1358 patients showed that mortality was 12% lower for COVID-19 patients treated with TCZ compared to COVID-19 patients who were not treated with TCZ. The NNT was 11, suggesting that for every 11 (severe) COVID-19 patients treated with TCZ, 1 death is prevented. Given the observational design of the included studies, these results should be interpreted with caution and require confirmation by RCTs.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted

materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Author contributions.*** All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

***Potential conflicts of interest.*** The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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