Tocilizumab as treatment for COVID-19: A systematic review and meta-analysis

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Tocilizumab as treatment for COVID-19: A systematic review and meta-analysis

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Abstract

BACKGROUND
The majority of patients with coronavirus disease 2019 (COVID-19) have good prognoses, but some develop a critical illness that can lead to death. Evidence shows severe acute respiratory syndrome is closely related to the induced cytokine storm. Interleukin-6 is a key player; its role in systemic inflammation is well known.

AIM
To evaluate the effect of tocilizumab (TCZ), an interleukin-6 receptor antagonist, on the outcomes for patients with COVID-19 pneumonia.

METHODS
PubMed, EMBASE, SCOPUS, Web of Science, MedRxiv, Science Direct, and the Cochrane Library were searched from inception to 9th June 2020 for observational or prospective studies reporting results of hospitalized adult patients with COVID-19 infection treated with TCZ. Effect sizes were reported as odds ratios (ORs) with 95% confidence intervals (CIs), and an OR less than 1 was associated with a better outcome in those treated with TCZ.

RESULTS
Overall 13476 patients (33 studies; \( n = 3264 \) received TCZ) with COVID-19 pneumonia and various degree of severity were included. Outcome was improved with TCZ. In the primary analysis (\( n = 19 \) studies reporting data),
mortality was reduced in patients treated with TCZ (OR = 0.64, 95% CI: 0.47-0.87; \( P < 0.01 \)). In 9 studies where risk of death with TCZ use was controlled for other variables mortality was reduced by 57% (OR = 0.43, 95% CI: 0.27-0.7; \( P < 0.01 \)). Intensive care need (mechanical ventilation) was also reduced (OR = 0.36, 95% CI: 0.14-0.89; \( P = 0.02 \)).

**CONCLUSION**

In COVID-19-infected patients treated with TCZ, outcome may be improved compared to those not treated with TCZ.

**Key Words:** Tocilizumab; COVID-19; Pandemic; Treatment; Meta-analysis; Review

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**INTRODUCTION**

Severe acute respiratory syndrome coronavirus 2 emerged in Wuhan, China in December 2019 and a pandemic was declared by the World Health Organization on March 11, 2020. The pandemic rapidly became a major global health concern. The vast majority of patients with coronavirus disease 2019 (COVID-19) have good prognoses, but some develop a critical illness that can lead to death. The data show that approximately 20% become severe or critical and require hospitalization\[1\]. Evidence shows that severe deterioration following severe acute respiratory syndrome coronavirus 2 infection is closely related to the associated cytokine storm\[2\]. Tocilizumab (TCZ) is an immunomodulatory therapeutic, an interleukin (IL)-6 receptor antagonist approved by the United States Food and Drug Administration and the European Medicine Agency for treating cytokine release syndrome. One of the key cytokines described in the cytokine storm induced by COVID-19 is IL-6, and its role in systemic inflammation is well known. Following an intriguing biological rationale, several institutions have proposed using TCZ off-label to treat COVID-19\[3\]. Thus far, randomized controlled trials have not been reported in the literature, but observational studies and case reports describe the compassionate use of TCZ. Results leave the efficacy of TCZ controversial. We performed a meta-analysis of the studies available to date.

**MATERIALS AND METHODS**

**Literature search and selection criteria**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for evaluating records identified during the literature search\[4\].

The search included MEDLINE, EMBASE, Scopus, the medRxiv preprint server, Science Direct, Web of Science, and the Cochrane Controlled Register of Trials for articles published up to June 9, 2020 describing trials or observational series about the efficacy of TCZ in patients with COVID-19 pneumonia. Search terms were tocilizumab and COVID-19. The inclusion criteria were: (1) Randomized or single-arm prospective
studies, observational or retrospective case series of patients with COVID-19 and treated with TCZ outside of clinical trials; (2) written in the English language; (3) reporting patient clinical characteristics; and (4) including at least 5 patients. Animal studies, case reports, editorials, commentaries, and clinical or pharmacological reviews were excluded. If multiple studies reported on the same population and met the inclusion criteria, the newest study was selected unless different endpoints or subgroup analyses were performed or updated.

**Data extraction and endpoints**
Two authors (Ghidini A, Petrelli F) determined article eligibility based on the abstracts. A third (Zaniboni A) independently read the articles, and agreement for trial inclusion was reached. Two authors (Petrelli F, Ghidini A) independently extracted data to a standard form constructed using Microsoft Word and compared results for agreement. Extracted data were author, publication year, number of participants treated, study design, patient group demographics and clinical characteristics (e.g., median age, sex, country, comorbidities), median follow-up, laboratory and clinical parameters (symptoms) of participants, rate of admission to the intensive care unit (ICU) before and after TCZ use, associated drugs, imaging (baseline and improvements shown in imaging), number of cycles with TCZ and resulting adverse events, death rate, median hospitalization time, rate of discharge from the ICU and/or hospital, and hazard ratios for mortality or other events associated with TCZ use.

Eligible studies were critically appraised by two independent reviewers at the study level for methodological and reporting bias by adapting the ROBIN-I tool[5] for assessing risk of bias in selected observational studies. By definition, single-arm or observational trials have a high risk of bias due to the absence of a control group and randomization. Otherwise, the Nottingham-Ottawa-Scale was used as a quality check for retrospective studies.

**Statistical analysis**
The primary endpoints were mortality (%) and ventilatory improvement (defined as the proportion of participants relieved from ICU admission or from non-invasive ventilation defined at the time from initiation of the study treatment) among those treated with TCZ. The outcome data extracted for each study were analyzed using random-effects models and were reported as weighted measures of any event. Event rates reported in individual studies were aggregated into pooled rates. All other continuous variables were analyzed using descriptive statistics. We used the procedures of the comprehensive meta-analysis (CMA) software to calculate the effect size using dichotomous outcomes; and if these were not available either, we used other statistics (such as t-value or P value) to calculate the effect size. A random-effects meta-analysis of odds ratios (ORs) was used to aggregate efficacy outcomes reported across trials. A meta-analysis of adjusted ORs attained from multivariate analysis only was also provided.

Heterogeneity was assessed using the $\chi^2$ test. Statistical significance and the magnitude of $I^2$ were considered. When $I^2$ was less than 50%, low to moderate heterogeneity was assigned; otherwise, substantial heterogeneity was assigned. A significance threshold of $P < 0.05$ was adopted. All analyses were performed using CMA software version 2.2 (Biostat).

We tested publication bias by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie’s trim and fill procedure yields an estimated effect size after publication bias has been taken into account (as implemented in CMA). We also conducted Egger’s test of the intercept to quantify the bias captured by the funnel plot and to test whether it was significant.

**RESULTS**

Thirty-three studies met inclusion criteria among 604 retrieved (Figure 1). The demographic and clinical characteristics of included studies are reported in Tables 1-3 (references reported in Supplementary material). Overall 13476 patients ($n = 3264$ received TCZ) with COVID-19 pneumonia and various degree of severity were included. The median age was 62 years. Almost all received treatments consisting of antibiotics (e.g., azithromycin), antivirals, steroids plus or minus hydroxychloroquine. Mortality was 22.4% [95% confidence intervals (CIs): 17.9%-26.8%]. Ventilatory status improved in 63.9% (95% CI: 50.4%-75.6%).
### Table 1 Baseline characteristics of tocilizumab treated patients

| Ref. | Country | Type of study | No. of pts | Median follow up (d) | Male/Female, % | Median age (yr) | CV Comorbidities, % | Respiratory/diabetes, % | Other/cancer, % | Other medications, % | Ventilatory status (Baseline to end of follow up, %) | ICU admission %/time to ICU admission (d) |
|------|---------|---------------|------------|----------------------|----------------|----------------|--------------------|-----------------------|----------------|----------------|-----------------------------------------------|--------------------------------------|
| Alattar et al [11], 2020 | Qatar | Retrospective | 25 | 14 | 92/8 | 58 | 12 HTN | -/48 | CKD 16/4 | HCQ (100), AZITRO (96), lopinavir/ritonavir (96), ribavirin (88), and INF-1-α2a (60) | 56 (invasive) | 100/1 |
| Alberici et al [12], 2020 | Italy | Retrospective | 6 | 4 | - | - | - | -/- | -/- | Steroids, antivirals, HCQ | 33 (16 worsened) | -/ - |
| Capra et al [13], 2020 | Italy | Retrospective (with ctr arm) | 82 (n = 62 TCZ) | 9 | 73/27 | 63 | 63 HTN | -/16 | -/- | HCQ (100), lopinavir/ritonavir (100) | 35.2 (27% worsened) | 4.8/ - |
| Colaneri et al [14], 2020 | Italy | Retrospective with prop. score | 112 (n = 21 TCZ) | 7 | 90/10 | 62.3 | 47.6 HTN | 0/9.5 | 19/4.7 | HCQ, AZITRO, steroids (100) | - | 14/ - |
| Hassoun et al [15], 2020 | United States | Retrospective | 9 | - | 66/33 | 60 | 55 HTN | 11/11 | 66/- | HCQ, AZITRO (100) steroids (33), antibiotics (66) | - | 89/- |
| Klopfenstein et al [16], 2020 | France | Case control | 45 (n = 20 TCZ) | - | - | 76.8 | 55 HTN/70 CVS disease | 20/25 | -/35 | HCQ or lopinavir/ritonavir + antibiotics ± steroids (100) | - | 0/- |
| Luo et al [17], 2020 | China | Retrospective | 15 | - | 80/20 | 73 | 66 HTN | -/26.6 | -/- | Steroids (53) | 6.6 (33.3% worsened) | -/ - |
| Quartuccio et al [18], 2020 | Italy | Retrospective (with ctr arm) | 111 (n = 42 TCZ) | 17.8 | 78.6/21.4 | 62.4 | 47.6 HTN | -/- | -/- | Antivirals (100), HCq (92.9) steroids (40); antibiotics (28.6) | 65 (invasive) | 57/- |
| Sciascia et al [19], 2020 | Italy | Prospective | 63 | - | 89/11 | 62.6 | 45 | 4.7/9.5 | - | Lopinavir/ritonavir (71), darunavir/cobicistat (29) | 95 | 7.9/- |
| Toniati et al [20], 2020 | Italy | Prospective | 100 | 10 | 88/12 | 62 | 62 | 9/17 | 11/6 | HCQ, lopinavir/ritonavir or remdesivir, antibiotic, steroids (n = 23 worsened) | 69 | 43/- |
| Xu et al [21], 2019 | China | Retrospective | 21 | - | 86/14 | 56.8 | 57.2 | 9.6/23.8 | CKD 4.8/- | Lopinavir/ritonavir, IFN-α, ribavirin, steroids (100) | 100 | -/ - |
| Ramaswamy et al [22], 2020 | United States | Case control | 86 (n = 21 TCZ) | - | 61.9/38.1 | 63.2 | 14.3 HTN-heart disease, AF or stroke 19.1 | 28.6/14.3 | -/0 | HCQ (81), AZITRO (23.8), steroids (42.9) | - | 47.6/- |
| Rimland et al [23], 2020 | United States | Retrospective | 11 | 17 | 82/18 | 59 | 73 HTN/18 CVS | 27/36 | Renal or liver 18/9 | HCQ (36), AZITRO (64) | 54 (10% worsened) | 73/- |
| Study Authors          | Country | Study Type        | n (TCZ) | Sex (M/F) | Age (median) | Comorbidities | Antiviral Therapy | Mortality Rate |
|------------------------|---------|-------------------|---------|-----------|--------------|----------------|------------------|---------------|
| Sanchez-Montalva et al | Spain   | Prospective       | 82      | -         | 63/37        | 59.1           | 39 HTN/6.1 heart failure/12.2 AF | 23.5/19.5     |
| Wadud et al            | United States | Case control | 94 (n = 44 TCZ) | - | - | 55.5 | - | - |
| Campochiaro et al[26], 2020 | Italy | Retrospective | 65 (n = 32 TCZ) | 28 | 91/9 | 64 | 37 HTN/12 CAD | 3/12 |
| Morena et al           | Italy   | Prospective       | 51      | 30        | 78.4/21.6    | 60             | 29.4 HTN/49 CVS disease | 9.8/11.8     |
| Kimmig et al           | United States | Retrospective (with ctr arm) | 60 (n = 28 TCZ) | - | - | 46.8/53.2 | 63.8 | 53.6 HTN/43 other | 35.7/14.3     |
| Roumier et al          | France  | Compassionate use | 59 (n = 30 TCZ) | 8 | 80/20 | 50 | 20 HTN/13 CVS | 13/23     |
| Ip et al[30], 2020     | United States | Retrospective | 547 (n = 134 TCZ) | 30 | 78/22 | 62 | 71.6 HTN and coronary artery disease | 15/35       |
| Perrone et al          | Italy   | Phase 2 and expansion cohort | 1231 (n = 708 TCZ) | 30 | 82/18 | 61% > 60 | 68 heart disease or HTN | -/15     |
| Perez-Tanoira et al[32], 2020 | Spain | Cohort study | 562 (n = 36 TCZ) | - | - | - | - | - |
| Somers et al           | United States | Observational | 154 (n = 78 TCZ) | 47 | 68/32 | 55 | 85 HTN or heart failure | 54/13 |
| Heili-Frades et al[34], 2020 | Spain | Cohort study | 4712 (n = 366 TCZ) | - | - | - | - | - |
| Issa et al[35], 2020   | France  | Retrospective     | 10      | -         | 100/0        | 66             | 60 HTN | -/30         |
| Garcia et al[36], 2020 | Spain   | Retrospective     | 171 (n = 77 TCZ) | - | 58.8/51.2 | 61.5 | 61 HTN or heart disease | 10.3/15.6    |
| Ayerbe et al           | United Kingdom | Retrospective | 2075 (n = 421 TCZ) | - | - | - | - | - |

**Note:** TCZ refers to Tocilizumab, HTN is hypertension, CAD is coronary artery disease, CVS is cardiovascular system, AF is atrial fibrillation, HCQ is Hydroxychloroquine, AZITRO is Azithromycin, Lopinavir/Ritonavir, Remdesivir, CKD is Chronic Kidney Disease, Anti-virals are antiviral medications.
Outcome was improved with TCZ. In the primary analysis (n = 19 studies reporting data), mortality was reduced in patients treated with TCZ (OR = 0.64, 95% CI: 0.47-0.87; P < 0.01; Figure 2). In 9 studies where risk of death with TCZ use was controlled for other variables mortality was reduced by 57% (OR = 0.43, 95% CI: 0.27-0.7; P < 0.01). Intensive care need (mechanical ventilation) was also reduced (OR = 0.36, 95% CI: 0.14-0.89; P = 0.02). In all cases, a random effect model was used.

Egger’s test indicated a significant publication bias (P = 0.01). Duval and Tweedie’s trim and fill procedure indicated 4 missing studies (see the funnel plot with imputed studies in Supplementary material). The adjusted effect size (after imputation of the missing studies) was 0.84 (95% CI: 0.63-1.14).

DISCUSSION

A large part of the ongoing research into COVID-19 infection is concentrated on finding an immunomodulatory therapy to down-regulate the cytokine storm, usually combining it with antiviral agents[6]. In fact, IL-6 binds either with transmembrane IL-6 receptors or soluble IL-6 receptors, and the resulting complex can combine with the
| Ref.                  | Fever (baseline) °C/% | O₂ sat. % | Cough | Dyspnea % | Leucocytes 10⁹/L | Lymphocytes/Neutrophil 10⁹/L | PLT 10⁹/L | Hb g/dL | LDH Liver tests IU/L | CRP mg/L | PCT ng/L | D-dimer | IL6 ng/L | Imaging %                                                                 |
|----------------------|-----------------------|-----------|-------|-----------|------------------|-----------------------------|------------|--------|---------------------|----------|----------|--------|----------|---------------------------------------------------------------------------|
| Alattar et al[11], 2020 | 38/92                | -         | 84    | 72        | 6.0              | 0.9/5.0                     | 208        | -      | 46/30               | 95.2     | 0.38     | -      | -        | Infiltrates and ground glass opacities 100                                |
| Alberici et al[12], 2020 | -/-                  | -         | -     | -         | -                | -                           | -          | -      | -                   | -        | -        | -      | -        | Bilateral pulmonary opacities 100                                        |
| Capra et al[13], 2020  | 38/-                 | -         | -     | -         | -                | 0.6/8.4                     | 303        | -      | 445                 | 38/72    | 21.3     | 0.24   | -        | Interstitial lung disease 100                                            |
| Colaneri et al[14], 2020 | -/-                  | -         | -     | -         | -                | -                           | -          | -      | -                   | -        | -        | -      | -        |                                                                         |
| Hassoun et al[15], 2020 | -/-                  | -         | -     | -         | -                | -                           | -          | -      | -                   | -        | -        | -      | -        |                                                                         |
| Klopfenstein et al[16], 2020 | -/-                  | 90        | -     | -         | -                | 0.67/-                      | -          | -      | -                   | -        | 158      | -      | -        | ≥ 50% lung involvement                                                  |
| Luo et al[17], 2020    | -/-                  | -         | -     | -         | -                | -                           | -          | -      | -                   | -        | 96       | -      | 71       |                                                                         |
| Quartuccio et al[18], 2020 | -/-                 | -         | -     | -         | -                | 5540                        | 157        | -      | 625                 | -/-      | 79.05    | -      | 835      | 63.5                                                     |
| Sciascia et al[19], 2020 | <38/39.7             | -         | -     | -         | -                | -                           | -          | -      | -                   | -        | -        | -      | -        | Bilateral pulmonary infiltrates                                          |
| Toniati et al[20], 2020 | >37.5/85             | -         | 55    | 73        | 6                | 0.78                        | 177        | 13.6   | 413                 | 55/39    | 97       | -      | 525      | 41                                  | Ground glass opacities and consolidation, bilateral pulmonary infiltration |
| Xu et al[21], 2019     | -/-100               | -         | 66.7  | -         | 6.3              | 0.97                        | 170        | -      | 370                 | 31/29    | 75       | 0.33   | 0.8      | 153                             | Ground glass opacities and focal consolidation, peripheral and subpleural |
| Ramaswamy et al[22], 2020 | -/-                  | -         | -     | -         | -                | 1.1/6.7                     | 200        | -      | 60/43.5             | 15.9     | 2.2      | 2900   | 371      |                                                                         |
| Rimland et al[23], 2020 | -/-                  | -         | -     | -         | 8.5              | -/0.8                       | 230        | -      | 1203                | 51/35    | 197.3    | -      | 343.5    | 30.65                                             |
| Sanchez-Montalva et al[24], 2020 | 37.7/91.5           | 94        | 86.6  | 65.9      | 9.2              | 0.86/-                      | 199        | 13.3   | 446                 | 53/41    | 17.98    | -      | 295      | 74.8                                                   |
| Wadud et al[25], 2020  | -                    | -         | -     | -         | -                | -                           | -          | -      | -                   | -        | -        | -      | -        |                                                                         |
| Campochiaro et al[26], 2020 | 37.6/-              | -         | -     | -         | -                | -                           | -          | -      | -                   | -        | 156      | -      | -        |                                                                         |
| Study                     | Age | Male | Female | Severe | IL-6 | CRP | PCT | IL-6 | CRP | PCT | LDH | Platelets | Hb | Saturation | LDH | Number | Description                           |
|--------------------------|-----|------|--------|--------|------|-----|-----|------|-----|-----|-----|-------|------|------------|-----|--------|-------|--------|---------------------------------------|
| Morena et al [27], 2020  | 74.5/- | 62.7 | 54.9   | 9.1    | 0.8/-| 7.3 | 230 | -    | 470 | 48/39 | 189 | 1706 | 116 | Bilateral pulmonary opacities 100 |
| Kimmig et al [28], 2020  | -   | -    | -      | -      | -    | -   | -   | -    | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |
| Roumier et al [29], 2020 | -   | -    | -      | -      | -    | -   | -   | -    | 189 | 3712 | -   | -     | -   | -          | -   | -      | -     |                    |
| Ip et al [30], 2020      | 80  | 78   | 80     | -      | -/-  | -   | -   | -    | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |
| Perrone et al [31], 2020 | -/- | -    | -      | -      | -/-  | -   | -   | -    | 30  | -    | -   | -     | -   | -          | -   | -      | -     |                    |
| Perez-Tanoira et al [32], 2020 | -/- | -    | -      | -      | -/-  | -   | -   | -    | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |
| Somers et al [33], 2020  | -/- | -    | -      | 12.1   | 0.9/-| -   | 627 | 50/76 | 185 | 2400 | -   | -     | -   | -          | -   | -      | -     |                    |
| Heili-Frades et al [34], 2020 | -/- | -    | -      | -      | -/-  | -   | -   | -    | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |
| Isa et al [35], 2020     | -/- | 100  | -      | -      | -/-  | -   | -   | -    | 246 | 1354 | -   | -     | -   | Ground glass opacities              | -   | -      | -     |                    |
| Garcia et al [36], 2020  | -/- | 98.7 | -      | 93     | -    | 0.87/- | -   | -    | -    | 97  | 918  | -   | -     | -   | -          | -   | -      | -     |                    |
| Ayerbe et al [37], 2020  | -/- | -    | -      | -      | -/-  | -   | -   | -    | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |
| Borku Uysal et al [38], 2020 | -/- | 92   | 100    | 67     | 6.1  | 1.09/- | 180 | 13.8 | 259  | 33/39 | 54  | 599  | -   | Ground glass opacities              | -   | -      | -     |                    |
| Fernandez-Cruz et al [39], 2020 | -/- | -    | -      | -      | -/-  | -   | -   | -    | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |
| Garibaldi et al [40], 2020 | -/- | -    | -      | -      | -/-  | -   | -   | -    | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |
| Martinez-Sanz et al [41], 2020 | 36.8/- | 91   | -      | -      | 0.89/5.4 | -  | 669  | 32/32 | 113 | 809  | 70  | -     | -   | -          | -   | -      | -     |                    |
| Petrak et al [42], 2020  | -   | -    | -      | -      | -    | -   | 538 | 53.3 | -   | 1.3  | -   | -     | -   | -          | -   | -      | -     |                    |
| Rossi et al [43], 2020   | 37.5/- | 94   | -      | -      | 1.128/- | -  | -    | 168  | -   | -   | -   | -     | -   | -          | -   | -      | -     |                    |

<: Not available; PLT: Platelets; Hb: Hemoglobin; CRP: C reactive protein; PCT: Procalcitonin C; IL-6: Interleukin-6; sat: Saturation; LDH: Lactate dehydrogenase.

Signal-transducing component gp130 to activate the inflammatory response. In an emergent situation where no approved drugs are available and supportive measures are available only for critically ill patients, any new promising agent merits attention. A meta-analysis has correlated IL-6 concentration with COVID-19 severity. Those with severe cases show a 2.9-fold higher concentration than those without complications[7].
## Table 3: Outcome of patients treated with tocilizumab therapy

| Ref. | N° TCZ administered (median doses) | Death % | Dismissed % | Median hospitalization (d) | TCZ AEs % | Comparison with other medications or no TCZ | NOS Scale | ROBIN risk |
|------|----------------------------------|---------|-------------|--------------------------|-----------|----------------------------------------|-----------|------------|
| Alattar et al[11], 2020 | 1 | 12 | 36 (from ICU) | - | Anemia 64; ALT ↑ 44 | HR for discharge from ICU 0.64 (0.37-1.11) | 8 | Low |
| Alberici et al[12], 2020 | 1 | 33 | 16 | - | - | - | 6 | Moderate |
| Capra et al[13], 2020 | 1 | 8 | 92 | 12.5 | - | OR for OS 0.036 (0.07-0.18)* | 7 | Low |
| Colaneri et al[14], 2020 | 2 | 23.8 | 85.7 (from ICU) | 2 | 0 | OR for OS 0.78 (0.06-9.34); OR for ICU 0.11 (0-3.38) | 7 | Low |
| Hassoun et al[15], 2020 | 1 | 22 | 55 | 13.5 (n = 7) | - | OR for OS and ICU admission 0.36 (0.1-1.3) and 0.03 (0.002-0.56); OR for mechanical vent 0.05 (0.003-0.95) | 5 | Low |
| Klopfenstein et al[16], 2020 | 1 or 2 | 25 | 55 | 13 | - | - | 5 | Low |
| Luo et al[17], 2020 | 1 | 20 | - | - | - | - | 5 | High |
| Quartuccio et al[18], 2020 | 1 | 9.5 | 28.5 | - | - | OR for OS 14.5 (0.76-279.3); OR for ICU admission 220.9 (12.7-3826.1) | 8 | Moderate |
| Sciascia et al[19], 2020 | 1 (2 in 82.5%) | 11 | - | - | - | - | 6 | Moderate |
| Toniati et al[20], 2020 | 1 (2 in 87%) | 20 | 15 | - | Septic shock (n = 2), GI perforation (n = 1) | - | 8 | Low |
| Xu et al[21], 2019 | 1 (2 in 14.3%) | 0 | 100 | 15.1 | - | - | 5 | Moderate |
| Ramaswamy et al[22], 2020 | 1 (2 in 38%) | 14.3 | - | - | - | HR for OS 0.25 (0.07-0.9) | 5 | Moderate |
| Rimland et al[23], 2020 | 1 | 27 | 18 | 18 | - | - | 7 | Low |
| Sanchez-Montalva et al[24], 2020 | 1 | 26.8 | 41.5 | - | - | - | 6 | Low |
| Wadud et al[25], 2020 | - | 38.6 | - | - | - | OR for OS 0.58 (0.25-1.32) | 6 | Moderate |
| Campochiaro et al[26], 2020 | 1 (2 in 28%) | 15 | 63 | 13.5 | SAEs (25) | OR for OS 0.38 (0.11-1.27); OR for ICU admission 0.33 (0.13-8.5) | 8 | Low |
| Morena et al[27], 2020 | - | 27 | 61 | - | AST/ALT ↑ 29, PLT 14, neutropenia 6, rash 2 | - | 8 | Low |
| Kimmig et al[28], 2020 | 1 (2 in 10.7%) | 42.9 | 25 | - | Infections 71.4 | OR for OS 2.25 (0.75-2.24) | 6 | Moderate |
| Roumier et al[29], 2020 | 1 | 10 | 20 | - | - | OR for OS 0.25 (0.05-1.03); OR for ICU 0.17 (0.06-0.48) | 7 | Low |
| Ip et al[30], 2020 | 1 (78%) | 46 | - | - | Bacteriemia (13), secondary pneumonia (9) | OR for OS 0.66 (045-0.99) | 8 | Low |
| Perrone et al[31], 2020 | 1 (59.8), 2 (54.5) | 20 | - | - | 26.4 G3-5; 14.4 G1-2 | OR for 30-d OS 0.7 (0.41-1.22) and 1.22 (0.86-1.92) in phase 2 and validation cohort | 8 | Low |
| Perez-Tanoira et | - | 27.7 | - | - | - | OR for OS 1.015 (0.47-2.18) | 5 | Moderate |
Siltuximab, a chimeric monoclonal antibody acting and blocking IL-6, is being tested in the SISCO study, including patients with acute respiratory distress syndrome related to COVID-19 infection (NCT04322188). Preliminary data from 21 patients showed a reduction in the C-reactive protein levels in 16 patients, a clinical improvement in 33% and disease stabilization in 43% of cases[8].

In this pooled analysis of 31 studies including 2898 patients treated with TCZ, we found a strong trend toward improved survival with the use of TCZ (a significant reduction in acute mortality risk by 36%). Tocilizumab administration was also independently associated with a 57% reduced risk of death in multivariable analysis. Tocilizumab reduced also the risk of mechanical ventilation and ICU admission by 64%. Overall mortality rate was 22%.

The limitations of these data are related to the observational nature of the studies, primarily monocentric and non-controlled. The population treated with TCZ was negatively selected for the worst clinical and inflammatory conditions. Also, due to the non-randomized design of all studies, final results might have been biased, and the added value of TCZ might not have been formally proven. However, despite a likely imbalance among clinical and laboratory baseline variables between the 2 groups, the effect of TCZ on clinical outcomes appears sustained. We finally recognize that some papers reported in the primary analysis were pre-printed in MedRxiv archive and not still finally reviewed and published in full.

At this time, 45 trials are underway to explore the contribution of TCZ when added to the standard of care for COVID-19. Four are in phase 3 trials: the COVACTA study (NCT04320615), in which TCZ is compared with placebo, the NCT04361552 study in which the control arm is represented by best practices, the COV-AID study (NCT04330638), a six-arm study including anakinra and the association of anakinra + TCZ, and the RECOVERY study (NCT04381936), also a six-arm study, including hydroxychloroquine, lopinavir/ritonavir, and low doses of steroids.

Recently, the use of hydroxychloroquine or chloroquine with or without a macrolide was associated with decreased survival and increased rate of ventricular arrhythmias in COVID-19 hospitalized patients[9]. Despite this alarming concern, article and data purity were subsequently questioned and article retracted. Similarly, results of a separate study with data attained from a different database, showed that hydroxychloroquine failed to reduce infection risk in people exposed to patients with confirmed COVID-19. Results indicated that the incidence of new illness compatible with

| Study | Country | Age | Sex | Disease Risk | Mortality | Mortality Rate | Effect | Confidence Intervals | Risk of Death |
|-------|---------|-----|-----|-------------|-----------|---------------|--------|---------------------|--------------|
| Somers et al[33], 2020 | 1 | 18 | 56 | 20.4 | Superinfection (54) | OR 0.39 (0.18-0.82) | 8 | Low |
| Heili-Frades et al[34], 2020 | - | 22.4 | - | - | - | - | 6 | Moderate |
| Isa et al[35], 2020 | 1 | 10 | - | 11 (ICU) | - | - | 5 | High |
| Moreno-Garcia et al[36], 2020 | - | 10.3 | 84.4 | - | - | OR for ICU 0.3 (0.12-0.71) and OR for OS 0.52 (0.21-1.29) | 5 | Moderate |
| Ayerbe et al[37], 2020 | - | 21.1 | - | - | - | OR for OS 1.9 (1.44-2.51) | 5 | High |
| Borku Uysal et al[38], 2020 | 2 | 0 | 100 | - | - | - | 6 | Moderate |
| Fernandez-Cruz et al[39], 2020 | - | - | - | - | - | OR for OS 0.69 (0.41-1.19) | 5 | High |
| Garibaldi et al[40], 2020 | - | 5 | - | - | - | OR for OS 1.14 (0.46-2.81) | 5 | Moderate |
| Martinez-Sanz et al[41], 2020 | 1 | 23 | - | 13 | - | OR for OS 2.19 (1.54-3.1) | 5 | Low |
| Petrak et al[42], 2020 | 1 (84.8), 2 (15.2) | 28.3 | 48.3 | - | - | - | 5 | Moderate |
| Rossi et al[43], 2020 | 1 | 28.9 | - | - | - | HR for OS 0.29 (0.17-0.49) | 8 | Low |

< Not available; NOS: Nottingham-ottawa-scale; ROBIN: Risk of bias of non-randomized studies; ALT: Alanine aminotransferase.
COVID-19 did not differ significantly between those who received hydroxychloroquine and those who received placebo[10]. Therefore, new combinations of potentially active drugs need to be tested, and efficacy confirmed in these patients[11-43].

**CONCLUSION**

In conclusion, we provide the first evidence that TCZ can improve the respiratory and clinical outcomes of patients with COVID-19 pneumonia in clinical practice, but its use merits further confirmatory trials.
Figure 2 In the primary analysis, mortality was reduced in patients treated with tocilizumab.

ARTICLE HIGHLIGHTS

Research background
Coronavirus disease 2019 (COVID-19) infection is associated with a cytokine storm during acute phase.

Research motivation
Interleukin-6 is a key player in this systemic inflammation.

Research objectives
We evaluated the effect of tocilizumab (TCZ) on the outcomes of COVID-19 pneumonia.

Research methods
We performed a systematic review and pooled analysis of published literature.

Research results
Mortality was reduced in patients treated with TCZ (Odds ratio = 0.64, 95%CI: 0.47-0.87; P < 0.01).

Research conclusions
We conclude that TCZ may improve outcome of COVID-19 infected patients.

Research perspectives
Current use of tocilizumab in clinical practice has to be validated further through large randomized trials.
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