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SYSTEMATIC REVIEWS

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),

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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

Core Tip: Coronavirus disease 2019 (COVID-19) infection is associated with a citokine storm during acute phase. Interleukin-6 is a key player in this systemic inflammation. We evaluated the effect of tocilizumab (TCZ) on the outcomes of COVID-19 pneumonia. Mortality was reduced in patients treated with TCZ (Odds ratio =0.64, 95% confidence intervals: 0.47-0.87; $P < 0.01$). We conclude that TCZ may improve outcome of COVID-19 infected patients.

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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 χ^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 Comorbities, %	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	Quatar	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[1])	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	Retrospctive	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[1])	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	69 (*n* = 23 worsened)	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/-

Sanchez-Montalva *et al* [24], 2020	Spain	Prospective	82	-	63/37	59.1	39 HTN/6.1 heart failure/12.2 AF	23.5/19.5	Liver 1.2/-	HCQ (98.9), lopinavir/ritonavir (76.8), AZITRO (96.3), darunavir/cobicistat (25)	53 (52% worsened)	2.9/-
Wadud *et al* [25], 2020	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	CKD 9/6	HCQ, AZITRO, lopinavir/ritonavir (100)	91	0/-
Morena *et al* [27], 2020	Italy	Prospective	51	30	78.4/21.6	60	29.4 HTN/49 CVS disease	9.8/11.8	5.9/5.9	HCQ (98), antibiotics (76), lopinavir/ritonavir (82), remdesivir (42)	66.6 (33% worsened)	11.8/-
Kimmig *et al* [28], 2020	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	14/14.3	-	-	-
Roumier *et al* [29], 2020	France	Compassionate use	59 (*n* = 30 TCZ)	8	80/20	50	20 HTN/13 CVS	13/23	33/-	HCQ (6.6), steroids (6.6)	-	23.3/-
Ip *et al*[30], 2020	United States	Retrospective	547 (*n* = 134 TCZ)	30	78/22	62	71.6 HTN and coronary arthery disease	15/35	15/9	HCQ + AZITRO (92), steroids (66)	-	100/-
Perrone *et al* [31], 2020	Italy	Phase 2 and expansion cohort	1221 (*n* = 708 TCZ[3])	30	82/18	61% > 60	68 heart disease or HTN	-/15	-/-	HCQ (75), anti-retroviral (65), antibiotics (50), steroids (28)	-	16 invasive ventilation/-
Perez-Tanoira *et al*[32], 2020	Spain	Cohort study	562 (*n* = 36 TCZ)	-	-/-	-	-	-/-	-/-	-	-	-
Somers *et al* [33], 2020	United States	Observational	154 (*n* = 78 TCZ)	47	68/32	55	85 HTN or heart failure	54/13	CKD 35/-	HCQ (26), steroids (29), remdesivir (3)	56 (18 and worsened)	100/41 < 24 h, 36 > 48 h
Heili-Frades *et al*[34], 2020	Spain	Cohort study	4712 (*n* = 366 TCZ)[2]	-	-/-	-	-	-/-	-/-	-	-	40.7/-
Issa *et al*[35], 2020	France	Retrospective	10	-	100/0	66	60 HTN	-/30	-/-	HCQ (100), steroids (30)	50	70/7 d
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	-/-	Antivirals (100, steroids (50)	90	10.3/-
Ayerbe *et al* [37], 2020	United Kingdom	Retrospective	2075 (*n* = 421	8	-/-	-	-	-/-	-/-	-	-	-/-

			TCZ)									
Borku Uysal *et al*[38], 2020	Turkey	Retrospective	12	22	50/50	65.8	58 HTN	16/58	CKD 8/16	HCQ and antivirals (100), AZITRO (50), antibiotics (58)	82	17/-
Fernandez-Cruz *et al*[39], 2020	Spain	Retrospective	463 (*n* = 189 TCZ)	-	-/-	-	-	-/-	-/-	Steroids (100), other not available	-	-/-
Garibaldi *et al* [40], 2020	United States	Cohort study	832 (*n* = 39 TCZ)	-	-/-	-	-	-/-	-/-	-	-	-/-
Martínez-Sanz *et al*[41], 2020	Spain	Cohort study	1229 (*n* = 260 TCZ)	-	73/27	65	17 HTN, 8 CAD, 2 heart failure	18/15	CKD 4/-	-	-	19/6 d
Petrak *et al*[42], 2020	United States	Retrospective	145	-	64/36	58.1	-	-	-	Corticosteroids (60), HCQ + AZITRO (98.6)	-	-/-
Rossi *et al*[43], 2020	France	Case control	246 (*n* = 106 TCZ)	28	66/34	64	60 HTN, 23.6 CVS	16/45	-/5.7	Antibiotics (100), HCQ (83), steroids (40), lopinavir/ritonavir (0.9)	-	-/-

[1]Control arm consisted in patients treated with hydroxycloroquine + lopinavir/ritonavir before tocilizumab availability.
[2]Hospitalized cohort only.
[3]Modified intent to treat analysis. CVS: Cardiovascular disease; CAD: Coronary arthery disease; AF: Atrial fibrillation; HTN: Hypertension; CKD: Chronic kidney disease; pts: Patients; HCQ: Hydroxycloroquine; AZITRO: Azitromycin; -: Not availble; TCZ: Tocilizumab; ICU: Intensive care unit.

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). Duvall 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

Table 2 Laboratory and radiological characteristics of patients treated with tocilizumab

Ref.	Fever (baseline) °C/%	O_2 sat. %	Cough %	Dyspnea %	Leucocytes 10^9/L	Lymphocites/Neutrophil 10^9/L	PLT 10^9/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	-/-	-	-	-	-	-/-	-	-	-	-	-	-	-	-	-
Capra *et al*[13], 2020	38/-	-	-	-	-	-/-	-	-	-	-	123	0.6	-	-	Bilateral pulmonary opacities 100
Colaneri *et al*[14], 2020	-/-	-	-	-	-	0.6/8.4	303	-	445	38/72	21.3	0.24	-	-	Interstitial lung disease 100
Hassoun *et al*[15], 2020	-/-	-	-	-	-	-/-	-	-	-	-/-	-	-	-	-	-
Klopfenstein *et al*[16], 2020	-/-	90	-	-	-	0.67/-	-	-	-	-/-	158	-	-	-	≥ 50% lung involvement 60
Luo *et al*[17], 2020	-/-	-	-	-	-	-/-	-	-	-	-/-	96	-	-	71	-
Quartuccio *et al*[18], 2020	-/-	-	-	-	5540	0.68/4.5	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/-	-	-	-	-	-/-	-	-	469	-/-	156	-	-	-	-

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	-/-	-	-	-	-	-/-	-	-	-	-/-	-	-	-	-	-
Issa *et al*[35], 2020	-/100	-	-	-	-	-/-	-	-	-	-/-	246	-	1354	-	Ground glass opacities
Garcia *et al*[36], 2020	-/98.7	-	83	43	-	0.87/-	-	-	-	-/-	97	-	918	-	-
Ayerbe *et al*[37], 2020	-/-	-	-	-	-	-/-	-	-	-	-/-	-	-	-	-	-
Borku Uysal *et al* [38], 2020	-/92	92	100	67	6.1	1.09/4.3	180	13.8	259	33/39	54	-	599	-	Ground glass opacities
Fernandez-Cruz *et al* [39], 2020	-/-	-	-	-	-	-/-	-	-	-	-/-	-	-	-	-	-
Garibaldi *et al*[40], 2020	-/-	-	-	-	-	-/-	-	-	-	-/-	-	-	-	-	-
Martínez-Sanz *et al* [41], 2020	36.8/-	91	-	-	-	0.89/5.4	-	-	669	-/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)	-	-	5	Low
Klopfenstein *et al*[16], 2020	1 or 2	25	55	13	-	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 (0.003-0.93)	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 (0.76-278.3); 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

al[32], 2020								
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
Issa *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
Martínez-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 availble; NOS: Nottingham-ottawa-scale; ROBIN: Risk of bias of non-randomized studies; ALT: Alanine aminotransferase.

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 hydroxycloroquine 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 hydroxycloroquine failed to reduce infection risk in people exposed to patients with confirmed COVID-19. Results indicated that the incidence of new illness compatible with

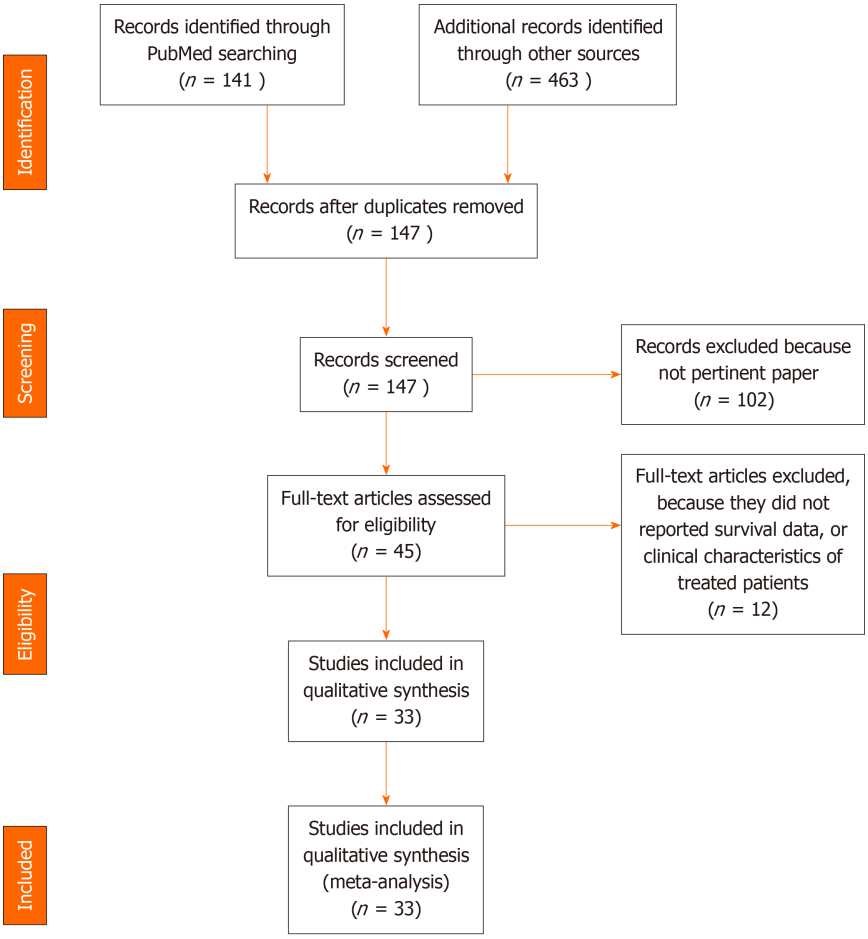

Figure 1 Thirty-three studies met inclusion criteria among 604 retrieved.

COVID-19 did not differ significantly between those who received hydroxycloroquine 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.

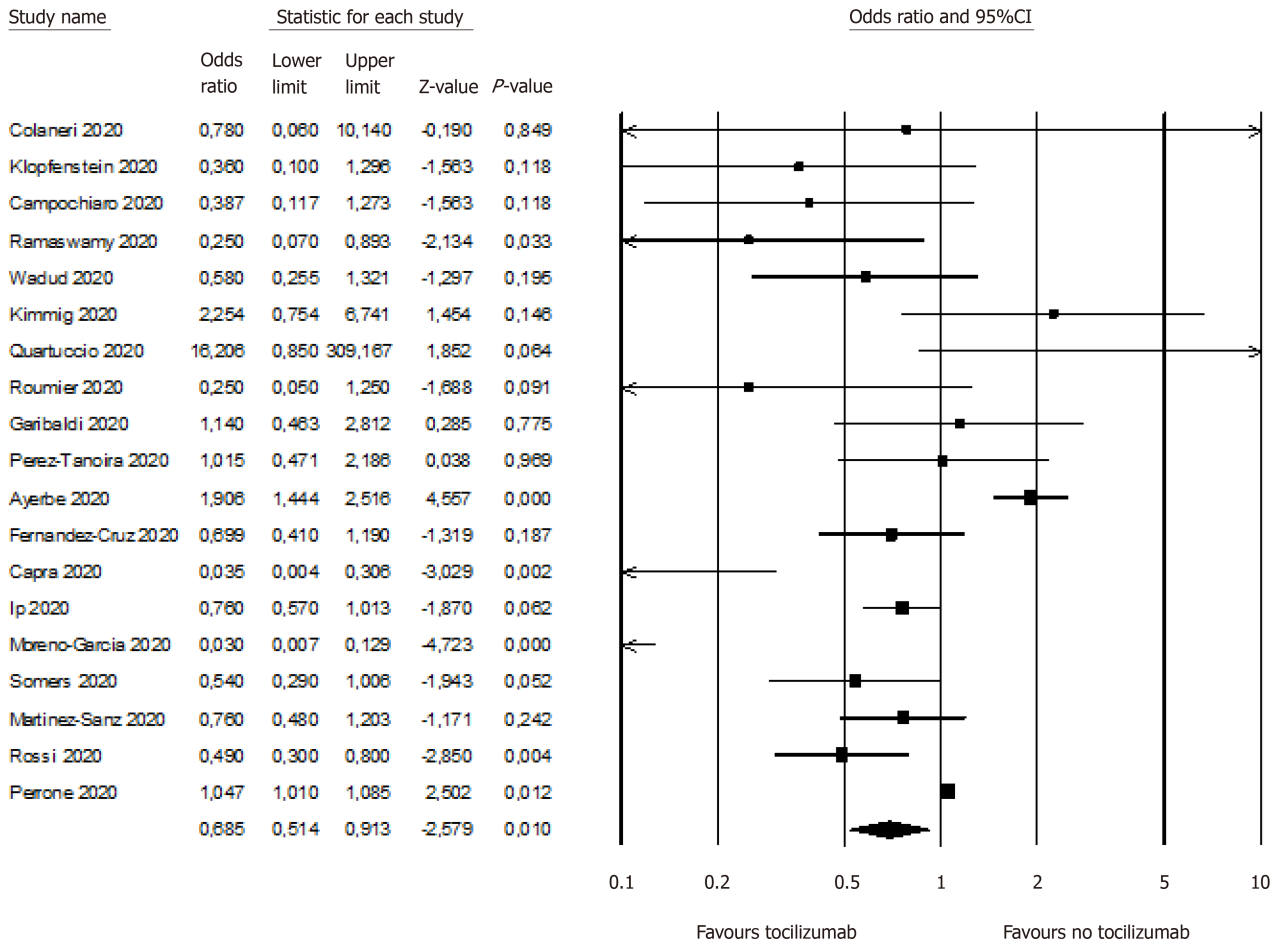

Figure 2 In the primary analysis, mortality was reduced in patients treated with tocilizumab.

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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