

Efficacy and Safety of Tocilizumab for Coronavirus Disease 2019 (COVID-19) Patients: A Systematic Review and Meta-analysis

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ABSTRACT

Background Currently, the data regarding the effectiveness and safety of tocilizumab as treatment for COVID-19 infection is still conflicting. This study aims to give clear evidence regarding the potential benefit and safety of tocilizumab in improving the outcome of COVID-19 patients.

Methods We systematically searched the PubMed and Europe PMC database using specific keywords related to our aims until November 1st, 2020. All articles published on COVID-19 and tocilizumab were retrieved. Statistical analysis was done using Review Manager 5.4 software.

Results A total of 38 studies with a total of 13 412 COVID-19 patients were included in our analysis. Our meta-analysis showed that tocilizumab treatment is associated with reduction of mortality rate from COVID-19 [OR 0.54 (95% CI 0.42–0.71), $p < 0.00001$, $I^2 = 79\%$, random-effect modelling], but did not alter the severity of COVID-19 [OR 1.05 (95% CI 0.92–1.20), $p = 0.47$, $I^2 = 84\%$, random-effect modelling] and length of hospital stay [Mean Difference 1.77 days (95% CI –0.61–4.14 days), $p = 0.15$, $I^2 = 97\%$, random-effect modelling]. Tocilizumab also does not associated with serious adverse events compared with standard of care treatment [OR 0.91 (95% CI 0.71–1.15), $p = 0.42$, $I^2 = 46\%$, random-effect modelling].

Conclusion Our study does not support the routine use of tocilizumab for COVID-19 patients. Future studies should focus more on other potential therapies for COVID-19 patients.

Introduction

Until now, the number of positive and death cases from coronavirus disease 2019 (COVID-19) is still increasing. This disease has caused significant health and economic burden across the world. The manifestations of the disease may vary from mild respiratory symptoms such as fever, nasal obstruction, and cough to severe life-threatening symptoms such as respiratory distress, shock, arrhythmia, and heart failure [1]. Several comorbid diseases has been demonstrated to be associated with severe COVID-19 infections,

such as hypertension, diabetes, dyslipidemia, thyroid disease, cardiovascular disease, anemia, and pulmonary disease [2–4]. Currently, there are no widely accepted drugs for the management of COVID-19 patients. Several potential agents have been proposed to help in achieving faster recovery time and reducing the mortality rate in COVID-19 patients, and one of the agents is tocilizumab, an IL-6 inhibitor. Tocilizumab has been approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and giant cell arteritis [5]. Recently, tocilizumab has been offered to help in re-

ducing the pro-inflammatory cytokines in COVID-19 and preventing the cytokine storm syndrome that could contribute to the development of the severe outcome. Unfortunately, the evidence regarding the potential benefit and safety of tocilizumab in COVID-19 patients is still conflicting. Therefore, a meta-analysis is required to aid in solving this problem. This article aims to explore the efficacy and safety of tocilizumab administration in patients with COVID-19.

Materials and Methods

Eligibility criteria

Studies were included in this review if met the following inclusion criteria: representation for clinical questions (P: positive/confirmed cases of COVID-19; I: receiving tocilizumab as their treatment; C: did not receive tocilizumab or receive only standard of care treatment; O: efficacy of tocilizumab (rate of severe COVID-19, mortality, and length of hospital stay) and serious adverse events of tocilizumab (thromboembolism incident and secondary infection); S: type of study was a randomized control trial, cohort, clinical trial, case-cohort, and cross-over design) and if the full-text article was available. The following types of articles were excluded: articles other than original research (e. g., review articles or commentaries); case reports; articles not in the English language; articles on research in pediatric populations (17 years of age or younger); and articles on research in pregnant women.

Search strategy and study selection

A systematic search of the literature was conducted on PubMed and Europe PMC using the keywords “tocilizumab” OR “anti-IL-6” OR “IL-6 inhibitor” AND “coronavirus disease 2019” OR “COVID-19”, between 2019 and present time (November 1st, 2020) with language restricted to English only. Duplicate results were removed. The remaining articles were independently screened for relevance by its abstracts with two authors. The full text of residual articles was assessed according to the inclusion and exclusion criteria. The references of all identified studies were also analyzed (forward and backward citation tracking) to identify other potentially eligible articles. The study was carried out per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6].

Data extraction and quality assessment

Data extraction was performed independently by two authors, we used standardized forms that include author, year, study design, number of participants, age, gender, number of patients who receive tocilizumab and who did not, tocilizumab dose, and proportion of patients with each outcome of COVID-19.

The outcome of interest was severe COVID-19, mortality, length of hospital stay, and serious adverse events which comprised of thromboembolism incident and secondary infection. Severe COVID-19 was defined as patients who had any of the following features at the time of, or after, admission: (1) respiratory distress (≥ 30 breaths per min); (2) oxygen saturation at rest $\leq 93\%$; (3) ratio of the partial pressure of arterial oxygen (PaO₂) to a fractional concentration of oxygen inspired air (fiO₂) ≤ 300 mmHg; or (4) critical

complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure) or admission into ICU. Mortality outcome from COVID-19 was defined as the number of patients who were dead because of COVID-19 infection.

Two investigators independently evaluated the quality of the included cohort and case-control studies using the Newcastle–Ottawa Scale (NOS) [7]. The selection, comparability, and exposure of each study were broadly assessed and studies were assigned a score from zero to nine. Studies with scores ≥ 7 were considered of good quality. They also independently evaluated the quality of the included clinical trial studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [8].

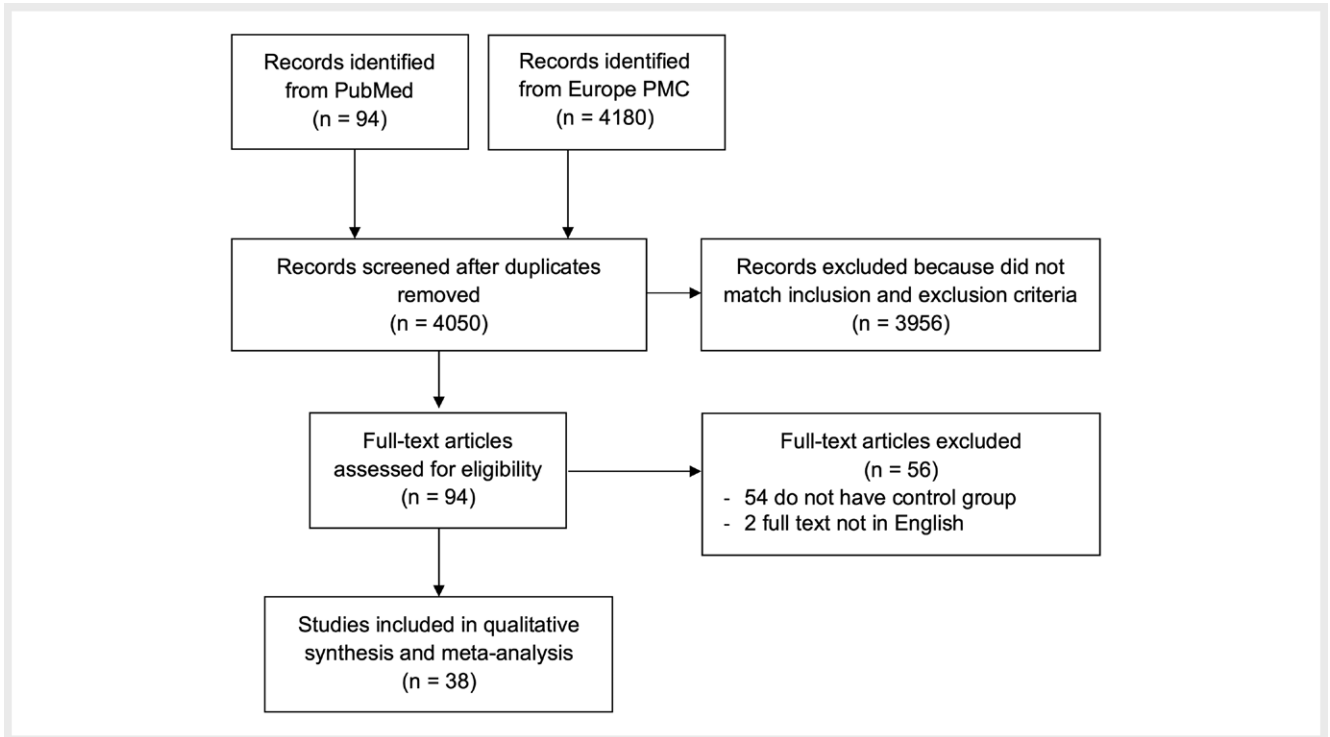
Statistical analysis

A meta-analysis was performed using Review Manager 5.4 (Cochrane Collaboration) software. Dichotomous variables were calculated using the Mantel-Haenszel formula with a random-effects model regardless of heterogeneity. The effect estimate was reported as risk ratio (RR) along with its 95% confidence intervals (CIs) for dichotomous variables, respectively. For continuous variables, the inverse variance method was used to obtain mean differences (MDs) and its standard deviations (SDs). P-value was two-tailed, and the statistical significance was set at ≤ 0.05 . A funnel plot, Begg's rank correlation method [9], and Egger's weighted regression method [10] were adopted to statistically assess publication bias ($P < 0.05$ was considered statistically significant). When data were reported as medians and interquartile ranges, we would convert them to means and standard deviations for meta-analytical pooling using the formula by Wan X, et al [11].

Results

Study selection and characteristics

A total of 4274 records were obtained through systematic electronic searches and other ways. After the removal of duplicates, 4050 records remained. A total of 3956 records were excluded after screening the titles/abstracts because they did not match our inclusion and exclusion criteria. After evaluating 94 full-texts for eligibility, 54 full-text articles were excluded because they do not have the control/comparison group, 2 full-text articles were excluded because the articles were not in English, and finally, 38 studies [12–49] with a total of 13 412 COVID-19 patients were included in the meta-analysis (► Fig. 1). Of a total of 38 included studies, 3 were double-blind randomized-controlled trial (RCT), 4 were open-label RCT, 23 were retrospective cohort, 3 studies were prospective cohort, while the remaining 5 studies was a case-control study. The dose and preparation of tocilizumab used were varied among the included studies. Most of the included studies (24 studies) use intravenous tocilizumab at dosage 8 mg/kg, 1–2 doses, while the remaining studies use tocilizumab at 400 mg, 1–2 doses, and subcutaneous tocilizumab at a dosage of 324 mg given as two consecutive injections. The essential characteristics of the included studies are summarized in ► Table 1.



► **Fig. 1** PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

► **Table 1** Characteristics of included studies.

Study	Sample size	Design	Tocilizumab dose	Tocilizumab patients		Non-tocilizumab patients	
				n (%)	Age (years)	n (%)	Age (years)
Campochiaro C et al. [12] 2020	65	Retrospective cohort	IV: 400 mg, 1–2 doses	32 (49.2%)	64 ± 16.2	33 (50.8%)	63.5 ± 15.1
Canziani LM et al. [13] 2020	128	Case-control	IV: 8 mg/kg, 1–2 doses	64 (50%)	63 ± 12	64 (50%)	64 ± 8
Capra R et al. [14] 2020	85	Retrospective cohort	IV: 400 mg, 1 dose	62 (72.9%)	63.3 ± 14.1	23 (27.1%)	68.3 ± 18.5
Chilimuri S et al. [15] 2020	1225	Retrospective cohort	IV: 400 mg, 1–2 doses	87 (7.1%)	61.6 ± 15.5	1138 (92.9%)	63 ± 14.8
Colaneri M et al. [16] 2020	112	Retrospective cohort	IV: 400 mg, 1 dose	21 (18.7%)	62.3 ± 18.6	91 (81.3%)	63.7 ± 16.3
De Rossi et al. [17] 2020	158	Retrospective cohort	IV: 400 mg, 1 dose SC: 324 mg, 1 dose	90 (56.9%)	62.9 ± 12.5	68 (43.1%)	71 ± 14.6
Eimer J et al. [18] 2020	87	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	29 (33.3%)	56.6 ± 10.3	58 (66.7%)	57.2 ± 9.4
Enzmann MO et al. [19] 2020	150	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	12 (15.3%)	N/A	66 (84.7%)	N/A
Gokhale Y et al. [20] 2020	269	Retrospective cohort	IV: 400 mg, 1 dose	151 (56.1%)	52.3 ± 11.8	118 (43.9%)	55.3 ± 12.5
Guaraldi G et al. [21] 2020	544	Retrospective cohort	IV: 8 mg/kg, 2 doses SC: 162 mg, 2 doses	179 (32.9%)	63.3 ± 13.3	365 (67.1%)	68 ± 15.5
Gupta S et al. [22] 2020	3924	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	433 (11%)	57 ± 12.5	3491 (89%)	62.3 ± 14.8
Hermine O et al. [23] 2020	130	Open-label RCT	IV: 8 mg/kg, 1–2 doses	63 (48.6%)	65.1 ± 12.7	67 (51.4%)	64.2 ± 11.2
Holt GE et al. [24] 2020	62	Retrospective cohort	IV: 400 mg, 1 dose	32 (51.6%)	N/A	30 (48.4%)	N/A

► **Table 1** Continued.

Study	Sample size	Design	Tocilizumab dose	Tocilizumab patients		Non-tocilizumab patients	
				n (%)	Age (years)	n (%)	Age (years)
Ip A et al. [25] 2020	547	Retrospective cohort	IV: 400 mg, 1 dose	134 (24.4%)	61.6 ± 12.5	413 (75.6%)	68 ± 14.1
Kewan T et al. [26] 2020	51	Retrospective cohort	IV: 8 mg/kg, 1 dose	28 (54.9%)	62 ± 13.3	23 (45.1%)	66.6 ± 14.8
Klopfenstein T et al. [27] 2020	206	Case-control	IV: 8 mg/kg, 1–2 doses	30 (14.5%)	75.6 ± 11.3	176 (85.5%)	74.3 ± 11
Lengnan X et al. [28] 2020	19	Retrospective cohort	IV: 400 mg, 1 dose	5 (26.3%)	73.2 ± 4.4	14 (73.7%)	66.2 ± 5
Masia M et al. [29] 2020	138	Prospective cohort	IV: 400 mg if <75 kg and 600 mg if ≥ 75 kg	76 (55%)	65.2 ± 14.9	62 (45%)	65.9 ± 16.8
Martinez-Sanz J et al. [30] 2020	1229	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	260 (21.1%)	65.3 ± 15.5	969 (78.9%)	68.3 ± 17
Menzella F et al. [31] 2020	79	Prospective cohort	IV: 8 mg/kg, 2 doses SC: 162 mg, 2–4 doses	41 (51.8%)	63.3 ± 10.6	38 (48.2%)	70.3 ± 11.3
Mikulska M et al. [32] 2020	196	Prospective cohort	IV: 8 mg/kg, 1–2 doses SC: 162 mg, 1–2 doses	130 (66.3%)	64.5 ± 12.4	66 (33.7%)	73.5 ± 14.4
Moiseev S et al. [33] 2020	137	Retrospective cohort	IV: 400 mg, 1 dose	83 (60.5%)	55.6 ± 11.1	54 (39.5%)	56.3 ± 14
Moreno-Perez O et al. [34] 2020	236	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	77 (32.6%)	62.3 ± 14	159 (67.4%)	57 ± 19.2
Perrone F et al. [35] 2020	301	Open-label RCT	IV: 8 mg/kg, 1–2 doses	180 (59.8%)	N/A	121 (40.2%)	N/A
Potere N et al. [36] 2020	80	Case-control	SC: 162 mg, 2 doses	40 (50%)	59.8 ± 16.9	40 (50%)	59.1 ± 17
Price CC et al. [37] 2020	239	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	153 (64%)	N/A	86 (46%)	N/A
Rodriguez-Bano J et al. [38] 2020	432	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	88 (20.3%)	64.6 ± 11.8	344 (79.7%)	68 ± 12.5
Rojas-Marte G et al. [39] 2020	193	Case-control	IV: 8 mg/kg, 1–2 doses	96 (49.7%)	58.8 ± 13.6	97 (50.3%)	62 ± 14
Roomi S et al. [40] 2020	176	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	134 (78.8%)	65.4 ± 10.5	36 (21.2%)	58 ± 13.2
Rosas I et al. [41] 2020	438	Double-blind RCT	IV: 8 mg/kg, 1–2 doses	294 (67.1%)	60.9 ± 14.6	144 (32.9%)	60.6 ± 13.7
Rossi B et al. [42] 2020	246	Case-control	IV: 400 mg, 1 dose	106 (43%)	64.3 ± 13	140 (57%)	70.1 ± 16.5
Roumier M et al. [43] 2020	59	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	30 (50.8%)	58.8 ± 12.4	29 (49.2%)	71.2 ± 15.4
Ruiz-Antoran B et al. [44] 2020	506	Retrospective cohort	IV: 8 mg/kg, 1–2 doses	268 (52.9%)	65 ± 11.7	238 (47.1%)	71.3 ± 14.2
Salama C et al. [45] 2020	377	Double-blind RCT	IV: 8 mg/kg, 1–2 doses	249 (66%)	56 ± 14.3	128 (34%)	55.6 ± 14.9
Salvarani C et al. [46] 2020	126	Open-label RCT	IV: 8 mg/kg, 1–2 doses	60 (47.6%)	62.1 ± 16.2	66 (52.4%)	61.6 ± 14
Somers EC et al. [47] 2020	154	Retrospective cohort	IV: 8 mg/kg, 1 dose	78 (50.6%)	55 ± 14.9	76 (49.4%)	60 ± 14.5
Stone JH et al. [48] 2020	243	Double-blind RCT	IV: 8 mg/kg, 1 dose	161 (66.2%)	59.2 ± 17.2	82 (33.8%)	56.3 ± 17.1
Wang D et al. [49] 2020	65	Open-label RCT	IV: 400 mg, 1–2 doses	34 (52.3%)	64.1 ± 9.6	31 (47.7%)	62 ± 11.1

Quality of study assessment

Studies with various study designs including a clinical trial, cohort, and case-control were included in this review and assessed accord-

ingly with the appropriate scale or tool. Newcastle Ottawa Scales (NOS) were used to assess the cohort and case-control studies (► **Table 2**). All included studies were rated 'good'. For clinical trial

► **Table 2** Newcastle-Ottawa quality assessment of observational studies.

First author, year	Study design	Selection	Comparability	Outcome	Total score	Result
Campochiaro C et al. [12] 2020	Cohort	****	**	***	9	Good
Canziani LM et al. [13] 2020	Cohort	****	**	***	9	Good
Capra R et al. [14] 2020	Cohort	***	**	**	7	Good
Chilimuri S et al. [15] 2020	Cohort	***	**	***	8	Good
Colaneri M et al. [16] 2020	Cohort	****	**	***	9	Good
De Rossi N et al. [17] 2020	Cohort	****	**	***	9	Good
Eimer J et al. [18] 2020	Cohort	**	**	***	7	Good
Enzmann MO et al. [19] 2020	Cohort	**	**	***	7	Good
Gokhale Y et al. [20] 2020	Cohort	***	**	***	8	Good
Guaraldi et al. [21] 2020	Cohort	****	**	***	9	Good
Gupta S et al. [22] 2020	Cohort	****	**	***	9	Good
Holt GE et al. [24] 2020	Cohort	**	**	***	7	Good
Ip A et al. [25] 2020	Cohort	***	**	***	8	Good
Kewan T et al. [26] 2020	Cohort	***	**	***	8	Good
Klopfenstein T et al. [27] 2020	Cohort	***	**	**	7	Good
Lengnan X et al. [28] 2020	Cohort	***	**	***	8	Good
Masia M et al. [29] 2020	Cohort	***	**	***	8	Good
Martinez-Sanz J et al. [30] 2020	Cohort	****	**	***	9	Good
Menzella F et al. [31] 2020	Cohort	***	**	***	8	Good
Mikulska M et al. [32] 2020	Cohort	****	**	***	9	Good
Moiseev S et al. [33] 2020	Cohort	**	**	***	7	Good
Moreno-Perez O et al. [34] 2020	Cohort	**	**	***	7	Good
Potere N et al. [36] 2020	Cohort	***	**	**	7	Good
Price CC et al. [37] 2020	Cohort	***	**	***	8	Good
Rodriguez-Bano J et al. [38] 2020	Cohort	****	**	***	9	Good
Rojas-Martel G et al. [39] 2020	Case-control	***	**	***	8	Good
Roomi S et al. [40] 2020	Cohort	***	**	***	8	Good
Rossi B et al. [42] 2020	Case-control	***	**	***	8	Good
Roumier M et al. [43] 2020	Cohort	***	**	**	7	Good
Ruiz-Antoran B et al. [44] 2020	Cohort	***	**	***	8	Good
Salama C et al. [45] 2020	Cohort	***	**	***	8	Good
Somers EC et al. [46] 2020	Cohort	***	**	***	8	Good

studies, the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used and all of the included trials showed a low risk of bias (► **Table 3**). In conclusion, all studies were deemed fit to be included in the meta-analysis.

Tocilizumab and outcomes

Tocilizumab efficacy

Our pooled analysis showed that tocilizumab administration was associated with reduction of mortality rate from COVID-19 [OR 0.54 (95% CI 0.42–0.71), $p < 0.00001$, $I^2 = 79\%$, random-effect modelling] (► **Fig. 2a**). However, tocilizumab administration did not alter the severity of COVID-19 [OR 1.05 (95% CI 0.92–1.20), $p = 0.47$, $I^2 = 84\%$, random-effect modelling] (► **Fig. 2b**) and length of hospital stay [Mean Difference 1.77 days (95% CI –0.61–4.14 days), $p = 0.15$, $I^2 = 97\%$, random-effect modelling] (► **Fig. 2c**).

Tocilizumab safety

Our meta-analysis showed that tocilizumab administration was not associated with serious adverse events [OR 0.91 (95% CI 0.71–1.15), $p = 0.42$, $I^2 = 46\%$, random-effect modelling] (► **Fig. 2d**). Subgroup analysis showed that tocilizumab administration was not associated with thromboembolism incident [OR 1.02 (95% CI 0.69–1.50), $p = 0.93$, $I^2 = 12\%$, random-effect modelling], nor secondary infection [OR 0.86 (95% CI 0.63–1.18), $p = 0.36$, $I^2 = 57\%$, random-effect modelling].

Subgroup analysis

Subgroup analysis for clinical trial studies showed a higher OR for mortality rate outcome [OR 0.90 (95% CI 0.64–1.26), $p = 0.54$, $I^2 = 0\%$, random-effect modelling] compared to observational studies [OR 0.50 (95% CI 0.38–0.67), $p < 0.00001$, $I^2 = 80\%$, random-effect modelling].

► **Table 3** Risk of bias assessment for clinical trial studies using RoB-2 tool.

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Hermine O et al. ^[23] 2020	+	+	+	+	+	+
Perrone F et al. ^[35] 2020	+	+	+	+	+	+
Rosas I et al. ^[41] 2020	+	+	+	+	+	+
Stone JH et al. ^[48] 2020	+	+	+	+	+	+
Wang D et al. ^[49] 2020	+	+	+	+	+	+

+ Low risk
 ? Some concerns
 - High risk

► **Table 4** Summary of meta-analysis.

Outcomes	Effect size (95 % Confidence Interval), p-value	Heterogeneity (I^2), p-value	Begg's test	Egger's test	Number of Studies
Mortality	OR = 0.54 [0.42–0.71], <0.00001	79%, <0.00001	0.968	0.284	37
Severe COVID-19	OR = 1.05 [0.92–1.20], 0.47	84%, <0.00001	0.464	0.150	30
Length of hospital stay	Mean Difference = 1.77 [–0.61–4.14], 0.15	97%, <0.00001	0.836	0.213	17
Thrombosis incident	OR = 1.02 [0.69–1.50], 0.93	12%, 0.33	0.916	0.978	9
Secondary infection	OR = 0.86 [0.63–1.18], 0.36	57%, 0.02	0.558	0.451	16

fect modelling]. Subgroup analysis for clinical trial studies showed a lower OR for severe COVID-19 outcome [OR 0.81 (95 % CI 0.53–1.23), $p = 0.32$, $I^2 = 23\%$, random-effect modelling] compared to observational studies [OR 1.11 (95 % CI 0.96–1.28), $p = 0.15$, $I^2 = 86\%$, random-effect modelling]. Subgroup analysis for clinical trial studies showed a lower Mean Difference for length of hospital stay outcome [Mean Difference –1.43 days (95 % CI –5.13–2.26 days), $p = 0.45$, $I^2 = 95\%$, random-effect modelling] compared to observational studies [Mean Difference 2.70 days (95 % CI –0.59–5.99 days), $p = 0.11$, $I^2 = 97\%$, random-effect modelling]. Subgroup analysis for clinical trial studies showed a lower OR for serious adverse events outcome [OR 0.52 (95 % CI 0.29–0.92), $p = 0.02$, $I^2 = 38\%$, random-effect modelling] compared to observational studies [OR 1.04 (95 % CI 0.80–1.35), $p = 0.76$, $I^2 = 41\%$, random-effect modelling].

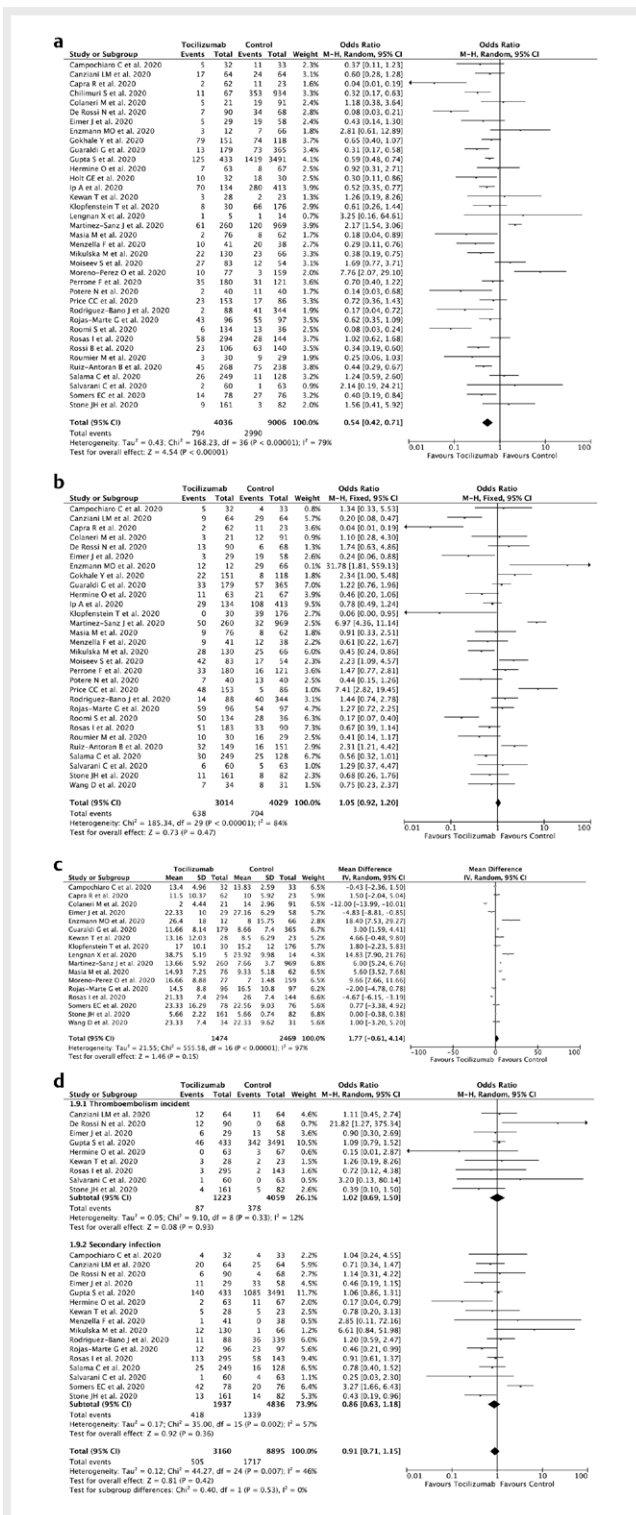
Publication Bias

The funnel-plot analysis showed a qualitatively symmetrical inverted funnel-plot for the association between tocilizumab administration and mortality (► **Fig. 3a**), severe COVID-19 (► **Fig. 3b**), length of hospital stay (► **Fig. 3c**), and serious adverse events

(► **Fig. 3d**). Meanwhile, rank-correlation Begg's test and regression-based Egger's test were not statistically significant for all outcomes, showing no indication of publication bias (► **Table 4**).

Discussion

Based on a contrite meta-analysis of available data, tocilizumab seems to be beneficial only in reducing the mortality rate from COVID-19 infection, but it did not alter the severity outcome of COVID-19 and the duration of hospital stay. However, our subgroup analysis that involves only clinical trial studies showed that tocilizumab failed to reduce the mortality rate from COVID-19 and cannot alter the severity outcome and length of hospital stay in COVID-19 patients. Tocilizumab also appears to be relatively safe in COVID-19 patients, compared with standard of care treatment as it is not associated with serious adverse events such as thromboembolism incident and secondary infection. Several reasons may be proposed to explain the lack of efficacy from tocilizumab administration in COVID-19 patients. First, interleukin-6 and other inflammatory proteins that are observed



► **Fig. 2** Forest plot that demonstrates the association of tocilizumab with the mortality **a**, severe COVID-19 **b**, length of hospital stay **c**, and serious adverse events **d** in COVID-19 infection.

to be present at elevated levels in patients with COVID-19 represent host responses to the infection, similar to the elevations in cytokine

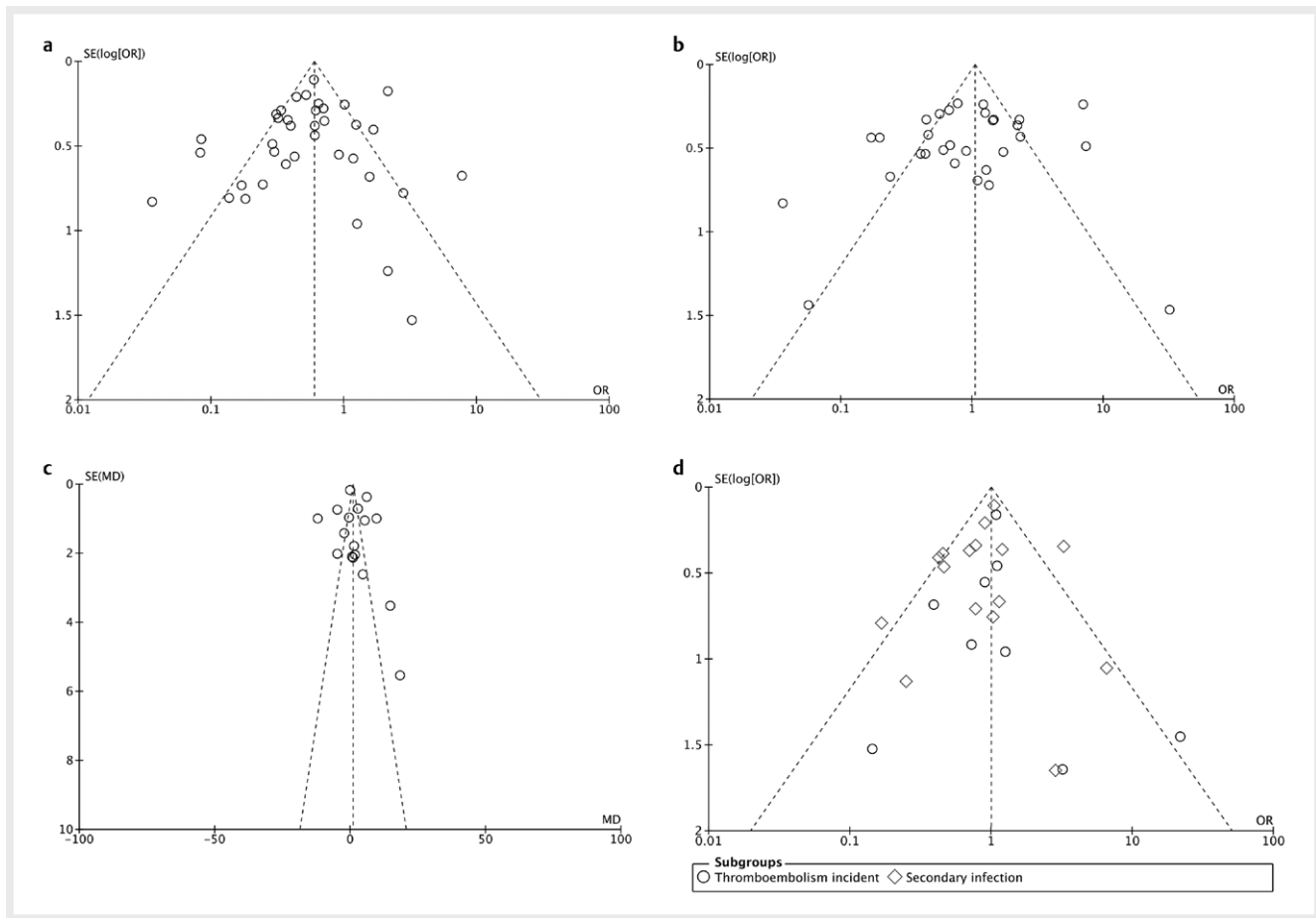
levels seen in patients with endocarditis, sepsis, and other infections, rather than components of a self-amplifying inflammatory loop that would benefit from suppression [49]. Second, severe COVID-19 symptoms may not be caused by cytokine storm syndrome like we used to think before. Recently published systematic review and meta-analysis showed that the descriptor cytokine storm does not appropriately describe the milieu in COVID-19-induced organ dysfunction. The mean IL-6 concentration in COVID-19 patients is relatively low (36.7 pg/mL (95% CI 21.6–62.3 pg/mL), when compared with other conditions which received benefit from tocilizumab administration such as chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (difference 3074 pg/mL, 95% CI 325–26735 pg/mL; $p < 0.0001$), or when compared with other severe conditions such as ARDS unrelated to COVID-19 (mean 460.1 pg/mL, 95% CI 216.3–978.7 pg/mL; difference 423.4 pg/mL, 95% CI 106.9–1438.1 pg/mL; $p < 0.0001$), and sepsis (mean 983.6 pg/mL, 95% CI 550.1–1758.4 pg/mL; difference 947 pg/mL, 95% CI 324–2648 pg/mL; $p < 0.0001$). Even in patients with hypoinflammatory ARDS, the mean IL-6 was still 5 times higher than the concentration in patients with COVID-19 [50]. Alternative mechanisms of COVID-19-induced organ dysfunction may play a part. Therefore, IL-6 may not play such a significant role in the pathogenesis of COVID-19, and inhibiting IL-6 through tocilizumab administration will not significantly alter the outcomes of COVID-19.

Our study was not without limitations. First, there was significant heterogeneity noted in our studies. One plausible rationale for this is the fact that the therapies for COVID-19 are rapidly evolving and hence the SOC differed significantly from one study to another. Moreover, the unaccounted confounders, especially in the included observational studies can also explain the heterogeneity noted in our study. Second, there was a significant variation in the follow-up of patients. Third, the studies did not consistently measure serum IL-6 and hence a correlation between IL-6 level and drug activity could not be established. Last, there was no standardization in the number of medication dosage, route of administration, and timing of administration. This can also account for the difference in outcomes noted across studies.

Despite the limitations, our study has significant strengths. First, we included a total of 38 studies with over 13 000 COVID-19 patients. This is by far the largest analysis comparing the addition of tocilizumab to the standard of care treatment. Moreover, we also included 5 recently published clinical trial studies in our analysis and performed a subgroup analysis that only consist of clinical trial studies to give more complete data regarding the benefit of tocilizumab administration in COVID-19 patients.

Conclusion

In conclusion, tocilizumab is not effective and failed to improve the outcome of COVID-19 patients compared with standard of care treatment, although it is relatively safe and did not cause significant serious adverse events. Our study does not support the routine use of tocilizumab for COVID-19 patients. Physicians may hence consider giving other potential agents for the treatment of COVID-19 patients, in addition to standard of care treatment.



► **Fig. 3** Funnel plot analysis for mortality **a**, severe COVID-19 **b**, length of hospital stay **c**, and serious adverse events **d** outcome.

Future studies should focus more on other potential therapies besides tocilizumab.

Conflict of Interest

The authors declare that they have no conflict of interest.

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