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ORIGINAL RESEARCH

Efficacy and Safety of Tocilizumab Treatment COVID-19 Patients: A Case-Control Study and Meta-Analysis

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ABSTRACT

Introduction: As the pandemic progresses, the pathophysiology of COVID-19 is becoming more apparent, and the potential for tocilizumab is increasing. However, the clinical efficacy and safety of tocilizumab in the treatment of COVID-19 patients remain unclear.

Methods: To assess the efficacy and safety of tocilizumab treatment in COVID-19 patients, we performed a retrospective case-control study. The study was conducted, including 95 patients treated with tocilizumab plus standard treatment and matched controls with 95 patients treated with standard treatment therapy by propensity score from February to April 2020. We searched some databases using the search terms for studies published from January 1, 2020, to June 1, 2021.

Results: Our case-control study found a lower mortality rate in the tocilizumab treatment group than in the standard treatment group (9.47% versus 16.84%, $P = 0.134$), but the results were not statistically significant. We also found that the mortality rate in tocilizumab treatment groups was significantly lower than in the standard treatment group in the stratified ICU analysis (OR 0.52, 95% CI 0.44–0.61, $P = 0.048$ and OR 0.31, 95% CI 0.10–0.99, $P = 0.044$). We selected 49 studies (including 6568 cases and 11,660 controls) that met the inclusion criteria in the meta-analysis. In the overall analysis, we performed a meta-analysis that showed significantly decreased mortality after patients received tocilizumab (OR 0.81, 95% CI 0.69–0.95, $P = 0.008$). We also revealed significant associations within some subgroups. The sequential trial analysis showed a true-positive result. No significant associations were observed between tocilizumab and elevated secondary infection risk, discharge, adverse events, and mechanical ventilation in the overall analysis.

Conclusion: Tocilizumab significantly decreased mortality in COVID-19 patients with no increased discharge, secondary infection risk, adverse events, and mechanical ventilation in a meta-analysis. Our data suggest that clinicians should pay attention to tocilizumab

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therapy as an effective and safe treatment for COVID-19 patients.

Keywords: COVID-19; Efficacy; Meta-analysis; Safety; Tocilizumab

Key Summary Points

Why carry out this study?

As the pandemic progresses, the pathophysiology of COVID-19 is becoming more apparent, and the potential for tocilizumab is increasing.

However, the clinical efficacy and safety of tocilizumab in the treatment of COVID-19 patients remain unclear.

What was learned from the study?

The study was conducted, including 95 patients treated with tocilizumab plus standard treatment and matched controls with 95 patients treated with standard treatment therapy by propensity score from February to April 2020. We searched some databases using the search terms for studies published from January 1, 2020, to June 1, 2021.

Our case-control study found a lower mortality rate in the tocilizumab treatment group than in the standard treatment group (9.47% versus 16.84%, $P = 0.134$), but the results were not statistically significant.

We selected 49 studies (including 6568 cases and 11,660 controls) that met the inclusion criteria in the meta-analysis. In the overall analysis, we performed a meta-analysis that showed significantly decreased mortality after patients received tocilizumab (OR 0.81, 95% CI 0.69–0.95, $P = 0.008$). We also revealed significant associations within some subgroups. The sequential trial analysis showed a true-positive result.

No significant associations were observed between tocilizumab and elevated secondary infection risk, discharge, adverse events, and mechanical ventilation in the overall analysis.

Our data suggests that clinicians should pay attention to tocilizumab therapy as an effective and safe treatment for COVID-19 patients.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14785560.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) may be associated with a dysregulated immune response and hyperinflammation, which can lead to or exacerbate acute respiratory distress syndrome (ARDS) and multiple organ failure [1–3]. As the pandemic progressed, there was an unfounded enthusiasm surrounding the use of tocilizumab. However, the clinical efficacy and safety of tocilizumab treatment of COVID-19 patients have been controversial.

Epidemiologic studies and earlier recent retrospective studies have demonstrated that patients infected with SARS-CoV-2 exhibited high plasma levels of circulating interleukin 6 (IL-6), IL-1Ra, IL-1β, IL-10, IL-17, IL-18, interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), C-reactive protein (CRP), granulocyte colony-stimulating factor (G-CSF), and macrophage colony-stimulating factor (M-CSF), suggesting a rapid activation of the innate immune response [4–11]. Several studies have shown that plasma IL-6 levels are elevated in COVID-19 patients in the intensive care unit (ICU), and they appear to be positively correlated with mortality [12–17]. In an observational study, tocilizumab, an anti-IL-6 receptor monoclonal antibody, has

been approved for the treatment of various inflammatory diseases and appeared to improve outcomes in COVID-19 patients in several countries [2]. Some recent studies have suggested that tocilizumab may be intensively related to a lower risk of intubation or death in severe and critically ill patients with COVID-19 pneumonia. Since the clinical severity of COVID-19 patients appears to be associated with a cytokines storm and an overproduction of soluble inflammatory mediators, tocilizumab is currently under investigation. Still, the results were inconsistent [18–25].

Amid the shortage of robust evidence regarding the use of tocilizumab in COVID-19 patients, we aimed to evaluate the efficacy and safety of tocilizumab treatment for COVID-19 patients in a case-control study and meta-analysis, which will help inform clinical management of COVID-19 patients.

METHODS

Patients

The retrospective case-control study was performed between February to April 2020 and was conducted in Wuhan, China. All participants were admitted to the Huoshenshan Hospital and were confirmed COVID-19 cases according to quantitative real-time polymerase chain reaction (qRT-PCR). We received approval from the ethics committee of Huoshenshan Hospital and conducted the study following the tenets of the Declaration of Helsinki and its amendments.

All participants voluntarily provided written informed consent for sample collection and their subsequent analysis. Intravenous tocilizumab was administered at a dose of 8 mg/kg body weight (up to 800 mg), up to twice, 12 h apart. Matched control patients were retrospectively identified within the electronic information database of Huoshenshan Hospital. The primary endpoint was 60 days' mortality, improvement, and discharge, and critical secondary endpoints were hospital stay, secondary infection, and mechanical ventilation. All participants received standard treatment, including hydroxychloroquine and antiviral therapy, including lopinavir/ritonavir, antimicrobial agents, and corticosteroids.

Study Selection

We searched PubMed, Web of Science, and MedRxiv using the search terms severe acute respiratory syndrome coronavirus 2, COVID-19, SARS-CoV-2, 2019-nCoV interleukin-6 inhibitors, tocilizumab, and coronavirus for studies published from January 1, 2020, to June 1, 2021 (Fig. 1).

Data Extraction and Verification

The inclusion criteria of the meta-analysis were: (1) research focus on tocilizumab and COVID-19; (2) studies on humans; (3) the number of cases and controls; (4) papers with full text available. The exclusion criteria of the meta-analysis were: (1) review, (2) case report; (3) animal study; (4) incomplete data and unclear outcome effects; (5) repeat of the report.

Specific information about the included studies is listed in Table 3, including (1) the author's last name and country, (2) publication and online time, (3) 3thnicity or race, (4) severity of disease, (5) dose of tocilizumab, (6) study design, (7) journal, (8) case size, (9) number of cases and controls, (10) number of discharges in cases and controls, (11) number of deaths in cases and controls, (12) number of secondary infections in cases and controls, and (13) number of mechanical ventilations in cases and controls. First, three authors (Weijun Jiang, Weiwei Li, and Ying Han) independently screened the studies that met inclusion and exclusion criteria and extracted all data. If two or three of the three agreed, the study was included in the meta-analysis. Next, each of the three authors pulled the data, while the other two cross-checked the data. Disagreements were resolved through review and discussion.

Statistical Analysis

Categorical variables were summarized as counts and percentages (%). For the continuous

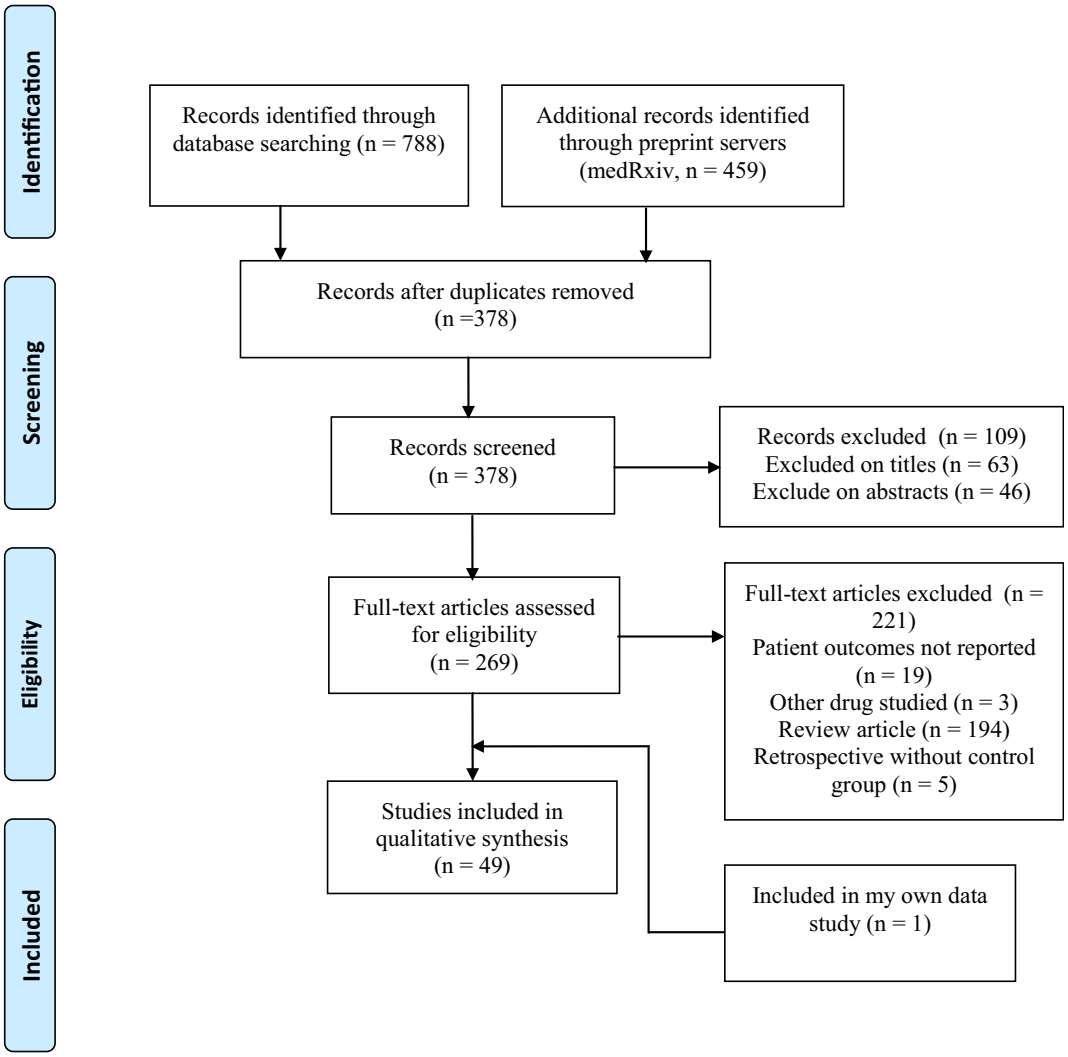

Fig. 1 Flow diagram of the study selection process

measurement, we used the Kolmogorov-Smirnov test to evaluate the distribution type. We also used mean ± standard deviation (SD) to express the customarily distributed data and otherwise used median and interquartile ranges (IQR) to describe the continuous variables. Continuous variables of different groups of data were compared using independent sample double-tailed *t*-test and Mann-Whitney test. Chi-square and Fisher's exact test was used to compare the frequencies of categorical variables. We used a 1:1 propensity score matching (PSM) analysis to reach patients who underwent tocilizumab with those who did not. We used SPSS (v.20.0; SPSS Inc., Chicago, IL, USA) to perform statistical analysis.

We used the DerSimonian and Laird method data in the random-effects model and used the Mantel-Haenszel method in the fixed-effects model. *Z*-test was used to determine the pooled odds ratio (OR) statistical significance, with *P* values < 0.05 being considered statistically significant. When the *P* value for heterogeneity was ≤ 0.10 or $I^2 \geq 50\%$, there was heterogeneity between comparative studies. Conversely, if $I^2 < 50\%$ and the *P* value for heterogeneity was > 0.10, this indicated that there was no heterogeneity between comparative studies. We used funnel plots and Egger's linear regression

test to evaluate publication bias. We used STATA version 11.0 (Stata Corp., College Station, TX, USA) to carry statistical analyses. Similarly, we used novel statistical analysis software, known as trial sequence analysis (TSA), to examine the reliability and conclusiveness of the existing evidence.

RESULTS

Basic Characteristics and Demographics

We analyzed a total of 190 participants who were determined to have COVID-19 in the clinical study. Ninety-five patients received standard treatment alone, and 95 received treatment with tocilizumab in addition to standard treatment. Of all patients, 63 (66.32%) cases and 56 (58.95%) controls had coexisting conditions, including hypertension, hyperlipidemia, hyperuricemia, diabetes, chronic cardiac disease, cancer, etc.

Interestingly, we found that both hospital stay and secondary infection risk in the case group were significantly higher than in the control group ($P < 0.001$). However, the rate of mortality in the tocilizumab treatment group was lower than that in the standard treatment group, but no statistically significant difference was found. We also found that the mortality rate in tocilizumab treatment groups was significantly lower than in the standard treatment group in the stratified ICU analysis (OR 0.52, 95% CI 0.44–0.61, $P = 0.048$ and OR 0.31, 95% CI 0.10–0.99, $P = 0.044$). In the subgroup without secondary infection, the tocilizumab treatment group's mortality rate was significantly lower than that in the standard treatment group (OR 0.35, 95% CI 0.12–1.00, $P = 0.040$).

However, no significant differences in age, disease severity, rate of cure, and basic disease between the tocilizumab group and standard treatment group were found. Our results showed that tocilizumab treatment did not significantly reduce the rate of COVID-19 mortality and the increased secondary infection risk. Clinicians are advised to use this therapy with caution. The clinical characteristics and demographic data of all participants are shown in Tables 1 and 2.

Study Selection and Characteristics

The combination of search terms produced all the related articles. A preliminary review of titles and abstracts found 157 articles that required a full manuscript review. According to the inclusion criteria, we selected 49 papers with potential relevance through literature retrieval and screening (Fig. 1). In our meta-analysis, a total of 49 studies, including 6568 cases and 11,660 controls, met the inclusion criteria. Table 3 summarizes the characteristics of the selected studies.

Mortality

In the overall analysis, we performed a meta-analysis of 49 studies (6568 tolcizumab plus standard treatment COVID-19 patients and 11,660 standard treatment COVID-19 patients) that reported that significantly decreased mortality after patients received tocilizumab (OR 0.81, 95% CI 0.69–0.95, $P = 0.008$). We also revealed significant associations within the mix of race subgroup (OR 0.86, 95% CI 0.79–0.94, $P = 0.001$), Caucasian subgroup (OR 0.64, 95% CI 0.45–0.89, $P = 0.008$), severe subgroup (OR 0.65, 95% CI 0.52–0.82, $P = 0.001$), critical subgroup (OR 0.77, 95% CI 0.66–0.89, $P < 0.001$), dose of 800 mg subgroup (OR 0.81, 95% CI 0.70–0.94, $P = 0.006$), no specific dose subgroup (OR 0.74, 95% CI 0.62–0.89, $P = 0.001$), case-control study subgroup (OR 0.72, 95% CI 0.56–0.91, $P = 0.006$), journal of published subgroup (OR 0.78, 95% CI 0.64–0.94, $P = 0.011$), and case size of < 100 subgroup (OR 0.77, 95% CI 0.61–0.98, $P = 0.030$), but not the remaining subgroups. In addition, there was an edge effect in dose of the ≤ 400 mg subgroup (OR 0.66, 95% CI 0.42–1.03, $P = 0.067$) and the multicenter case-control subgroup (OR 0.69, 95% CI 0.45–1.05, $P = 0.081$). For mortality, the number of patients did not reach the optimal information size. However, the blue cumulative Z curve crossed both the traditional boundary and the

Table 1 Clinical characteristics of all COVID-19 patients

Characteristics	All (N = 190)	Case (N = 95)	Control (N = 95)	P value
Age (mean ± SD) years	67.27 ± 34.51	68.55 ± 11.50	66 ± 13.64	0.183
Hospital stay (mean ± SD) days	24.13 ± 12.67	12.75 ± 27.68	11.55 ± 20.58	**0.000**
ICU no. (%)				0.163
No	139 (71.16%)	66 (69.47%)	73 (76.84%)	
Yes	51 (36.84%)	29 (30.53%)	22 (23.16%)	
Gender group no. (%)				0.765
Male	120 (61.16%)	59 (62.11%)	61 (64.21%)	
Female	70 (36.84%)	36 (37.89%)	34 (35.79%)	
Basic disease no. (%)				0.296
No	71 (37.37%)	32 (33.68%)	39 (41.05%)	
Yes	119 (62.63%)	63 (66.32%)	56 (58.95%)	
Outcome no. (%)				0.134
Cure	165 (86.84%)	86 (90.53%)	79 (83.16%)	
Death	25 (13.16%)	9 (9.47%)	16 (16.84%)	
Disease severity no. (%)				0.789
Moderate	25 (13.16%)	13 (13.68%)	12 (12.63%)	
Severe	108 (56.84%)	52 (54.74%)	56 (58.95%)	
Critical	57 (30.00%)	30 (31.58%)	27 (28.42%)	
Secondary infection no. (%)				
No	172 (90.53%)	79 (83.16%)	93 (97.89%)	**0.000**
Yes	18 (9.47%)	16 (16.84%)	2 (2.11%)	

Bold values indicate statistically significant results
SD, standard deviation; ICU, intensive care unit

TSA boundary showing that no more tests are needed to reach a positive conclusion in advance. Specific data are summarized in Figs. 2, 3 and Table 4.

Secondary Infection Risk

No significant associations were observed between tocilizumab and an elevated secondary infection risk in the overall analysis. However, we found significantly increased secondary infection risk after COVID-19 patients received tocilizumab in the dose of 400–800 mg subgroup (OR 1.43, 95% CI 1.06–1.92, P = 0.018), dose of ≤ 400 mg subgroup (OR 1.92, 95% CI 1.40–2.63, $P < 0.001$), retrospective observational study subgroup (OR 2.00, 95% CI 1.15–3.47, P = 0.013), and case-control study subgroup (OR 1.98, 95% CI 1.14–3.45, P = 0.016). In addition, there was an edge effect in the RCT subgroup (OR 0.79, 95% CI 0.61–1.03, P = 0.079). Figure 4 and Table 4

Table 2 Outcome of tocilizumab treatment COVID-19 patients in stratified analysis

	Outcome	Tocilizumab		adjOR	95% CIs	*P*
		Case (*N* = 95)	Control (*N* = 95)			
Disease						
No	Cure	29	35	0.91	0.19–4.38	0.901
	Death	3	4			
Yes	Cure	57	44	0.39	0.13–1.11	0.069
	Death	6	12			
Severity						
Moderate	Cure	13	12			-
	Death	0	0			
Severe	Cure	52	54			0.103
	Death	0	2			
Critical	Cure	21	13	0.40	0.13–1.18	0.092
	Death	9	14			
ICU						
No	Cure	66	70	0.52	0.44–0.61	**0.048**
	Death	0	3			
Yes	Cure	20	9	0.31	0.10–0.99	**0.044**
	Death	9	13			
Gender						
Female	Cure	32	30	0.94	0.22–4.09	0.932
	Death	4	4			
Male	Cure	54	49	0.38	0.12–1.12	0.075
	Death	5	12			
Secondary infection						
No	Cure	74	78	0.35	0.12–1.00	**0.040**
	Death	5	15			
Yes	Cure	12	1	0.33	0.02–6.65	0.478
	Death	4	1			

Bold values indicate statistically significant results

ICU, intensive care unit; P_h, *P* value of heterogeneity, *P* value of *Q*-test for the heterogeneity test; OR, odds ratio; CI, confidence interval

Table 3 Characteristics of all studies describing tocilizumab treatment COVID-19 patients in the meta-analysis

Author (country)	Time	Race	Disease severity	Dose	Study type	Journal	Case size	Case/control	Discharge case/control	Mortality case/control	Adverses events case/control	Secondary infection case/control	MV case/control
Roumier (France) [31]	20200420	Caucasian	Severe	8 mg/kg	Retrospective Observational study	Unpublished	< 100	30/29		3/9			10/16
Colaneri (Italy) [32]	20200509	Caucasian	Critical	8 mg/kg	Case-control study	Published	< 100	21/91		5/19	0/0		
Capra (Italy) [14]	20200513	Caucasian	Severe	≤ 400 mg	Retrospective observational study	Published	< 100	62/23	57/10	2/11		0/0	5/4
Wadud (USA) [33]	20200513	Mix	Severe	≤ 400 mg	Case-control study	Unpublished	< 100	44/50		17/26			
Ramaswamy (USA) [34]	20200514	Mix	Mix	8 mg/kg	Case-control study	Unpublished	< 100	21/65		3/8			13/10
Kimmig (USA) [24]	20200515	Mix	Critical	≤ 400 mg	Retrospective observational study	Published	< 100	54/57	18/34	19/11		29/16	
Quartuccio (Italy) [26]	20200515	Caucasian	Severe	≤ 400 mg	Case-control study	Published	< 100	42/69	30/21	7/0		17/0	26/0
Ip (USA) [35]	20200521	Mix	Critical	≤ 400 mg	Multicenter cohort study	Published	> 100	134/413		62/231		18/44	
Campochiaro (Italy) [6]	20200522	Caucasian	Severe	≤ 400 mg	Cohort study	Published	< 100	32/33	20/16	5/11	8/9	4/4	4/2
Moreno-Garcia (Spain) [36]	20200605	Caucasian	Mix	NA	Cohort study	Unpublished	< 100	77/94	65/71	8/17			3/14
Martinez-Sanz (Spain) [37]	20200608	Caucasian	Mix	400–800 mg	Multicenter cohort study	Unpublished	> 100	260/969		61/120			
Kewan (USA) [23]	20200620	Mix	Severe	8 mg/kg	Cohort study	Published	< 100	28/23	11/13	3/2	5/5	5/5	21/11
Guaraldi (Italy) [21]	20200624	Caucasian	Severe	8 mg/kg	Multicenter cohort study	Published	> 100	179/365		13/73	1/1	24/14	33/57

Table 3 continued

Author (country)	Time	Race	Disease severity	Dose	Study type	Journal	Case size	Case/control	Discharge case/control	Mortality case/control	Adverses events case/control	Secondary infection case/control	MV case/control
Canziani (Italy) [13]	20200708	Caucasian	Mix	8 mg/kg	Case-control study	Published	< 100	64/64		17/24		20/25	9/29
Potere (Italy) [25]	20200709	Caucasian	Severe	≤ 400 mg	Case-control study	Published	< 100	40/40		2/11	0/0	1/3	
Somers (USA) [28]	20200711	Mix	Severe	8 mg/kg	Cohort study	Published	< 100	78/76	44/30	7/20		42/20	31/43
Carvalho (Brazil) [38]	20200715	Caucasian	Critical	≤ 400 mg	Case-control study	Unpublished	< 100	29/24		5/4		11/4	15/7
Gokhale (India) [39]	20200716	Caucasian	Severe	≤ 400 mg	Cohort study	Published	< 100	70/91	26/30	33/61			19/9
De Rossi (Italy) [15]	20200717	Caucasian	Severe	≤ 400 mg	Cohort study	Published	< 100	90/68		7/34	0/0	6/4	13/6
Rojas-Marte (USA) [19]	20200801	Mix	Severe	NA	Case-control study	Published	< 100	96/97		43/55		16/26	1/0
Eimer (Sweden) [40]	20200803	Caucasian	Severe	8 mg/kg	Cohort study	Published	< 100	51/80		10/26	0/0	9/20	42/74
Patel (USA) [41]	20200803	Mix	Mix	NA	Cohort study	Published	< 100	42/41	23/11	11/12			
Potere (Italy) [18]	20200805	Caucasian	Moderate	≤ 400 mg	Case-control study	Published	< 100	10/10		0/0	0/0	0/0	0/1
Pettit (USA) [42]	20200813	Mix	NA	≤ 400 mg	Retrospective observational study	Published	< 100	74/74		29/17		17/6	25/23
Rodríguez-Bano (Spain) [27]	20200826	Caucasian	NA	400–800 mg	Multicenter cohort study	Published	< 100	88/339		2/41		11/36	
Roomi (USA [43])	20200901	Mix	NA	NA	Cohort study	Published	< 100	32/144	25/38	6/13			47/31
Albertini (France) [4]	20200910	Caucasian	Severe	8 mg/kg	Cohort study	Published	< 100	22/22	10/10	3/2	0/0	0/0	2/6

Table 3 continued

Author (country)	Time	Race	Disease severity	Dose	Study type	Journal	Case size	Case/control	Discharge case/control	Mortality case/control	Adverses events case/control	Secondary infection case/control	MV case/control
Galvan-Roman (Spain) [16]	20200930	Caucasian	Severe	8 mg/kg	Cohort study	Published	< 100	58/88		14/16		3/7	
Zheng (China) [44]	20201008	Asian	Mix	400–800 mg	Retrospective Observational study	Published	< 100	92/89	83/88	9/1	0/0	0/0	
Holt (USA) [45]	20201013	Mix	NA	≤ 400 mg	Cohort study	Published	< 100	32/31		10/9			
Guisado-Vasco (Spain) [46]	20201015	Caucasian	Severe	8 mg/kg	Cohort study	Published	> 100	132/475		44/97			
Klopfenstein (France) [47]	20201016	Caucasian	Severe	8 mg/kg	Case-control study	Published	< 100	30/176	16/82	8/66			0/39
Rossi (France) [48]	20201017	Caucasian	Severe	8 mg/kg	Case-control study	Published	> 100	106/140		23/63			
Gupta (USA) [22]	20201020	Mix	Critical	NA	Multicenter cohort study	Published	> 100	433/3491		125/1419		140/1085	
Hermine (France) [8]	20201020	Caucasian	Mix	8 mg/kg	RCT	Published	< 100	63/67		7/8	28/36	2/14	5/14
Salvarani (Italy) [11]	20201020	Caucasian	NA	8 mg/kg	RCT	Published	< 100	60/66	54/58	2/1		1/4	
Stone (USA) [12]	20201021	Mix	Mix	8 mg/kg	RCT	Published	> 100	161/82	147/72	9/3	2/2	13/14	11/8
Tsai (USA) [20]	20201105	Mix	Severe	400–800 mg	Cohort study	Published	< 100	66/66		18/18		4/4	
Hill (USA) [17]	20201117	Mix	Severe	≤ 400 mg	Cohort study	Published	< 100	43/45	26/27	9/15		4/2	9/18
Ruiz-Antora'n (Spain) [29]	20201206	Caucasian	Severe	400–800 mg	Multicenter cohort study	Published	> 100	268/238		45/75		124/72	
Tian (China) [30]	20201209	Asian	Severe	400–800 mg	Multicenter cohort study	Published	< 100	65/130		14/42			18/41
Rosas (USA) [49]	20201212	Mix	Severe	8 mg/kg	RCT	Unpublished	> 100	294/144		58/28		113/58	

Table 3 continued

Author (country)	Time	Race	Disease severity	Dose	Study type	Journal	Case size	Case/control	Discharge case/control	Mortality case/control	Adverses events case/control	Secondary infection case/control	MV case/control
Salama (USA) [1]	20201217	Mix	NA	8 mg/kg	RCT	Published	> 100	249/128		26/11	38/25	25/16	
Veiga (Brazil) [50]	20210120	Mix	Mix	8 mg/kg	RCT	Published	< 100	65/64	35/31	14/6	29/21	10/10	11/10
Kumar (India)[51]	20210316	Caucasian	Mix	≤ 400 mg	RCT	Published	< 100	20/10	16/6	0/3	18/4	1/3	
Peter W Horby (UK) [52]	20210211	Mix	Severe	400–800 mg	RCT	Unpublished	> 100	2022/2094	1093/999	596/694			
Arvinder (India) [53]	20210504	Caucasian	Mix	8 mg/kg	RCT	Published	< 100	91/88		11/15	30/22	5/5	14/13
Gordon (UK) [54]	20210225	Mix	Critical	8 mg/kg	RCT	Published	> 100	353/402	163/218	87/134	9/11	1/0	104/121
Jiang (China)	20210701	Asian	Mix	8 mg/kg	Case-control study	Unpublished	< 100	95/95	86/79	9/16		16/2	

The mix of severity, symptoms of the disease include moderate, severe, and critical; mix of race, including Asian, Caucasian, African, and so on; ICU, intensive care unit; NA, no appearance

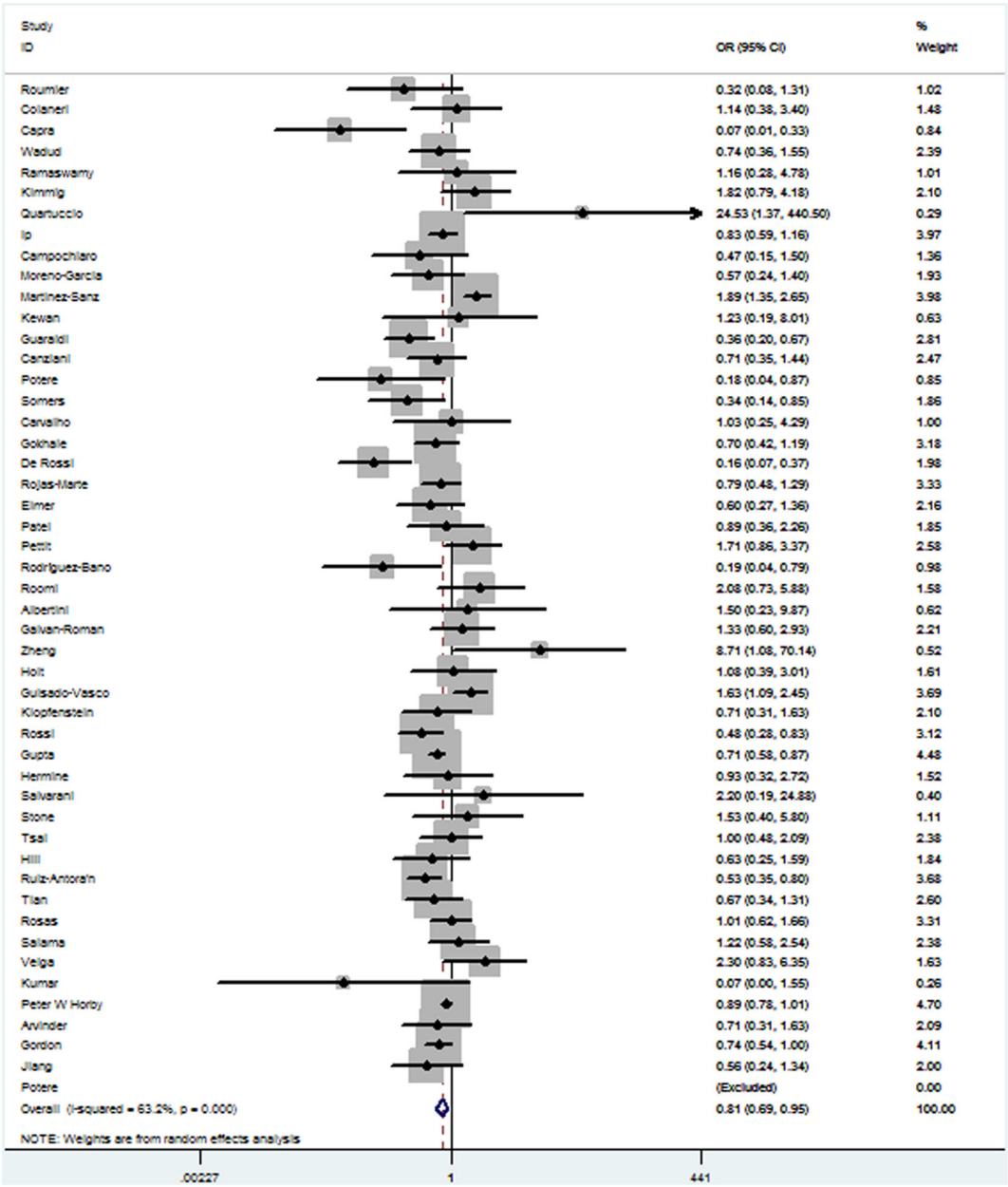

Fig. 2 Forest plot of mortality and tocilizumab treatment COVID-19 patients

summarize the data associated with tocilizumab and secondary infection risk.

Discharge

We also failed to find significantly increased discharge after COVID-19 patients received tocilizumab in the overall analysis (OR 1.13, 95% CI 0.98–1.32, $P = 0.100$). We revealed significantly increased discharge in tocilizumab treatment COVID-19 patients in the cohort study subgroup (OR 1.32, 95% CI 1.06–1.65, $P = 0.014$). We revealed significantly decreased discharge in tocilizumab treatment COVID-19 patients in the dose of 400–800 mg subgroup (OR 0.88, 95% CI 0.80–0.98, $P = 0.018$). However, we also found an edge effect in Caucasian subgroup analysis (OR 1.24, 95% CI 1.00–1.55,

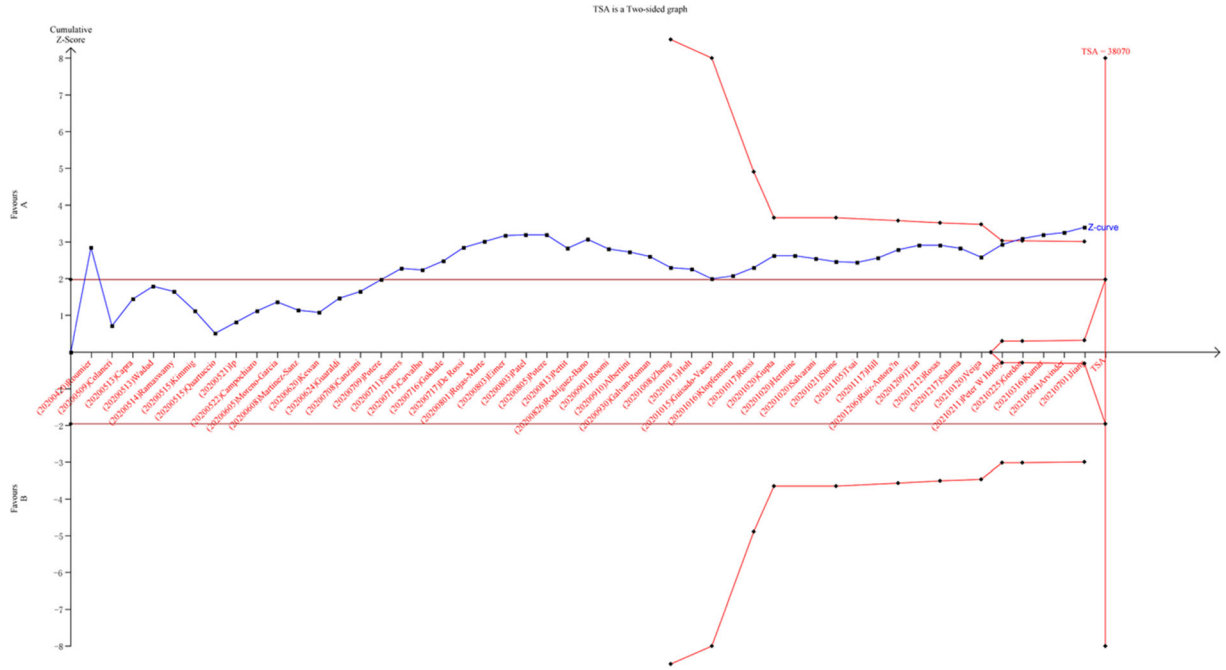

Fig. 3 Trial sequential analysis of mortality and tocilizumab treatment COVID-19 patients

$P = 0.051$), the no specific dose subgroup (OR 1.82, 95% CI 0.95–3.47, $P = 0.069$), case-control study subgroup (OR 1.37, 95% CI 1.00–1.89, $P = 0.051$), journal of unpublished subgroup (OR 0.91, 95% CI 0.0.82–1.00, $P = 0.055$), journal of published subgroup (OR 1.18, 95% CI 0.99–1.41, $P = 0.060$), and case size of < 100 subgroup (OR 1.19, 95% CI 0.99–1.44, $P = 0.060$). Specific data are summarized in Fig. 4 and Table 5.

Adverse Events and Mechanical Ventilation

No significant association was found between tocilizumab and adverse events and mechanical ventilation in COVID-19 patients in the overall analysis. We found significantly increased adverse events risk in tocilizumab treatment COVID-19 patients in the RCT subgroup (OR 1.32, 95% CI 1.00–1.74, $P = 0.049$). Subgroup analyses were performed to clarify the effects of potential ethnicity, disease severity, drug dose, study type, and case size and whether the article is officially published. There was no significant association between tocilizumab treatment and estimated risk of adverse events and mechanical ventilation, as shown in Fig. 4 and Table 5.

Publication Bias and Sensitivity Analysis

We performed Egger's test and Begg's funnel plot to assess the publication bias of the meta-analysis. We also conducted sensitivity analysis by omitting one study at a time when calculating summary results. Although the size of the sample of cases in all included studies varied, corresponding pooled ORs and 95%CIs did not qualitatively change with or without studies on small pieces.

DISCUSSION

The World Health Organization (WHO) announced COVID-19 may progress to a pandemic associated with substantial morbidity and mortality and is a public health emergency of globalized concern as of 1 February 2020 [1, 3, 12]. At the time of this writing, over 174 million laboratory-diagnosed COVID-19 patients had been reported spanning 212

Table 4 The mortality and risk of infection of tocilizumab treatment COVID-19 patients

Mortality	OR (95% CI)	*P*	P_h	I^2%	P_b	Secondary infection risk	OR (95% CI)	*P*	P_h	I^2%	P_b
Total	**0.81 (0.69–0.95)**	**0.008**	< 0.001	63.2	0.767	*Total*	1.16 (0.94–1.45)	0.170	0.001	48.4	0.880
Race						*Race*					
MIX	**0.86 (0.79–0.94)**	**0.001**	0.155	24.5		Caucasian	1.14 (0.76–1.70)	0.530	0.006	51.5	
Asian	0.97 (0.34–2.76)	0.952	0.048	67.2		MIX	1.07 (0.92–1.23)	0.378	0.102	34.1	
Caucasian	**0.64 (0.45–0.89)**	**0.008**	< 0.001	75.1		Asian	**5.50 (1.59–19.09)**	**0.007**	0.188	42.3	
Severity						*Severity*					
MIX	1.03 (0.68–1.56)	0.886	0.009	56.3		Severe	1.23 (0.87–1.74)	0.248	0.008	51.9	
Severe	**0.65 (0.52–0.82)**	**< 0.001**	< 0.001	67.4		Critical	1.12 (0.93–1.34)	0.226	0.319	15.0	
Critical	**0.77 (0.66–0.89)**	**0.001**	0.346	10.9		MIX	0.97 (0.48–1.97)	0.934	0.010	62.3	
NA	1.11 (0.77–1.60)	0.586	0.103	45.5		Moderate	1.00 (0.05–18.30)	1.000	-	-	
						NA	1.13 (0.75–1.72)	0.559	0.115	49.5	
Dose						*Dose*					
8 mg/kg	**0.81 (0.70–0.94)**	**0.006**	0.100	45.8		8 mg/kg	0.98 (0.67–1.44)	0.932	0.001	60.9	
400–800 mg	0.90 (0.58–1.40)	0.633	< 0.001	82.8		400–800 mg	**1.43 (1.06–1.92)**	**0.018**	0.561	0.0	
≤ 400 mg	*0.66 (0.42–1.03)*	*0.067*	< 0.001	71.4		≤ 400 mg	**1.92 (1.40–2.63)**	**< 0.001**	0.228	21.9	

Table 4 continued

Mortality	OR (95% CI)	*P*	P_h	I^2%	P_b	Secondary infection risk	OR (95% CI)	*P*	P_h	I^2%	P_b
NA	**0.74 (0.62–0.89)**	**0.001**	0.346	10.5		NA	1.00 (0.82–1.21)	0.973	0.157	50.0	
Study type						*Study type*					
Retrospective observational study	0.89 (0.27–2.95)	0.845	< 0.001	81.5		Retrospective observational study	**2.00 (1.15–3.47)**	**0.013**	0.545	0.0	
Case-control study	**0.72 (0.56–0.91)**	**0.006**	0.247	20.7		Case-control	**1.98 (1.14–3.45)**	**0.016**	0.001	73.1	
Multicenter cohort study	*0.69 (0.45–1.05)*	*0.081*	< 0.001	85.3		Cohort study	1.22 (0.85–1.77)	0.285	0.663	0.0	
Cohort study	0.78 (0.54–1.11)	0.167	0.001	62.0		Multicenter cohort	1.67 (0.63–4.41)	0.302	0.010	69.8	
RCT	**0.89 (0.80–0.99)**	**0.032**	0.372	7.6		RCT	*0.79 (0.61–1.03)*	*0.079*	0.173	30.6	
Journal						*Journal*					
Unpublished	0.93 (0.66–1.29)	0.642	0.004	64.7		Unpublished	2.21 (0.64–7.64)	0.212	0.013	77.1	
Published	**0.78 (0.64–0.94)**	**0.011**	< 0.001	60.9		Published	1.12 (0.89–1.41)	0.322	0.003	45.7	
Case size						*Case size*					
< 100	**0.77 (0.61–0.98)**	**0.030**	< 0.001	51.3		< 100	1.18 (0.86–1.62)	0.314	0.015	41.4	
> 100	0.86 (0.69–1.08)	0.200	< 0.001	79.8		> 100	1.15 (0.84–1.56)	0.384	0.003	67.3	

Bold values indicate statistically significant results

The mix of severity, symptoms of the disease include moderate, severe and critical; mix of race, including Asian, Caucasian, African, and so on; ICU, intensive care unit; NA, no appearance; OR, odds ratio; CI, confidence interval; P_h, *P* value of heterogeneity, *P* value of *Q*-test for the heterogeneity test; I^2, 0–25, no heterogeneity; 25–50, modest heterogeneity; 50, high heterogeneity

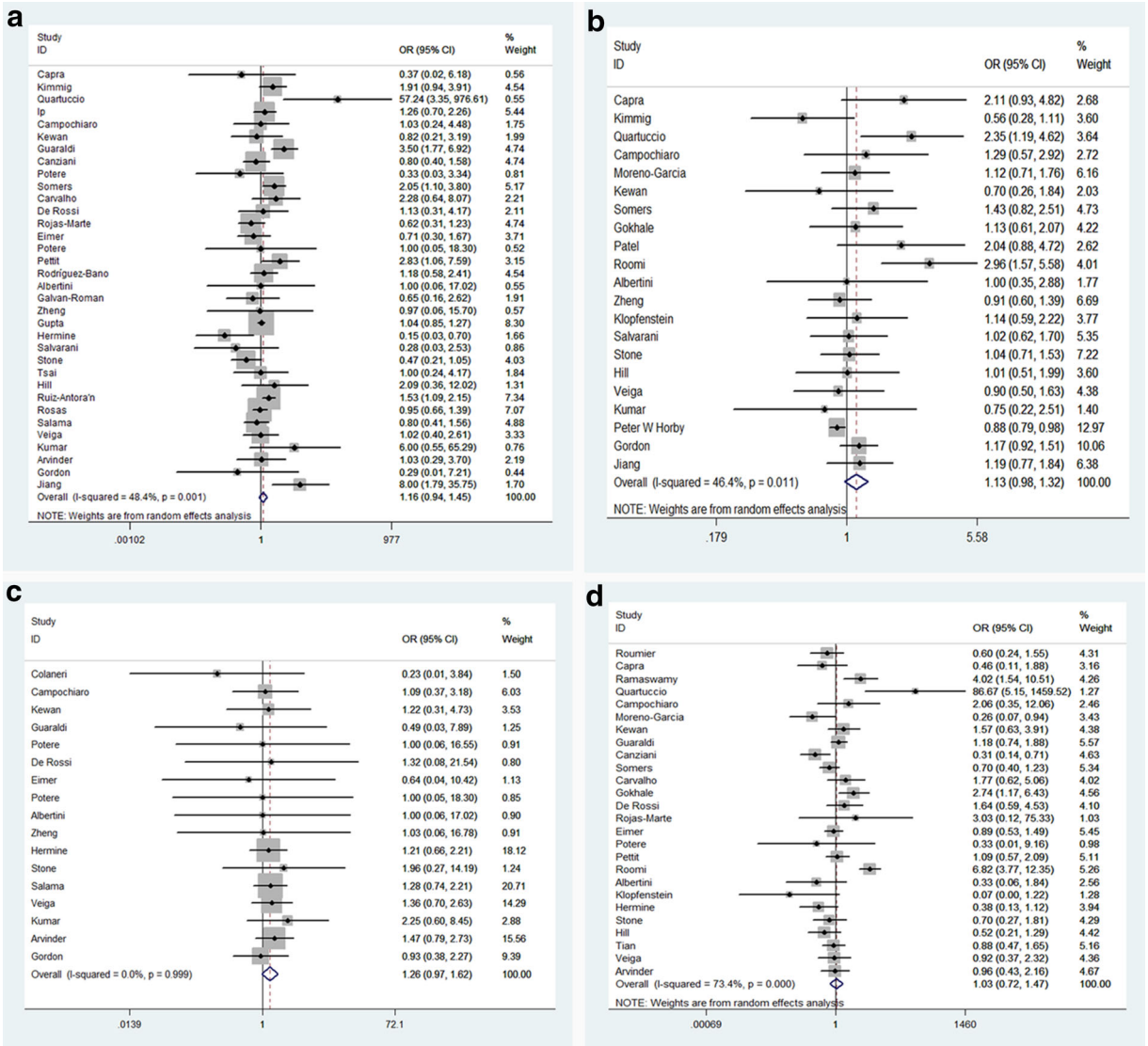

Fig. 4 Forest plot of safety of tocilizumab treatment COVID-19 patients. **a** Forest plot of tocilizumab and secondary infection risk in COVID-19 patients. **b** Forest plot of tocilizumab and discharge in COVID-19 patients. **c** Forest plot of tocilizumab and adverse events in COVID-19 patients. **d** Forest plot of tocilizumab and mechanical ventilation in COVID-19 patients

countries and regions and contributing to > 3,730,000 death.

SARS-CoV-2 brings about a broad spectrum of clinical manifestations, ranging from asymptomatic or paucisymptomatic forms (with malaise, myalgia, dry cough, and fever) to full-blown viral pneumonia ARDS, multiorgan failure, and death [2, 25]. The serum cytokine profiles of some moderate to severe COVID-19 patients overlap with secondary hemophagocytic lymphocytosis (sHLH) and macrophage activation syndrome (MAS). Viruses are known as solid triggers of MAS/sHLH, and serum ferritin levels are associated with mortality in MAS and COVID-19 patients. Endogenous IL-1 is a proinflammatory cytokine that induces the production of IL-6 by macrophages and monocytes and is elevated in MAS, COVID-19 disease, and other diseases, such as severe chimerical antigen receptor T-cell (CAR-

Table 5 The rate of discharge, adverse events and mechanical ventilation of tocilizumab treatment COVID-19 patients

Discharge	OR (95% CI)	*P*	P_h	I^2%	P_b	Adverse event	OR (95% CI)	*P*	P_h	I^2%	P_b	Mechanical ventilation	OR (95% CI)	*P*	P_h	I^2%	P_b
Total	1.13 (0.98–1.32)	0.100	0.011	46.4	0.367	*Total*	*1.26 (0.97–1.62)*	*0.078*	0.999	0.0	0.075	*Total*	1.03 (0.72–1.47)	0.866	< 0.001	73.4	0.657
Race						*Race*						*Race*					
Caucasian	*1.24 (1.00–1.55)*	*0.051*	0.564	0.0		Caucasian	1.27 (0.88–1.81)	0.197	0.976	0.0		Caucasian	0.85 (0.55–1.32)	0.472	< 0.001	63.3	
MIX	1.11 (0.88–1.39)	0.397	0.003	64.3		MIX	1.25 (0.87–1.79)	0.226	0.953	0.0		MIX	1.40 (0.71–2.76)	0.327	< 0.001	82.6	
Asian	1.03 (0.77–1.40)	0.824	0.393	0.0		Asian	1.03 (0.06–16.78)	0.981	–	–		Asian	0.88 (0.47–1.65)	0.685	–	–	
Severity						*Severity*						*Severity*					
Severe	0.94 (0.86–1.04)	0.228	0.069	43.5		Severe	1.04 (0.52–2.08)	0.920	0.998	0.0		Severe	1.01 (0.70–1.45)	0.968	0.008	53.4	
Critical	0.87 (0.43–1.78)	0.701	0.045	75.2		Critical	0.84 (0.36–1.96)	0.679	0.353	0.0		Critical	1.77 (0.62–5.06)	0.284	–	–	
MIX	1.07 (0.88–1.29)	0.514	0.707	0.0		Moderate	1.00 (0.05–18.30)	1.000	–	–		MIX	0.71 (0.36–1.40)	0.326	0.002	71.3	
NA	1.71 (0.60–4.84)	0.312	0.010	84.7		MIX	*1.40 (0.99–1.96)*	*0.054*	0.969	0.0		Moderate	0.33 (0.01–9.16)	0.516	–	–	
						NA	1.28 (0.74–2.21)	0.377	–	–		NA	2.74 (0.45–16.58)	0.273	< 0.001	94.0	
Dose						*Dose*						*Dose*					
8 mg/kg	1.12 (0.96–1.30)	0.163	0.953	0.0		8 mg/kg	1.24 (0.95–1.63)	0.118	0.981	0.0		8 mg/kg	0.82 (0.57–1.16)	0.256	0.007	55.7	
400–800 mg	**0.88 (0.80–0.98)**	**0.018**	0.880	0.0		400–800 mg	1.03 (0.06–16.78)	0.981	–	–		400–800 mg	0.88 (0.47–1.65)	0.685	–	–	
≤ 400 mg	1.19 (0.81–1.76)	0.380	0.079	47.0		≤ 400 mg	1.38 (0.67–2.88)	0.385	0.937	0.0		≤ 400 mg	1.41 (0.74–2.70)	0.295	0.007	62.1	
NA	*1.82 (0.95–3.47)*	*0.069*	0.041	68.6								NA	1.71 (0.13–22.61)	0.684	< 0.001	90.7	
Study type						*Study type*						*Study type*					

Table 5 continued

Discharge	OR (95% CI)	*P*	P_h	I^2%	P_b	Adverse event	OR (95% CI)	*P*	P_h	I^2%	P_b	Mechanical ventilation	OR (95% CI)	*P*	P_h	I^2%	P_b
Retrospective observational study	0.98 (0.52–1.83)	0.950	0.051	66.5		Retrospective Observational study	1.03 (0.06–16.78)	0.981	–	–		Retrospective Observational study	0.83 (0.50–1.36)	0.462	0.415	0.0	
Case-control study	*1.37 (1.00–1.89)*	*0.051*	0.210	36.0		Case-control study	0.65 (0.13–3.34)	0.603	0.706	0.0		Case-control study	1.43 (0.36–5.65)	0.611	< 0.001	80.7	
Cohort study	**1.32 (1.06–1.65)**	**0.014**	0.221	25.1		Cohort study	1.09 (0.52–2.31)	0.813	0.996	0.0		Cohort study	1.18 (0.61–2.26)	0.625	< 0.001	82.9	
RCT	0.93 (0.85–1.02)	0.116	0.424	0.0		Multicenter cohort study	0.49 (0.03–7.89)	0.615	–	–		Multicenter cohort study	1.06 (0.73–1.54)	0.755	0.458	0.0	
						RCT	**1.32 (1.00–1.74)**	**0.049**	0.954	0.0		RCT	0.73 (0.46–1.16)	0.183	0.551	0.0	
Journal												*Journal*					
Unpublished	*0.91 (0.82–1.00)*	*0.055*	0.281	21.1								Unpublished	1.07 (0.34–3.35)	0.905	0.003	78.9	
Published	*1.18 (0.99–1.41)*	*0.060*	0.081	33.8								Published	1.02 (0.69–1.50)	0.921	< 0.001	73.7	
Case size						*Case size*						*Case size*					
< 100	*1.19 (0.99–1.44)*	*0.060*	0.087	32.9		< 100	*1.30 (0.95–1.76)*	*0.099*	0.997	0.0		< 100	1.04 (0.69–1.56)	0.851	< 0.001	75.3	
> 100	0.99 (0.81–1.22)	0.953	0.097	57.1		> 100	1.18 (0.75–1.84)	0.480	0.803	0.0		> 100	1.07 (0.70–1.63)	0.758	0.333	0.0	

Bold values indicate statistically significant results

The mix of severity, symptoms of the disease include moderate, severe and critical; mix of race, including Asian, Caucasian, African, and so on; ICU, intensive care unit; NA, no appearance; OR, odds ratio; CI, confidence interval; P_h, *P* value of heterogeneity, *P* value of *Q*-test for the heterogeneity test; I^2, 0–25, no heterogeneity; 25–50, modest heterogeneity; 50, high heterogeneity

T)-mediated cytokine release syndrome (CRS) [2, 26–28].

IL-6 inhibitors or their receptor inhibitors have been successfully treated with other cytokine storm syndromes or CRS secondary to CAR T-cell therapies. We already have several drug options available, including IL-6 inhibitors (siltuximab, sirukumab, clazakizumab) and IL-6 receptor inhibitors (tocilizumab, sarilumab). It is noteworthy that tocilizumab has been officially included in the National Health Commission of the People's Republic of China COVID-19 Guidelines for diagnosis and treatment program (7th edition) since March 2020: "Tocilizumab can be used in COVID-19 patients with extensive ground-glass lesions opacity in bilateral lungs or critically ill COVID-19 patients, who have elevated laboratory detected serum IL-6 levels" [2]. The Infectious Diseases Society of America (IDSA) has also recently published guidelines and suggested that tocilizumab should only be used in clinical trials of hospitalized COVID-19 patients because of the lack of reliable clinical treatment data [2].

The Infectious Diseases Society of America (IDSA) has also recently published guidelines and suggested that tocilizumab should only be used in clinical trials of hospitalized COVID-19 patients because of the lack of reliable clinical treatment data [1, 11, 12]. However, several retrospective observational studies have found that, in addition to standard treatment, tocilizumab is a safe and promising treatment to prevent disease progression in hospitalized COVID-19 patients with moderate and hyperinflammation [13–16, 28–30]. Our case-control study also found a lower mortality rate in the tocilizumab treatment group than in the standard treatment group (9.47% versus 16.84%), but the results were not statistically significant. However, we found that tocilizumab significantly decreased mortality and increased discharge in COVID-19 patients but no increased secondary infection risk, adverse event, and mechanical ventilation in a meta-analysis of 49 studies (6568 cases and 11,660 controls). We additionally found similar results in several subgroups. Therefore, our data suggest that clinicians should pay attention to tocilizumab therapy as an effective and safe treatment for COVID-19 patients.

Some limitations of the study need to be noted. First, in the absence of clinical test data of every patient, it is not clear which patients with high clinical indicators will benefit most when treated with tocilizumab. Second, subgroup analyses involved relatively small groups, which may not provide sufficient statistical power to explore accurate correlations. Third, every doctor has a different treatment for clinical diagnostics, which would allow for adjustment by other factors. Finally, the inclusion of zero-event trials can sometimes reduce effect size estimates and narrow confidence intervals.

CONCLUSION

To our knowledge, it is the systematic review and meta-analysis to investigate the efficacy and safety of tocilizumab treatment in COVID-19 patients in the the biggest sample size. Tocilizumab significantly decreased mortality in COVID-19 patients but no increased discharge, secondary infection risk, adverse event, and mechanical ventilation in a meta-analysis. Our data suggest that clinicians should pay attention to tocilizumab therapy as an effective and safe treatment for COVID-19 patients.

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Disclosures. All authors declare that they have no competing interests in the work.

Compliance with Ethics Guidelines. All participants voluntarily provided written informed consent for sample collection and their subsequent analysis. We have the approval of the ethics committee of Huoshenshan Hospital and have conducted it following the tenets of the Declaration of Helsinki and its amendments.

Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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