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The effect of tocilizumab on COVID-19 patient mortality: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: This systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to investigate the clinical efficacy and safety of tocilizumab for treating patients with COVID-19.
Methods: The PubMed, Embase, Cochrane Library, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform and the preprint server of medRxiv.org were searched from their inception to February 20, 2021. Only RCTs that compared the treatment efficacy and safety of tocilizumab with the placebo or the standard of care for adult patients with COVID-19 were included in this meta-analysis. The primary outcome was 28-day mortality.
Results: This meta-analysis included eight RCTs which enrolled a total of 6314 patients for randomization, in which 3267 and 3047 patients were assigned to the tocilizumab and control groups, respectively. The mortality at day 28 was 24.4% and 29.9% in patients in the tocilizumab and control groups, respectively, meaning there was no significant difference observed between these two groups (OR, 0.92; 95% CI, 0.66–1.28; $I^2 = 62$). This finding did not change in the subgroup analysis according to the initial use of MV or steroid while enrollment. The patients receiving tocilizumab had a lower rate of mechanical ventilation (MV) and intensive care unit (ICU) admission at day 28 compared with the control group (MV use: OR, 0.75; 95% CI, 0.62–0.90; $I^2 = 11$; ICU admission: OR, 0.51; 95% CI, 0.28–0.92; $I^2 = 30$). There were no significant differences between these two treatment groups in terms of the risk of treatment-emergent adverse events (AEs) (OR, 1.03; 95% CI, 0.71–1.49; $I^2 = 43$), serious AEs (OR, 0.86; 95% CI, 0.67–1.12; $I^2 = 0$) or infection (OR, 0.87; 95% CI, 0.63–1.20; $I^2 = 0$).
Conclusions: Tocilizumab does not provide a survival benefit for patients with COVID-19, but it may help reduce the risk of MV and ICU admission. In addition, tocilizumab is a safe agent to use for the treatment of COVID-19.

1. Introduction

From the end of 2019 until now, coronavirus disease 2019 (COVID-19) has had a terrible impact on global public health [1]. As of November 19th 2020 more than 56 million patients had been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 has caused more than 1.3 million deaths [2]. Although patients infected with SARS-CoV-2 can present as either asymptomatic or with acute respiratory diseases which have favorable outcomes, patients with severe COVID-19 may develop acute respiratory distress syndrome, cytokine release syndrome (CRS) or even death [3–5]. However, effective treatment options in this fight against COVID-19 are limited.

In severe COVID-19 disease, increased levels of cytokines, especially interleukin-6 (IL-6) have been found to be a key factor associated with inflammation [6]. As tocilizumab is widely used in the treatment of IL-6-induced CRS, it has been proposed as a promising agent for the treatment of patients with moderate to severe COVID-19 disease and its usefulness has been demonstrated in many studies and associated meta-analyses [7–11]. A retrospective observational study of 96 COVID-19 admitted to ICU showed that fewer deaths were observed among tocilizumab-treated patients than control group (15% vs. 37%; p = 0.02) [12]. Another matched retrospective cohort analysis showed the similar

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findings – tocilizumab was associated with a lower mortality rate (27.8% vs 34.4%) and reduced hazards of death (aHR, 0.47; 95% CI, 0.25 to 0.88) [13]. Although these studies showed that the addition of tocilizumab could help reduce COVID-19 patient mortality, their conclusions were based on the meta-analysis of observational studies with low levels of evidence [7–10]. Recently, the results of several randomized controlled trials (RCTs) investigating the effect of tocilizumab for COVID-19 patients have been published [14–21]. However, their findings regarding the mortality benefit of tocilizumab were not consistent. Therefore, we conducted this systematic review and meta-analysis of the RCTs to provide updated information based on strong evidence.

2. Methods

2.1. Data sources and search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines when searching for articles, selecting studies, evaluating article quality, and analyzing data [22]. The protocol was registered at PROSPERO with the reference number: CRD42020220003.

We searched for eligible articles and studies in PubMed, Embase, Cochrane Library, Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) from their inception to February 20, 2021. The search terms used were "COVID-19", "tocilizumab" and "RCT". Detailed information on key words and the search strategy are described in supplemental Table 1. The reference lists of the relevant articles, Google Scholar, and the preprint server of medRxiv.org were also searched manually for additional eligible articles. No publication year or language limitations were considered during the literature review.

Two investigators (WTL and SHH) independently screened and reviewed each study. Studies were included if they met the following criteria: (1) studied patients with COVID-19 infection; (2) patients were aged ≥18 years; (3) included intervention with tocilizumab; (4) compared tocilizumab with a placebo, or standard of care; (5) RCT, either blinded or open labelled; (6) study outcomes of clinical efficacy, including mortality or clinical improvement. Studies including additional treatments which were received in both the intervention and comparison arms were not excluded. If there were any disagreements between the investigators, the third investigator (CHC) was consulted and made the final decision.

Three investigators reviewed the full texts of the candidate articles to finalize the experimental and control groups for the meta-analysis. The investigators reviewed the study methods, sites, durations, populations, and treatment regimens reported in the articles. Two investigators

Table 1
Characteristics of the included studies.

Study, published year	Study design	Study sites	Study populations	No of patients		Regimen of TCZ
				Tocilizumab (TCZ)	Control	
Stone et al, 2020	Randomized, double-blind, placebo-controlled trial	7 hospitals in US	Patients with confirmed SARS-CoV-2 infection, hyperinflammatory states and at least two of the following signs: fever (body temperature >38 °C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%.	161	82	1 TCZ at 8 mg/kg but not to exceed 800 mg)
Hermine et al, 2020	Cohort-embedded, investigator-initiated, open-label, randomized clinical trial	9 hospitals in France	Patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min oxygen but without ventilation or admission to the ICU	63	67	TCZ 8 mg/kg D1 and if no response (no decrease of oxygen requirement) a second injection of 400 mg at D3.
Salvarani et al, 2020	Prospective, open-label, randomized clinical trial	24 hospitals in Italy	Hospitalized patients with COVID-19 pneumonia, PaO_2/FiO_2 between 200 and 300 mmHg, and an inflammatory phenotype defined by fever and elevated CRP	60	66	TCZ within 8 h from randomization (8 mg/kg up to a maximum of 800 mg), followed by a second dose after 12 h
Salama et al, 2020	Randomized, double-blind, placebo-controlled, phase III study	61 hospital in 6 countries	Nonventilated patients hospitalized with COVID-19 pneumonia	249	128	1 TCZ at 8 mg/kg (but not exceeding 800 mg), but up to one additional dose may be given.
Rosas et al, 2020	Randomized, double-blind, placebo-controlled trial	67 hospital in 9 countries	Hospitalized patients with severe COVID-19 pneumonia and a blood oxygen saturation ≤93% or PaO_2/FiO_2 <300 mm/Hg	294	144	1 IV infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose may be given if clinical symptoms worsen or show no improvement.
REMAP-CAP Investigator, 2021	Randomized, adaptive platform trial	113 sites in 6 countries	Critically ill patients, 18 years of age or older, with either clinically suspected or microbiologically confirmed COVID-19 who were admitted to ICU and receiving respiratory or cardiovascular organ support	353	402	1 TCZ at 8 mg/kg (but not exceeding 800 mg), but up to 1 additional dose may be given after 12 to 24 h
RECOVERY Collaborative Group, 2021	Randomized, controlled, open-label, platform trial	131 sites in UK	Hospitalized patients with clinical suspected or laboratory confirmed SARS-CoV-2 infection and with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L)	2022	2094	1 IV infusion of TCZ, dose up to a maximum dose 800 mg. Up to 1 additional dose may be given after 12 – 24 h
Viega et al, 2021	Randomized, open label trial	9 hospitals in Brazil	Adults with confirmed COVID-19 who were receiving supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (C reactive protein, D dimer, lactate dehydrogenase, or ferritin)	65	64	1 TCZ at 8 mg/kg

PaO_2/FiO_2: partial pressure of arterial oxygen to fraction of inspired oxygenation; CRP, C-reactive protein; TCZ, tocilizumab.

initially independently examined the publications to avoid bias, and the third investigator resolved any disagreements. Data including the author name, year of publication, study design, site and duration, demographic characteristics of the study subjects, intervention regimens, comparative therapy types, outcomes and adverse events were extracted from each included study.

2.2. Definitions and outcomes

The primary outcome was all-cause mortality at 28–30 days. Secondary outcomes included the use of mechanical ventilation (MV), intensive care unit (ICU) admission, survival to discharge and risk of adverse events.

2.3. Quality assessment and data analysis

The Cochrane risk-of-bias tool was used to assess the quality and associated risk of bias for the enrolled RCTs [23]. Two reviewers subjectively reviewed all the included studies and rated them "low risk," "high risk," or "unclear" based on the following items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and inclusion of intention-to-treat analyses. A random-effects model in Review Manager version 5.3 was used for the statistical analyses. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for outcome analyses.

3. Results

3.1. Literature search and study evaluation

A total of 697 articles were identified from the search of PubMed (n = 131), Embase (n = 258), Cochrane CENTRAL (n = 129), the Cochrane Database of Systematic Reviews (CDSR) (n = 5), Clinicaltrials.gov (n = 75) and WHO ICTRP (n = 99). Fifty-seven articles remained after the removal of duplicates (n = 248) and ineligible articles as determined by a review of the titles and abstracts (n = 392). A total of eight studies [14–21] were included after 49 articles were removed following a full-text review process (Fig. 1).

3.2. Study characteristics

All eight RCTs [14–21] were multicenter studies. Three [14,17,18] were multinational studies, while the other five trials were conducted solely in the US [20], France [15], Brazil [21], UK [16] and Italy [19]. Overall, a total of 6314 patients were included in this meta-analysis, in which 3267 and 3047 patients were assigned to the tocilizumab and control groups, respectively. Except one RCT [20] used only a single dose of tocilizumab, other 7 RCTs [14–19,21] allowed one additional dose if needed. The characteristics of the study populations varied and are summarized in Tables 1 and 2. Their mean or medium age ranged from 56 to 64 years and men comprised more than 60% of patients. Diabetes, hypertension and cardiovascular disease were the most common underlying diseases, followed by chronic obstructive pulmonary diseases, asthma, chronic kidney disease and malignancy.

3.3. Quality assessment

There was a risk of performance and detection bias due to the open labelled design in five of the studies [14–16,19,21]. Risk of bias for the included studies is depicted in Fig. 2.

3.4. Clinical outcomes

The pooled analysis of the eight RCTs [14–21] showed that the mortality rate at day 28 was 24.4% and 29.9% among patients in the tocilizumab and control groups, respectively, and therefore no significant difference was observed between these two groups (OR, 0.92; 95% CI, 0.66–1.28; I^2 = 62, Fig. 3). The leave-one-out sensitivity analysis showed that the magnitude of association for tocilizumab with mortality

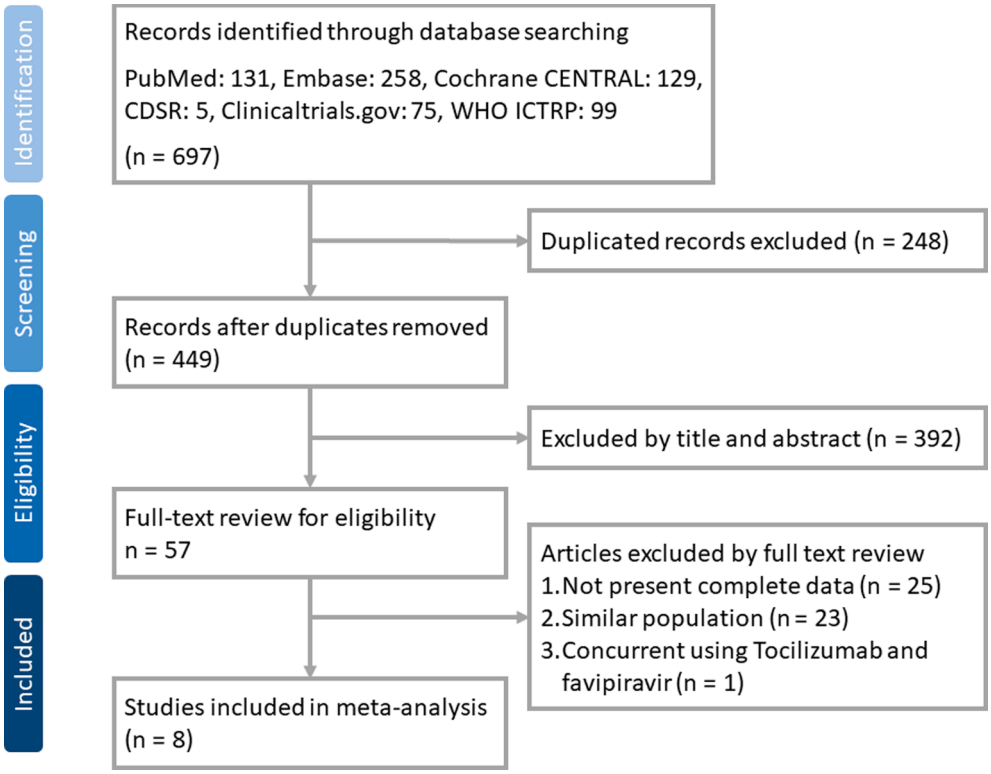

Fig. 1. PRISMA flow diagram for the selection of RCTs. CDSR: Cochrane database of systematic reviews, ICTRP: international clinical trials registry platform.

Table 2
Demographic features of the study populations between tocilizumab (TCZ) and control group in each study.

Study, publish year	Age, year*		Male sex, no (%)		BMI*		Underlying disease, no (%)		Time from symptom onset to randomization, day*	
	TCZ	Control	TCZ	Control	TCZ	Control	TCZ	Control	TCZ	Control
Stone et al, 2020	61.6 (46.4–69.7)	56.5 (44.7–67.8)	96 (60)	45 (55)	29.9 (26.0–34.2)	30.2 (25.7–33.8)	HTN: 80 (50); DM: 45 (28); CKD: 29 (18); cancer: 22 (14); heart failure: 17 (11); myocardial infarction: 15 (9); COPD: 15 (9); asthma: 15 (9)	HTN: 38 (46); DM: 30 (37); CKD: 13 (16); cancer: 8 (10) heart failure: 7 (9); myocardial infarction: 6 (7); COPD: 7 (9); asthma: 7 (9)	9 (6.0–13.0)	10.0 (7.0–13.0)
Hermine et al, 2020	64.0 (57.1–74.3)	63.3 (57.1–72.3)	44 (70)	44 (66)	27.9 (23.3–30.8)	27.4 (24.5–31.3)	Chronic cardiac disease: 20 (33); DM: 30 (33); CKD: 5 (8); asthma: 5 (8); COPD: 3 (5); cancer: 4 (7)	Chronic cardiac disease: 20 (30); DM: 23 (34); CKD: 13 (19); asthma: 3 (5); COPD: 3 (5); cancer: 5 (8)	10 (7–13)	10 (8–13)
Salvarani et al, 2020	61.5 (51.5–73.5)	60.0 (54.0–69.0)	40 (66.7)	37 (56.1)	BMI $\geq$ 30: 16 (28.1)	BMI $\geq$ 30: 22 (36.1)	DM: 10 (17); HTN: 27 (45); COPD: 2 (3)	DM: 9 (14); HTN: 29 (44); COPD: 2 (3)	7.0 (4.0–11.0)	8.0 (6.0–11.0)
Salama et al, 2020	56.0 (14.3)	55.6 (14.9)	150 (60)	73 (57)	32.0 (7.9)	33.1 (7.2)	HTN: 119 (48); DM: 105 (42); hyperlipidemia: 70 (29); asthma: 27 (11); COPD: 12 (5)	HTN: 63 (50); DM: 48 (38); hyperlipidemia: 34 (27); asthma: 16 (13); COPD: 5 (4)	8.0 (0.0–31.0)	8.0 (0.0–36.0)
Rosas et al, 2020	60.9 (14.6)	60.6 (13.7)	205 (70)	101 (70)	NA	NA	DM: 105 (36); cardiovascular disease: 88 (30); HTN: 178 (61); chronic lung disease: 49 (17)	DM: 62 (43); cardiovascular disease: 35 (24); HTN: 94 (65); chronic lung disease: 22 (15)	11.0 (1.0–49.0)	10.0 (2.0–50.0)
REMAP-CAP Investigator, 2021	61.5 (12.5)	63.4 (13.4)	261 (74)	283 (70)	30.5 (26.9–34.9)	30.9 (27.1–34.9)	DM: 123 (35); respiratory disease: 82 (23); severe cardiovascular disease: 34 (10)	DM: 150 (37); respiratory disease: 98 (24); severe cardiovascular disease: 47 (12)	NA	NA
RECOVERY Collaborative Group, 2021	63.3 (13.7(	63.9 (13.6)	1335 (66)	1437 (69)	NA	NA	DM: 569 (28); heart disease: 435 (22); chronic lung disease: 473 (23); severe kidney impairment: 118 (6)	DM: 600 (18); heart disease: 497 (24); chronic lung disease: 484 (23); severe kidney impairment: 99 (5)	9 (7–13)	10 (7–14)
Viega et al, 2021	57.4 (15.7)	57.5 (13.5)	44 (68)	44 (69)	NA	NA	HTN: 30 (46); DM: 22 (34); heart failure: 4 (6); CKD: 5 (8); myocardial infarction: 4 (6); asthma: 4 (6); COPD: 2 (3)	HTN: 34 (53); DM: 20 (31): heart failure: 3 (5); myocardial infarction: 3 (5); COPD: 2 (3); asthma :1 (2); CKD: 1(2)	10.0 (3.1)	9.5 (3.0)

Study, publish year	Other treatments, n (%)		Use of corticosteroid, n (%)		Use of NIV or high flow and MV, n (%)		CRP, mg/L*		IL-6, pg/ml*	
	TCZ	Control	TCZ	Control	TCZ	Control	TCZ	Control	TCZ	Control
Stone et al, 2020	Remdesivir: 55 (33); HCQ: 6 (4)	Remdesivir: 24 (29); HCQ: 3 (4)	18 (11)	5 (6)	NIV or high flow oxygen: 5 (3); MV: 0 (0)	NIV or high flow oxygen: 5 (6); MV: 1 (1)	116.0 (67.1–190.6)	94.3 (58.4–142.0)	23.6 (14.0–49.9)	25.4 (14.6–40.3)
Hermine et al, 2020	Antiviral drug: 7 (11)	Antiviral drug: 16 (24)	21 (33)	41 (61)	NIV: 0 (0); MV: 0 (0)	NIV: 0 (0); MV: 0 (0)	119.5 (74.5–219.5)	127.0 (84.0–171.0)	NA	NA
Salvarani et al, 2020	Antiviral drug: 21 (35)	Antiviral drug: 31 (47)	NA	NA	NIV: 0 (0); MV: 0 (0)	NIV: 0 (0); MV: 0 (0)	82 (37–135)	105 (50–146)	42.1 (20.6–74.9)	50.4 (28.3–93.2)
Salama et al, 2020	Antiviral drug: 196 (79)	Antiviral drug: 101 (79)	200 (80.3)	112 (87.5)	NIV or high flow oxygen: 64 (25.7); MV: 0 (0)	NIV or high flow oxygen: 36 (28.1); MV: 0 (0)	151.9 (177.2)	202.8 (404.9)	NA	NA
Rosas et al, 2020	Antiviral drug: 71 (24.1); convalescent plasma: 5 (1.7)	Antiviral drug: 42 (29.2); convalescent plasma: 1 (0.7)	57 (19.4)	41 (28.5)	NIV or high flow oxygen: 94 (32); MV: 111 (37.8)	NIV or high flow oxygen: 39 (27.1); MV: 54 (37.5)	168.4 (101.4)	172.6 (114.0)	201.9 (418.4)	195.4 (368.2)
REMAP-CAP Investigator, 2021	Antiviral drug: 169 (48)	Antiviral drug: 217 (54)	50 (14.2)	52 (12.9)	High flow oxygen: 101 (29); NIV: 147 (42); MV: 104 (29)	High flow oxygen: 110 (27); NIV: 169 (42); MV: 121 (30)	150 (85–221)	137 (71–208)	NA	NA
RECOVERY Collaborative Group, 2021	Lopinavir/ritonavir: 51 (3); HCQ: 37 (2); azithromycin: 197 (10)	Lopinavir/ritonavir: 64 (3); HCQ: 38 (2); azithromycin: 177 (8)	1664 (82)	1721 (82)	NIV: 819 (41); MV: 268 (13)	NIV: 867 (41); MV: 294 (14)	143 (107–203)	144 (106–205)	NA	NA
Viega et al, 2021	HCQ: 11 (17); azithromycin: 41 (63)	HCQ: 9 (14); azithromycin: 31 (48)	45 (69)	47 (73)	NIV or high flow oxygen: 15 (23); MV: 11 (17)	NIV or high flow oxygen: 26 (41); MV: 10 (16)	160 (104)	193 (283)	NA	NA

TCS, tocilizumab; HTN, hypertension; DM, diabetes; COPD, chronic obstructive pulmonary disease; NIV: non-invasive ventilation; MV: mechanical ventilation; HCQ: hydroxychloroquine; NA, not applicacble; CRP, C-reactive protein; IL-6, interleukin-6.

* Presented as the median (IQR) or mean (SD).

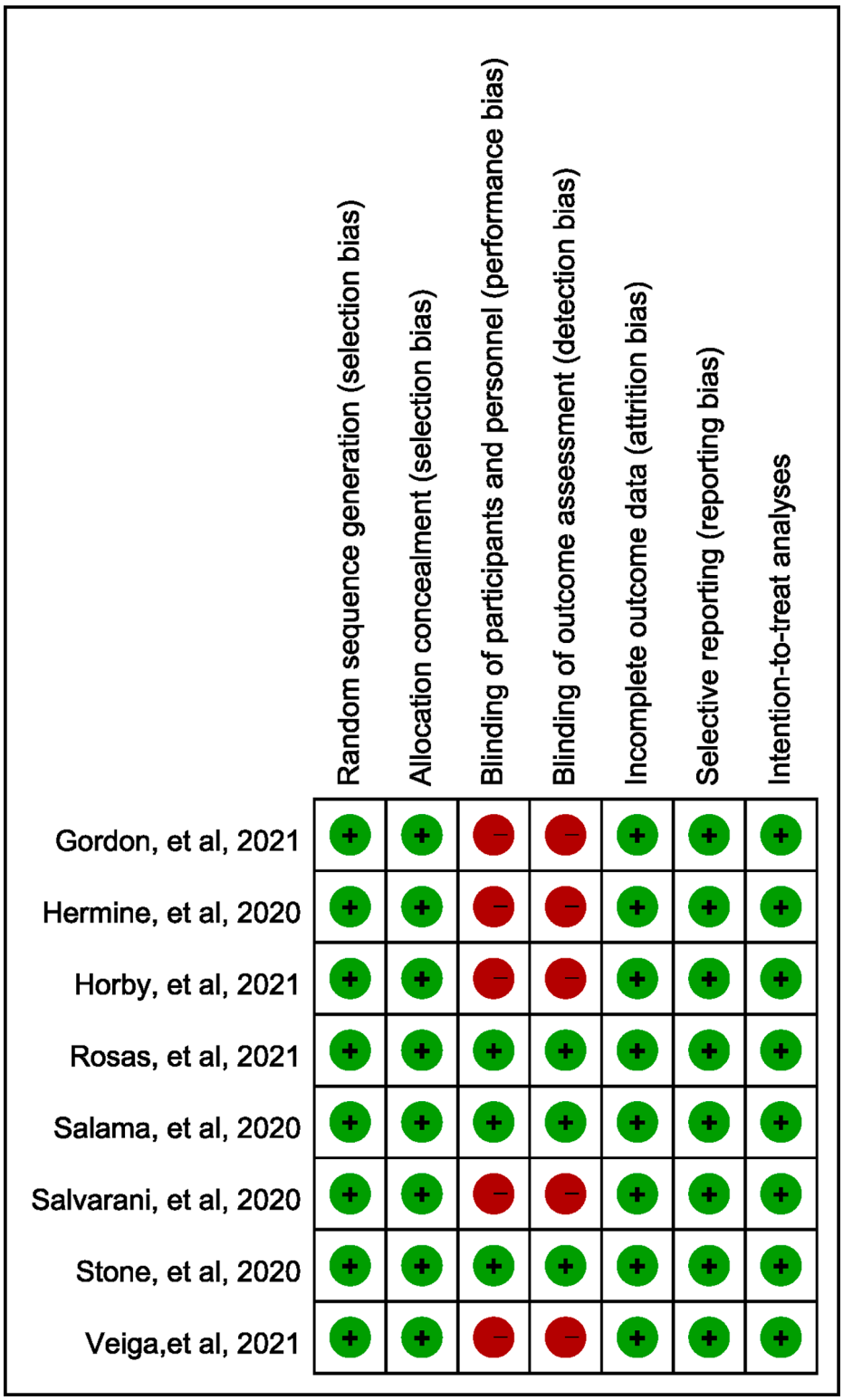

Fig. 2. Summary of the risks of bias in each domain in each study. High risk of bias red (−); low risk of bias: green color (+).

was not influenced by any individual study. In addition, this finding did not change according to the initial use of MV or steroid use while enrollment. The pooled analysis of 4 RCTs, which did not include MV patients showed mortality rate at day 28 was 7.7% and 6.5% among patients in the tocilizumab and control groups, respectively (OR, 1.21; 95% CI, 0.69–2.11; I^2 = 0) [15,18,19,24]. The pooled analysis of another 4 RCTs [14,16,17,21], which also included MV patients showed mortality rate at day 28 was 27.6% and 32.8% among patients in the tocilizumab and control groups, respectively (OR, 0.86; 95% CI, 0.56–1.31; I^2 = 81). The pooled analysis of 4 RCTs [14,16,18,21], in which more than 50% of patients using steroid showed mortality rate at day 28 was 26.9% and 32.4% among patients in the tocilizumab and control groups, respectively (OR, 0.89; 95% CI, 0.56–1.43; I^2 = 81). The pooled analysis of 4 RCTs [15,17,19,20], in which less than 50% of

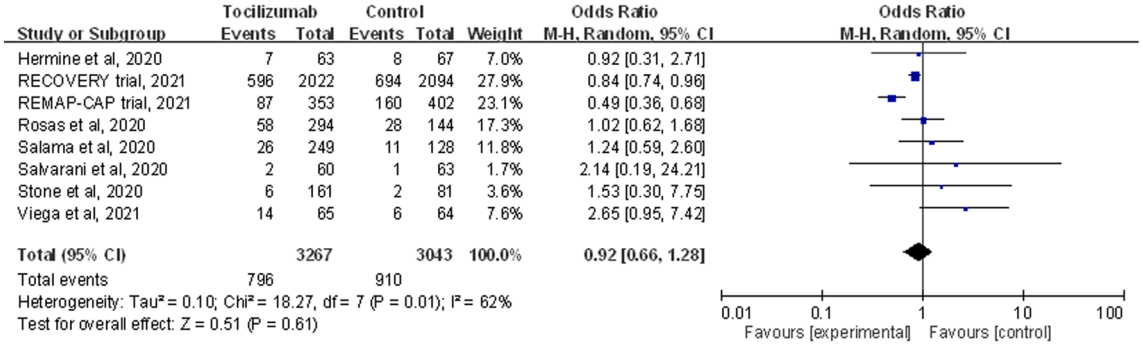

Fig. 3. Forest plot for 28-day mortality between the tocilizumab and control groups.

patients using steroid showed mortality rate at day 28 was 12.6% and 11.0% among patients in the tocilizumab and control groups, respectively (OR, 1.06; 95% CI, 0.69–1.63; $I^2 = 0$).

Moreover, the rate of death at day 14 was 11.3% and 13.1% in the tocilizumab and control groups, respectively and no significant difference was observed (OR, 1.57; 95% CI, 0.63–3.92; $I^2 = 59$) in the pooled analysis of five RCTs [14,15,19–21]. In addition, the rate of survival to discharge at day 14 remained similar between the tocilizumab and control groups (48.2% vs 38.6%; OR, 1.38; 95% CI, 1.12–1.70; $I^2 = 0$) in the pooled analysis of six RCTs [14,15,17,19–21]. However, patients receiving tocilizumab had a lower rate of MV and ICU admission at day 28 compared with the control group (MV use: OR, 0.75; 95% CI, 0.62–0.90; $I^2 = 11$; ICU admission: OR, 0.51; 95% CI, 0.28–0.92; $I^2 = 30$). Three RCTs [16,18,20] reported the composite outcome of MV or death at day 28, and lower rate of this composite outcome was observed in the tocilizumab group than the control group (28.6% vs 35.6%; OR, 0.78; 95% CI, 0.68–0.89; $I^2 = 0$).

3.5. Risk of adverse events (AEs)

Fig. 4 shows a comparison of the risk of AEs between the tocilizumab and control groups. There was no significant difference between these two groups in terms of the risk of treatment-emergent AEs (OR, 1.03; 95% CI, 0.71–1.49; $I^2 = 43$), serious AEs (OR, 0.86; 95% CI, 0.67–1.12; $I^2 = 0$) or infection (OR, 0.87; 95% CI, 0.63–1.20; $I^2 = 0$). However, the tocilizumab group was associated with a lower rate of serious infection compared with the control group (OR, 0.57; 95% CI, 0.36–0.89; $I^2 = 21$).

4. Discussion

In this meta-analysis, eight RCTs [14–21] were reviewed to compare the use of tocilizumab with a control group to determine its efficacy and safety for the treatment of hospitalized patients with COVID-19. From the pooled analysis of these 8 RCTs, we could not find an additional survival benefit of tocilizumab, compared with the control group and this finding was supported by the following evidence. First, the overall 28-day mortality of the hospitalized patients with COVID-19 was not significantly different between the tocilizumab and control groups in this study. Second, the similarities between the two groups remained unchanged following the leave-one-out sensitivity analysis. Third, the findings of the subgroup analysis according to the use of MV or steroid while enrollment remained the same. Finally, no significant difference was observed between the tocilizumab and control groups in terms of 14-day mortality. All these findings were consistent with previous meta-analyses [25,26] which included 5 and 6 RCTs, respectively and indicate that tocilizumab does not improve the mortality rate of hospitalized patients with COVID-19, compared with the control group.

Although several previous meta-analyses [7,8,27] showed that tocilizumab could help reduce mortality among critically ill COVID-19 patients, their level of evidence was lower than the present study as most of them only included observation studies in their analysis. By contrast, our study was based on the analysis of RCTs. Therefore, our findings provide more solid evidence regarding this issue than previous studies [7–11,27], and suggests that tocilizumab does not reduce the short-term mortality of hospitalized patients with COVID-19.

Despite the fact that our findings showed that tocilizumab did not have a positive impact on COVID-19 patient mortality, we found that tocilizumab was associated with a lower rate of MV and ICU admission compared with the control group. This is consistent with the findings of previous studies [9,27]. A previous meta-analysis of seven case-controlled studies, which included 766 patients (351 in the tocilizumab arm and 414 in the control arm), demonstrated that the need for artificial invasive ventilation was significantly lower in the tocilizumab group (risk ratio, 0.34; 95% CI: 0.12–0.99; $I^2 = 0\%$) compared with the control group [27]. Zhao *et al* reported similar findings as a lower risk of admission to the ICU (OR: 0.53; 95% CI: 0.26–1.09), and use of ventilation (OR: 0.66; 95% CI, 0.46–0.94) were found in the tocilizumab treatment group compared with the control [9]. Overall, the findings of this study and previous meta-analyses suggest that tocilizumab may help to reduce the rate of MV and ICU admission.

Finally, this meta-analysis also assessed the risk of AEs associated with tocilizumab. We found that tocilizumab was not associated with a higher risk of treatment emergent AEs, serious AEs or infection compared with the control group. In fact, a lower rate of serious infections was found in patients receiving tocilizumab compared with those in the control group. These findings are consistent with the results of previous meta-analyses of observational studies [9,11,27]. Therefore, together these findings indicate that tocilizumab is a tolerable agent for the treatment of COVID-19 patients.

Although a major strength of this meta-analysis was that only RCTs were included, this study also had several limitations. First, the number of included studies and the total number of patients was limited. Second, the design of each study and the patient populations were varied. Some findings were associated with high heterogeneity. However, we did leave-one-out sensitivity analysis and subgroup analysis, and found that the results did not change. Finally, we could not assess the effect of tocilizumab on the time to clinical improvement, length of hospital stays or MV duration due to the associated data was limited. More large-scale RCTs are needed to clarify these issues. However, many RCTs investigating the usefulness of tocilizumab are still ongoing or being prepared (Appendix Table 2). In the near future, we will be able to obtain more data to validate our findings and to perform more subgroup analyses to determine if there are some types of COVID-19 cases which respond well to tocilizumab.

In conclusion, tocilizumab does not appear to provide a survival benefit for hospitalized patients with COVID-19, but it may help reduce the risk of MV and ICU admission. In addition, tocilizumab is a safe agent to use in the treatment of COVID-19.

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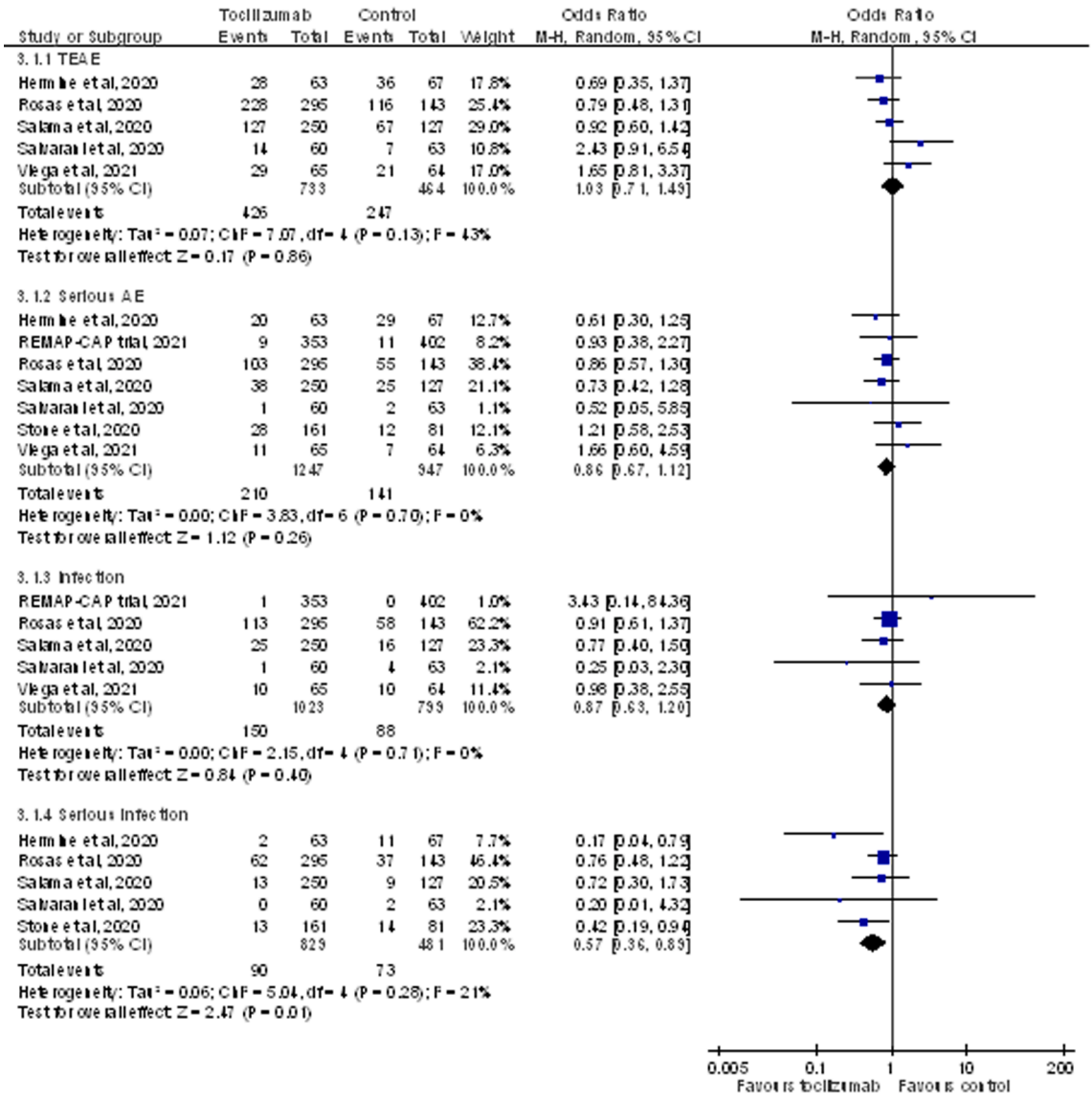

Fig. 4. The risk of adverse events between the tocilizumab and control groups.

Authors' contributions

Study concept and design: WTL, SHH, CCL, CYW, and CHC. Acquisition of data: WTL, SHH, CCL, and CHC. Analysis and interpretation of data: All, Drafting of the manuscript: WTL, SHH, CCL, and CHC. Critical revision of the manuscript for important intellectual content: All. Statistical analysis: CYW, and CHC. Guarantor: CHC. Approval of final manuscript: All.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2021.107602.

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