Tocilizumab in Hospitalized Patients with COVID-19: A Meta Analysis of Randomized Controlled Trials

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Abstract

Background To date, only dexamethasone has been shown to reduce mortality in coronavirus disease-19 (COVID-19) patients. Tocilizumab has been recently added to the treatment guidelines for hospitalized COVID-19 patients, but data remain conflicting.

Study Design and Methods Electronic databases such as MEDLINE, EMBASE, and Cochrane central were searched from March 1, 2020, until March 10, 2021, for randomized controlled trials evaluating the efficacy of tocilizumab in hospitalized COVID-19 patients. The outcomes assessed were all-cause mortality, mechanical ventilation, and time to discharge.

Results Nine studies (with 6490 patients) were included in the analysis. In total, 3358 patients received tocilizumab, and 3132 received standard care/placebo. Pooled analysis showed a significantly decreased risk of all-cause mortality (RR 0.89, 95% CI 0.80–0.98, $p = 0.02$) and progression to mechanical ventilation (RR 0.80, 95% CI 0.71–0.89, $p < 0.0001$) in the tocilizumab arm compared to standard therapy or placebo. In addition, there was a trend towards improved median time to hospital discharge (RR 1.28, 95% CI 1.12–1.45, $p = 0.0002$).

Conclusions Tocilizumab therapy improves outcomes of mortality and need for mechanical ventilation, in hospitalized patients with COVID-19 infection compared with standard therapy or placebo. Our findings suggest the efficacy of tocilizumab therapy in hospitalized COVID-19 patients and strengthen the concept that tocilizumab is a promising therapeutic intervention to improve mortality and morbidity in COVID-19 patients.

Abbreviations

BACC	Boston Area COVID-19 Consortium
RCT-TCZ-COVID-19	Randomized controlled trial-tocilizumab-COVID-19
CORIMUNO-TOCI-1	Cohort multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients
EMPACTA	Evaluating Minority Patients with Actemra
REMAP-CAP	Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia
RECOVERY	Randomized evaluation of COVID-19 therapy
MEDLINE	Medical literature analysis and retrieval system online
EMBASE	Excerpta Medica database

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Introduction

The coronavirus disease-19 (COVID-19) pandemic has resulted in hospitalization in many cases. In severe and critical cases of COVID-19, which occurs in 13.8% and 6.1% of the patient population, COVID-19-associated pneumonia can lead to acute respiratory distress syndrome (ARDS) and rapid deterioration, sometimes leading to invasive mechanical ventilation and death [1]. The clinical spectrum of COVID-19 continues to evolve along with the emergence of new severe acute respiratory syndrome-coronavirus-2 (SARS-CoV2) variants.

The pathophysiology of COVID-19 involves an initial viremic phase where patients mostly have mild constitutional symptoms, followed by a pulmonary and then hyperinflammatory phase where patients have shortness of breath and hypoxemia [2]. The median time from onset of symptoms to hospital admission is five to seven days and nine to ten days for acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure [3, 4]. The hyperinflammatory phase of COVID-19 is associated with elevated C-reactive protein (CRP) levels, ferritin, lactate dehydrogenase (LDH), and interleukin-6 (IL-6) and causes edema and inflammatory cell infiltration in the lungs [5, 6]. IL-6 appears to play a significant role in endothelial dysfunction and the development of vascular permeability and has been associated with the vascular dysfunction seen in severe disease [7]. This dysregulated and excess immune response plays an important role in the disease course of COVID-19 [8, 9]. Elevated levels of IL-6 have been associated with prolonged viral shedding, increased viremia, and progression to mechanical ventilation and death [10–13]. A meta-analysis of 6 studies revealed that mean IL-6 levels were 2.9-fold higher in patients with complicated COVID-19 than non-complicated disease [14].

Dexamethasone therapy has shown mortality benefit in patients of COVID-19 infection [15, 16]. Nevertheless, in some severely ill patients, dexamethasone therapy alone might not be sufficient to quell the cytokine storm in the hyperinflammatory phase. Tocilizumab is a recombinant monoclonal antibody indicated for treating giant cell arteritis, rheumatoid arthritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor T-cells [17–19]. Its mode of action is by inhibiting IL-6 signaling by binding soluble IL-6R and membrane IL-6R [20]. A recent study also showed there might be genetic variants in the interleukin-6 inflammatory pathway that may be associated with life-threatening disease in COVID-19 patients [21]. It is reasonable to assume that early intervention with tocilizumab through IL-6 blockade could abrogate progression to hypoxemic respiratory failure

and decreases the duration of supplemental oxygen use [22]. However, randomized controlled trials (RCTs) and systematic reviews evaluating the role of tocilizumab in COVID-19 patients have yielded disparate results [23–29].

We, therefore, conducted a meta-analysis of the RCTs to synthesize the current evidence on the efficacy of tocilizumab in hospitalized COVID-19 patients.

Methods

Data Sources and Search Strategy

This study was conducted according to the Cochrane Collaboration and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [30]. We conducted a systematic search in MEDLINE, EMBASE, Cochrane Central, and preprint databases to identify all relevant articles using the following search terms: ("SARS-CoV2" OR "COVID-19") AND ("tocilizumab" OR "IL6" OR "Anti-IL6"). Results were limited to humans and the English language. Databases were searched from March 1, 2020, to March 10, 2021, to identify all relevant RCTs including preprint, non-peer reviewed studies as well. Review articles, case reports, observational studies, opinion articles, letters, abstracts, conferences, brief reports, and non-English publications were excluded. The reference lists of the identified articles were also perused to find additional pertinent studies. All results were imported into End-Note × 8.2 (Clarivate Analytics) and duplicate results were identified and removed.

Study Selection and Eligibility

Two independent reviewers (V.S. and M.S.K.) screened the retrieved papers based on the title and abstract. If the paper contained relevant data, the full paper was retrieved if it was not clear from the title and abstract. Any disagreements between the two reviewers were discussed with a third reviewer (K.D.A.) and resolved by consensus. A study was considered eligible for inclusion in the analysis if it was 1) randomized controlled trial 2) reported outcomes of interest in hospitalized COVID-19 patients with tocilizumab therapy compared to standard treatment or placebo. The outcomes assessed were all-cause mortality, progression to mechanical ventilation, and the median time to hospital discharge. If more than one study reported data from the same population, then the largest study was included.

Data Extraction

From the included studies, two reviewers (V.S. and M.S.K.) independently extracted the data. Extracted data included (1)

study characteristics—design, site of study, dates of study, and type of randomization (2) details of the study population and the interventions utilized, including demographics of participants in both intervention and control arms, presence of comorbidities, concomitant treatment, CRP levels (3) primary outcome, and follow-up. In the REMAP-CAP trial, data from only the tocilizumab arm were included. Data from the sarilumab arm of the trial were excluded from the meta-analysis [31].

Risk of Bias Assessment

Two authors (V.S. and M.S.K.) reviewed each selected trial for quality assessment, including the risk of bias using the Cochrane criteria for systematic review of interventions [32]. This methodology explores the adequacy of sequestration, allocation sequence concealment, blinding of participants and study personnel, blinding for outcome assessment, incomplete outcome or selective outcome reporting, and another potential bias. Any disagreement between the authors was resolved with mutual agreement after discussion.

Data Synthesis and Statistical Analysis

Outcomes were used in the meta-analysis only if at least three studies reported usable data. The Mantel-Haenszel method for dichotomous data was used to calculate aggregated risk ratios (RRs) with corresponding 95% confidence intervals (CIs). A 2-tailed alpha level of 0.05 was set as the threshold for statistical significance. The I^2 statistic was used to assess unexplained statistical heterogeneity among studies. The meta-analysis was performed with a random-effects model. Subgroup analysis was done to evaluate the effect of disease severity, dexamethasone use, and sample size on all-cause mortality. Statistical analysis was performed using Review Manager, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Search Results and Characteristics of Included Trials

Figure 1 shows the PRISMA flow chart summarizing the search strategy. The literature search identified 38 full-text articles, of which nine RCTs were eligible for inclusion in this study after full read [24–29, 31, 33]. A total of 6490 patients were included, of which 3358 patients received tocilizumab, and 3132 received standard care/placebo. Baseline characteristics were similar across the intervention and standard care or placebo groups. Detailed characteristics of the studies are described in Table 1.

All trials included in the analysis studied hospitalized patients with COVID-19 and were multicenter in design. One study was conducted in Italy, one in Brazil, one in India, one in France, one in the United Kingdom, and one in the United States of America (USA). Three international trials were conducted across multiple countries in Europe, Mexico, Kenya, South Africa, Peru, and Brazil [25, 26, 31]. Six trials had open-label design and three were double-blinded. Detailed study designs and study criteria are described in Table 2.

Risk of Bias Assessment

The risk of bias assessment for the included trials is presented in Fig. 2. All trials were reported using random sequence generation. Concealment of allocation was not mentioned in six trials and therefore risk of allocation concealment remains high in these trials [27–29, 31, 33, 34]. Also, six trials had open-label study design [27–29, 31, 33, 34]. The risk of performance and selection bias was high in these trials as participants and personnel were not blinded to the assigned treatment. Bias due to selective reporting was deemed high in one study because it was a preliminary report and data were not presented for some outcomes [31]. Risk of attrition bias was deemed high in one trial due to incomplete outcome [29]. In the rest of the studies, risk of attrition bias was low [24–28, 31, 33, 34].

Assessment of Outcomes

All-Cause Mortality

All nine RCTs reported the outcome of all-cause mortality [24–29, 31, 33, 34]. A total of 846 deaths out of 3358 participants were reported in the tocilizumab arm compared to 943 deaths out of 3132 participants in the standard care or placebo arm. Pooled analysis showed a significant reduction in all-cause mortality with tocilizumab therapy than standard therapy or placebo (RR 0.89, 95% CI 0.80–0.98, $p = 0.02$) (Fig. 3A).

Progression to Mechanical Ventilation

Eight RCTs reported the outcome of progression to mechanical ventilation [24, 25, 27–29, 31, 33, 34]. 440 out of 2622 participants progressed to mechanical ventilation in the tocilizumab group compared to 536 out of 2526 participants in the other group. Statistical significance was observed with RR of 0.80 and 95% CI 0.71–0.89 with a p value < 0.0001 (Fig. 3B).

Fig. 1 PRISMA flow chart outlining literature search
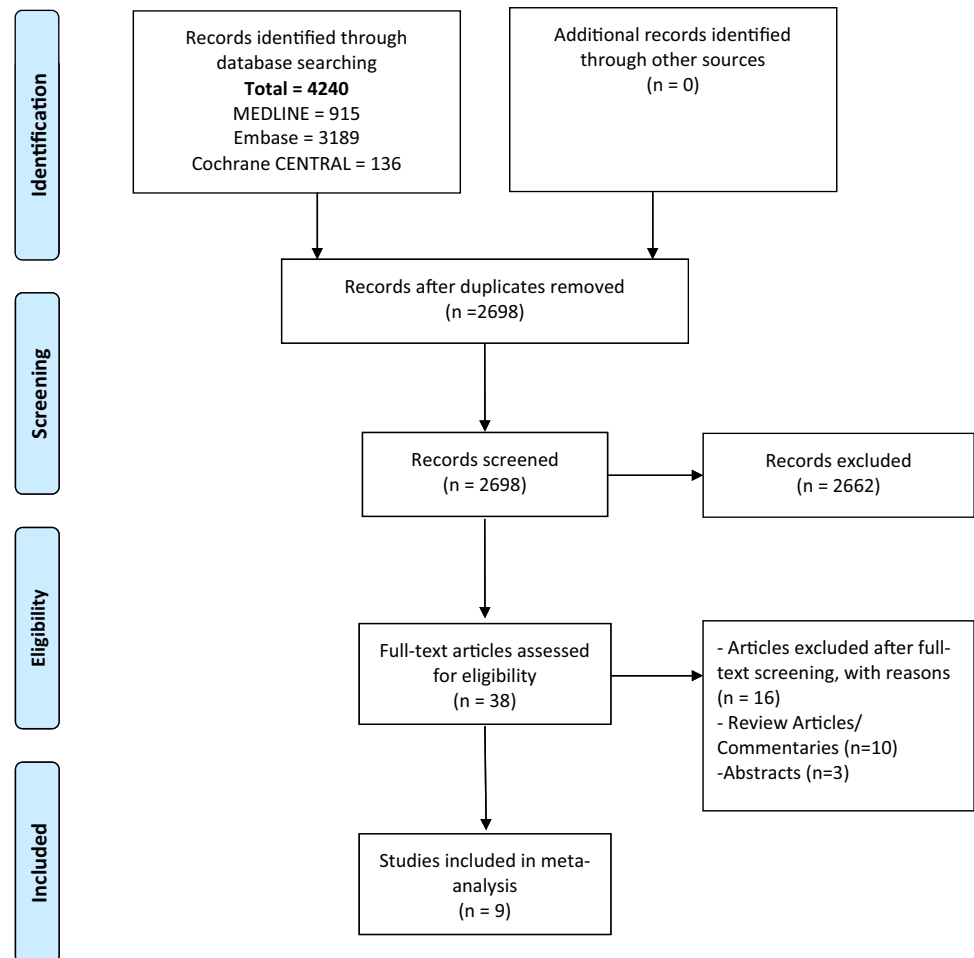
Progression to Mechanical Ventilation or Death

Six RCTs reported the outcome of progression to mechanical ventilation or death [24, 26, 28, 29, 31, 33]. 795 out of 2534 participants progressed to mechanical ventilation or died in the tocilizumab group compared to 951 out of 2414 participants in the standard care or placebo group. (RR 0.84, 95% CI 0.77–0.92, $p < 0.0001$) (Fig. 3C).

Time to Hospital Discharge

Four RCTs reported hazard ratios for median time to hospital discharge [24–26, 31]. Pooled analysis showed significantly improved outcome of median time to hospital discharge with tocilizumab therapy than standard therapy or placebo (HR 1.28, 95% CI 1.12–1.45, $p = 0.0002$) (Fig. 3D).

Subgroup Analysis

To improve the selection of patients who are most likely to benefit from tocilizumab, we examined the effect of disease severity, concomitant dexamethasone use, and sample

size on all-cause mortality. Five trials reported all-cause mortality in patients with severe or critical disease (on non-invasive or invasive ventilation). A total of 802 deaths out of 2825 participants were reported in the tocilizumab arm compared to 920 deaths out of 2792 participants in the standard care or placebo arm (RR 0.89, 95% CI 0.75–1.04, $p = 0.14$) [25, 29, 31, 33, 34]. In patients with mild or moderate disease, 44 deaths out of 533 participants were reported in the tocilizumab arm compared to 23 deaths out of 340 participants in the standard care or placebo arm (RR 1.20, 95% CI 0.73–1.96, $p = 0.47$) [24, 26–28] (Supplementary figure 1).

Three trials reported all-cause mortality in patients who received tocilizumab and dexamethasone. In patients that received dexamethasone along with tocilizumab, a total of 745 deaths out of 2624 participants were reported in the tocilizumab arm compared to 882 deaths out of 2624 participants in the standard care or placebo arm. Pooled analysis showed a significant reduction in all-cause mortality with tocilizumab therapy than standard therapy or placebo (RR 0.87, 95% CI 0.80–0.95, $p = 0.0009$) [26, 31, 33] (Supplementary figure 2).

Table 1 Study characteristics

Reference	Groups	Sample size	Median age (years)	Race or ethnic group—white %	Males (%)	DM2 (%)	HTN (%)	CRP (mg/L)	Mortality (%)	Concomitant treatment
BACC Bay Tocilizumab	TCZ	161	61.6 (46.4–69.7)	44	60%	28	50	110 (64.9–175.3)	5.59	Antivirals Hydroxychloroquine Glucocorticoids
	Placebo	82	56.5 (44.7–67.8)	40	55%	37	46	94.3 (58.4–142)	3.65	
RCT-TCZ-COVID	TCZ	60	61.5 (51.5–73.5)	N/A	66.7	16.7	27	105 (50–146)	3.33	Hydroxychloroquine Azithromycin Antiretrovirals Anticoagulation
	Standard care	63	60.0 (54–69)	N/A	56.1	13.6	29	65 (32–118)	1.59	
CORIMUNO-TOCI-1	TCZ	63	64.0 (57.1–74.3)	N/A	70	33	33	119.5 (74.5–219.5)	11.11	Antivirals Antiretrovirals Anakinra Eculizumab Glucocorticoids Anticoagulation Azithromycin
	Usual care	67	63.3 (57.1–72.3)	N/A	66	34	30	127 (84–171)	11.9	
COVACTA	TCZ	294	60.9±14.6	59.9	69.7	35.7	60.5	168.4±101.4	19.73	Glucocorticoids Antivirals Hydroxychloroquine Convalescent plasma
	Placebo	144	60.6±13.7	52.8	70.1	43.1	65.3	172.6±114.0	19.44	
REMAP-CAP	TCZ	353	61.5±12.5	70	74	N/A	N/A	150 (85–221)	27.76	Hydrocortisone Antivirals Immunoglobulin Macrolide Antiplatelet Statins Anticoagulation
	Control	402	61.1±12.8	74	70	N/A	N/A	130 (71–208)	35.32	
EMPACTA	TCZ	249	56.0±14.3	11.2	60.2	N/A	N/A	124.5 (2.5–2099)	10.44	Glucocorticoids Antivirals
	Placebo	128	55.6±14.9	15.6	57	N/A	N/A	143.4 (9–3776)	8.59	
RECOVERY	TCZ	2022	63.3 (13.7)	67	66	28	22	143 (107–204) mg/L	30.71	Hydroxychloroquine Antiviral Azithromycin Antiretrovirals
	Usual care	2094	63.9 (13.6)	68	69	29	24	144 (106–205)	34.81	
TOCIBRAS	TCZ	65	57.4 (15.7)	68	N/A	34	46	160±104	21.54	Corticosteroids Anticoagulation Other Immunosuppressants
	Control	64	57.5 (13.5)	69	N/A	31	53	193±283	9.37	Hydroxychloroquine Azithromycin
COVINTOC	TCZ	91	56 (47–63)	N/A	84	34	40	110.7	12.0	Corticosteroids Antivirals
	Control	88	54 (43–63)	N/A	86	49	39	88.1	17.04	

Table 2 Study design and criteria

Reference	Site	Design	Dates	Follow-up	Inclusion criteria	Primary outcome
BACC Bay Tocilizumab	USA	Randomized, double-blind, placebo-controlled trial	April 20 to June 15, 2020	28 days	SARS-CoV2 + fever + pulmonary infiltrates or need for supplemental oxygen. At least one of the following laboratory criteria also had to be fulfilled: a CRP 50 mg/L, ferritin > 500 ng/ml, D-dimer level > 1000 ng/ml, or LDH level > 250 U/L	Intubation (or death, for patients who died before intubation)
RCT-TCZ-COVID	Italy	Cohort-embedded, investigator-initiated, multicenter, open-label, randomized clinical trial	March 31 to June 11, 2020	28 days	SARS-CoV2 + fever + (PaO2/FiO2) ratio between 200 and 300 mg Hg, and/or CRP levels of > 10 mg/dL and/or CRP level increased to at least twice the admission measurement	Entry into ICU with invasive mechanical ventilation, death from all causes, or PaO_2/FiO_2 ratio less than 150 mm Hg
CORIMUNO-TOCI-1	France	Prospective, open-label randomized clinical trial	March 31 to April 18, 2020	60 days	SARS-CoV2 + or CT chest findings + moderate, severe, or critical pneumonia $O_2 > 3$ L/min, WHO-CPS score ≥ 5	Scores higher than 5 on the WHO-CPS scale on day 4 and survival without need of ventilation (including non-invasive ventilation) at day 14
COVACTA	Global	Multicenter, randomized, double-blind, placebo-controlled phase III trial	Apri 3 to May 28, 2020	28 days	SARS-CoV2 + chest Xray or CT findings + SpO2 < 93% or PaO2/FiO2 ratio < 300	Clinical status at day 28, as assessed on the seven-category ordinal scale
REMAP-CAP	Global	International, adaptive platform, open-label randomized controlled trial	April 19 to November 19, 2020	90 days	Confirmed COVID-19 who were admitted to the ICU and were receiving respiratory or cardiovascular organ support	Number of respiratory and cardiovascular organ support–free days up to day 21
EMPACTA	Global	Double-blinded, placebo-controlled, multicenter trial	N/A	60 days	Confirmed COVID-19 along with radiologic features who were saturating below 94% while breathing ambient air	Mechanical ventilation (invasive mechanical ventilation or extracorporeal membrane oxygenation) or death by day 28
RECOVERY	UK	Randomized, controlled, open-label, platform trial	N/A	28 days	Clinical evidence of progressive COVID-19 (defined as oxygen saturation < 92% on room air or receiving oxygen therapy, and CRP ≥ 75 mg/L)	All-cause mortality

Table 2 (continued)

| Reference	Site	Design	Dates	Follow-up	Inclusion criteria	Primary outcome
TOCIBRAS	Brazil	Multicenter, randomized, open-label, parallel group, superiority trial	May 8 to July 17, 2020	15 days	Confirmed severe or critical COVID-19 + receiving supplemental or receiving mechanical ventilation for < 24 h before analysis + At least two of the following criteria had to be met: D-dimer > 1000 ng/mL, CRP > 50 mg/L, ferritin > 300 µg/L, or LDH greater than the upper limit of normal	Clinical status at 15 days evaluated with the use of a seven-level ordinal scale
COVINTOC	India	Open-label, randomized, multicenter, controlled phase III trial	May 30 to August 31, 2020	28 days	Confirmed COVID-19 + moderate to severe disease (moderate defined as respiratory rate 24/min and SpO2 90-94%; and severe defined as respiratory rate ≥ 30/min or SpO2 < 90% in ambient air or ARDS or septic shock)	Proportion of patients with progression of COVID-19 from moderate to severe or from severe to death up to day 14
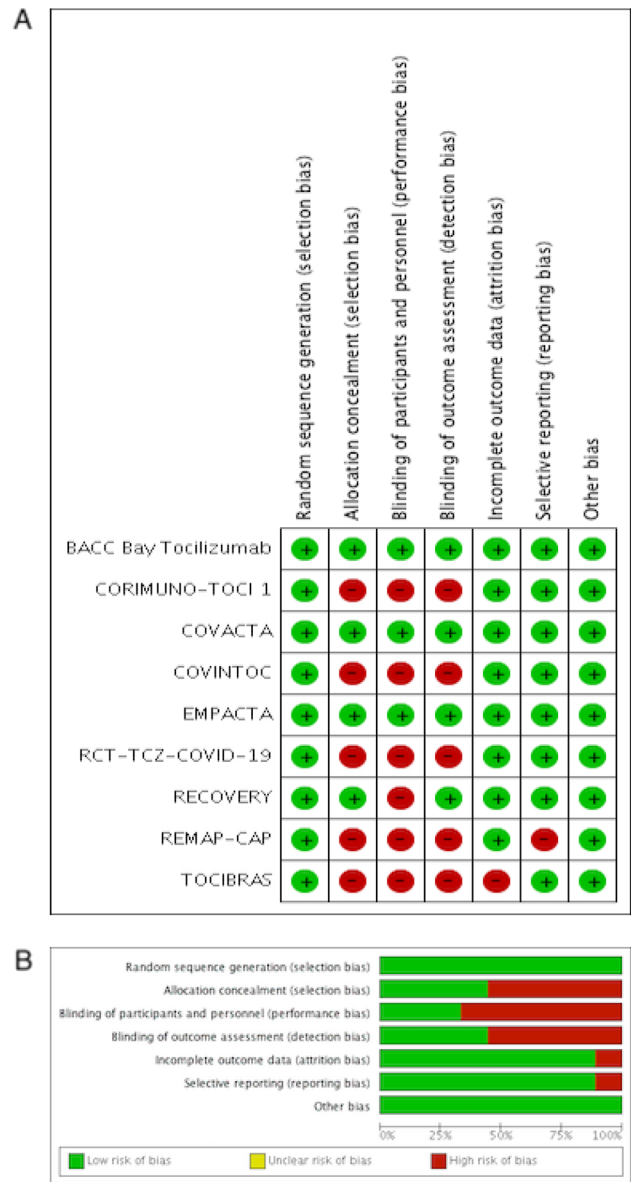
Fig. 2 Risk of bias assessment of trials included in the study

Four RCTs enrolled more than 100 patients in each arm. In these trials, there was a statistically significant reduction in all-cause mortality in patients who received tocilizumab compared to standard care or placebo (RR 0.88, 95% CI 0.81–0.95, $p = 0.001$) [25, 26, 31, 33]. However, in RCTs with less than 100 patients in each arm, all-cause mortality outcomes were not statistically significant (RR 1.16, 95% CI 0.68–1.98, $p = 0.59$) [24, 27–29, 34] (Supplementary figure 3).
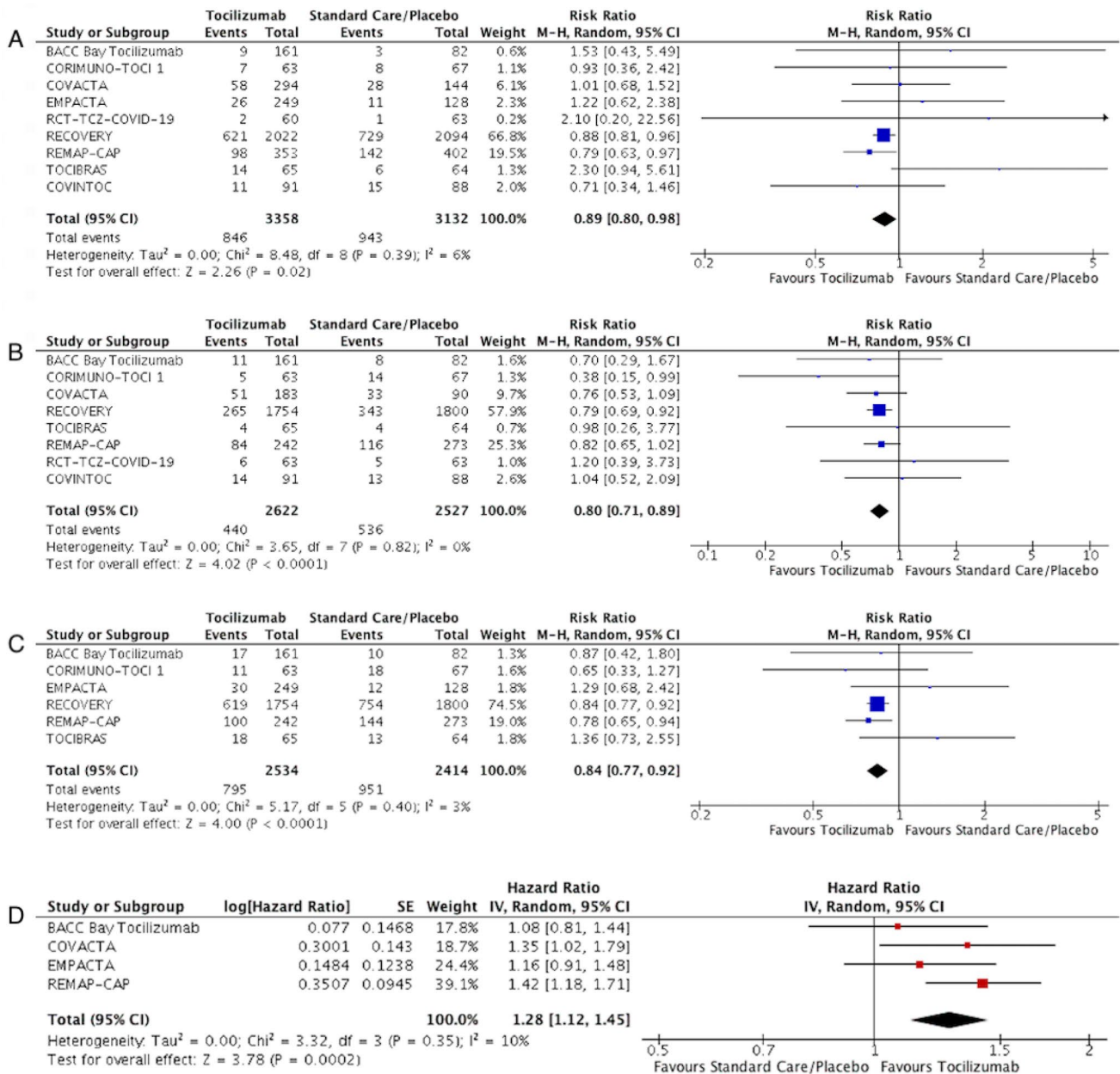
Fig. 3 Forest plots for primary and secondary outcomes. **A** Mortality outcome. **B** Progression to mechanical ventilation. **C** Progression to mechanical ventilation or death. **D** Time to discharge

Discussion

This meta-analysis provides a comprehensive aggregate analysis of the available randomized trials to date on the efficacy and safety of tocilizumab therapy in hospitalized patients with COVID-19 Infection. The results of this study favored mortality benefit with tocilizumab treatment in hypoxemic COVID-19 patients, even though they were not statistically significant. Tocilizumab therapy was also associated with reduced progression to mechanical ventilation and early hospital discharge or readiness to discharge

than standard therapy or placebo in hospitalized COVID-19 patients.

Recent Infectious Diseases Society of America (IDSA) guidelines conditionally suggest the use of tocilizumab in addition to standard of care rather than standard care alone among hospitalized patients with progressive severe or critical COVID-19 [35]. The National Institutes of Health (NIH) guidelines also recommend the use of tocilizumab along with dexamethasone in hospitalized patients who have been admitted to the intensive care unit within the prior 24 h and who require invasive mechanical ventilation, non-invasive

mechanical ventilation, or high-flow nasal cannula oxygen (> 0.4 FiO2/30 L/min of oxygen flow). They also recommend the use of tocilizumab in hospitalized patients with rapidly increasing oxygen needs and with significantly increased markers of inflammation [36]. Our study findings support these guidelines, especially in patients with severe or critical disease in whom tocilizumab use favored improved mortality.

The hyperinflammation phase in COVID-19 involves several cytokines and chemokines. However, tocilizumab only inhibits one cytokine, IL-6. In the RCT-TCZ-COVID study, only 4% of the patient population received steroids. Tocilizumab use did not reduce the risk of clinical worsening in the study population [27]. Also, in the BACC Bay Tocilizumab study, only 10% of the study population received glucocorticoids [24]. There was no significant effect on the risk of intubation or death, on disease worsening, on time to discontinuation of supplemental oxygen. With concomitant dexamethasone administration, there appears to be a synergistic or additive effect on numerous inflammatory pathways. In the EMPACTA trial, 55.4% of the patients in the tocilizumab group and 67.2% of those in the placebo group received concomitant dexamethasone [26]. Patients who received tocilizumab were less likely than those who received placebo to undergo mechanical ventilation or die by day 28. In the REMAP-CAP trial, steroid use increased to 88%, and tocilizumab was found to improve mortality and time to clinical improvement [31]. In the RECOVERY trial, 82% of the patients received dexamethasone and tocilizumab resulted in a 6% reduction in mortality when combined with dexamethasone but had no impact on mortality given alone [33].

The severity of illness seems to play an important role in determining the benefit of tocilizumab in this population. In the RCT-TCZ-COVID study, only patients with PaO2/FiO2 ratios between 200 and 300 mm were included [27]. In the BACC Bay tocilizumab study, patients requiring > 10 L/min oxygen were excluded [24]. In both studies, primary outcomes were not met. In the CORIMUNO-TOCI-1 trial, patients with a WHO-CPS score of 5 with O2 levels of 3 L/min or higher but without non-invasive ventilation (NIV) or mechanical ventilation (MV) were enrolled. Survival without invasive or non-invasive mechanical ventilation by day 14 was met, but mortality at day 28 was not different between the groups. Effects of tocilizumab may have also been diminished due to greater steroid use in the control group [28]. In the COVACTA trial, 38% of the patients were mechanically ventilated. There was no significant difference between the tocilizumab and placebo groups concerning clinical status or mortality at day 28, although the time to hospital discharge was shorter with tocilizumab (HR 1.35; 95% CI 1.02–1.79). Besides, patients initially located outside the ICU were less likely to be transferred to the ICU

if treated with tocilizumab [25]. In the REMAP-CAP trial, the greatest benefit was seen in patients admitted to the ICU for organ support (e.g., high-flow nasal cannula or ventilation) [31].

Our meta-analysis has certain limitations. Firstly, the number of patients in the RECOVERY trial was much higher than other RCTs (study weight 66.8%) [33]. Secondly, there were differences in enrollment criteria, the time at which anti–interleukin-6 therapy was initiated, the primary outcome, and background care. Thirdly, five studies enrolled less than 100 patients in each arm of the trial. Due to the small sample size, they may not have been powered adequately to detect a statistical difference in outcomes. Lastly, six of the included studies had an open-label design, implying high risk of performance and selection bias due to lack of blinding of participants and personnel to intervention, limiting our ability to interpret the results.

In conclusion, our meta-analysis suggests tocilizumab, when used along with dexamethasone, could be an effective therapeutic option with promising evidence on reduced mortality, progression to mechanical ventilation, and early discharge from hospital. Variations in inflammatory cascade pathophysiology make the timing of initiating treatment with tocilizumab crucial. Future studies could assess the timing of intervention based on associated comorbidities and inflammatory markers, the economic benefits of tocilizumab and other IL-6 inhibitors in patient outcomes, and critical healthcare resource usage.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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