REVIEW ARTICLE

Comparing the efficacy of tocilizumab with corticosteroid therapy in treating COVID-19 patients: a systematic review and meta-analysis

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Abstract

Purpose Tocilizumab has shown equivocal outcomes in reducing mortality in COVID-19. The corticosteroids appear to be an affordable alternative to tocilizumab. This study aims to estimate the efficacy of tocilizumab and the corticosteroids particularly dexamethasone and methylprednisolone and to identify possible determinants of their efficacy.

Methods Five electronic databases were searched for studies involving tocilizumab, dexamethasone, and methylprednisolone in treating COVID-19. We included case–control and randomized or partially randomized trials. Meta-regression for patient baseline characteristics, co-medications, and tocilizumab dose regimens was performed to identify contributing factors to drug efficacy.

Results Thirteen randomized controlled trials (RCTs) and twenty-four case–control studies were included in our meta-analysis involving 18,702 patients. Meta-analysis among the RCTs showed that a summary estimate favoring mortality reduction (OR 0.71, 95%CI 0.55 – 0.92) contributed mainly by tocilizumab and dexamethasone. Among case–control studies, meta-analysis showed mortality reduction (OR 0.52, 95%CI 0.36 – 0.75) contributed by tocilizumab and tocilizumab-methylprednisolone combination. Methylprednisolone alone did not reduce mortality except for one study involving high dose pulse therapy. Meta-analysis also found that all three drugs did not significantly reduce mechanical ventilation (OR 0.72, 95%CI 0.32 – 1.60).

Conclusion Tocilizumab and dexamethasone emerge as viable options in reducing mortality in severe COVID-19 patients. A tocilizumab-corticosteroid combination strategy may improve therapeutic outcome in cases where single therapy fails.

Keywords COVID-19 · Tocilizumab · Dexamethasone · Methylprednisolone · Meta-analysis

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Introduction

The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to challenge the capacity of healthcare systems and government public health policies worldwide. As of mid-January 2021, the coronavirus disease 2019 (COVID-19) pandemic has resulted in over 94 million cases and over 2 million deaths globally. The mortality rate has clearly increased in last three months which recorded approximately 1 million deaths in that period alone [1]. An updated re-evaluation of efficacy of the current COVID-19 treatment strategies to reduce disease mortality is important at this juncture of the pandemic.

Mortality attributable to SAR-CoV-2 infection occurs mainly through the development of viral pneumonia-induced acute respiratory distress syndrome (ARDS), multi-organ failure, and blood clots. Accumulating evidence suggests

these severe and potentially fatal clinical manifestations are associated with increased levels of inflammatory mediators including cytokines and chemokines such as interleukin-2 (IL-2), IL-6, IL-10, tumor necrosis factor (TNF), macrophage inflammatory protein alpha (MIPα or also known as CCL), C-reactive protein (CRP), ferritin, and D-dimer in the blood of severely ill COVID-19 patients [2–4]. The high correlation between blood IL-6 and disease mortality suggests that fatal COVID-19 is characterized as a cytokine release syndrome (CRS) induced by a cytokine storm with high mortality [5]. These notable features provide the basis for the use of anti-inflammatory and immunomodulatory agents to counter the hyperinflammation in severe COVID-19. These immune system-modulating drugs already in clinical use for other inflammatory and autoimmune disorders have been repurposed to treat COVID-19. Among them, the interleukin-6 receptor antagonists including tocilizumab and sarilumab, and the less costly corticosteroids such as methylprednisolone and dexamethasone are the current prominent examples most frequently reported [6]. Despite the theoretically sound rationale supporting the use of the IL-6 inhibitors and corticosteroids, early studies investigating them as COVID-19 treatments have shown mixed outcomes [6]. In addition, there still lingers the controversy of using immunomodulatory drugs in an infection which may reduce the immune system's ability to overcome the viral infectious agent and may instead worsen disease outcome and increase the risk of secondary infections [7, 8].

In this systematic review, we aimed to collate studies investigating the use of tocilizumab and corticosteroids particularly dexamethasone and methylprednisolone in COVID-19 treatment and sought for summative evidence for their efficacy in treating the disease. Particularly, we assessed the ability of the drugs to reduce mortality and prevent events of needing invasive mechanical ventilation in severe COVID-19 cases. By including both tocilizumab and the corticosteroids in our analysis, we also aimed to compare the efficacy of tocilizumab, an expensive drug with the less costly dexamethasone and methylprednisolone. Finally, we aimed to determine the possible predictors that may explain the efficacy (or non-efficacy) of the drugs.

Methods

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [9] on available quantitative studies that reported on treatment of COVID-19 with tocilizumab and corticosteroids. The study was registered with the National Medical Research Register of Malaysia (No: NMRR-20–2263-56296). This study did not require ethical

approval as all analyses were performed on data extracted from published studies.

Literature search strategy

An extensive search of literature published in the electronic databases PubMed, Google Scholar, Scopus, Wiley and Science Direct was conducted from January 2020 to October 2021 using the following search terms: 'Covid-19' OR 'SARS-CoV-2' AND 'tocilizumab', 'interleukin 6', 'IL-6', 'corticosteroid', 'dexamethasone' and 'methylprednisolone'. In addition, the bibliography of each retrieved article was screened for relevant articles.

Study selection and data collection

Randomized controlled trials (RCTs) and case–control studies in the English language on anti-IL-6 receptor antibody tocilizumab or corticosteroids (methylprednisolone and dexamethasone) in comparison to standard of care (SOC) for the treatment of COVID-19, and reporting at least one of four outcomes (mortality, requirement for mechanical ventilation, admission to intensive care unit and day of hospitalization) were included. Publications which only involved a single arm (treatment without SOC), editorials, reviews, notes, comments, conference proceedings and letters were excluded. A standardized data collection sheet was used to extract the data. The following information was collected: first author, publication title, year of publication, country, study design, description of the study population and the outcomes.

Potentially eligible studies were selected by screening the titles and abstract independently by two investigators (LPC, RR). After removal of duplications, the full text articles were obtained and assessed for eligibility by two investigators (CMF, WKL) by applying the predefined inclusion and exclusion criteria. Decisions to include or exclude were compared between the two investigators. When disagreements arose and primary reviewers could not reach a consensus, the other investigators were consulted to resolve the disagreement.

Quality assessment

Quality assessment of eligible studies was performed by two reviewers (LPC, RR) independently using the modified Jadad scale [10, 11] for RCTs and the Newcastle–Ottawa scale [12] for case–control studies. The modified Jadad scale consists of eight items measuring representativeness. These including two items each for grading randomization and blinding and one item each for grading withdrawal and dropout, inclusion or exclusion criteria, adverse effect and statistical analysis. The score ranges from 0 (lowest quality)

to 8 (highest quality) with scores ranging from 0 to 3 denoting poor to low quality and 4 to 8 indicating good to excellent quality. On the other hand, the Newcastle–Ottawa scale contains three domains to assess the quality of the selection of case and control, the comparability of case and control and the ascertainment of exposure [12]. The scoring was a star for each item in selection and exposure and a maximum of two stars for comparability for a total score that ranges from 0 to 9 stars [13].

Statistical analysis

Heterogeneity among the studies was determined using I^2 statistic. I^2 value of 25%, 50% and 75% were considered low, moderate and considerable heterogeneity respectively [14]. Data was pooled using the Mantel–Haenszel method and the Hartung-Knapp-Sidik-Jonkman random-effects model. Odd ratios of each study were generated and forest plots constructed. Subsequently, meta-regression analysis was performed to explore a priori variables that possibly affect the overall efficacy of the drugs in reducing mortality. These variables include the baseline characteristics of the populations (age, gender composition, comorbidities, and levels of CRP, ferritin, and IL-6), time of treatment initiation, tocilizumab dose and number of doses given, and the SOC co-medications given. Other variables were not included because of missing data. Additionally, for studies that showed significant reduction in mortality, independent t-tests were performed comparing the treatment versus SOC arms for each of the variables. Finally, a funnel plot was constructed and Egger's test of asymmetry performed to assess for publication biases.

Meta-analysis, meta-regression and generation of the plots were performed using R software version 4.0.3 (The R Core Team, Vienna, Austria) and the metafor v2.4.0 package [15]. Paired t-tests were done using SPSS 16.0 (IBM Corp., New York, US).

In addition, trial sequential analysis was conducted using TSA software version 9.5.10 (Copenhagen Trial Unit, Copenhagen, Denmark) for included RCTs in this meta-analysis to determine whether the cumulative evidences were reliable. The adjusted required information size was calculated using alpha = 0.05 (two-sided) and beta = 0.20 (80% power).

Results

Electronic database searches initially identified 5,852 potentially relevant publications (Fig. 1). After removal of duplications, exclusion of irrelevant publications based on title and abstract and further exclusion of articles based on the
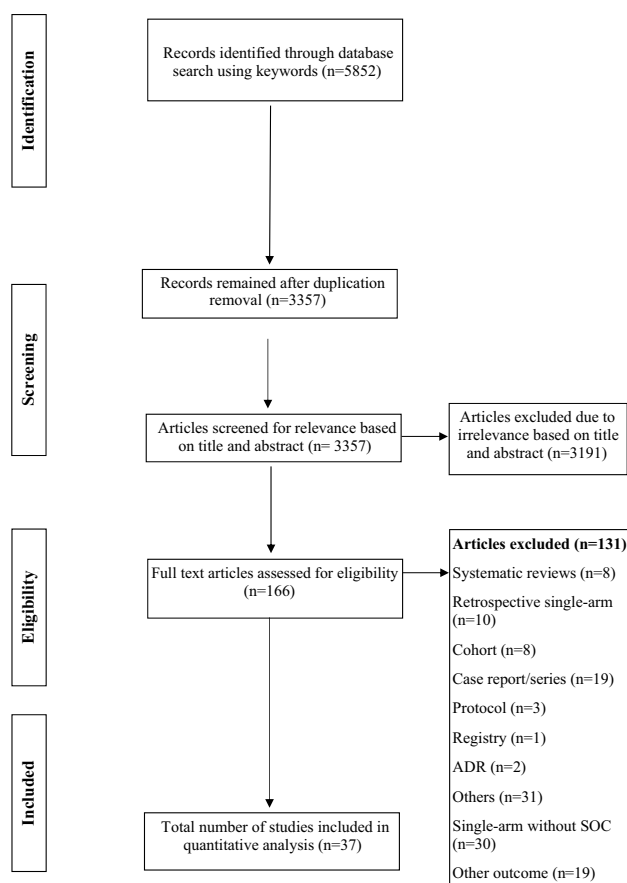

Fig. 1 Flow chart for study screening and selection according to PRISMA guidelines

eligibility criteria, 13 RCTs [16–28] and 24 case–control studies [29–52] were included in the meta-analysis.

The studies included were conducted in single-centres or multi-centres in several countries namely Canada, United States of America, Mexico, Brazil, United Kingdom, France, Germany, Denmark, the Netherlands, Italy, Spain, Kenya, Iran, India and China. A total of 18,702 COVID-19 patients, a majority of them being male (69.5%) were included in this systematic review. All the patients included in the analysis were hospitalized and were having stage 3 severe COVID-19 infection (having one or more of these characteristics: $SpO_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%) as well as stage 5 patients requiring invasive mechanical ventilation. The evidence is summarized in Tables 1 and 2.

The quality assessment tables for the RCTs and case–control studies included in the systematic review are given in Supplementary Data Tables S1 and S2. Ten RCTs did not mention the assessment of adverse events in their methodology but reported the adverse events in the result. Majority

Table 1 Evidence summary of included randomised controlled trials

Date of publication[a]	Study	Study design	Number of patients	Patient characteristics	Disease severity (stage 1- 5)[b]	Tocilizumab/ Methylprednisolone/ Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
Preprint June 2020	Corral-Gudino et al. [16]	Partially randomised, open label trial, multi-centre, Spain	85	Mean age 68 ± 12 years 58% male, 46% hypertensive 15% diabetic	4	**Methylprednisolone** 40 mg IV every 12 h for 3 days followed by 20 mg every 12 h for 3 days N=56	Lopinavir-ritonavir, hydroxychloroquine, azithromycin, low molecular weight heparin N=29
July 2020	Horby et al (RECOVERY) [17]	Randomised, open label trial, multicentre, UK	6425	Mean age 66.1 ± 15.7 64% male 24% diabetic	3—5	**Dexamethasone** 6 mg oral or IV once daily for up to 10 days N=2104	25% were given azithromycin, 0 to 3% were given lopinavir-ritonavir and hydroxychloroquine. 2% were given tocilizumab or sarilumab N=4321
August 2020	Jeronimo et al. [18]	Randomised, double-blind, placebo-controlled trial, single-centre Brazil	393	Mean age 55 ± 15 62.6% male 48.9% hypertensive, 29.1% diabetic	4—5	**Methylprednisolone** 0.5 mg/kg IV twice daily for 5 days N=194	Azithromycin, another antibiotic (ceftriaxone) N=199
September 2020	Tomazini et al. [19]	Randomised, open label, multi-centre, Brazil	299	Mean age 61 ± 14 63% male, 66% hypertensive, 21% diabetic	5	**High dose Dexamethasone** 20 mg IV once daily for 5 days followed by 10 mg IV once daily for 5 days or until ICU discharge N=151	Not stated N=148
Preprint September 2020	Salama et al. (EMPACTA) [20]	Randomised, double-blind, placebo-controlled, Multi-centre, six countries	377	Mean age 56 ± 14. 60.2% male 48.3% hypertensive, 40.6% diabetic. Multiple ethnicities including minor ethnicities	4	**Tocilizumab** 8 mg/kg one to doses N=249	Dexamethasone (59%), remdesivir (54.6%) N=128
Preprint September 2020	Rosas et al (COVACTA) [21]	Randomised, double-blind, placebo-controlled, Multi-centre, nine countries	438	Mean age 60.9 ± 14.6 in treatment group and 60.6 ± 13.7 in placebo group 69.9% male 60.5% hypertensive, 35.7% diabetic	3—5	**Tocilizumab** 8 mg/kg one to two doses N=294	Lopinavir–ritonavir, remdesivir, lopinavir, ritonavir, chloroquine, hydroxy-chloroquine, systemic glucocorticoids N=144

Table 1 (continued)

Date of publication[a]	Study	Study design	Number of patients	Patient characteristics	Disease severity (stage 1 - 5)[b]	Tocilizumab/ Methylprednisolone/ Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
September 2020	Edalatifard et al. [22]	Single-blind, randomized controlled, three centres, Iran	62	Mean age 58.5 ± 16.6, 62.9% male, 53.5% diabetic, 32.3% hypertensive	3	**High dose methylprednisolone** 250 mg/d for 3 days N=34	Hydroxychloroquine, lopinavir, naproxen N=28
October 2020	Salvarani et al. [23]	Italy	126	Median age 60 (53-72), 61% male, 15.1% diabetic, 44.4% hypertensive	4	**Tocilizumab** 8 mg/kg up to 800 mg N=60	N=63
Preprint January 2021	REMAP-CAP [24]	Double-blind, placebo-controlled, multi-centre, UK	755	Mean age 61.4 ± 12.7 72.7% male 35.4% diabetic and 10.2% have severe cardiovascular disease	3—5	**Tocilizumab** 8 mg/kg one to two doses N=353	Dexamethasone, remdesivir N=402
April 2021	Jamaati et al. [25]	Single centre, Iran	50	Median age 54 (37 – 63) in treatment group, 61.5 (54 – 62) in SOC group. 67% male. 44% hypertensive, 56% diabetic	**3—5**	**High dose dexamethasone** 20 mg/day days 1—5, followed by 10 mg/day on days 6 – 10 N=25	N=25
May 2021	RECOVERY [26]	Single centre, open label, UK	2022	Mean age 63.3 ± 13.7 in treatment group, 63.9 ± 13.6 in SOC group. 28% diabetic	3—5	**Tocilizumab** 800 mg if weight > 90 kg; 600 mg if weight > 65 and ≤90 kg; 400 mg if weight > 40 and ≤ 65 kg; and 8 mg/kg if weight ≤ 40 kg) N=2022	N=2094
May 2021	Hermine et al. [27]	Multi-centred, open-label, France	130	Median age 64.0 (57.1 – 74.3) in treatment group, 63.3 (57.1— 72.3) in SOC group. 70% male. 33% diabetic	3—5	**Tocilizumab** 8 mg/kg IV on day 1, an additional fixed dose of 400 mg IV on day 3 if oxygen requirement was not decreased N=63	N=67

Table 1 (continued)

Date of publication[a]	Study	Study design	Number of patients	Patient characteristics	Disease severity (stage 1 - 5)[b]	Tocilizumab/ Methylprednisolone/ Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
May 2021	Soin et al.[28]	Multi-centred, open label, India	179	Median age 56 46–62 in treatment group, 54 43–62 in SOC group.84% male, 34% diabetic and 40% hypertensive in treatment group	3—5	**Tocilizumab** A single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. An additional dose of 6 mg/kg (max 480 mg/kg) could be administered if clinical symptoms worsened N=91	Remdesevir, corticosteroids N=88

[a]Date of publication online. "Preprint" is stated if the study was first found and included in its preprint version

[b]COVID-19 severity stage 1: asymptomatic; stage 2: symptomatic but without pneumonia; stage 3: mild pneumonia without need of oxygen supplementation; stage 4: acute respiratory distress syndrome with one or more the following characteristics: $SpO_2 < 94\%$ on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%; stage 5: Critical disease needing invasive mechanical ventilation

of the studies performed web-based block-randomization but did not blind the clinicians and patients (open-label) while only two RCTs were double blinded. Patients in the control group were not informed about the study in studies conducted by Hermine et al. [27] and Salvarani et al. [23]. All randomized control studies were of good to excellent quality except for the study by Coral-Gudino et al. [16] that only scored 3. The studies by Tomazini et al. [19], Edalatifard et al. [22], Hermine et al. [27], RECOVERY [26] and Salvarani et al. [23] scored 5 while the studies by Jeronimo et al. [18], Horby et al. [17], Salama et al. [20], Rosas et al. [21], REMAP-CAP [24] and Soin et al. [28] scored 6 each. Meanwhile, the study by Jamaati et al. [25] scored 4 as there was no description on blinding, withdrawal and also no mention on the method of assessing adverse effects. The study by Corral-Gudino et al. [16] was graded poor quality as there was no description on blinding and partial randomization was practiced since there was a clinician preference arm. All the case–control studies were graded good quality with 6 to 9 stars except for the studies by Wadud et al. [34] and Huang et al. [50]. Wadud et al. [34] scored 3 stars because there was no mention of study selection and in terms of comparability, no data on gender and co-morbidities. On the other hand, the study by Huang et al. [50] scored 5 stars because of selection bias.

A meta-analysis pooling data from the 13 RCTs (Fig. 2) yielded a summative odds ratio for mortality of 0.71 (95%CI 0.55—0.92) with considerable heterogeneity ($I^2 = 79\%$, $\tau^2 = 0.07$, $p < 0.01$). This summative odds ratio for mortality indicated that when all studies involving the three drugs were considered in a single analysis, the treatments showed a significant reduction in mortality. Individually examining each RCT however, we identified two studies involving tocilizumab that contributed to this favourable outcome: REMAP-CAP (OR 0.63 95%CI 0.46—0.86) and RECOVERY (OR 0.83 95%CI 0.73 – 0.95). Among studies involving the corticosteroids, only the study by Horby et al. [17] involving dexamethasone stood out to reduce mortality significantly (OR 0.45, 95% CI 0.39 – 0.52). None of the trials involving methylprednisolone indicated COVID-19 mortality reduction except for the study by Edalatifard et al. [22] which used high-dose (> 1.5 mg/kg/day) pulse methylprednisolone.

All-treatment meta-analysis of the 24 case–control studies (Fig. 3) yielded an overall summative odds ratio indicating mortality reduction (OR 0.53 95%CI 0.37 -0.77). Of these 24 studies, seven studies that showed favourable outcomes involved tocilizumab [30, 32, 37–41]. The one study involving dexamethasone, Fusina et al. [51] failed to reduce COVID-19 mortality (OR 1.28 95% CI 0.99 -1.67) while the two studies included that used methylprednisolone alone (Mikulska et al., OR 0.32, 95% CI 0.10 – 1.03; Nelson

Table 2 Evidence summary of included case–control studies

Date of publication[a]	Study	Country, single or multi centre	Number of patients	Patient characteristics	Disease severity (stage 1 - 5)[b]	Tocilizumab/ Methylprednisolone/ Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
May 2020	Campochiaro et al. [29]	single-centre, Italy	65	Median age 64 [53–75] in treatment arm, 60 [55–75.5] in SOC arm 86.5% male 42.5% hypertensive 15% diabetic	4	**Tocilizumab** All received 400 mg IV infusion. 72% received one dose only N = 32	Lopinavir-ritonavir, hydroxychloroquine, azithromycin, other antibiotics, enoxaparin N = 33
May 2020	Capra et al. [30]	single-centre, Italy	85	Median age 65 [54.5–73] 75% male 46% hypertensive 16% diabetic	4	**Tocilizumab** 33 received 400 mg IV infusion while 27 received 324 mg subcutaneously. All received one dose only N = 62	Lopinavir-ritonavir, hydroxychloroquine N = 23
May 2020	Colaneri et al. [31]	single-centre, Italy	112	Median age 63.55 IQR 16.95 73% male, 25% hypertensive 9% diabetic	4	**Tocilizumab + methylprednisolone** > 400 mg (8 mg/kg) IV + methylprednisolone 1 mg/kg IV. A second dose of tocilizumab was given if no adverse effect reported N = 21	Hydroxychloroquine, azithromycin, low molecular weight heparin N = 91
May 2020	Klopfenstein et al. [32]	single-centre, France	45	Mean age 76.8 ± 11 years in treatment arm, 70.7 ± 15 in SOC arm 49.5% hypertensive 28.5% diabetic	4	**Tocilizumab** > 400 mg (8 mg/kg) one to two doses N = 20	Lopinavir-ritonavir, hydroxychloroquine, antibiotics N = 25
May 2020	Quartuccio et al. [33]	Single-centre, Italy	111	Mean age 62.4 ± 11.8 in treatment group, 56.2 ± 14.2 I SOC group 71.2% male 39% hypertensive	4	**Tocilizumab** > 400 mg (8 mg/kg) IV infusion one dose only N = 42	Lopinavir-ritonavir, other antivirals (darunavir-cobicistat, remdesivir) hydroxychloroquine, low molecular weight heparin N = 69
Preprint May 2020	Wadud et al. [34]	Single-centre, USA	94	Median age was 55.5 years in the treatment group and 66 in the control group No co-morbidities are given	4—5	**Tocilizumab** No dose and number of doses were mentioned N = 44	Not stated N = 50

Table 2 (continued)

Date of publication[a]	Study	Country, single or multi centre	Number of patients	Patient characteristics	Disease severity (stage 1 - 5)[b]	Tocilizumab/Methylprednisolone/Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
June 2020	Rojas-Marte et al. [35]	Single-centre, USA	193	Mean age 60.4 ± 13.8, 71% male, 53.9% hypertensive, 34.7% diabetic	3—5	**Tocilizumab** Dose used was not stated. All patients received one dose only N=96	93 – 95% received hydroxychloroquine, 93% received azithromycin, 11–12% received remdesivir, 48 -59% received prophylactic anticoagulant N=97
July 2020	Canziani et al. [36]	Multicentre, Italy	128	Mean age 63 ± 10, 73% male, 52% hypertensive	4	**Tocilizumab** >400 mg (8 mg/kg) IV infusion followed by a second dose 24 h later N=64	Lopinavir-ritonavir, hydroxychloroquine, azithromycin, other antibiotics (ceftriaxone, piperacillin-tazobactam), darunavir, enoxaparin N=64
July 2020	Ramiro et al (CHIC study) [37]	Single-centre, The Netherlands	172	Mean age 67 ± 11, 79% male, 26.5% hypertensive, 19% diabetic	4—5	**Tocilizumab+methylprednisolone (high dose on day 1)** Methylprednisolone 250 mg on day 1 followed by 80 mg on days 2–5 (N=49) When no improvement, tocilizumab was added on as a single 8 mg/kg (>400 mg) infusion post day 2 (N=37) N=86	80% received chloroquine 300 mg bd following a loading dose of 600 mg, 99% received antibiotic (ceftriaxone), 91% received prophylactic low molecular weight heparin N=86
July 2020	Rosotti et al. [38]	Single-centre, Italy	222	Median age 59 [51–71] in treatment group, 59 [52–70] in SOC group 81.8% male Comorbidities given as Charlson index 2 1–4	4—5	**Tocilizumab** >400 mg (8 mg/kg) IV infusion, a second dose was given in cases of persistent fever N=74	Ritonavir/lopinavir, hydroxychloroquine, remdesivir N=148
July 2020	Somers et al. [39]	Single-centre, USA	154	Mean age 58 ± 14.9 66% male, 66% hypertensive 16.5% diabetic	5	**Tocilizumab** >400 mg (8 mg/kg) IV infusion. Second dose was discouraged N=78	Hydroxychloroquine (23%), remdesivir N=76

Table 2 (continued)

Date of publication[a]	Study	Country, single or multi centre	Number of patients	Patient characteristics	Disease severity (stage 1 - 5)[b]	Tocilizumab/Methylprednisolone/Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
August 2020	Biran et al. [40]	Multicentre, USA	630	Median 62 [53–71] in treatment arm, 65 [56–74] 69.2% male 59.7% hypertensive 37.3% diabetic	4	**Tocilizumab** 98% received 400 mg IV infusion. 88% received one dose only N = 210	Hydroxychloroquine, azithromycin N = 420
August 2020	De Rossi et al. [41]	Single-centre, Italy	158	Mean age 62.9 ± 12.5 in treatment arm, 71 ± 14.6 in SOC arm 72% male, 44% hypertensive 23% diabetic	4	**Tocilizumab** 43 received 400 mg IV. once and 47 received 324 mg subcutaneously once. All received one dose only N = 90	Lopinavir-ritonavir 800/200 mg once daily, hydroxychloroquine 400 mg daily N = 68
August 2020	Klopfenstein et al. [42]	Single-centre, France	206	Mean age 75.6 ± 11.3 in treatment group, 74.3 ± 11 in SOC group 64.5% male 55.6% hypertensive 22.6% diabetic	4	**Tocilizumab** > 400 mg (8 mg/kg) one to two doses N = 30	Lopinavir-ritonavir, hydroxychloroquine, antibiotics, and corticosteroids N = 176
August 2020	Mikulska et al. [43]	Single centre, Italy	196	Mean age 67.5 ± 13.7 67.4% male 39.3% hypertensive 15.3% diabetic	4	Three treatment groups were observed: **Tocilizumab arm** > 400 mg (8 mg/kg) IV one to two doses, N = 29 **Methylprednisolone arm** 1 mg/kg IV for 5 days followed by 0.5 mg/kg IV for 5 days, N = 45 **Tocilizumab + methylprednisolone arm** N = 56	Hydroxychloroquine, darunavir-ritonavir, low molecular weight heparin N = 66
August 2020	Nelson et al. [44]	Single-centre, USA	84	Median age 60 46–67 in treatment group, 62 [55–70] in SOC group 69% male Comorbidities were given as Charlson index of 3 1–4	5	**Methylprednisolone** 80 mg/day (1 mg/kg/day) IV for 5 days N = 42	Hydroxychloroquine, azithromycin N = 42

Table 2 (continued)

Date of publication[a]	Study	Country, single or multi centre	Number of patients	Patient characteristics	Disease severity (stage 1 - 5)[b]	Tocilizumab/Methylprednisolone/Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
September 2020	Ruiz-Irastoza et al. [45]	single centre, Spain	242	Mean age 64.4 ± 14.3 62.0% male 21.1% diabetic, 48.4% hypertensive	4	**High dose methylprednisolone** 125–250 mg/d for 3 days N = 61	Hydroxychloroquine, lopinavir/ritonavir, low molecular weight heparin N = 181
November 2020	Roumeir et al (TOCICOVID study) [46]	Single- centre, France	96	Mean age 59.9 ± 12.5. 81% male, 25% hypertensive, 27% diabetic	4—5	**Tocilizumab** 8 mg/kg IV up to maximum of 800 mg IV N = 49	Hydroxychloroquine, azithromycin, beta-lactams, lopinavir-ritonavir N = 47
November 2020	Tsai et al. [47]	Single-centre, USA	132	Mean age 62.38 ± 13.49 in treatment group, 61.35 ± 16.09 in SOC group 73% male, 54.6% hypertensive, 30.3% diabetic	4—5	**Tocilizumab** 80.3% received 400 mg while 19.6% received > 400 mg. Four patients received second dose N = 66	Hydroxychloroquine, azithromycin, antibiotics (cephalosporins, piperacillin/tazobactam) N = 66
December 2020	Tian et al.[48]	Multi-centre, China	195	Median age 69.0 [62.0 – 75.0] 67% male, 52.8% hypertensive, 16.9% diabetic	4—5	**Tocilizumab** 4 - 8 mg/kg IV up to 800 mg IV N = 65	Antibiotic therapy, Antiviral therapy (lopinavir-ritonavir, ganciclovir, oseltamivir) N = 130
January 2021	Rajendram et al.[49]	Multi-centre, USA	444	Mean age 64 ± 12 in treatment group, 64 ± 13 in control group.33% diabetic,	4—5	**Tocilizumab** Doses not stated N = 102	Remdesivir, lopinavir-ritonavir, hydroxychloroquine, azithromycin N = 342
April 2021	Huang et al.[50]	Single centre, USA	96	Mean age 66.59 ± 19.10 in treatment group, 63.22 ± 16.29 in SOC group. 80% male, 60% hypertensive and 49% diabetic in treatment group	4—5	**Tocilizumab** A single 400 mg IV infusion N = 55	Hydroxychloroquine, remdesivir, azithromycin N = 41
June 2021	Sanchez-Rovira et al. [52, 51]	Spain	50	Mean age 60.9 ± 10.4 in treatment group, 65.2 ± 10.2 in SOC group. 86.1% male, 41.7% hypertensive and 33.3% diabetic in treatment group	4 -5	**Tocilizumab** a single dose of 400 mg if they weighed <75 kg, or 600 mg if they weighed ≥ 75 kg N = 36	N = 14

Table 2 (continued)

Date of publication[a] Study	Country, single or multi centre	Number of patients	Patient characteristics	Disease severity (stage 1 - 5)[b]	Tocilizumab/ Methylprednisolone/ Dexamethasone, N, number of patients	Standard of care (SOC), N, number of patients
June 2021 Fusina et al. [52]	Single centre, Italy	1311	Mean age 69 ± 12 in treatment group, 69 ± 15 in control group 24% diabetic and 44% hypertensive in treatment group	3—4	**Dexamethasone** Median dose 8 mg/day for 5 days N = 480	N = 831

[a]Date of publication online. "Preprint" is stated if the study was first found and included in its preprint version

[b]COVID-19 severity stage 1: asymptomatic; stage 2: symptomatic but without pneumonia; stage 3: mild pneumonia without need of oxygen supplementation; stage 4: acute respiratory distress syndrome with one or more the following characteristics: $SpO_2 < 94\%$ on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen $(PaO_2/FiO_2) < 300$ mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50%; stage 5: Critical disease needing invasive mechanical ventilation

et al., OR 0.42 95% CI 0.16—1.15) did not show significant mortality reduction [43, 44].

Interestingly, two studies involving tocilizumab co-treated with methylprednisolone gave positive outcomes in reducing mortality [37, 43]. The study by Mikulska et al. [43] involved three treatment arms: (i) treatment with tocilizumab alone, (ii) treatment with methylprednisolone alone, and (iii) tocilizumab co-treated methylprednisolone (1 mg/kg/d, low dose). Both tocilizumab only and methylprednisolone only treatment arms failed to show mortality reduction (OR 0.32, 95%CI 0.10 – 1.03 and OR 0.81, 95%CI 0.36 – 1.36, respectively). The tocilizumab co-treated with low dose methylprednisolone, in contrast significantly reduced COVID-19 mortality (OR 0.20, 95%CI 0.07 – 0.56). A similar outcome was shown in the study by Ramiro et al. [37], also known as the CHIC study. This study employed a strategy in which high dose pulse methylprednisolone (250 mg) was given on day 1 and followed by lower doses (80 mg) on days 2 to 5, with tocilizumab added when no improvement was seen. A significant positive outcome in mortality reduction was seen in this study (OR 0.21, 95%CI 0.10 -0.43).

Only one study by Horby et al. [17] with dexamethasone 6 mg/d (low dose) gave significant positive outcome (OR 0.45 95%CI 0.39 – 0.52). None of the studies involving methylprednisolone alone showed significant mortality reduction while the trial by Jamaati et al. [25] and Tomazini et al. [19] involving high dose dexamethasone (20 mg/d) failed to show mortality reduction. An exception was the study by Edalatifard et al. [22] which treated mild, non-ARDS COVID-19 patients with high dose methylprednisolone (250 mg/d). The larger number of studies favouring tocilizumab versus that of the corticosteroids in our analysis appeared to suggest that tocilizumab was a superior drug to the corticosteroids in reducing mortality among severe COVID-19 patients. To determine how tocilizumab would fare by itself, we combined all studies, both RCTs and case–control that only involved tocilizumab. A meta-analysis of this combination yielded favourable outcome towards mortality reduction (OR 0.63 95% CI 0.44—0.88) (Fig. 4).

A meta-analysis was also performed on a secondary outcome: the efficacy of tocilizumab and the corticosteroids in preventing events in which disease conditions deteriorate toward needing invasive mechanical ventilation (IMV). 12 studies provided data on events of IMV needed for this analysis. Hence, an analysis was run on these 12 studies with the result shown in Fig. 5. The summative odds ratio (0.72, 95%CI 0.32 -1.60) in this analysis indicated all treatments (tocilizumab, methylprednisolone, and dexamethasone) did not significantly prevent the events of patient conditions worsening towards IMV. On individual examination, only the studies of Canziani et al. [36] involving tocilizumab IV infusion of 8 mg/kg (> 400 mg), using up to two doses (OR 0.11, 95%CI 0.05—0.27), Ramiro et al. [37] using

Fig. 2 Forest plot for the effect for all treatments (tocilizumab, methylprednisolone, and dexamethasone) on mortality in randomised controlled trials
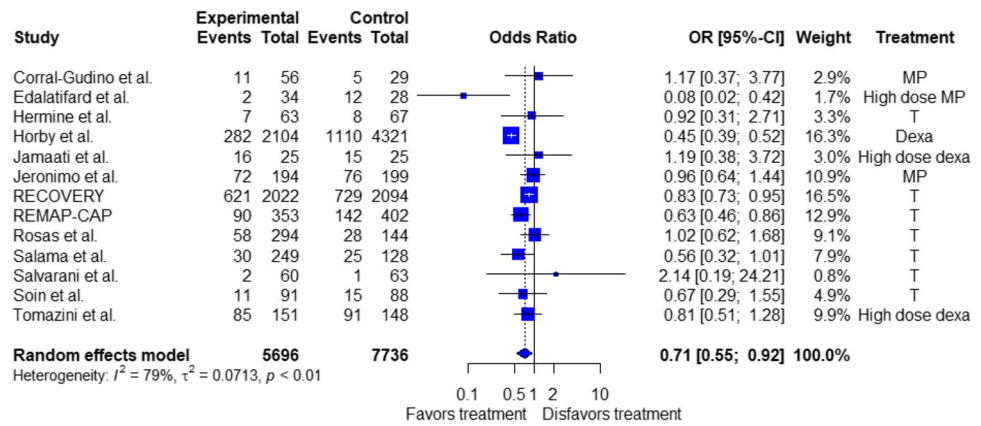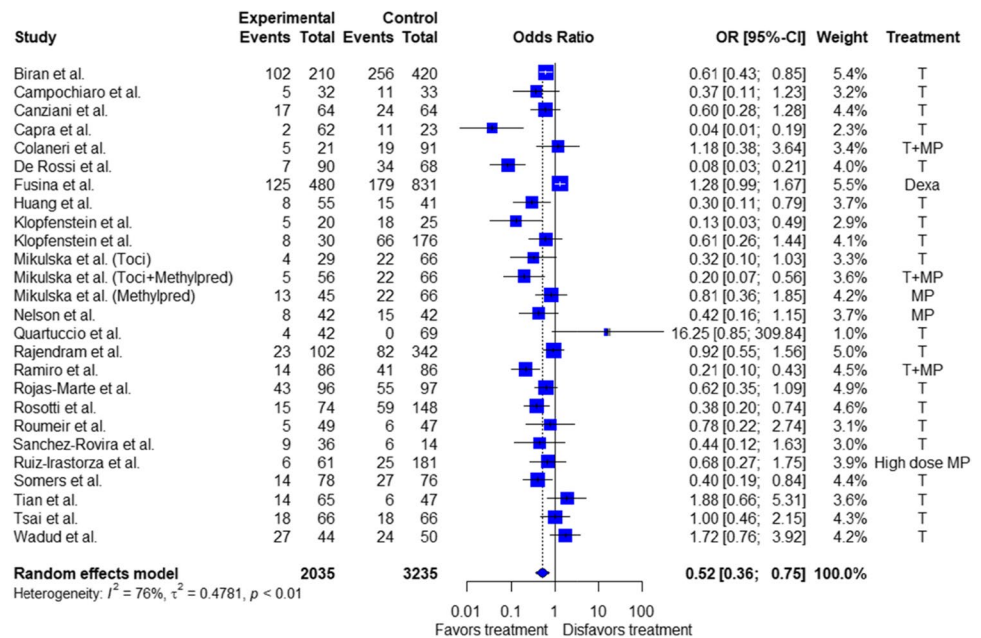

Fig. 3 Forest plot for the effect of all treatments (tocilizumab, methylprednisolone, and dexamethasone) on mortality in case–control studies

tocilizumab co-treated with methylprednisolone (OR 0.34, 95%CI 0.15 – 0.76), and Horby et al. [17] involving dexamethasone (OR 0.72, 95%CI 0.57—0.90) gave favourable outcome in reducing events of IMV (Fig. 5).

We next examined the possible contributing factors that may have affected the mortality outcomes of the drugs. Factors such as whether the patients were co-medicated with other drugs, most commonly antiviral drugs (lopinavir-ritonavir, remdesivir), azithromycin, hydroxychloroquine, and prophylactic anticoagulants, were included in the analysis. The result of the meta-regression analysis is given in Table 3.

We found that of all the variables analysed, only co-medication with azithromycin showed significant contribution ($p < 0.01$) to the mortality outcome of the treatment with tocilizumab or dexamethasone. All patients' baseline characteristics (age, high percentage of male patients, substantial number of hypertensive patients, high levels of CRP) did not

contribute to mortality outcome of the drugs. The time to initiate the drugs was also not significant. Higher doses of tocilizumab (> 400 mg) as well as number of tocilizumab doses given (up to 2 doses) did not significant affect the mortality outcome of tocilizumab. The sole significant predictor (co-medication with azithromycin) led us to examine the studies in which azithromycin was given. It was observed that of 11 studies that included azithromycin as co-medication, only two studies (Biran et al., tocilizumab [40] and Horby et al., dexamethasone [17]) showed significant mortality reduction. The remainder were studies which showed unfavourable mortality outcomes. Independent t-test of the possible factors associated to the reduction in mortality using tocilizumab demonstrated no significant differences among both treatment and SOC arms in terms of age, hypertension, heart disease, CRP and ferritin. Nevertheless, the percentage of patients with diabetes in the tocilizumab arm was significantly lower than the SOC arm ($23.0 \pm 10.0\%$

Fig. 4 Forest plot for the effect of tocilizumab alone on mortality
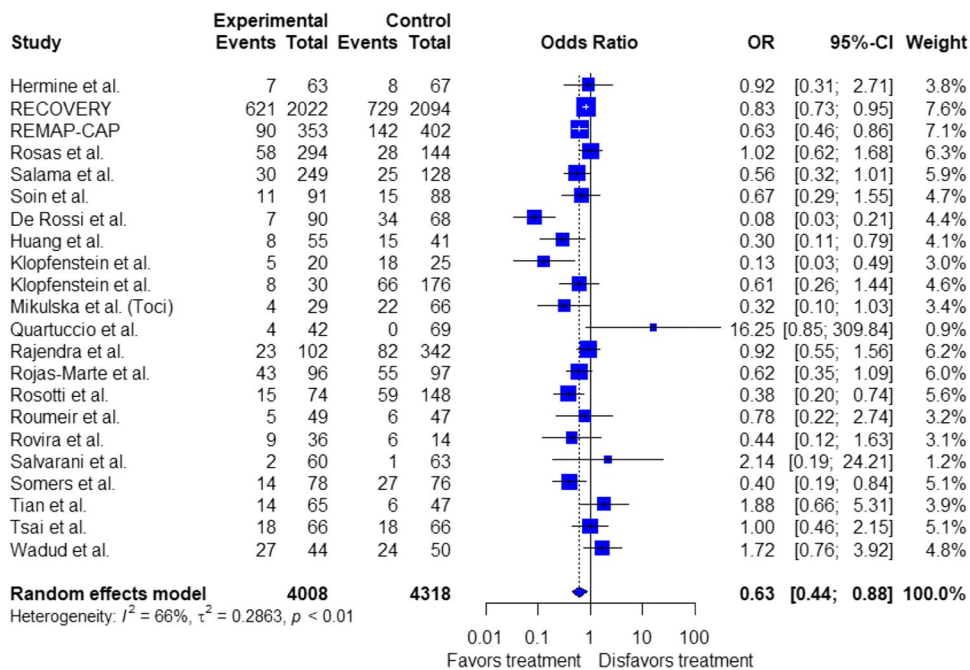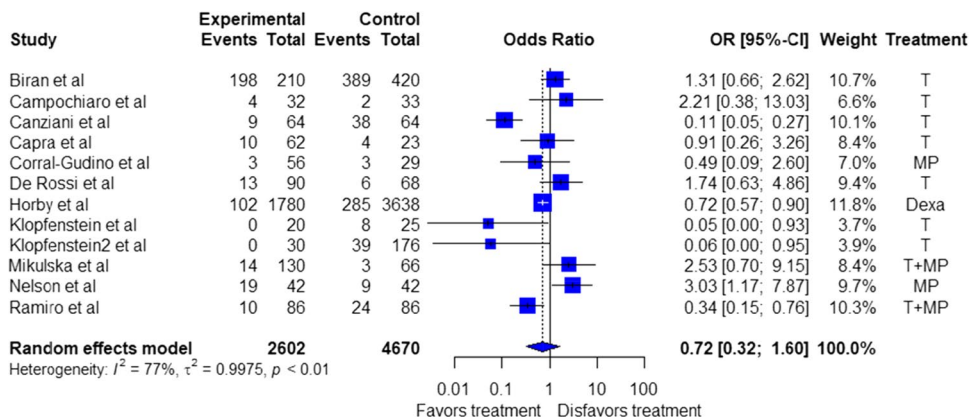

Fig. 5 Forest plot for effect of all treatments (tocilizumab, methylprednisolone, and dexamethasone) on the event of invasive mechanical ventilation

vs. 29.2 ± 10.1%, $p = 0.002$). Three studies (Biran et al. [40], Canziani et al. [36] and Mikulska et al. [43]) reported significantly lower number of diabetic patients in their tocilizumab arms. In addition, there were significantly more male patients in the tocilizumab arm compared to the SOC arm (74.7 ± 8.1% vs. 70.9 ± 8.8%, $p = 0.028$).

A funnel plot was constructed to detect publication bias (Fig. 6). Majority of the studies formed a coherent cluster symmetrically around the summative odds ratio at the top of the plot indicating that most studies contained small standard errors and the absence of publication bias. Egger's test of asymmetry confirmed no significant asymmetry ($p > 0.05$).

In addition, in view of studies that continue to appear, a trial sequential analysis (TSA) was conducted to determine that the included RCTs were significantly adequate. TSA on all RCTs involving the corticosteroids and tocilizumab showed that firm evidence was lacking and more trials were

still needed (Supplementary data, Figure S1). Hence, it could not be concluded that the interventions were unlikely to reduce mortality. A second TSA was conducted on RCTs involving tocilizumab only. This analysis showed statistical significance (Supplementary data, Figure S2). However, the required information size to detect or reject the reduction in mortality with certainty has yet to be reached.

Discussion

This systematic review demonstrated that tocilizumab was better than the corticosteroids in treating COVID-19. Corticosteroids that are also immunomodulators are inexpensive and widely available in most healthcare systems worldwide compared to tocilizumab. It would have been desirable if methylprednisolone and dexamethasone have comparable

Table 3 Meta-regression analysis of variables against the summative odds ratio of mortality. Significant contribution at $p < 0.01$ is indicated by **

Variables	p-value
Co-medications	
Lopinavir-ritonavir	0.1397
Hydroxychloroquine	0.6799
Azithromycin	0.0065**
Other antibiotics	0.9212
Other antivirals (including remdesivir)	0.9765
Prophylactic anticoagulants (LMW heparin, enoxaparin)	0.5517
Time of initiating treatment from symptoms onset (day)	0.7462
Number of tocilizumab dose given	0.4789
Dose of tocilizumab given (400 mg or > 400 mg)	0.4310
Age of treatment arm (year)	0.4406
Age of the SOC arm (year)	0.0873
Percentage of male in treatment arm (%)	0.7939
Percentage of male in the SOC arm (%)	0.0696
Percentage of hypertension in treatment arm (%)	0.2233
Percentage of hypertension in SOC arm (%)	0.5380
Percentage of diabetes mellitus in treatment arm (%)	0.1213
Percentage of diabetes mellitus in SOC arm (%)	0.8781
C-reactive protein level in treatment arm	0.9329
C-reactive protein level in SOC arm	0.7683
IL-6 level in treatment arm	0.8973
IL-6 level in SOC arm	0.8993
Ferritin level in treatment arm	0.4851
Ferritin level in SOC arm	0.5674

efficacy to tocilizumab. Nevertheless, none of the studies that involved methylprednisolone including one highly powered, randomized, double-blinded, placebo-controlled trial by Jeronimo et al. [18] demonstrated significant reduction in mortality. While for the three RCTs involving dexamethasone [17, 19, 25], only the study by Horby et al. [17], also known as the RECOVERY trial, showed significant reduction in mortality of severely ill (stages 4 to 5) COVID-19 patients. In the two studies involving high dose pulse (> 1.5 mg/kg/day) methylprednisolone therapy, the results were equivocal. Edalatifard et al. [22] showed significant mortality reduction but the study by Ruiz-Irastorza et al. [45] failed to show positive outcome in preventing death or intubation.

The mixed outcomes shown by the corticosteroids particularly methylprednisolone in these studies may be due to the heterogeneity of (i) the doses and treatment protocols employed, and (ii) the stage of disease severity experienced by the patients. Compared to the fixed dose of 6 mg once daily (a low dose regimen) of dexamethasone in the RECOVERY trial, the dexamethasone trial of Tomazini et al. [19] failed to reduce mortality in contrast to the

RECOVERY trial probably because of the higher dose of intravenous dexamethasone (40 mg) used in the Tomazini et al. study to treat the critically ill (stage 5) COVID-19 patients. The degree of inflammatory response as indicated by biomarkers such as CRP and IL-6 may have affected the outcome of the corticosteroid treatment. Patients who were less inflamed and had low CRP levels (< 100 mg/L) as seen in studies by Jeronimo et al. [18] and Mikulska et al. [43] did not benefit from methylprednisolone treatment. In the RECOVERY trial, it was also noted that treating less severe, stage 3 patients (who did not need oxygen support) with dexamethasone resulted in a trend toward increased mortality [17]. A hypothesis to explain this phenomenon is that early corticosteroid use in patients with less severe disease could lead to increased viral load due to more viral shedding which in turn lead to more inflammation and delayed viral clearance as suggested by several researchers [53, 54].

On the other hand, the summative odds ratio showed tocilizumab reduced mortality significantly, even though tocilizumab was found to reduce mortality in two out of six RCTs and six out of the twenty case–control studies. Univariate meta-regression analysis was used to identify if age, gender, underlying co-morbidities such as arterial hypertension and diabetes mellitus, surrogate markers of disease severity such as CRP, IL-6 and ferritin levels, as well as co-medications may have affected the efficacy of the drug. These variables were selected because of their reported strong association with disease prognosis and severity [55–58].

We did not find any variables that significantly correlate with tocilizumab efficacy except for co-treatment with azithromycin. Majority of the tocilizumab studies that involved azithromycin in their treatment regimen (nine out eleven) showed inefficacy of tocilizumab to reduce mortality. This suggested that adding azithromycin in COVID-19 treatment with tocilizumab did not benefit treatment outcome and may even be deleterious. The rationale for azithromycin as a part of COVID-19 treatment regimen mainly stemmed from its role as empirical treatment against community acquired pneumonia in COVID-19 patients possibly co-infected with bacteria. The drug has been shown to have antiviral and immunomodulatory properties in in vitro and animal experiments but clinical evidence supporting these attributes is absent [59]. Our finding concurs with the finding of one RCT assessing efficacy of adding azithromycin in the SOC treatment of COVID-19 (COALITIONII) which showed that the drug did improve therapeutic outcome [60].

We found that factors characterizing how tocilizumab was used in these studies particularly the dose (400 mg or > 400 mg), the number of doses (only one dose or two doses given) and the time of the drug were also insignificant to tocilizumab efficacy. Contrary to the general notion on the importance of initiating the drug at a crucial time to capture the therapeutic "window", the time of drug initiation

Fig. 6 Funnel plot for (**a**) randomised clinical trials, and (**b**) case–control studies included in the meta-analysis
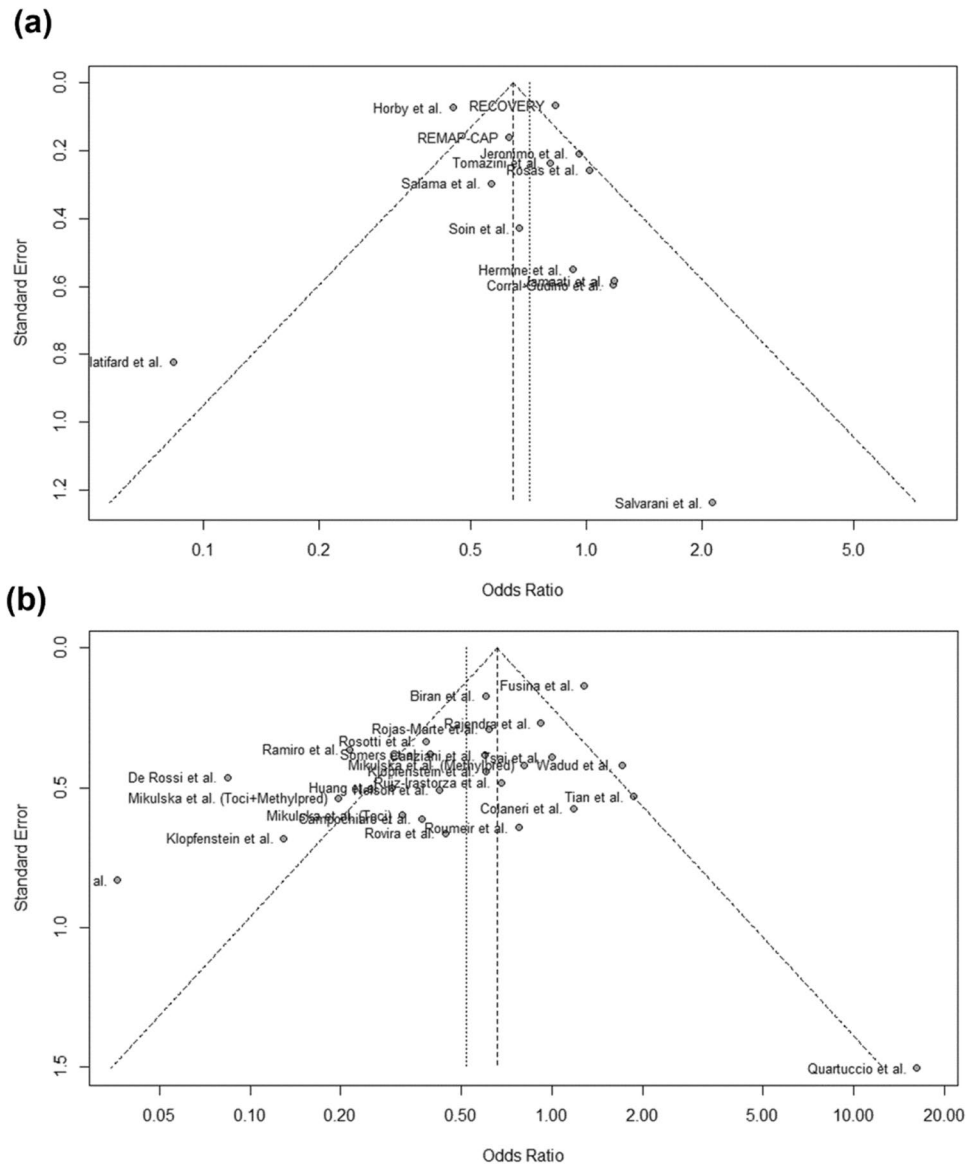
from symptoms onset was insignificant. This failure to detect the significance of this factor may have stemmed from the time of drug initiation between the studies were not varied significantly (average time 9.3 ± 2.0 days from symptoms onset). Moreover, the decisions to start treatment were in practice, governed by the clinical manifestations of the patients such as chest CT scans and lung functions as indication of severity rather than a pre-determined time [61]. The other parameters indicating baseline severity especially inflammation severity such as IL-6, ferritin and CRP levels also were insignificant to tocilizumab efficacy. It may be due to these parameters being fluid and dynamic in nature and the values that we have extracted were recorded at variable timepoints in the disease evolution of the patients and as such were not sufficiently robust to show significance. Nevertheless, patients in most studies [20, 21, 24, 30, 32,

39, 41] with positive mortality reduction outcome had CRP values ranging from 90 to 150 mg/L which are potential signals to initiate tocilizumab. This implicates that the time to initiate tocilizumab should best be dictated by the levels of inflammatory markers such as CRP levels. This finding has presently been established in tocilizumab protocols which recommend the initiation when CRP levels exceed 75 mg/L [62, 63].

A notable modulator to tocilizumab efficacy in both reducing mortality that we have found in this study is the concomitant treatment with a corticosteroid such methylprednisolone. This is most evident in the positive outcomes shown by Ramiro et al. or CHIC study which used a 3- to 6-day course of methylprednisolone with the addition of tocilizumab in the later stage of the disease. The benefit of combination therapy with a corticosteroid and tocilizumab

has also been confirmed by RECOVERY and REMAP-CAP. The small study by Malgorzata et al. in which the tocilizumab + methylprednisolone treatment arm showed positive outcome in both preventing death and intubation versus single treatment arms was an early indication to this trend. This finding again is in line with the latest knowledge regarding the use of tocilizumab in COVID-19 [62, 63].

No factors of patient co-morbidities were found to affect the outcome of tocilizumab treatment although there were significantly less diabetic patients in the treatment arms of tocilizumab studies that showed positive outcome. This may suggest that in the face of ARDS and the cytokine storm syndrome experienced by the COVID-19 patients, the chronic diseases did not affect the outcome of tocilizumab treatment. The effect of diabetes mellitus toward disease prognosis and tocilizumab efficacy may be important here and requires a more focused approach to confirm its significance.

Meta-analysis on the efficacy of the three drugs (tocilizumab and the corticosteroids) in lowering events of IMV found that overall, the drugs were ineffective in reducing events of disease progression towards being mechanically ventilated. On a study-level, only two studies (Canzani et al. and Ramiro et al.) involving tocilizumab showed positive outcome in IMV event reduction. The RECOVERY trial [17] was the sole study among those assessing corticosteroid efficacy in preventing IMV that showed dexamethasone to be effective. Dexamethasone was relatively consistent in this respect in addition to its mortality reduction. We propose that the corticosteroid was efficacious in both respects possibly because it was used as a single, defined dose and was used in the patients who presented highly inflamed conditions and were critically ill and requiring assisted ventilation.

Immunosuppressive adverse effects ensuing the use of immunomodulators such as tocilizumab and corticosteroids have always been the concern when they are used for an infectious disease such as COVID-19. There are occurrences of secondary bacterial infections that came with tocilizumab use but these cases had not led to deaths [63]. The corticosteroids in contrast, despite their immune-modulating action, seldom led to secondary infections but may cause hyperglycemia and may potentially lead to the onset of diabetes [64–66]. But weighed against the almost equal benefits of both drugs and the combination of the two in COVID-19 mortality reduction as seen in this review, their use as key COVID-19 treatment modalities is strongly justified.

This review included five databases search that involved two reviewers at every phase to minimise bias. However, there are a few limitations in this review. During data extraction, kappa to test reviewer reliability was not conducted. Nevertheless, the two reviewers discussed and when disagreement arose, other reviewers were consulted to resolve the disagreement. Besides, this review was a health-related study in which kappa interpretation might be too lenient

[67]. In addition, extensive search strategies were employed to identify the relevant literature but some studies may have been missed due to the terminology used to describe COVID-19 treatment with tocilizumab and corticosteroid particularly methylprednisolone and dexamethasone. Only English language studies were included for the review that may have reduced the representativeness of our findings. Besides, only RCTs and case–control studies were included so that we could synthesize the odds of the outcome of interest. Still, we might have missed the important reports of cohort studies.

Nevertheless, this review concludes that tocilizumab and dexamethasone were effective in reducing the mortality of severe COVID-19 patients but could not reduce the incidence of ventilation. This review also found that no factors affected the efficacy of tocilizumab and dexamethasone. Hence, dexamethasone being the less costly alternative may be the drug of choice in the treatment of severe COVID-19 patients.

Authors' contributions PCL designed and conceptualised the study. PCL, RR, KLW and MFC performed the literature search and extracted data. CYL and PCL performed the data analysis and wrote the original draft of the manuscript. All authors reviewed and edited the manuscript. SS contributed to project administration.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval Ethical approval was obtained from the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-20–2263-56296).

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