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META-ANALYSIS

Efficacy and safety of Tocilizumab in severe and critical COVID-19: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: Currently published papers and clinical guidelines regarding the effects of tocilizumab in severe and critical COVID-19 are contradictory. The aim of this meta-analysis was to combine the results of clinical studies of different designs to investigate the efficacy and safety of tocilizumab in severely-to-critically ill COVID-19 patients.

Methods: A systematic search was performed in PubMed, Embase, CENTRAL, ClinicalTrials.gov, Scopus, and preprint servers up to 26 December 2020. Since a substantial heterogeneity was expected, a random-effects model was applied to calculate the pooled effect size (ES) and 95% confidence interval (CI) for each study outcome.

Results: Forty-five comparative studies involving 13,189 patients and 28 single-arm studies involving 1,770 patients were analyzed. The risk of mortality (RR of 0.76 [95%CI 0.65 to 0.89], P < 0.01) and intubation (RR of 0.48 [95%CI 0.24 to 0.97], P = 0.04) were lower in tocilizumab patients compared with controls. We did not find any significant difference in secondary infections, length of hospital stay, hospital discharge before day 14, and ICU admission between groups.

Conclusion: Tocilizumab can improve clinical outcomes and reduce mortality rates in severe to critical COVID-19 patients. Large-scale randomized controlled trials are still required to improve the statistical power of meta-analysis.

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KEYWORDS
ARDS; covid-19; intubation; meta-analysis; mortality; tocilizumab

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly emerging pathogen. According to a World Health Organization (WHO) report, since its first identification in late 2019, SARS-CoV-2 has caused over 107.8 million confirmed infections and over 2.3 million deaths globally as of 13 February 2021. The WHO declared the coronavirus disease 2019 (COVID-19) a pandemic on 11 March 2020 [1].

The clinical manifestation of COVID-19 ranges from asymptomatic to severe pneumonia and acute respiratory distress syndrome (ARDS) [2]. Several studies have reported a massive release of inflammatory mediators, such as interleukin-6 (IL-6), in response to the SARS-COV-2 infection. This may lead to a cytokine storm in severely-to-critically ill COVID-19 patients [3]. The significant role of IL-6 in the COVID-19 inflammatory pathogenesis has been established in the early studies on severely-to-critically ill patients [4]. Hence, tocilizumab, an IL-6 inhibitor with an approved clinical indication in cytokine release syndrome (CRS) [5], has been evaluated in severe to critical COVID-19 patients by various clinical research teams around the world. The China National Health Commission Guidelines were the first to include tocilizumab in the treatment plan of COVID-19 patients [6]. The status of the National Institutes of Health (NIH) was neither for nor against tocilizumab until July 2020; however, NIH decided to recommend against the use of this medication on its later updates [7]. Most recently, the UK's National Institute for Health Research (NIHR) supported the use of tocilizumab for critically ill COVID-19 patients based on the results of the REMAP-CAP trial (they reported a 24% relative reduction in the risk of mortality; unpublished data) [8].

Data on the clinical safety and efficacy of tocilizumab in COVID-19 patients is rapidly growing. Hence, we performed an updated meta-analysis to combine the results of clinical studies of different designs to further investigate the potential benefits and harms of tocilizumab treatment in severely-to-critically ill COVID-19 patients.

2. Methods

2.1. Protocol and registration

This systematic review and meta-analysis study was conducted and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses checklists (PRISMA).

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The study protocol was prospectively registered in the PROSPERO database (CRD42020203461) and can be accessed on https://www.crd.york.ac.uk/prospero/.

2.2. Eligibility criteria

For this systematic review and meta-analysis, studies were selected based on the following population (P), intervention (I), comparison (C), and outcomes (O) (PICO) criteria: P, hospitalized patients with a confirmed diagnosis of COVID-19; I, intravenous tocilizumab; C, any comparator provided as standard-of-care (SOC) or placebo, and O, mortality rate. We included comparative studies, including randomized controlled trials (RCTs), case–control studies, and cohort studies. Moreover, we analyzed single-arm observational studies in separate analyses. Other published literature, including editorials, letters to the editor, commentaries, case series, case reports, specific populations, and reviews (of any type) were excluded.

COVID-19 patients with an oxygen saturation of 93% or less while breathing room air, a respiratory rate of 30 breaths/min or more, a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FIO2) of below 300 mmHg or lung infiltrates of more than 50% were considered as severe. COVID-19 patients with shock, organ failure, or ARDS requiring mechanical ventilation, and any patient requiring admission to the intensive care unit (ICU) were considered as critical [9,10].

2.3. Information sources

Potential studies were identified through a systematic search of online databases, including PubMed, Embase, CENTRAL, ClinicalTrials.gov, Scopus, and preprint servers, including medRxiv, bioRxiv, and SSRN up to 26 December 2020.

2.4. Search

Generally, following search keywords were used: 'tocilizumab', 'actemra', 'IL-6 blocker', 'IL-6 blockade therapy', 'anti-interleukin -6 therapy', 'IL-6 inhibitor', 'COVID19', 'COVID-19', 'SARS-CoV-2', 'severe acute respiratory syndrome Coronavirus type 2', 'Coronavirus disease 2019', '2019-nCoV', 'novel coronavirus', 'emerging coronavirus', and 'Wuhan coronavirus'. Search strategies used in these databases are available in Supplementary file 1.

2.5. Data collection process

Four reviewers (SR, BF, ZM, and HM) independently selected the eligible studies and collected the following data when available: study design, patient demographics, disease characteristics, and the outcomes of interest (mortality, ICU admission, intubation, length of hospital stay, hospital discharge before day 14, clinical improvement, and secondary infections). The reviewers extracted data from the texts, tables, and graphs of the included studies. Any disagreements were resolved by the two senior reviewers (SR and BF).

2.6. Risk of bias in individual studies

Four reviewers (SR, BF, ZM, and HM) independently assessed all the included studies for the risk of bias (RoB). Disagreements regarding RoB were resolved by discussion and consensus. The Cochrane risk-of-bias tool for RCTs (RoB 2) was used to assess the RoB in the RCTs; the Newcastle Ottawa Scale (NOS) tool was used to evaluate the RoB in the comparative observational studies; and an adjusted NOS tool was used to assess the RoB in the single-arm observational studies.

2.7. Summary measures

In this meta-analysis, we calculated the pooled proportions, standardized mean differences (SMDs), and relative risks (RRs) for the study outcomes based on the design of the included studies.

2.8. Synthesis of results

Heterogeneity across the included studies was evaluated using the inconsistency index I^2. We used the DerSimonian and Laird random-effects model because of the significant heterogeneity among studies [11–13]. The combined effect size (ES) and its 95% confidence interval (CI) for each outcome of interest were calculated using numbers of events in both tocilizumab cases (tocilizumab plus SOC) and controls (SOC). Subgroup meta-analysis of study outcomes was also performed based on the study design (RCT, cohort, and case–control studies). We also evaluated the single-arm observational studies in addition to the comparative studies to use all the available evidence. To achieve a better understanding of the results, a systematically matched SOC group was created for the single-arm studies using the SOC group of the included comparative studies. Patients in the single-arm studies and the systematically matched SOC group were statistically similar in terms of age, sex, and disease severity. Proportions and means were compared between the single-arm studies and the matched group using a two-proportion z-test and a Student's t-test, respectively.

2.9. Risk of bias across studies

The potential risk of publication bias was assessed by visually inspecting the funnel plots for each of the study outcomes. In this approach, we plotted the logarithm of the effect sizes against their standard errors.

2.10. Additional analyses

Meta-regression analyses were performed to evaluate the effects of sex, age, study design, and baseline disease stage. All the statistical analyses were conducted using STATA 14. Differences were considered significant if $P < 0.050$.

3. Results

3.1. Study selection

Figure 1 illustrates the results of our search strategy (PRISMA flow diagram). A total of 3364 articles was identified through

a systematic search of online databases. After removing duplications, 1224 articles remained. Based on the eligibility criteria, 73 articles were finally selected for this systematic review and meta-analysis.

3.2. Study characteristics

Of 1224 citations, 45 comparative studies, including four RCTs [14–17], 25 cohort studies [18–42], and 16 case–control studies [43–58], were included. A total of 13,189 patients were involved in these studies, of which 3,999 received tocilizumab plus SOC and 9,190 received SOC alone. All these studies assessed the effect of tocilizumab administration in patients with severe and/or critical COVID-19. Patel et al. [40] reported the clinical outcomes of the two groups of severe and critical COVID-19 patients separately. Therefore, we have considered them as two separate studies. Moreover, 28 single-arm observational studies [59–86] were included in this analysis. Knorr et al. [82] classified the patients into two groups of severe and critical COVID-19, and we have considered these two groups as two separate studies.

The mean age of patients in the studies was 63.14 ± 5.2 years, and more than half (64%) were male. The mean time of follow-up was 27.7 ± 13.4 days. Table 1 illustrates the baseline characteristics of patients in the included comparative studies. Increased serum levels of IL-6 and/or C-reactive protein (CRP), that indicate the presence of CRS, were among the main eligibility criteria for all the included studies.

Mortality was reported in all the included comparative studies. Secondary infections, hospital discharge before day 14, intubation, length of hospital stay, ICU admission, and

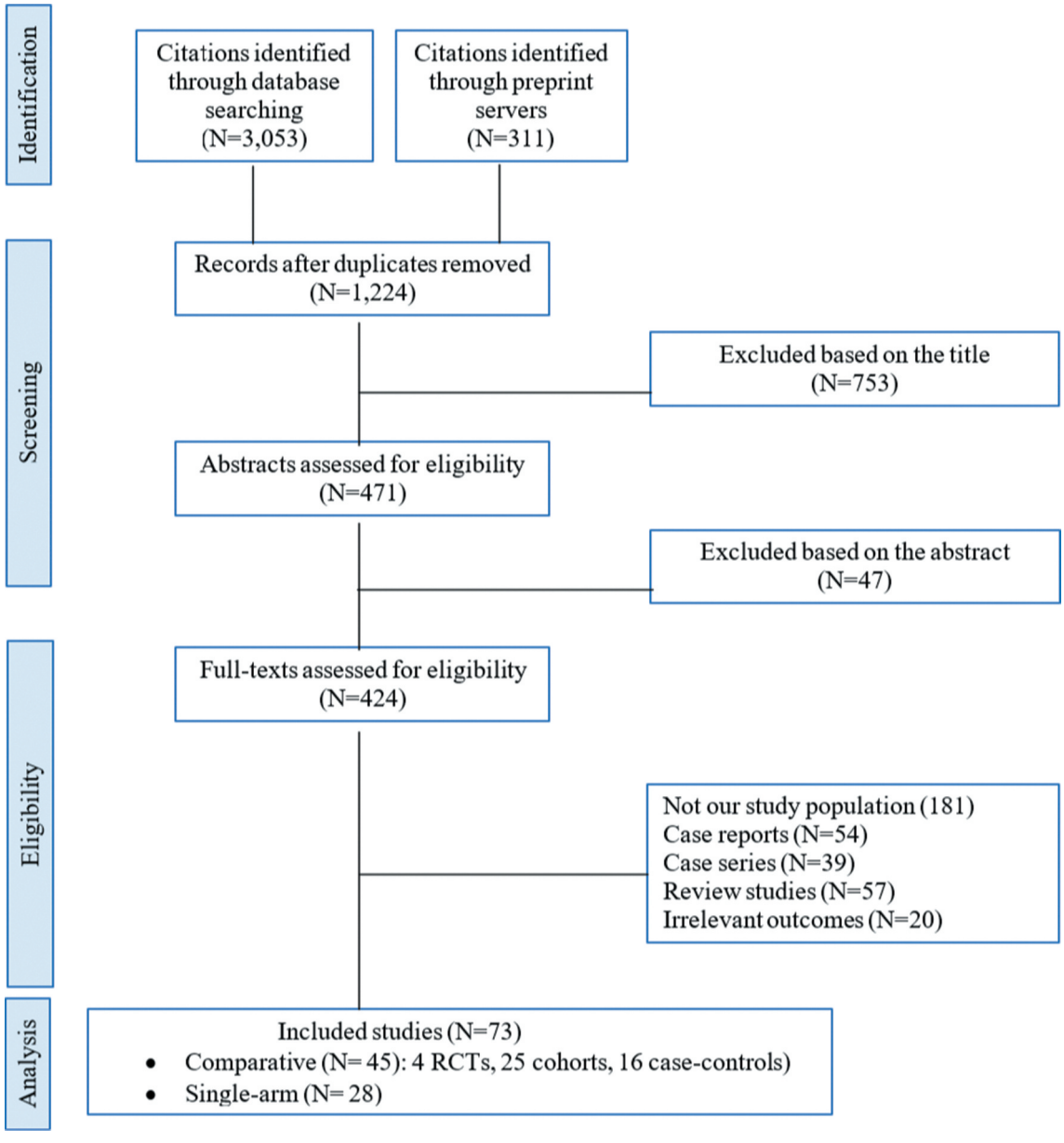


Figure 1. PRISMA Flow diagram of selecting studies for meta-analysis. RCT, randomized controlled trial.

Table 1. Baseline characteristics of included comparative studies.

					Age, mean (SD)		Group size, N		Sex, male, %	
No.	First author	Country	Study Design	Disease stage	TOZ+SOC	SOC	TOZ+SOC	SOC	TOZ+SOC	SOC
1	Salvarani	Italy	RCT	Severe	61 (16.7)	60 (11.3)	60	63	66.7	58.7
2	Stone	USA	RCT	Severe	61 (17.4)	56 (17.4)	161	82	59.6	54.9
3	Hermine	France	RCT	Severe	65.2 (13)	64.2 (11.5)	63	67	69.8	65.7
4	Rosas	USA	RCT	Severe-Critical	60.9 (14.6)	60.6(13.7)	294	144	69.7	70.1
5	Campochiaro	Italy	Cohort	Severe	64 (17)	60 (15.8)	32	33	90.6	81.8
6	Somers	USA	Cohort	Critical	55 (14.9)	60 (14.5)	78	76	67.9	64.5
7	Wadud	USA	Cohort	Critical	71.5 (13)	84.5 (15.6)	44	50	84.1	70.0
8	Guaraldi	Italy	Cohort	Severe	64 (13.4)	69 (15.6)	179	365	70.9	63.6
9	Ip	USA	Cohort	Critical	62 (12.7)	69 (14.1)	134	413	73.9	62.2
10	Kimmig	USA	Cohort	Critical	64 (14.2)	62 (15.9)	54	57	63.0	49.1
11	Maeda	USA	Cohort	Severe	66 (NA)	66 (NA)	23	201	NA	NA
12	Moreno-García	Spain	Cohort	Severe-Critical	61 (12)	61 (16)	77	94	68.8	62.8
13	Martínez-Sanz	Spain	Cohort	Severe-Critical	65 (15.6)	68 (17)	260	969	73.5	59.2
14	Mikulska	Italy	Cohort	Severe	64.5 (12.4)	73.5 (14.4)	130	66	71.5	62.1
15	Biran	USA	Cohort	Severe	62 (13.4)	65 (13.3)	210	420	73.8	66.9
16	Fisher	USA	Cohort	Critical	56.2 (14.7)	60.6 (13.4)	45	70	64.4	72.9
17	Gupta	USA	Cohort	Critical	62 (14.8)	62 (14)	443	3491	61.2	62.9
18	Rodríguez-Bano	Spain	Cohort	Severe	66 (12)	69 (12.6)	88	344	45.5	68.9
19	Roomi	USA	Cohort	Severe	65 (NA)	58 (NA)	32	144	187.5	16.0
20	Rossi	France	Cohort	Severe	64 (13)	70 (16.5)	106	140	66.0	57.9
21	Ruiz-Antoran	Spain	Cohort	Severe	66.6 (10.7)	67.3 (14.8)	268	238	68.7	58.8
22	Tsai	USA	Cohort	Severe-Critical	61 (13.5)	63 (17.2)	84	190	75.0	55.3
23	Zheng	china	Cohort	Severe-Critical	68 (12.5)	66 (12.2)	92	89	62.0	52.8
24	Hill	USA	Cohort	Severe	NA	NA	43	45	69.8	68.9
25	Kewan	USA	Cohort	Severe	62 (4.47)	68.6 (5.18)	28	23	71.4	47.8
26	Gould	USA	Cohort	Critical	59.8 (11.7)	58.8 (12.7)	52	41	86.5	68.3
27	Masia	Spain	Cohort	Severe	65.4 (15.2)	65.7 (17.3)	76	62	71.1	50.0
28	Patel	USA	Cohort	Severe	70.8 (18.7)	70.0 (18.7)	21	21	42.9	47.6
				Critical	60.1 (10.5)	60.3 (11.2)	21	20	52.4	55.0
29	Perrone	Italy	Cohort	Severe-Critical	63.3 (NA)	70.3 (NA)	41	38	70.7	71.1
30	Canziani	Italy	Case-control	Severe-Critical	63 (12)	64 (8)	64	64	73.4	73.4
31	Capra	Italy	Case-control	Severe	63.0 (4.0)	69.3 (6.4)	62	23	72.6	82.6
32	Colaneri	Italy	Case-control	Severe	62.3 (9.8)	63.7 (6.7)	21	91	90.5	69.2
33	Carvalho	Brazil	Case-control	Severe	54.6 (16.3)	60.2 (15.6)	29	24	62.1	75.0
34	Gokhale	India	Case-control	Severe	50.9 (9.8)	56 (12.8)	70	91	67.1	58.2
35	Rojas-Marte	USA	Case-control	Severe-Critical	58.8 (13.6)	62 (14)	96	97	77.1	64.9
36	Roumier	France	Case-control	Severe-Critical	58.8 (12.4)	71.2 (15.4)	30	29	80.0	79.3
37	Klopfensteina	France	Case-control	Severe	76.8 (11)	70.7 (15)	20	25	NA	NA
38	Rossotti	Italy	Case-control	Severe-Critical	60.4 (15.1)	60.4 (13.4)	74	148	82.4	81.1
39	Ramaswamy	USA	Case-control	Severe	63.2 (15.6)	63.8 (15.9)	21	65	61.9	55.4
40	Ramiro	Netherlands	Case-control	Severe-Critical	67 (12)	67 (11)	86	86	79.1	79.1
41	Klopfenstein	France	Case-control	Critical	75.6 (11.3)	74.3 (11)	30	176	70.0	59.1
42	Menzella	Italy	Case-control	Severe	63.3 (10.6)	70.3 (11.3)	41	38	70.7	71.1
43	Nasa	UAE	Case-control	Severe-Critical	51 (NA)	52 (NA)	22	63	100.0	95.2
44	Okoh	USA	Case-control	Severe	53.2 (19.1)	61.4 (19.2)	20	40	50.0	60.0
45	Pettit	USA	Case-control	Critical	66 (13.7)	65 (16.3)	74	74	58.1	44.6

NA, non-available; RCT, randomized controlled trial; SD, standard deviation; SOC, standard-of-care; TOZ, Tocilizumab; UAE, United Arab Emirates; USA, United States of America

clinical improvement were reported in 22, 15, 13, 10, 8, and 6 studies, respectively (Supplementary file 2).

The included single-arm observational studies involved 1,770 tocilizumab-treated patients (69.9% male) with a mean age of 61.3 ± 5.7 years and a mean follow-up time of 22.37 ± 12.64 days (Supplementary file 3). Mortality was reported in all these studies. Clinical improvement, hospital discharge before day 14, intubation, length of hospital stay, and secondary infections were reported in 12, 10, 9, 9, and 5 studies, respectively (Supplementary file 4).

3.3. Risk of bias within studies

Based on the RoB 2 tool, except for the RCT-TCZ-COVID-19 study [14] with a moderate risk of bias, all the included RCTs had a low risk (Supplementary file 5). Based on the NOS risk of bias tool, 22 of the 41 comparative observational studies were at moderate risk of bias, and the other 19 studies were at low risk of bias (Supplementary file 6). All the 28 single-arm studies had a fair methodological quality based on the adjusted NOS tool. Many of the comparative and single-arm trials did not report on patient withdrawals, and this was the main cause of bias among the included studies (Supplementary file 7).

3.4. Results of individual studies and synthesis of results

3.4.1. Mortality

Pooling all the 45 comparative reports (four RCTs, 25 cohorts, and 16 case-controls) yielded a RR of mortality of 0.76 (95% CI 0.65 to 0.89, $P < 0.01$, $I^2 = 75.7\%$), corresponding to a number needed to treat (NNT) of 10 (95% CI 9 to 11) (Figure 2).

Pooling all the 29 single-arm observational reports yielded a mortality rate of 0.20 (95% CI 0.15 to 0.26) in tocilizumab-treated patients. The systematically matched SOC group's

mortality rate was 0.27 (95% CI 0.22 to 0.33) (Supplementary file 8, parts A & B). There was no significant difference between tocilizumab-treated patients and the systematically matched SOC group in mortality rates (P = 0.49).

3.4.2. Clinical improvement

Six comparative studies (one RCT, four cohorts, and one case-control) with a total of 487 patients reported clinical improvement as a secondary outcome variable. The pooled RR of clinical improvement was 1.19 (95% CI 1.00 to 1.42; P = 0.05, I^2 = 81.2%) (Figure 3).

Twelve single-arm studies with a total of 633 patients reported the clinical improvement as a secondary outcome variable. The pooled proportion of clinical improvement in the tocilizumab-treated patients and the systematically matched SOC group were 0.58 (95% CI 0.44 to 0.71) and 0.55 (95% CI 0.35 to 0.75), respectively (P = 0.90) (Supplementary file 8, parts C & D).

3.4.3. Intubation

Ten comparative studies (two RCTs, one cohort, and seven case-controls) with a total of 1,612 patients reported the need for intubation as a secondary outcome variable. The pooled RR of intubation was 0.48 (95% CI 0.24 to 0.97; P = 0.04; I^2 = 74.5%) (Figure 4).

Nine single-arm observational studies with a total of 641 patients reported intubation as a secondary outcome variable. The pooled proportion of intubation in the tocilizumab-treated patients and the systematically matched SOC group were 0.15 (95%CI 0.09 to 0.20) and 0.17 (95% CI 0.10 to 0.26), respectively (P = 0.90) (Supplementary file 8, parts E & F).

3.4.4. Length of hospital stay

Ten comparative studies (one RCT, three cohorts, and six case-controls) involving 1,583 patients compared the length of hospital stay in the tocilizumab group with the SOC group. The pooled SMD was 0.10 (95% CI −0.38 to 0.58; P = 0.58; I^2 = 94.4%) (Figure 5).

Seven single-arm observational studies involving 506 patients reported length of hospital stay as a secondary outcome variable. The mean ± SD length of stay was 10.82 ± 5.18 days and 16.56 ± 11.13 days for the tocilizumab-treated and the systematically matched SOC patients, respectively (P = 0.23).

3.4.5. Hospital discharge before day 14

Fifteen comparative studies (two RCTs, nine cohorts, and four case-controls) involving 2,383 patients reported hospital discharge before day 14 as a secondary outcome variable. The pooled RR of hospital discharge before day 14 was 1.09 (95% CI 0.88 to 1.35; P = 0.44; I^2 = 79.6%) (Figure 6).

Ten single-arm studies involving 624 patients investigated hospital discharge before day 14 as a secondary outcome variable. The pooled proportion of patients discharged before day 14 in the tocilizumab and the systematically matched SOC groups were 0.43 (95% CI 0.28 to 0.60) and 0.42 (95% CI 0.22 to 0.60), respectively (P = 0.96) (Supplementary file 8, part G & H).

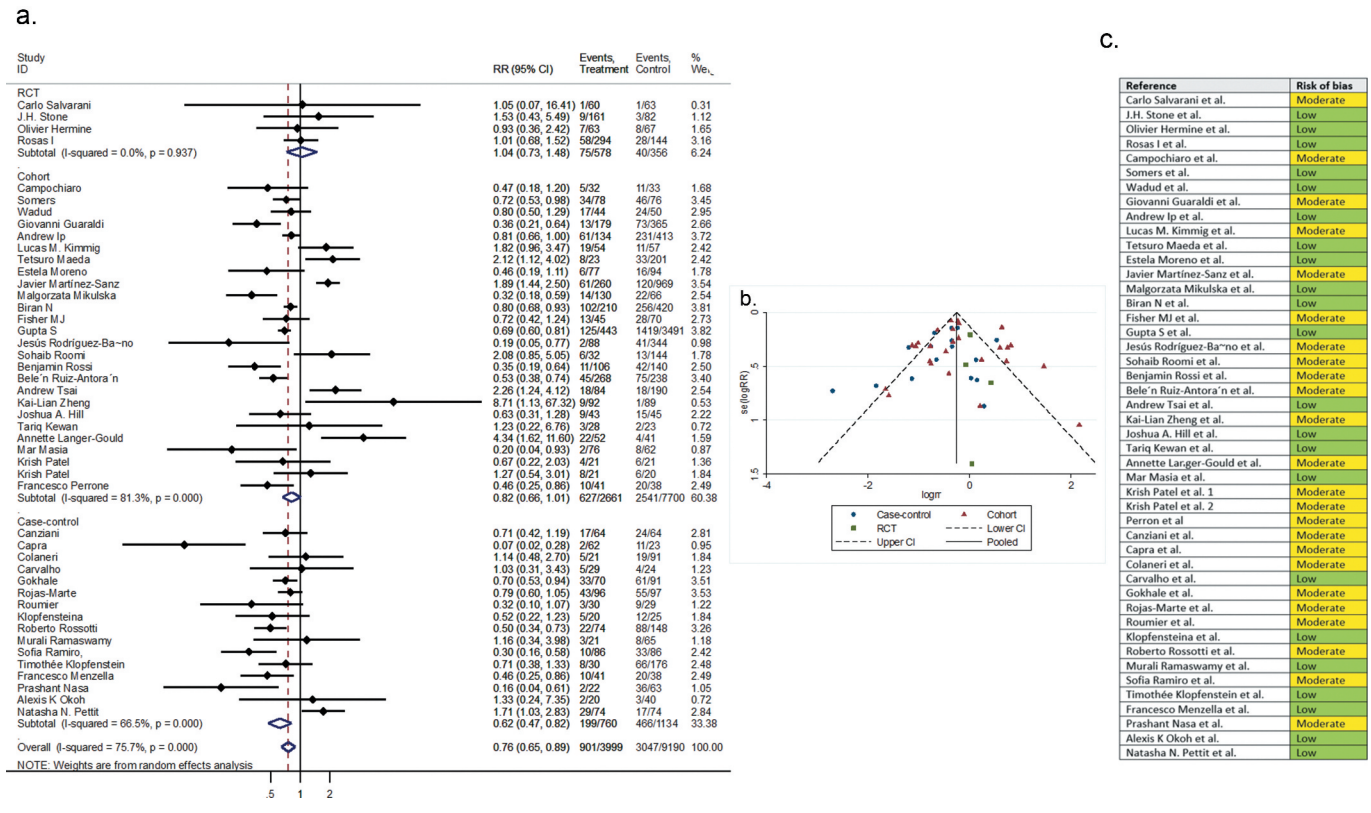
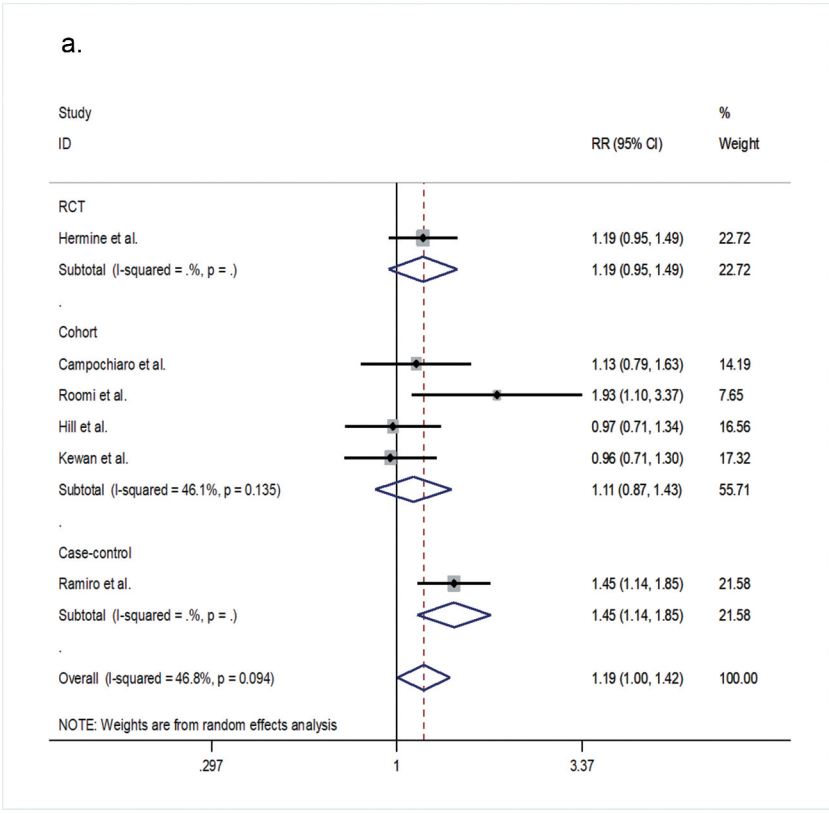


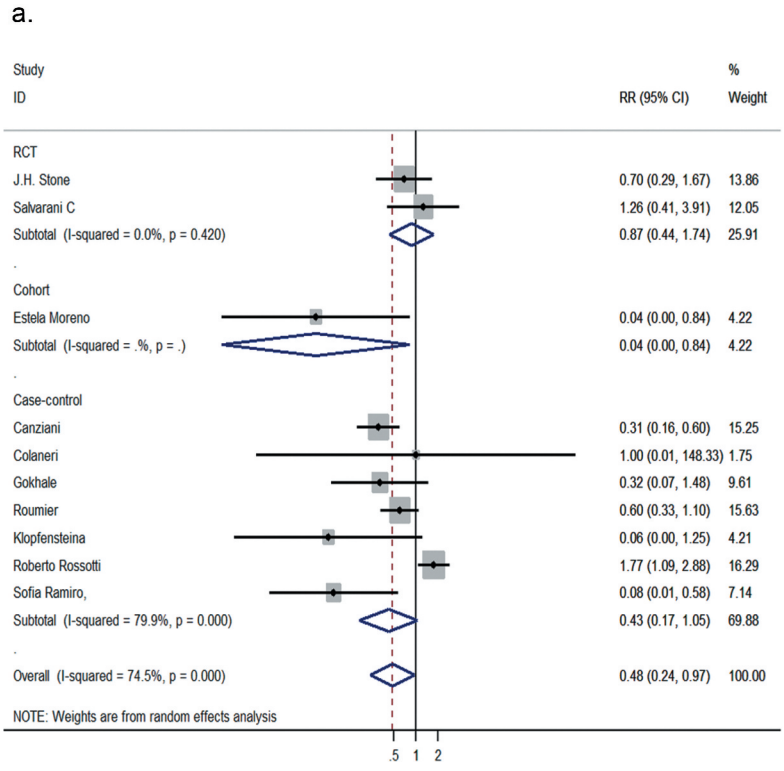
Figure 2. (A) Forest plot of pooled RR of mortality; (B) Funnel plot with pseudo 95% confidence limits; (C) Risk of bias across studies. CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.



c.

Reference	Risk of bias
Olivier Hermine et al.	Low
Campochiaro et al.	Moderate
Sohaib Roomi et al.	Moderate
Joshua A. Hill et al.	Low
Tariq Kewan et al.	Low
Sofia Ramiro et al.	Moderate

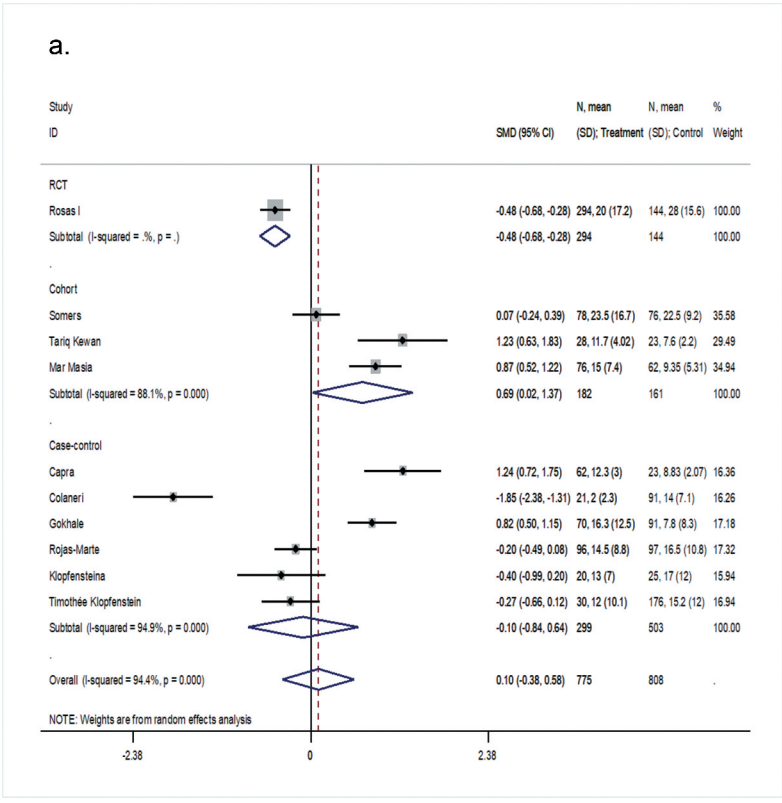
Figure 3. (A) Forest plot of pooled RR of clinical improvement; (B) Funnel plot with pseudo 95% confidence limits; (C) Risk of bias across studies. CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

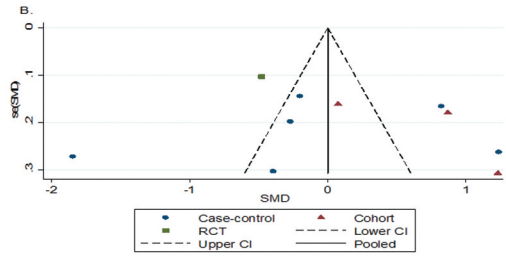


c.

Reference	Risk of bias
J.H. Stone et al.	Low
Salvarani C et al.	Moderate
Estela Moreno et al.	Low
Canziani et al.	Moderate
Colaneri et al.	Moderate
Gokhale et al.	Moderate
Roumier et al.	Moderate
Klopfensteina et al.	Low
Roberto Rossotti et al.	Moderate
Sofia Ramiro et al.	Moderate

Figure 4. (A) Forest plot of pooled RR of intubation; (B) Funnel plot with pseudo 95% confidence limits; (C) Risk of bias across studies. CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

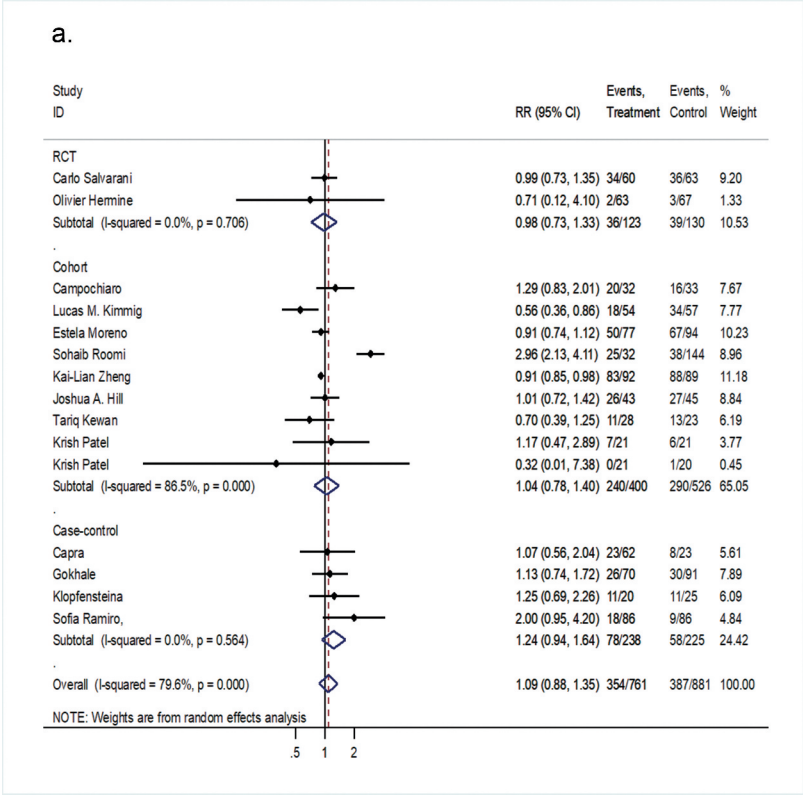


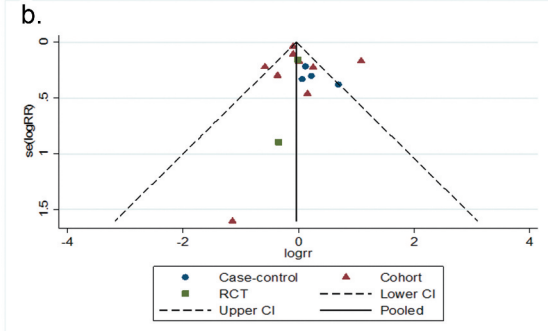


c.

Reference	Risk of bias
Rosas I et al.	Low
Somers et al.	Low
Tariq Kewan et al.	Low
Mar Masia et al.	Low
Capra et al.	Moderate
Colaneri et al.	Moderate
Gokhale et al.	Moderate
Rojas-Marte et al.	Moderate
Klopfensteina et al.	Low
Timothée Klopfenstein et al.	Low

Figure 5. (A) Forest plot of SMD of hospital length of stay; (B) Funnel plot with pseudo 95% confidence limits; (C) Risk of bias across studies. CI, confidence interval; RCT, randomized controlled trial; SMD, standardized mean difference.





c.

Reference	Risk of bias
Carlo Salvarani et al.	Moderate
Olivier Hermine et al.	Low
Campochiaro	Moderate
Lucas M. Kimmig et al.	Moderate
Estela Moreno et al.	Low
Sohaib Roomi et al.	Moderate
Kai-Lian Zheng et al.	Moderate
Joshua A. Hill et al.	Low
Tariq Kewan et al.	Low
Krish Patel et al.	Moderate
Krish Patel et al.	Moderate
Capra et al.	Moderate
Gokhale et al.	Moderate
Klopfensteina et al.	Low
Sofia Ramiro et al.	Moderate

Figure 6. (A) Forest plot of RR of discharging before day 14; (B) Funnel plot with pseudo 95% confidence limits; (C) Risk of bias across studies. CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

3.4.6. ICU admission

Eight comparative studies (two RCTs, three cohorts, and three case-controls) involving 2,233 patients reported ICU admission as a secondary outcome variable. The pooled RR of ICU admission was 0.98 (95% CI 0.36 to 2.66; P = 0.99; I^2 = 89.4%) (Figure 7).

Four single-arm studies involving 248 patients reported the ICU admission rates as a secondary outcome variable. The pooled proportion for the tocilizumab-treated patients and the systematically matched SOC group were 0.21 (95% CI 0.15 to 0.28) and 0.15 (95% CI 0.07 to 0.25), respectively (P = 0.79) (Supplementary file 8, part I & J).

3.4.7. Secondary infections

Twenty-three comparative observational studies (4 RCTs, 12 cohorts, and 7 case-controls) involving 8,660 patients reported infection as a secondary outcome variable. The pooled RR of infection was 1.24 (95% CI 0.98 to 1.56; P = 0.07; I^2 = 66.5%) (Figure 8).

Five single-arm studies involving 404 patients reported infection as a secondary outcome variable. The pooled proportion of infection in the tocilizumab-treated patients and the systematically matched SOC group were 0.16 (95% CI 0.05 to 0.31) and 0.13 (95% CI 0.07 to 0.19), respectively (P = 0.86) (Supplementary file 8, parts K & L).

3.5. Risk of bias across studies

In the assessment of mortality, the symmetry of the funnel plot suggested no publication bias (part B of Figure 2). However, in the assessment of clinical improvement, intubation, secondary infection, length of hospital stay, hospital discharge before day 14, and ICU admission, the asymmetry of the funnel plots suggested possible publication bias (part B of Figure 3–8). In addition, the risk of bias for each outcome of interest in each included study is shown in part C of Figure 2–8.

3.6. Additional analysis

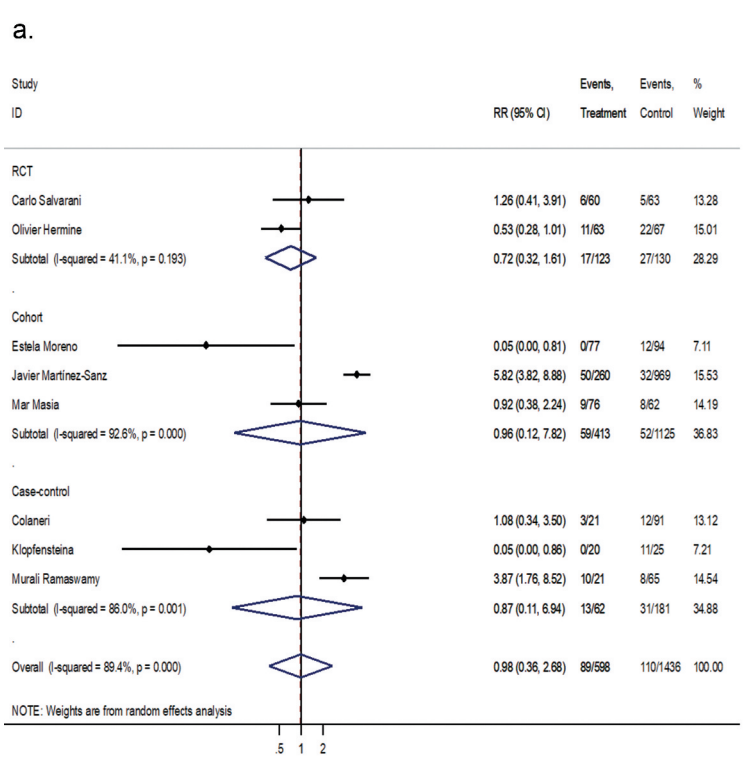
In meta-regression, we did not find any association between the RR of mortality between tocilizumab and control patients and the independent variables of sex, age, study design, and stage of the disease (P > 0.05).

4. Discussion

4.1. Summary of evidence

Since the beginning of the COVID-19 pandemic, several anti-inflammatory agents have been evaluated to dampen the cytokine storm following SARS-CoV-2 infection. Tocilizumab was among the most noticed immunomodulatory drugs. In this systematic review and meta-analysis study, we investigated the potential harms and benefits of the tocilizumab treatment in COVID-19 patients based on the most updated and comprehensive data available in the literature.

Our meta-analysis demonstrated a lower risk of mortality with tocilizumab treatment (RR [95%CI] of 0.76 [0.65, 0.89]). The NNT value of 10 in our analysis suggests that one death is prevented with every 10 severely-to-critically ill patients



c.

Reference	Risk of bias
Carlo Salvarani et al.	Moderate
Olivier Hermine et al.	Low
Estela Moreno et al.	Low
Javier Martínez-Sanz et al.	Moderate
Mar Masia et al.	Low
Colaneri et al.	Moderate
Klopfensteina et al.	Low
Murali Ramaswamy et al.	Low

Figure 7. (A) Forest plot of RR of ICU admission; (B) Funnel plot with pseudo 95% confidence limits; (C) Risk of bias across studies. CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

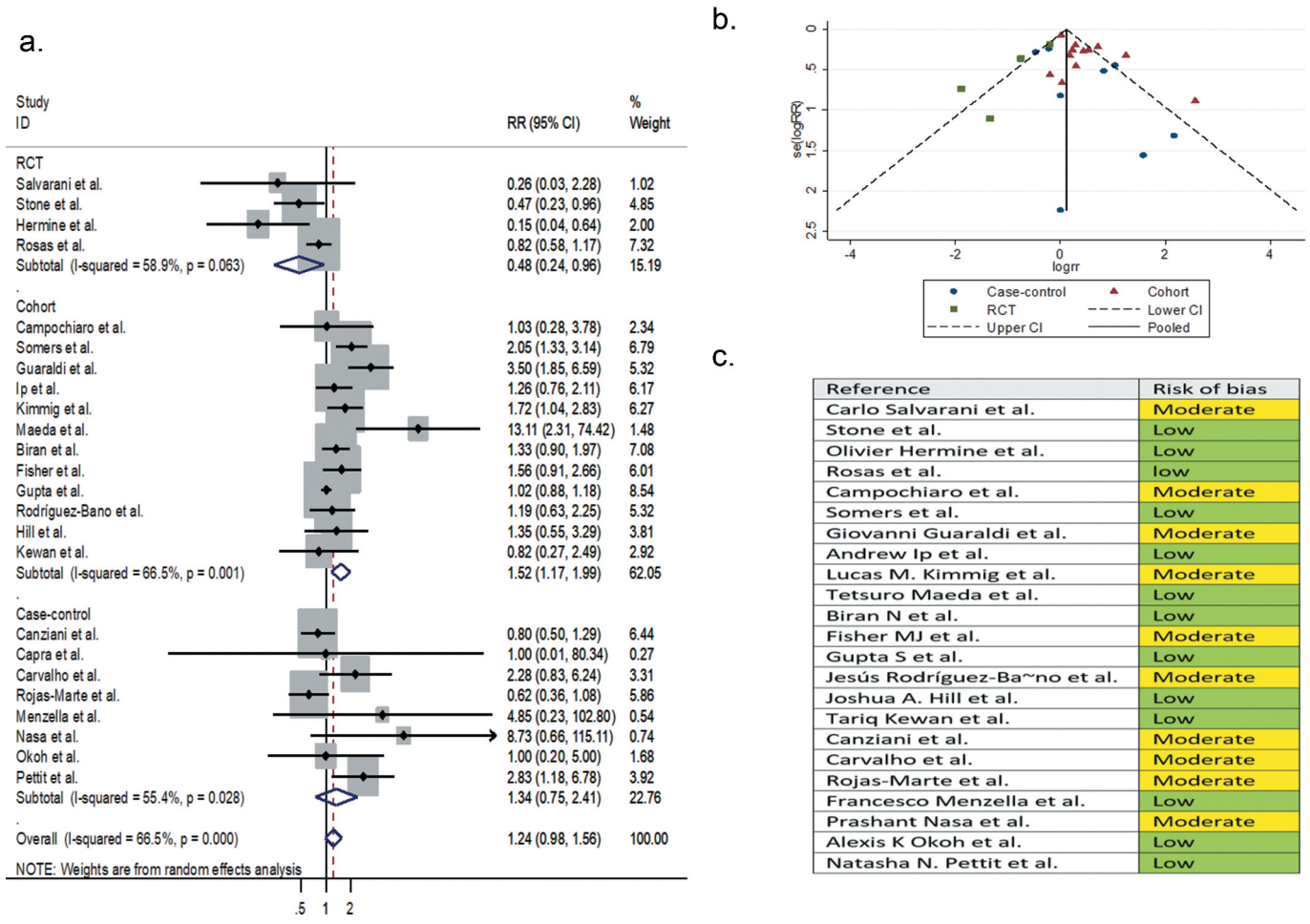


Figure 8. (A) Forest plot of pooled RR of infection; (B) Funnel plot with pseudo 95% confidence limits; (C) Risk of bias across studies. CI, confidence interval; RCT, randomized controlled trial; RR, relative risk.

treated with tocilizumab. Similar results were obtained by previous meta-analysis studies on the effect of tocilizumab treatment on the mortality risk of COVID-19 patients. Khan et al. [87], Rubio-Rivas et al. [88], and Kotak et al. [89] reported RRs [95%CIs] of 0.83 [0.72, 0.96], 0.73 [0.57, 0.93], and 0.56 [0.34, 0.92], respectively, and Zhao et al. [90] and Sarfraz et al. [91] reported odds ratios [95%CIs] of 0.44 [0.36, 0.55] and 0.42 [0.26, 0.69], respectively, with tocilizumab treatment compared with SOC. Despite the promising results in these meta-analysis studies, none of the four published RCTs found a significant beneficial effect on mortality rates for tocilizumab in COVID-19 patients. The subgroup meta-analysis of RCTs (Figure 2) for the risk of death yielded an RR [95%CI] of 1.04 [0.73, 1.48] in our study. Although RCTs and meta-analyses of RCTs are at the top of the hierarchy of evidence for treatment effectiveness, wide 95%CIs reported in the four included RCTs in our meta-analysis show the great levels of uncertainty in their results. Accordingly, these trials cannot rule out either the benefits or harms of tocilizumab treatment on mortality rates in severe to critical COVID-19. Hence, we conducted an updated meta-analysis by combining the results of comparative studies of different types (RCTs, cohort studies, and case–control studies) to provide further conclusions on the impact of tocilizumab treatment on COVID-19 outcomes. Moreover, the comparison of single-arm studies with the systematically matched group showed a 7% reduction in the risk of death with tocilizumab treatment; however, this reduction was not statistically significant.

Regarding secondary efficacy outcomes, our meta-analysis demonstrated that tocilizumab may have some beneficial impacts on the oxygen-support status of severely-to-critically ill COVID-19 patients as it decreased the need for invasive mechanical ventilation with a RR [95%CI] of 0.48 [0.24, 0. 97]. Tleyjeh et al. [92] in the meta-analysis of four RCTs reported a pooled RR [95%CI] of 0.71 [0.52, 0.96] for the effect of tocilizumab on mechanical ventilation. Similarly, Kotak et al. [89] demonstrated a lower risk of the need for intubation with a RR [95%CI] of 0.34 [0.12, 0.99]; and Aziz et al. [93] reported lower rates of mechanical ventilation with a risk difference [95%CI] of −0.11 [−0.19, −0.02] in tocilizumab patients. In a recent retrospective study, Salvati et al. [94] found improved alveolar-arterial oxygen gradient and pulmonary vascular radiologic score in severe COVID-19 patients 1 week after tocilizumab treatment. These data show that tocilizumab may have the potential to improve the lung perfusion in severe COVID-19 patients. Our results indicate no statistically significant differences in the ICU admission rates and length of hospital stay among treatment and control groups. However, Rosas

et al. [17] in the COVACTA trial reported a lower time to hospital discharge in the tocilizumab arm (median [95%CI] of 20 [16,26] days), compared to the control group (median [95% CI] of 28 [20, not evaluable] days) with a hazard ratio [95%CI] of 1.35 [1.02 to 1.79]. Single-arm studies indicated potential benefits of tocilizumab treatment in all secondary efficacy outcome measures; however, these differences were not statistically significant.

Regarding safety, almost all published meta-analysis studies reported no significant differences in the rate of clinically important infections between the tocilizumab and SOC groups [89,92,95,96]. Similarly, in our study, no significant association between tocilizumab administration and secondary infections was found (RR [95%CI] of 1.24 [0.98, 1.56]). Even lower rates of infection were reported in tocilizumab cases in the four published RCTs (pooled RR [95%CI] of 0.48 [0.24, 0.96]). In the CORIMUNO-19 trial [16], bacterial and fungal sepsis were more common in the control group (11/67 and 2/67, respectively) compared with the tocilizumab group (2/63 and 0/63, respectively). Similarly, in the RCT-TCZ-COVID-19 study [14], the rate of secondary infections was lower in the tocilizumab group (1.7%, 1/60) compared with the SOC group (6.3%, 4/63). However, the results of cohort and case–control studies regarding the impact of tocilizumab treatment on the rate of secondary infections were conflicting. Recently, Frigault et al. [97] analyzed the risk of infection in 391 patients with hematologic malignancies in the two groups of tocilizumab (n = 166) and control (n = 225) for the management of CRS following chimeric antigen receptor T (CAR T) cell therapy. After 100 days of follow-up, similar rates of clinically significant infections were reported in the tocilizumab (31.3%) and control (29.8%) groups (P = 0.85). Collectively, although mechanistically possible, available data suggest that the short-term use of tocilizumab in COVID-19 patients cannot be associated with a significant increase in the risk of clinically important infections.

4.2. Limitations

Our meta-analysis study carries several limitations. We were not able to conduct our meta-analysis based only on the published RCTs. The four RCTs lacked adequate power to detect any significant impact for tocilizumab on mortality rates and their pooled RR had a very wide 95%CI. Hence, we included observational clinical studies in addition to the RCTs to increase the power of the analysis [98]. The timing of tocilizumab administration with respect to the severity of the disease can significantly influence the effectiveness of the drug. The timing of treatment was not reported in many of the selected studies and, accordingly, could not be evaluated in our meta-analysis. Similarly, concomitant treatments, notably the corticosteroids, were not reported properly in many of the observational trials. Moreover, secondary outcome measures were not available for all the included studies. Accordingly, we performed the meta-analysis of the secondary outcome variables with the data on a lower number of patients compared with the primary outcome variable. Despite these limitations, our study further supports the administration of tocilizumab to decrease mortality rates in severely-to-critically ill COVID-19 patients. Our meta-analysis was strengthened by the large number of studies involving RCTs, cohort studies, case-controlled studies, and uncontrolled studies. So far, our study is the most updated and the most comprehensive meta-analysis on the effects of tocilizumab in severe and critical COVID-19.

5. Conclusions

Tocilizumab can potentially improve clinical outcomes and reduce mortality rates in patients with severe to critical COVID-19. Our meta-analysis involved a large number of studies of different designs. Published RCTs do not have adequate statistical power to detect possible impacts of tocilizumab on mortality rates and hence meta-analysis performed solely based on the RCTs cannot be considered as conclusive. Large-scale RCTs are still required to make more robust conclusions.

Declaration of interest

Nassim Anjidani is the head of the medical department of Orchid Pharmed company, which is in collaboration with AryoGen Pharmed company with respect to conducting clinical trials. Ali Taheri is an employee of Orchid Pharmed company. The remaining authors have no other relevant affiliations or financial involvement with any organization with a financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contributions

MP and FD contributed to conceptualization and design of study. SR and BF contributed to systematic searching, screaning, article selection, data extraction, data analysis, coordination, and drafing of manuscript. ZK and HM contributed to the data extraction and drafting of the manuscript. NA and AT contribute to the data analysis and drafting of the manuscript. MP, FD and RM contributed to the interpretation of results and supervision of execution. All authors critically revised the manuscript and have contributed to the final approval of the version to be submitted.

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•• **According to this paper, along with the randomized controlled trials, observational studies should be included in the meta-analysis studies in order to make use of all available evidence in the area.**