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REVIEW

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Efficacy of tocilizumab in the treatment of COVID-19: An umbrella review

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Abstract

Tocilizumab is an interleukin (IL)-6 receptor inhibitor that has been proposed as a therapeutic agent for treating coronavirus disease 2019 (COVID-19). The aim of this umbrella review was to determine the efficacy of tocilizumab in treating COVID-19, and to provide an overview of all systematic reviews on this topic. We systematically searched PubMed, Scopus, the Web of Science collection, the Cochrane library, Epistemonikos, and Google Scholar, as well as the medRxiv preprint server. These databases were searched up to 30 September 2021, using the following keywords: 'SARS-CoV-2', 'COVID-19', 'tocilizumab', 'RHPM-1', 'systematic review', and 'meta-analysis'. Studies were included if they were systematic reviews (with or without meta-analysis) investigating the efficacy or safety of tocilizumab in confirmed COVID-19 patients. The AMSTAR 2 checklist

Abbreviations: aHR, adjusted hazard ratio; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; CAR, chimaeric antigen receptor; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; ICU, intensive care unit; IL, interleukin; IQR, interquartile range; LDH, lactate dehydrogenase; MD, mean difference; MRA, myeloma receptor antibody; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; WBC, white blood cell; WMD, weighted mean difference.

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was used to assess quality of the included articles, while publication bias was examined using Egger's test. A total of 50 eligible systematic reviews were included. The pooled estimates showed significant reductions in clinical failure (risk ratio (RR) 0.75; 95% confidence interval (CI), 0.61–0.93), deaths (RR 0.78; 95%CI, 0.71–0.85) and the need for mechanical ventilation (RR 0.77; 95%CI, 0.64–0.92) for those receiving tocilizumab compared with the control group. Also, an emerging survival benefit was demonstrated for those who received tocilizumab, over those in the control group (adjusted hazard ratio (aHR) 0.52; 95%CI, 0.43–0.63). In addition, tocilizumab substantially increased the number of ventilator-free days, compared with the control treatments (weighted mean difference (WMD) 3.38; 95%CI, 0.51–6.25). Furthermore, lymphocyte count (WMD 0.26 $\times$ 10^9/L; 95%CI, 0.14–0.37), IL-6 (WMD 176.99 pg/mL; 95%CI, 76.34–277.64) and D-dimer (WMD 741.08 ng/mL; 95%CI, 109.42–1372.75) were all significantly elevated in those receiving tocilizumab. However, the level of lactate dehydrogenase (LDH) (WMD −30.88 U/L; 95%CI, −51.52, −10.24) and C-reactive protein (CRP) (WMD -104.83 mg/L; 95%CI, −133.21, −76.46) were both significantly lower after treatment with tocilizumab. Tocilizumab treatment reduced the risk of intubation, mortality and the length of hospital stay, without increasing the risk of superimposed infections in COVID-19 patients. Therefore, tocilizumab can be considered an effective therapeutic agent for treating patients with COVID-19.

KEYWORDS
COVID-19, efficacy, interleukin 6, SARS-CoV-2, tocilizumab, umbrella review

1 | INTRODUCTION

In late 2019, a pandemic of novel viral pneumonia occurred in China, which was later named coronavirus disease 2019 (COVID-19).[1] The alarming progression of the disease, and the severity of its clinical manifestations, motivated many researchers to try to develop vaccines and therapeutic approaches for controlling or treating this disease.[2] Several serology analyses have shown that patients with severe COVID-19 manifest higher serum Interleukin (IL)-6 levels, in comparison with those with milder forms of the disease, suggesting that elevated levels of IL-6 might be associated with greater disease severity and worse outcomes.[3–5] This hypothesis raised hopes that IL-6 receptor inhibitors would be effective in treating COVID-19.[6]

Tocilizumab, also known as myeloma receptor antibody (MRA), is a recombinant humanised antibody of the IgG1 subclass that acts as an IL-6 receptor inhibitor.[7] Its main use is for the treatment of autoimmune disorders, such as rheumatoid arthritis and systemic juvenile idiopathic arthritis.[8,9] Tocilizumab has also been found to be effective in treating cytokine release syndrome (CRS), which is associated with some types of immunotherapy, such as chimaeric antigen receptor (CAR)-T cell therapy.[10] These observations form the basis for considering tocilizumab as a therapeutic agent for COVID-19.[11]

There have been several systematic reviews and meta-analyses which have investigated the efficacy of tocilizumab for treating COVID-19, but they have reached different conclusions. For example, a living systematic review and meta-analysis showed that tocilizumab had no effect on the risk of short-term mortality.[12] In contrast, another meta-analysis revealed that all-cause mortality was significantly lower in those receiving tocilizumab.[13] Therefore, we conducted the present umbrella review in order to comprehensively evaluate all available evidence regarding the efficacy of tocilizumab in the treatment of COVID-19.

2 | METHOD

This umbrella review aimed to provide a comprehensive overview and to critically appraise the existing systematic reviews, which evaluated the efficacy and safety of tocilizumab treatment in patients with COVID-19. Our primary outcome was to evaluate the occurrence of “clinical failure”, which was defined as requiring intubation, admission to an intensive care unit (ICU), or death. Also, we evaluated the overall death rate. The secondary outcomes included the

need for mechanical ventilation, risk of ICU admission, hospital discharge rate, presence of a super-infection, length of the hospital stay, length of the ICU stay, number of ventilator-free days, and changes in laboratory parameters.

2.1 | Systematic search

The following databases were searched up to 30 September 2021: PubMed, Scopus, Web of Science collection, Cochrane library, Epistemonikos, and medRxiv. In addition, the first 100 pages of the Google Scholar search engine were manually searched to identify additional eligible studies. There were no limitations or restrictions used in any of the search fields, such as language, date and study type. Furthermore, backward and forward citation searching of all included studies were performed to discover whether there were any additional relevant articles. The search strategy comprised a combination of the following keywords (SARS-CoV-2 OR COVID-19) AND (tocilizumab OR RHPM-1) AND (systematic review OR meta-analysis). A detailed description of the search strategy used in each database is presented in Table S1.

2.2 | Selection of meta-analyses

All of the articles identified through the electronic and manual searches were exported to EndNote 20. After removing duplicates, two groups of authors independently screened the title and abstracts of the articles and excluded those that were irrelevant. In the next step, the same groups reviewed the full-texts of the remaining papers, in accordance with the eligibility criteria. Any discrepancies between the two groups were resolved by consulting other authors. Studies were included if they were: (1) conducted on patients with confirmed COVID-19, based on serological, molecular, or computed tomography (CT)-scan techniques; (2) used tocilizumab as the intervention; (3) used a standard of care treatment or placebo for the control group; (4) reported at least one of the outcomes of interest (i.e. clinical failure, overall death, need for mechanical ventilation, risk of ICU admission, hospital discharge rate, super-infection, length of the hospital stay, ICU stay, ventilator-free days, and changes in laboratory parameters); and (5) conducted a systematic review, with or without a meta-analysis. Studies were excluded if they were: (1) cross-sectional, case-control, cohort or clinical trials; (2) living systematic reviews and review articles that did not used a systematic approach (e.g. rapid or scoping reviews); (3) systematic reviews on preclinical or animal studies; and (4) investigated the effectiveness of tocilizumab combined with other IL-6 inhibitor therapies.

All eligible meta-analyses were reviewed and the primary studies were identified. Individual primary studies were selected for the recalculation of the summary effect, based on the following criteria: (1) retrospective and prospective observational studies with a matched control group, in terms of disease severity (i.e. similar proportions of patients receiving respiratory support in both the experimental and control groups), (2) randomized controlled trials, or (3) single-group studies which assessed the pattern of changes in laboratory measures before and after tocilizumab therapy.

2.3 | Data extraction

Data extraction was conducted using previously designed Microsoft Office Excel forms. Two researchers independently obtained the following information from each included study: (1) basic information about the study, including the first author's name, year of publication and the journal; (2) search date and names of the databases searched, number of included studies, total number of participants, study designs of the included studies, tools used for assessing the risk of bias, age and sex of the included participants, general summary, and summary effect size (95% confidence interval (CI)) for each outcome. Disagreements were resolved by discussing or consulting a third author and all of the extracted data were double-checked by other reviewers.

2.4 | Methodological quality

Two authors independently assessed the risk of bias and the quality of the included articles using the "A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)" checklist.[14] This checklist consists of 16 items, of which seven are considered critical domains: protocol registration, adequacy of the literature search, justification for excluding individual studies, risk of bias from the individual studies being included, appropriateness of the meta-analytical methods, consideration of the risk of bias when interpreting the results of the review, and assessment of the presence and likely impact of publication bias. The checklist does not create an overall score, but provides a total rating based on weaknesses detected in the critical domains. The overall confidence in the results of the review can be qualitatively rated as either "high" (no or one non-critical weakness), "moderate" (more than one non-critical weakness), "low" (one critical flaw, with or without non-critical weaknesses), and "critically low" (more than one critical flaw, with or without non-critical weaknesses). A third reviewer was consulted to resolve any discrepancies between the two authors.

2.5 | Statistical analysis

The crude data, multivariable adjusted hazard ratios (aHRs) that controlled for any confounders, and their 95% CIs were extracted from all primary studies included in the selected meta-analyses. Following this, we performed our own meta-analysis using the DerSimonian and Laird random-effects method. The binary outcomes were examined using summary risk ratios (RRs) and aHRs, while for continuous outcomes weighted mean differences (WMDs) and their corresponding

95% CIs were recalculated. Furthermore, whenever the continuous variables were reported as a median with a range or interquartile range (IQR), we converted them to a mean and standard deviation (SD) using the method proposed by Lue et al. and Wan et al.[15,16]

When recalculating the summary effect sizes, primary studies were excluded if: (1) the retrospective and prospective observational studies had unmatched control groups, (2) they were not conducted in the general population, such as studies that recruited COVID-19 patients with specific underlying disorders, or (3) they only reported unadjusted HRs. We excluded the aforementioned primary studies from the meta-analyses and then reanalysed the effect sizes using the random-effects model. This approach helped to ensure that the general population was targeted and that the risk of selection bias was minimised among the primary studies included. This is because tocilizumab was more likely to be given to those who presented with more severe forms of the disease, which may lead to a higher proportion of negative outcomes in the intervention group, relative to the controls.

The between study heterogeneity was assessed for each meta-analysis by estimating I^2 statistics and their 95% CIs,[17] while publication bias was examined using Egger's test.[18] All analyses were performed in STATA Statistical Software, version 17 (Stata Corporation, College Station, TX, USA). Statistical significance was defined as p-value <0.05.

3 | RESULTS

3.1 | Literature search

The systematic search identified a total of 709 records, which came from PubMed (n = 94), Scopus (n = 279), the Web of Science collection (n = 80), the Cochrane library (n = 1), Epistemonikos (n = 139), and medRxiv (n = 116). Following the removal of 197 duplicate records, the remaining 512 studies were screened and 93 publications were selected for full text review. One article was not accessible and thus it was excluded.[19] After evaluating the other 92 articles for eligibility, 42 were excluded for the following reasons: one study investigated tocilizumab combined with another IL-6 inhibitor,[20] two discussed therapies other than tocilizumab,[21,22] 37 were not systematic reviews,[23–59] and two were systematic reviews of preclinical or animal studies.[60,61] Finally, 50 articles met the eligibility criteria and were included in the present umbrella review[6,28,62–109] (Figure 1).

3.2 | Characteristics of the studies included in the meta-analysis

The 50 included studies were comprised of nine preprints and 41 published articles, which appeared in 37 different journals. They were all published in English and published in 2020 and 2021. Two studies did not report the search date, while in the remaining 48 comprehensive searches were performed from 1 December 2019 up to May 2021. Table 1 summarises the characteristics of the included studies.

A total of 70 primary studies were included in the published meta-analyses, including 55 retrospective cohorts, 11 randomized control trials (RCTs), and four prospective cohorts. Thirty-eight primary studies provided a matched control group and 37 studies reported the adjusted multivariate effect sizes. There were 24 studies conducted in the USA, 12 in Italy, 10 in Spain, and 24 in other countries.

3.3 | Primary outcomes

3.3.1 | Tocilizumab administration and risk of intubation, admission to ICU, or death

The first outcome was the combined outcome of either intubation, admission to ICU, or death, which was collectively called clinical failure. Ten publications, which were comprised of six retrospective studies, one prospective cohort study, and three clinical trials (n = 3318), were used for recalculating the summary aHR. The results of the pooled estimate showed that there was a significant 58% reduction in this composite outcome in the group receiving tocilizumab, relative to the control group (aHR 0.42; 95%CI, 0.30–0.59, I^2 = 61.0%). In a subgroup analysis, by study type, the risk of clinical failure was greatly reduced for the treatment group in retrospective cohort studies (aHR 0.31; 95%CI, 0.19–0.51, I^2 = 68.7%) and RCTs (aHR 0.62; 95%CI, 0.43–0.89, I^2 = 0.0%), but not for prospective cohorts (aHR 0.65; 95%CI, 0.23–1.83, I^2=NA) (Figure 2).

In order to recalculate the summary effect for clinical failure, in terms of RR, 5140 patients from ten studies (two retrospective cohorts and eight RCTs) were enroled. Participants who received tocilizumab had an overall significant 25% lower risk of clinical failure, as compared to their counterparts in the control group (RR 0.75; 95%CI, 0.61–0.93, I^2 = 44.1%). Furthermore, the advantage of tocilizumab administration in reducing the risk of clinical failure ranged from a 19% reduction in clinical trials (RR 0.81; 95%CI, 0.69–0.95, I^2 = 21.2%) to a 65% reduction in retrospective studies (RR 0.35; 95% CI, 0.13–0.99, I^2 = 49.6%) (Figure 3).

3.3.2 | Tocilizumab administration and the overall risk of mortality

A total of 33 primary studies, consisting of 18,538 participants, reported aHRs for mortality. These studies were comprised of 30 retrospective studies and three RCTs. After recalculating the summary effect, an emerging survival benefit was demonstrated for those receiving tocilizumab over the control group (aHR 0.52; 95%CI, 0.43–0.63, I^2 = 74.0%). When the pooled estimates were stratified, based on the study design, the summary effects remained statistically significant, with a larger benefit being found in retrospective studies (aHR 0.50; 95%CI, 0.41–0.61, I^2 = 75.9%), relative to clinical trials (aHR 0.67; 95%CI, 0.53–0.86, I^2 = 0.3%) (Figure 4).

In the next step, the mortality RRs were reanalysed using 38 primary studies, which included data for 16,072 COVID-19 patients.

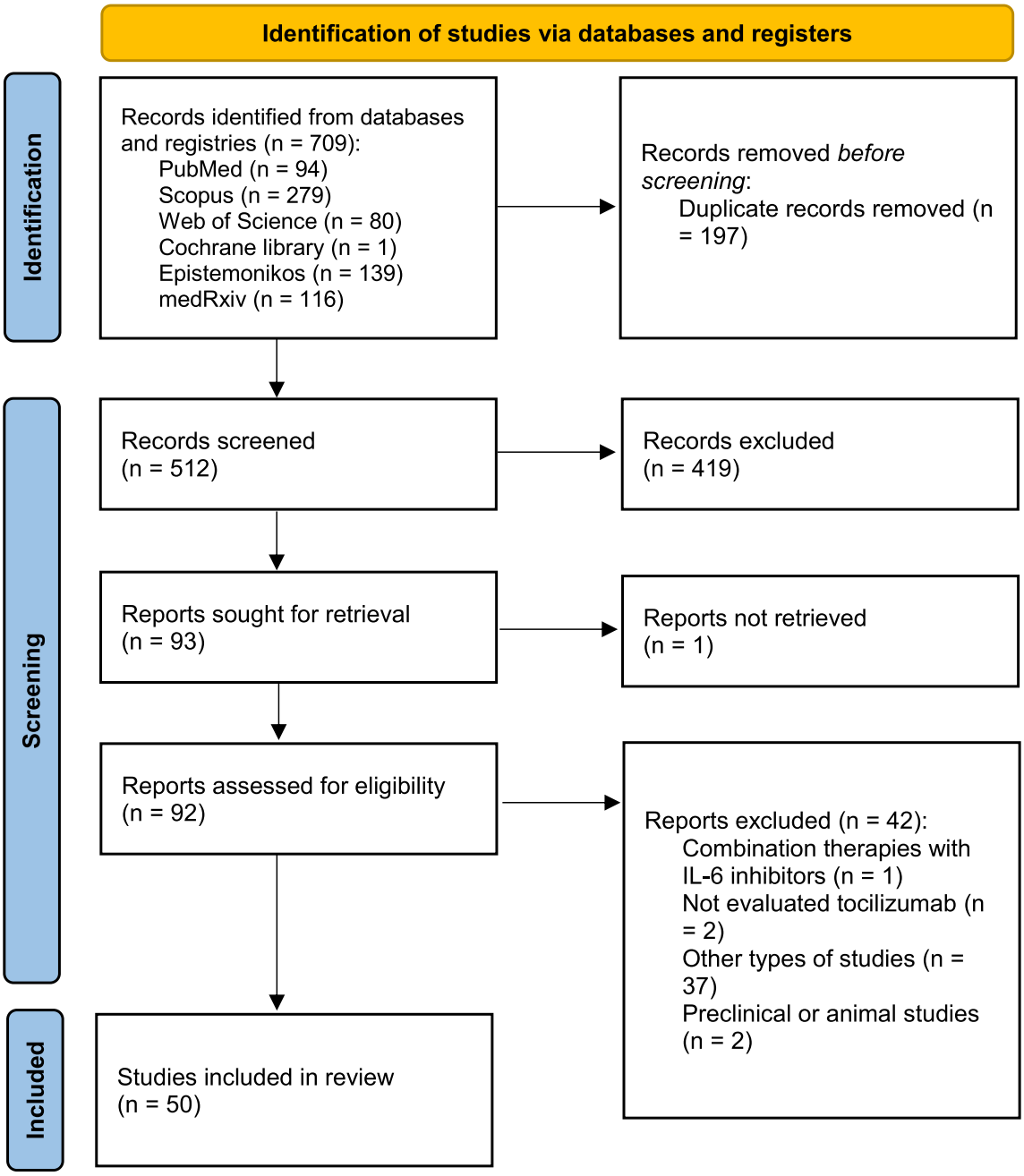

FIGURE 1 Study selection process

Twenty-eight publications were retrospective observational studies, one was a prospective cohort, and nine were RCT. Tocilizumab administration resulted in substantially lower odds of death, when compared to the control group (RR 0.78; 95%CI, 0.71–0.85, I^2 = 40.8%). Analysing the results by study design, tocilizumab therapy was associated with a lower risk of mortality, compared to the control groups, in retrospective studies (27%), prospective studies (80%), and RCTs (11%). The differences were statistically significant for all types of study designs (RR 0.73; 95%CI, 0.66–0.81, I^2 = 29.9%; RR 0.20; 95%CI, 0.04–0.93, I^2=NA; and RR 0.89; 95%CI, 0.80–0.98, I^2 = 5.9%, respectively) (Figure 5).

3.4 | Secondary outcomes

3.4.1 | Tocilizumab administration and the need for mechanical ventilation

Eight primary retrospective studies and seven RCTs, with a total population of 5792 COVID-19 patients, were used to recalculate the RR for requiring mechanical ventilation. Patients who were given tocilizumab had a significantly lower risk of requiring mechanical ventilation, than those who were treated with the control group medications (RR 0.77; 95%CI, 0.64–0.92, I^2 = 44.9%). However,

TABLE 1 Characteristics of the systematic reviews included in the present umbrella review

Study identification	Journal	Search date	Searched databases	Number of included studies/total number of participants	Study design of included studies	Tools for assessment of risk of bias	Age of included participants	Sex of included participants (the proportion of females)
Nugroho et al. 2021[74]	F1000Research	2 November 2020	PubMed, Embase, Medline, and Cochrane	26 studies/2112 in intervention group and 6160 in control group	Cohort, case-control, and RCT	NOS	A mean/median age from 29 to 77 in intervention group and from 21 to 73.5 in controls	Not reported
Aziz et al. 2020[62]	Journal of Medical Virology	1 January 2020 to 23 July 2020	PubMed/MEDLINE, Embase, Lit-COVID, WHO COVID, Cochrane, and Web of Science	23 studies/6279 patients (1897 in tocilizumab + standard therapy group and 4382 in standard therapy alone)	RCT and cohort studies	NOS, NCOS and ROBINS-I	62.2 ± 4.7 years in tocilizumab + standard therapy group and 64.8 ± 4.1 years in standard therapy group	39.4% in tocilizumab + standard therapy group and 28.0% in standard therapy group
Conti et al. 2021[110]	Journal of Personalised Medicine	May 2021	PubMed, Scopus, Embase, Cochrane, WILEY, and ClinicalTrials.gov	47 studies/9640 patients (3085 in tocilizumab + standard therapy and 6355 patients in standard therapy alone)	Observational studies and RCT	NOS	The mean age of all participants was 64.44 ± 13.89 years (range 53–78 years)	Not reported
Elangovan et al. 2020[66]	Preprint	1 August 2020	PubMed, medRxiv and Scopus	29 studies/684 patients	RCT, nRCT, and observational studies (cohort study and case series)	RoB 2.0 and ROBINS-I tools, NOS	Not reported	Not reported
Gupta et al. 2021[111]	Journal of Investigative Medicine	19 April 2021	Medline (PubMed), Embase, Google Scholar, and Cochrane	6 studies/3013 patients (1651 in tocilizumab + standard therapy and 1362 patients in standard therapy alone)	RCT	RoB 2	Not reported	Not reported
Hariyanto et al. 2020[112]	Drug Research	1 November 2020	PubMed and Europe PMC	38 studies/13,412 patients (4090 in tocilizumab group and 9322 in non-tocilizumab group)	RCT, nRCT, and observational studies (cohort study and case control)	NOS	Adult patients (at least 18 years old)	Not reported
Klopfenstein et al. 2021[70]	Infectious Diseases and Therapy	27 April 2021	Medline, the Cochrane Library, and Embase	9 studies/6482 patients (3357 in tocilizumab group and 3125 in placebo group)	RCT	RoB 2.0	Not reported	Not reported
Kyriakopoulos et al. 2021[113]	Preprint	31 March 2021	MEDLINE, CENTRAL and medRxiv	52 studies/27,004 patients (8048 in tocilizumab group and 18,956 in non-tocilizumab group)	RCT and observational studies	RoB 2.0 and ROBINS-I tools	Not reported	Not reported
Podmore et al. 2021[63]	Preprint	July 2020 to 1 March 2021	Embase and PubMed	41 studies/Not reported	RCT and observational studies	ROBINS-I tool	Not reported	Not reported
Wafa et al. 2021[114]	Preprint	January 25 to 5 February 2021	PubMed (MEDLINE), Science Direct, Cochrane Library, ProQuest and Springer	10 studies/Not reported	RCT	RoB 2.0	Not reported	Not reported
Kotak et al. 2020[115]	Cureus	29 June 2020	PubMed and Cochrane	7 studies/766 patients (351 in the tocilizumab group and 414 in the control group)	Observational studies	NOS	Not reported	Not reported
Abdulrahman et al. 2021[116]	Preprint	3 January 2021	PUBMED, EMBASE, and medRxiv	9 studies/6326 patients (3272 in the tocilizumab group and 3054 in the control group)	RCT	RoB 2.0	Adult patients (at least 18 years old)	Not reported
Lan et al. 2020[72]	International Journal of Antimicrobial Agents	24 May 2020	PubMed, Cochrane Library, Embase, medRxiv and bioRxiv.	7 studies/592 patients (240 in the tocilizumab group and 352 in the control group)	Observational studies	NOS	Adult patients (at least 18 years old)	Not reported

TABLE 1 (Continued)

Study identification	Journal	Search date	Searched databases	Number of included studies/total number of participants	Study design of included studies	Tools for assessment of risk of bias	Age of included participants	Sex of included participants (the proportion of females)
Rezaei et al. 2021[75]	Expert Review of Clinical Immunology	26 December 2020	PubMed, Embase, CENTRAL, ClinicalTrials.gov, Scopus, and preprints	73 studies (45 comparative studies and 28 single-arm studies)/Not reported	Comparative studies (RCT, case– control studies), single-arm observational studies	RoB 2.0 and NOS	63.14 ± 5.2 years	36%
Chandrasekar et al. 2020[117]	Journal of Medical Virology	1 December 2019 to 11 May 2020.	PubMed/MEDLINE, Embase, Cochrane Central, Google Scholar, MedRxiv	29 studies/5207 patients 3624 patients in the intervention arm (mean age: 55.9 ± 8.4 years, 62% males) and 1583 patients (mean age: 52.5 ± 8.5 years, 60.7% males) in the control arm	RCT, prospective cohorts, retrospective cohorts, and case series	RoB 2.0	55.9 ± 8.4 in intervention arm and 52.5 ± 8.5 in the control arm	62% in intervention arm and 60.7% in the control arm
Rubio-Rivas et al. 2021[118]	The Journal of Human Pharmacology and Drug Therapy	1 January 2020 to 13 April 2021	PubMed/MEDLINE, and Scopus	64 studies/20,616 patients (7668 in tocilizumab + standard therapy and 12,948 in standard therapy alone)	RCT and observational studies	NOS and RoB 2.0	62.4 ±15.1 in tocilizumab group and not reported in control group	31.2% in tocilizumab group and not reported in control group
Tleyjeh et al. 2021[12]	Clinical Microbiology and Infection	8 October 2020	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, Scopus up, preprint servers and Google	24 studies (five RCTs and 19 cohorts)/1325 patients in RCTs and 9850 in cohorts (detailed number of patients in intervention and control group was not reported)	RCT and cohort	RoB 2.0 and ROBINS-I tools	Not reported	Not reported
Viswanatha et al. 2021[119]	Clinical and Experimental Rheumatology	1 January 2020 to 30 September 2020	PubMed, Scopus, CENTRAL, and Google scholar	24 studies/5686 patients (1841in tocilizumab + standard therapy and 3454 in standard therapy alone)	Comparative studies (RCT, case– control studies)	NOS, RoB 2.0	Not reported	Not reported
Wei et al. 2021[79]	Infectious Disease of Poverty	20 March 2020	PubMed, PMC, Scopus, Google Scholar, and Web of Science	25 studies/10,201 patients (3135 in tocilizumab + standard therapy and 7066 in standard therapy alone)	RCT and observational studies	RoB 2.0	Not reported	Not reported
Zhao, J. et al. 2020[120]	Critical Care	25 July 2020	PubMed, Embase, Medline, Cochrane, and CNKI	10 studies/1675 patients (675 patients in tocilizumab + standard therapy, while 1000 in standard therapy alone)	RCT and cohort	Not reported	older/elderly (mean/median age ≥52 years)	Not reported
Berardicurti et al. 2020[121]	Clinical and Experimental Rheumatology	1 January 2020 to 21 July 2020	MEDLINE, Cochrane Library, SCOPUS, and Web of Science	22 studies/1520 tocilizumab-treated patients	RCT and observational studies	NOS	61 years (95% CI: 59–64)	29%

(Continues)

TABLE 1 (Continued)

Study identification	Journal	Search date	Searched databases	Number of included studies/total number of participants	Study design of included studies	Tools for assessment of risk of bias	Age of included participants	Sex of included participants (the proportion of females)
Boregowda et al. 2020[122]	Frontiers in Medicine	December 2019 to 14 June 2020.	PubMed, Embase, Cochrane library, Web of Science, and MedRxiv	16 studies/3641 (1153 in tocilizumab + standard therapy and 2488 in standard therapy alone)	RCT and observational studies	ROBINS-I	Not reported	36% (38.3% in standard therapy group and 31.3% in tocilizumab group)
Campbell et al. 2021[123]	Frontiers in Medicine	1 January 2020 to 25 February 2021	The global WHO database of Individual Case Safety Reports (ICSRs)/adverse drug reactions (ADRs) ("VigiBase"), searching Medline, Embase, and Web of Science	72 studies/Not reported	Cohort	RoB 2.0	Not reported	Not reported
Chen et al. 2020[124]	Leukemia	1 January 2020 to 27 October 2020	PubMed, Web of Science and Medline	32 studies/11,487 patients (detailed number of patients in intervention and control group was not reported)	RCT and observational studies	NOS, Jadad scale	Not reported	Not reported
Han et al. 2021[125]	Frontiers in Pharmacology	10 August 2020	PubMed, EMBASE, ISI Web of Science, Cochrane library, ongoing clinical trial registries (clinicaltrials.gov), and preprint servers (medRxiv, ChinaXiv)	33 studies/5630 patients (2132 in anti-IL-6 signalling (anti-IL6/IL-6 R/JAK) agents + standard therapy and 3498 in standard therapy alone)	RCT, and observational studies (cohort study and case control)	The MINORS index, NOS, RoB 2.0	Not reported	Not reported
Kaye et al. 2021[94]	PeerJ	4 August 2020	PubMed and SearchWorks	34 studies (16 case-control studies and 18 uncontrolled trials)/ 1008 in tocilizumab + standard therapy and 1537 in standard therapy alone)	Case-control studies and uncontrolled studies		Not reported	Not reported
Khan et al. 2021[126]	Respiratory Infection	7 January 2021	MEDLINE, and EMBASE and ongoing clinical trial registries (clinicaltrials.gov and EU Clinical Trials Register)	70 studies/20,972 patients (6563 in tocilizumab + standard therapy and 14,409 in standard therapy alone)	RCT and observational studies	RoB 2.0	Not reported	Not reported
Peng et al. 2021[100]	Reviews in Medical Virology	1 January 2020 to 20 December 2020	PubMed, Embase Medline, Web of Science and MedRxiv	29 studies/Sample size not reported	Observational studies	Not conducted	Not reported	Not reported
Petrelli et al. 2021[127]	World Journal of Methodology	9 June 2020	PubMed, EMBASE, SCOPUS, Web of Science, MedRxiv, Science Direct, and the Cochrane Library	33 studies/13,476 patients (3264 in tocilizumab + standard therapy and 10,212 in standard therapy alone)	RCT and observational studies	ROBIN-I, NOS	Median: 62	Not reported

TABLE 1 (Continued)

Study identification	Journal	Search date	Searched databases	Number of included studies/total number of participants	Study design of included studies	Tools for assessment of risk of bias	Age of included participants	Sex of included participants (the proportion of females)
Pinzon et al. 2021[128]	Journal of Infection and Public Health	November 2020	PubMed and medRxiv	16 studies/Not reported	RCT and observational studies	OCEBM	Not reported	Not reported
Singh et al. 2020[129]	Preprint	4 June 2020	PubMed, The Cochrane Central Register of Controlled Trials, preprint server (medRxiv) and international clinical trial register (clinicaltrials.gov)	13 studies/2750 patients (819 in tocilizumab + standard therapy and 1931 in standard therapy alone)	RCT, nRCT, and observational studies	ROBIN-I, RoB 2.0	Not reported	Not reported
Zhao et al. 2021[130]	European Journal of Clinical Pharmacology	27 September 2020	PubMed, Embase, Medline, and Cochrane	19 studies/2493 patients (detailed number of patients in intervention and control group was not reported)	Observational studies	Not conducted	Not reported	Not reported
Alunno et al. 2021[82]	Clinical Science	11 December 2020	MEDLINE, Embase, The Cochrane Database of Systematic Reviews, CENTRAL and CINAHL	4 studies/Not reported	RCT	RoB 2.0.	Not reported	Not reported
Elsokary et al. 2020[131]	Preprint	26 August 2020	ClinicalTrial.gov, ProQuest, PubMed, Embase, Cochrane, Google Scholar, Science direct, Chinese Clinical Trial Registry (ChiCTR), and medRxiv	6 studies/1473 patients (472 in tocilizumab + standard therapy and 1001 in standard therapy alone)	Cohort studies	ROBIN-I	Not reported	Not reported
Lin et al. 2021[85]	International Immunopharmacology	20 February 2021	PubMed, Embase, Cochrane Library, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform and the preprint server of medRxiv	8 studies/6314 patients (3267 in tocilizumab + standard therapy and 3047 in placebo or standard therapy alone)	RCT	RoB 2.0.	The mean or medium age ranged from 56 to 64 years	40%
Mathew et al. 2020[132]	Open access journal of biomedical science	May 25 to 16 June 2020	PubMed and Google Scholar	14 studies/Not reported	RCT, cohorts, case reports and case series.	Not conducted	Not reported	Not reported
Misra et al. 2020[86]	European Journal of Clinical Investigation	29 June 2020	PubMed, EMBASE, Medline, Google Scholar, Cochrane library and clinicaltrials.gov	4 studies/806 patients (294 in tocilizumab + standard therapy group and 512 in standard therapy alone)	RCT, nRCT, cohort and case-control studies	RoB 2.0., NOS	Not reported	Not reported

(Continues)

TABLE 1 (Continued)

Study identification	Journal	Search date	Searched databases	Number of included studies/total number of participants	Study design of included studies	Tools for assessment of risk of bias	Age of included participants	Sex of included participants (the proportion of females)
Ogiji et al. 2020[133]	EAS Journal of Pharmacy and Pharmacology	25 May 2020	PubMed, Google Scholar, Scopus	18 studies/Not reported	Cohort and case-control studies, case reports and case series	Joanna Briggs Institute's critical appraisal checklist	Not reported	Not reported
Putman et al. 2021[134]	Arthritis & Rheumatology	19 March 2020 and 7 May 2020	Ovid Medline and E-pub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, Web of Science, and ClinicalTrials.Gov	7 studies/339 patients (detailed number of patients in intervention and control group was not reported)	Cohort and case series	NOS	Not reported	Not reported
Russell et al. 2020[89]	Ecancermedicalscience	Not reported	Ovid MEDLINE	Not reported	Not reported	Not conducted	Not reported	Not reported
Talaie et al. 2020[135]	DARU Journal of Pharmaceutical Sciences	1 July 2020	PubMed, Embase, Scopus, Cochrane, and Scholar	11 studies/Not reported	All types of studies	RoB 2.0.,NOS, NIH Quality Assessment Tool	Not reported	Not reported
Zhang et al. 2020[136]	Frontiers in Public Health	19 December 2020	WHO COVID-19 Global Research Database, PubMed, PubMed Central, LitCovid, Proquest Central and Ovid	Not reported	RCT	RoB 2.0.	Not reported	Not reported
Antwi-Amoabeng et al. 2020[137]	Journal of Medical Virology	27 April 2020	PubMed, Embase, and Medline	11 studies/29 patients	Case reports and case series	ROBIN-I	63 ±12	17.2%
Chibber et al. 2020[138]	European Journal of Pharmacology	Not reported	Google Scholar, Embase, and PubMed	Not reported	Not reported	Not conducted	Not reported	Not reported
Kim et al. 2020[33]	PLOS MEDICINE	the beginning of 2020 to 24 August 2020	PubMed, Google Scholar, MEDLINE, the Cochrane Library, medRxiv, SSRN, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov	9 studies/Not reported	RCT and observational studies	RoB 2.0.	Not reported	Not reported

TABLE 1 (Continued)

Study identification	Journal	Search date	Searched databases	Number of included studies/total number of participants	Study design of included studies	Tools for assessment of risk of bias	Age of included participants	Sex of included participants (the proportion of females)
Mahroum et al. 2021[107]	International Journal of Environmental Research and Public Health	20 July 2020	PubMed, MEDLINE, Scopus, medRxiv and SSRN	39 studies/15,531 patients (3657 in tocilizumab + standard therapy group and 11,874 in standard therapy alone)	Case control, cohort	NOS	Ranged from 55 to 76.8	Not reported
Martinez-Vizcaino et al. 2020[108]	Preprint	22 April 2020	International Clinical Trials Registry Platform (WHO-ICTRP)	10 studies/2175 patients	RCT	Not conducted	Not reported	Not reported
POZO et al. 2020[139]	European Review for Medical and Pharmacological Sciences	18 April 2020	PubMed, Web of Science, Scopus, and clinicaltrials.gov	13 studies/Not reported	RCT and observational studies	Not conducted	Not reported	Not reported
Qayyumi et al. 2020[140]	Cancer Research, Statistics, and Treatment	23 May 2020	PubMed, Embase, and Google Scholar	One study/21 patients	Case series	Not conducted	Not reported	Not reported
Zeraatkar et al. 2021[141]	Preprint	9 October 2020	Medline Ovid, PubMed, PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane 138 Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO and CDC Covid-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv, medRxiv, chemRxiv, and SSRN	20 trials/7608 patients	RCT	RoB 2.0.	Ranged from 42.1 to 69.8	Not reported

Abbreviations: CDC, Centres for Disease Control and Prevention; NOS, The Newcastle-Ottawa scale; nRCT, non-randomized controlled trials; RCT, Randomized controlled trials; RoB 2.0, Cochrane risk of bias tool for RCTs; ROBINS-I, Risk of bias in nonrandomised studies of Interventions; WHO, World Health Organization.

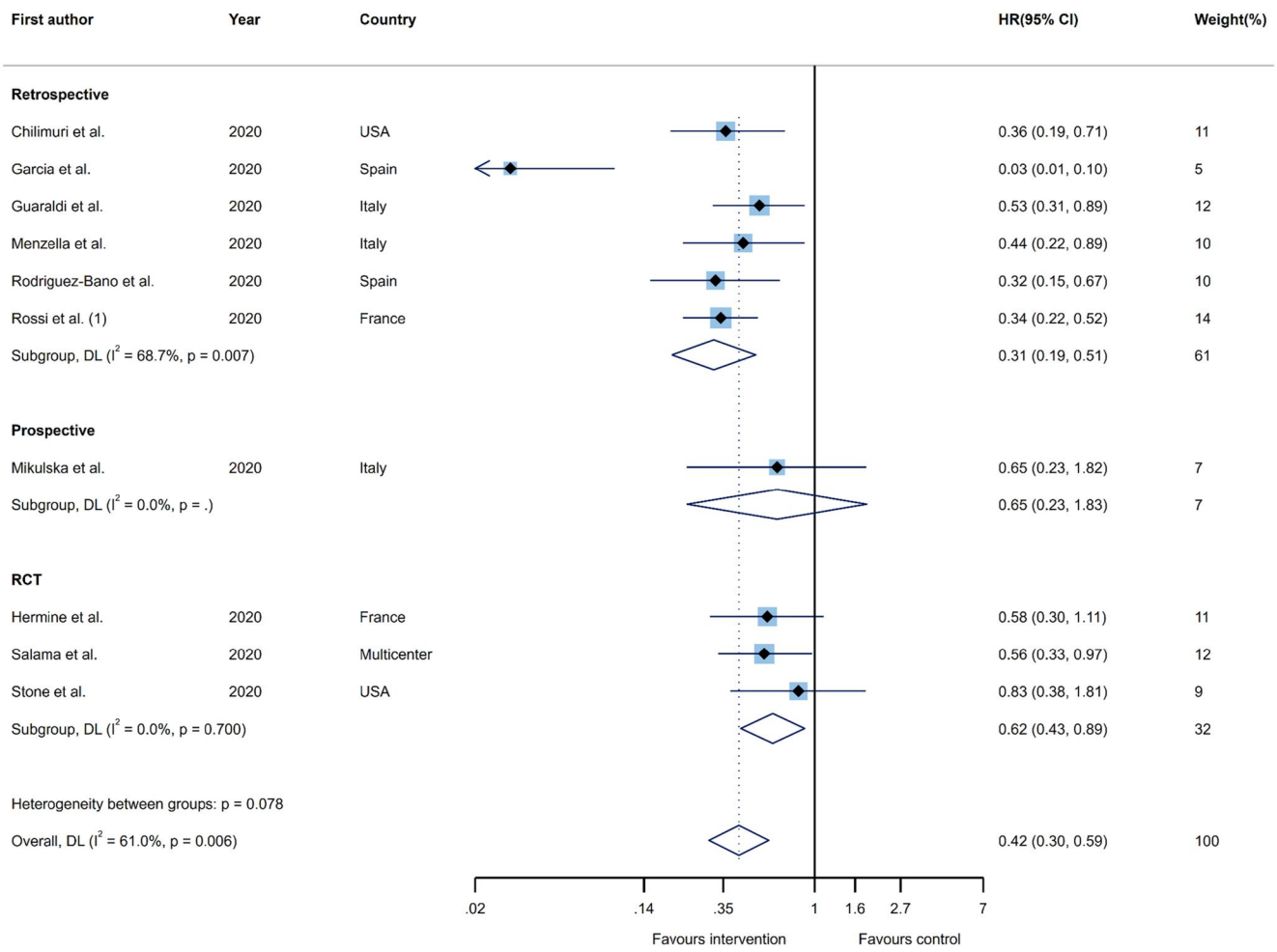

FIGURE 2 Forest plots of the pooled estimates for hazard ratios on the association between tocilizumab administration and risk of clinical failure (i.e. intubation, admission to ICU, or death) by study type. hazard ratio (HR); confidence interval (CI); DerSimonian and Laird (DL); randomized controlled trial (RCT)

although the beneficial impact of tocilizumab was found in clinical trials (RR 0.79; 95%CI, 0.71–0.89, I^2 = 0.0%), this was not the case in retrospective studies (RR 0.72; 95%CI, 0.43–1.21, I^2 = 68.5%) (Figure S1).

3.4.2 | Tocilizumab administration and the risk of ICU admission

The effect of tocilizumab on the probability of being admitted to ICU was examined in eight publications, which were comprised of three retrospective studies, one prospective cohort, and four RCTs (a total of 1052 COVID-19 patients). Reanalysis of the summary effect revealed that tocilizumab did not reduce the overall risk of ICU admission (RR 0.85; 95%CI, 0.65–1.11, I^2 = 57.7%). Furthermore, the sub-group analysis showed no reduced risk for retrospective cohorts, prospective cohorts or clinical trials (RR 0.77; 95%CI, 0.36–1.63, I^2 = 70.8%; RR 0.92; 95%CI 0.38–2.24, I^2=NA; and RR 0.79; 95%CI, 0.51–1.23, I^2 = 67.8%, respectively), in comparison to the control groups (Figure S2).

3.4.3 | Tocilizumab administration and hospital discharge

The outcome of being discharged from hospital after receiving tocilizumab, in comparison with the control treatments, was assessed in 15 primary investigations (11 retrospective cohorts and four RCTs) that recruited a total of 7159 COVID-19 patients. In general, administration of tocilizumab resulted in a significant higher rate of hospital discharge, relative to the control group (RR 1.12; 95%CI, 1.03–1.22, I^2 = 64.1%). Moreover, the subgroup analysis showed that although tocilizumab improved the chances of hospital discharge in patients enrolled in retrospective cohort studies (RR 1.23; 95%CI, 1.04–1.45, I^2 = 66.3%), no significant differences were found in RCTs (RR 1.07; 95%CI, 0.98–1.16, I^2 = 61.9%) (Figure S3).

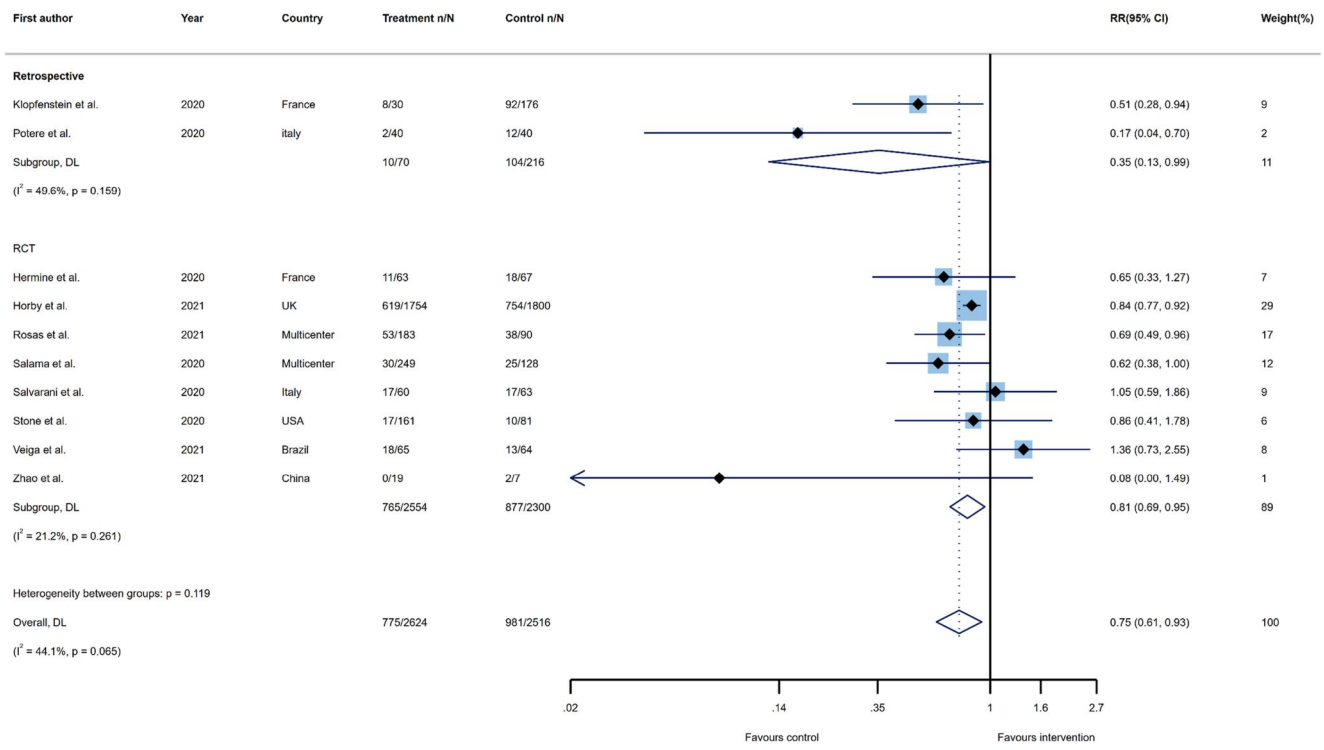

FIGURE 3 Forest plots of the summary effects for risk ratios on the association between tocilizumab administration and risk of clinical failure (i.e. intubation, admission to ICU, or death) by study type. risk ratio (RR); confidence interval (CI); DerSimonian and Laird (DL); randomized controlled trial (RCT)

3.4.4 | Tocilizumab administration and the risk of superadded infection

The summary effect was recalculated for 23 studies (8684 patients), in order to estimate the impact of tocilizumab therapy on the risk of superadded infections. No significant association was found between the administration of tocilizumab and an elevated risk of secondary infection (RR 1.00; 95%CI, 0.80–1.26, $I^2 = 77.1\%$). In both subgroups, which consisted of 16 retrospective cohorts and seven RCTs, there was no evidence that tocilizumab was related to a higher rate of co-infections (RR 1.13; 95%CI, 0.86–1.48, $I^2 = 80.4\%$ and RR 0.75; 95% CI, 0.54–1.04, $I^2 = 31.3\%$, respectively) (Figure S4).

3.4.5 | Tocilizumab administration and the length of the hospital stay, ICU stay, and ventilator-free days

The summary effects of the continuous outcomes were recalculated, in terms of the impact of tocilizumab therapy on the: length of hospital stay (10 studies), length of the ICU stay (five studies), and number of ventilator-free days (six studies). The pooled estimation revealed that receiving tocilizumab increased the number of ventilator free days, compared to the control treatments (WMD 3.38; 95% CI, 0.51–6.25, $I^2 = 75.8\%$). In contrast, no significant relationship was found between tocilizumab treatment and the length of the hospital or ICU stays (WMD −0.19; 95%CI, −3.34, 2.95; $I^2 = 97.3\%$ and WMD −0.49; 95%CI, −7.88, 6.91, $I^2 = 97.6\%$, respectively) (Figure S5–S7).

3.4.6 | Tocilizumab administration and the laboratory parameters

Data on the laboratory measures before and after tocilizumab therapy were available for the levels of: white blood cells (WBC), neutrophils, lymphocytes, IL-6, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, and ferritin. The time intervals between the baseline measurements and those after tocilizumab administration ranged from five to 14 days. Following the reanalysis of the summary effects, the level of lymphocytes (WMD 0.26×10^9/L; 95%CI, 0.14–0.37, $I^2 = 45.1\%$), IL-6 (WMD 176.99 pg/mL; 95%CI, 76.34–277.64, $I^2 = 94.3\%$), and D-dimer (WMD 741.08 ng/mL; 95%CI, 109.42–1372.75, $I^2 = 75.8\%$) were significantly higher after administration of tocilizumab. In contrast, the levels of LDH (WMD −30.88 U/L; 95%CI, −51.52, −10.24, $I^2 = 0.0\%$) and CRP (WMD −104.83 mg/L; 95%CI, −133.21, −76.46, $I^2 = 91.3\%$) were significantly lower after tocilizumab administration (Figure S8–S15).

3.5 | Publication bias

There was evidence of publication bias (Egger's p-value <0.05) for the outcomes of mortality ($p = 0.017$), level of IL-6 ($p = 0.012$), and level of CRP ($p = 0.003$). In contrast, publication bias was not found for: clinical failure (effect size of aHR, $p = 0.368$ and RR $p = 0.129$), mortality (effect size of RR $p = 0.719$), the need for mechanical

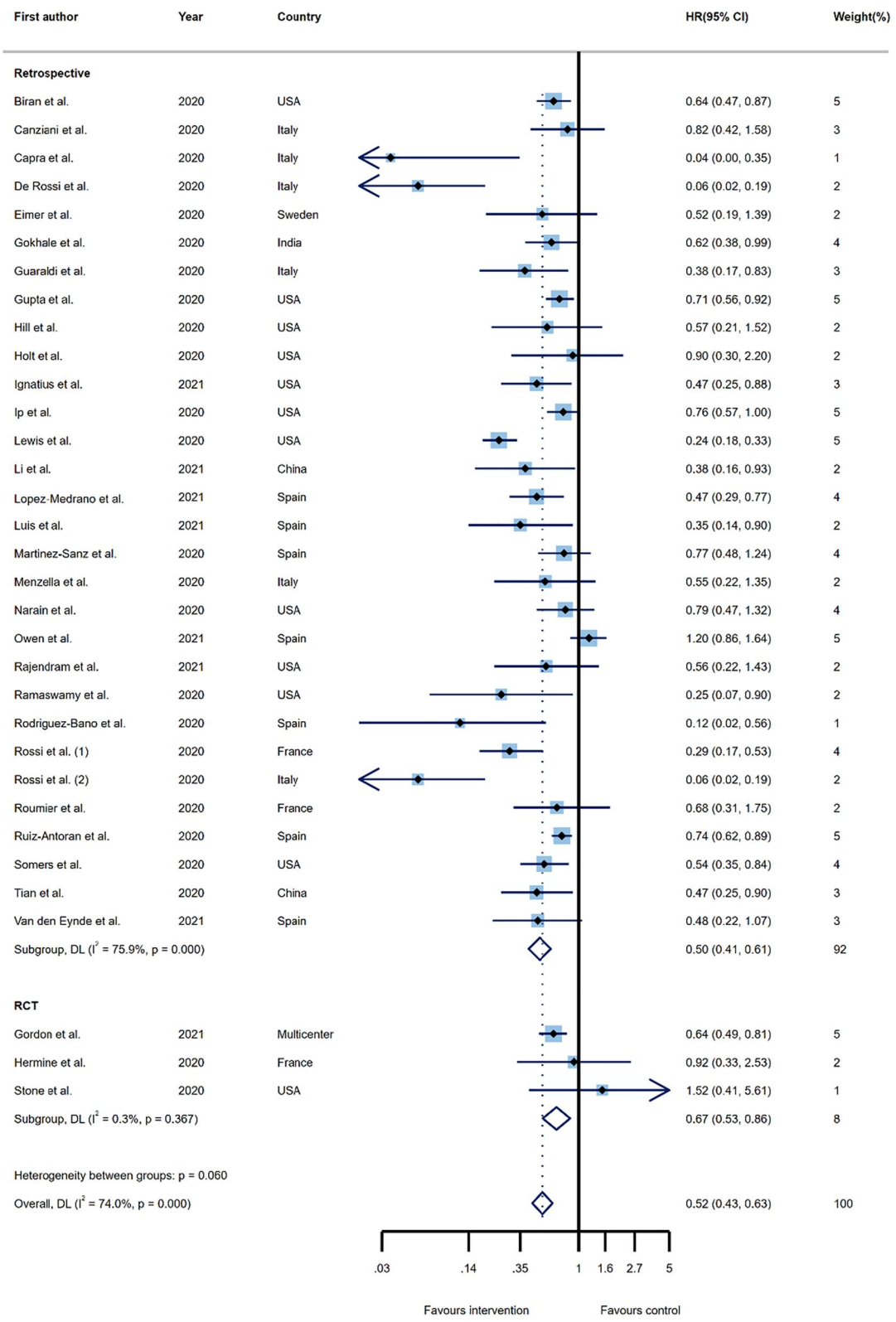

FIGURE 4 Forest plots of the pooled estimates for hazard ratios on the association between tocilizumab administration and risk of overall mortality by study type. hazard ratio (HR); confidence interval (CI); DerSimonian and Laird (DL); randomized controlled trial (RCT)

ventilation ($p = 0.439$), ICU admission ($p = 0.106$), hospital discharge rate ($p = 0.269$), superadded infection ($p = 0.192$), length of hospital stay ($p = 0.417$), length of ICU stay ($p = 0.128$), length of ventilator-free days ($p = 0.758$), WBC count ($p = 0.461$), neutrophil count ($p = 0.648$), lymphocyte count ($p = 0.295$), level of LDH ($p = 0.950$), level of ferritin ($p = 0.481$), and level of D-dimer ($p = 0.423$).

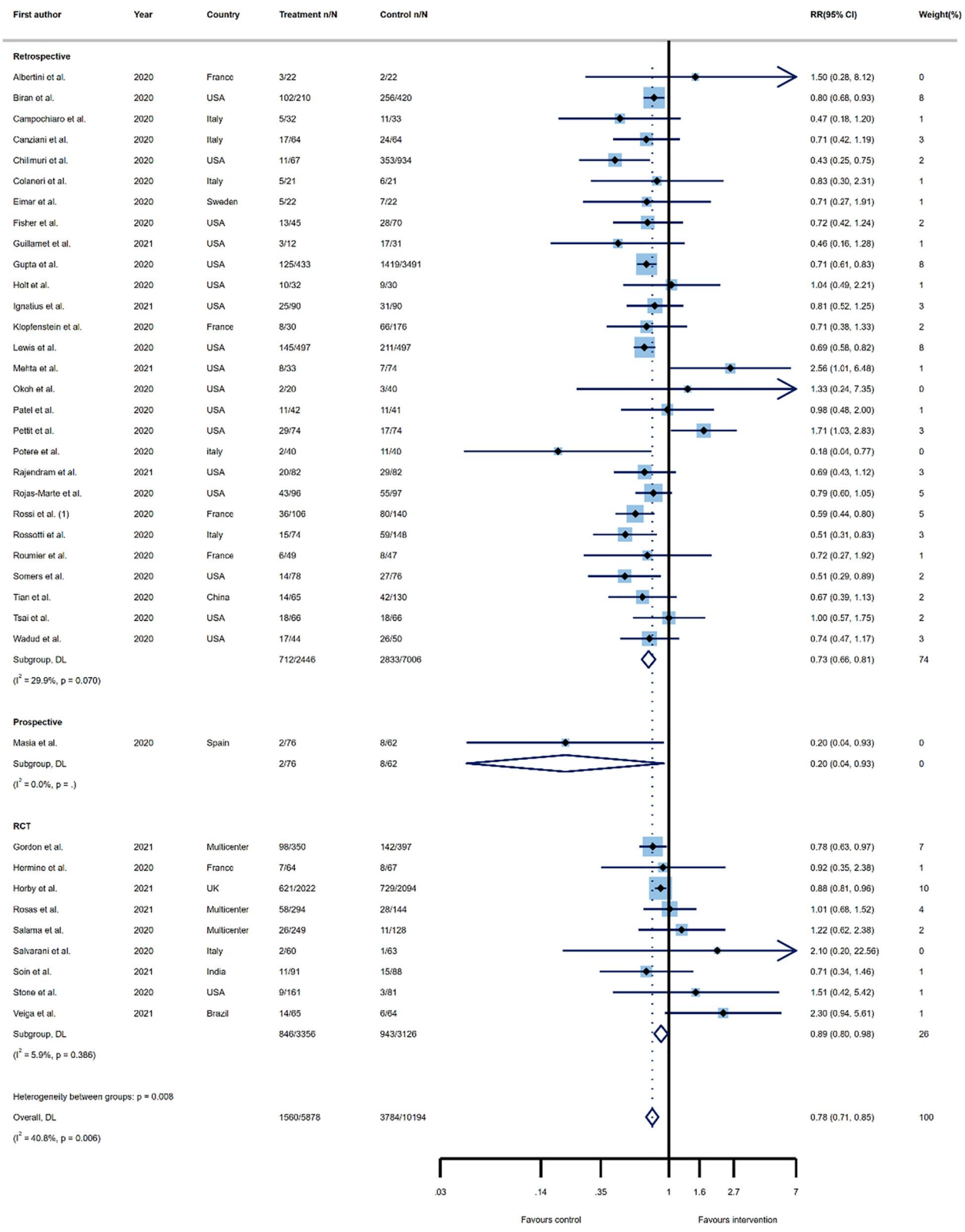

FIGURE 5 Forest plots of the summary effects for risk ratios on the association between tocilizumab administration and risk of overall mortality by study type. risk ratio (RR); confidence interval (CI); DerSimonian and Laird (DL); randomized controlled trial (RCT)

3.6 | Quality assessment

The results of the quality assessment showed that 29 (58%) were critically low, 12 (24%) were low, eight (1 were moderate, and 1 (2%) study was high quality. Among the critical domains, the most common problem was not taking into account the risk of bias when interpreting the results. Among the non-critical domains, most studies did not report the source(s) of funding for their study (Table S2).

4 | DISCUSSION

The present umbrella review found that tocilizumab administration significantly reduced the risk of requiring mechanical ventilation and dying in COVID-19 patients. Moreover, tocilizumab significantly increased the likelihood of hospital discharge and a higher number of ventilator-free days, without increasing the risk of super-imposed infections. In terms of the effects of tocilizumab treatment on laboratory measures, it significantly increased lymphocytes, IL-6 and D-dimer, and decreased LDH and CRP levels.

We found that tocilizumab treatment significantly decreased the risk of mortality by 48%. In addition, the risk of clinical failure, which was defined as a combination of intubation, ICU admission, or death, was 0.42 times lower in the tocilizumab group than among the controls. A systematic review of hospitalised COVID-19 patients showed that remdesivir decreased the 14-day mortality rate of COVID-19 patients by 36%, but not the 28-day mortality rate (RR = 1.14, 95%CI: 1.06, 1.22).[142] Furthermore, treatment with favipiravir showed no significant difference from the control group, in terms of COVID-19 mortality (RR 1.19; 95%CI, 0.85–1.66).[143] Moreover, an umbrella review revealed that treating COVID-19 patients with convalescent plasma significantly reduced the mortality rate, compared with the controls.[144] Another umbrella review, on the efficacy of hydroxychloroquine or chloroquine in patients with COVID-19, showed there was a lack of consistency in the clinical efficacy reported by the included articles.[145] A network meta-analysis on the efficacy of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies for treating COVID-19 revealed that bamlanivimab + etesevimab decreased mortality by 87% (95%CI, 0.02–0.77).[146] The differences in the mortality outcomes between the numerous strategies for treating COVID-19 could be due to differences in the inclusion criteria between the studies and features of the eligible populations, such as the prevalence of various underlying diseases and previous infection with SARS-CoV-2. However, comparing our results with the previously published studies shows that tocilizumab appears to be one of the most effective therapies for reducing COVID-19 mortality.

Tocilizumab reduced the need for mechanical ventilation by 23%, although it was not significantly associated with a reduced risk of ICU admission. In comparison, Deng et al. found no significant differences in the incidence of mechanical ventilation, ICU admission, and duration of ICU hospitalisation in COVID-19 patients treated with anti-SARS-CoV-2 antibodies (e.g., monoclonal antibodies and intravenous immunoglobulins) and those in the control group.[146] Furthermore, research by Yu et al. found that sarilumab was not significantly associated with a reduced risk of invasive mechanical ventilation (RR 1.15; 95%CI, 0.38–3.51), whereas tocilizumab reduced the risk by 21% (RR 0.79; 95%CI, 0.71–0.88).[147] The differences between the two may be due to the limited number of studies which have evaluated the effects of sarilumab, compared with tocilizumab, or the different mechanisms of action. Sarilumab blocks IL-6 and IL-6 receptors, but tocilizumab is only an IL-6 receptor antagonist.[148]

A systematic review evaluating the effects of five pharmacologic interventions (i.e., anti-inflammatory, antiviral, antiparasitic, antibody, and antibiotics) on the length of hospital stay showed that anti-inflammatory (mean difference (MD) −1.41; 95%CI, −1.75, −1.07) and antiparasitic drugs (MD −0.65; 95%CI, −1.26, −0.03) significantly reduced the length of hospital stay.[149] However, in the present study we did not find any significant differences between the tocilizumab and control groups, in terms of the length of hospital stay or ICU stay ($p > 0.05$). This discrepancy could be as a result of the different aims, methodologies, and therapies included in these two studies. Similar to our findings, in a review of 13 articles and 4770 patients, Ebrahimi Chaharom and colleagues showed that corticosteroids did not significantly reduce the duration of hospital stay (odds ratio (OR) 1.56; 95%CI, −0.29, 3.41).[150] A network meta-analysis on 196 trials, which included 76,767 participants and compared the efficacy of different COVID-19 treatments, revealed that IL-6 inhibitors significantly reduced the risk of mechanical ventilation (OR 0.72; 95%CI, 0.57–0.90) and also the length of hospital stay (MD −4.5; 95%CI, −6.7, −2.3), while no significant differences were found in the time to symptom resolution (MD −0.7; 95%CI, −2.7, 1.7) or the number of ventilator-free days (MD 1.6; 95%CI, −0.2, 3.3).[151] Similarly, we found a reduced risk of mechanical ventilation for those receiving tocilizumab (RR 0.77; 95%CI, 0.64–0.92), but in contrast we found a significant increase in the number of ventilator-free days (WMD 3.38; 95% CI, 0.51–6.25). These inconsistencies could be explained by differences in the number of included studies and due to the inclusion of all types of IL-6 inhibitors, compared with our study which only included tocilizumab. Moreover, the above-mentioned study showed no significant difference in the occurrence of adverse events between IL-6 inhibitors and the control group (MD −4.0; 95%CI, −9.0, 67.0),[151] while our study also found no increased risk for superadded infection in those treated with tocilizumab (RR 1.00; 95%CI, 0.80–1.26).

COVID-19 has been associated with increased platelet levels and CRP, as well as decreased lymphocytes.[152] Tocilizumab, which is also used to treat rheumatologic diseases like rheumatoid arthritis, has been found to reduce CRP and erythrocyte sedimentation levels.[153] The results of a systematic review of 11 studies, including 29 patients, showed that IL-6 and CRP levels were significantly higher and lower, respectively, after tocilizumab treatment ($p = 0.002$ for IL-6 and $p < 0.0001$ for CRP).[103] In addition, the results of another meta-analysis showed that tocilizumab was associated with significant reductions in CRP (MD −106.69 mg/L; 95%CI, −146.90, −66.49), D-dimer (MD −3.06 mg/L; 95%CI, −5.81, −0.31), ferritin (MD 532.80 ng/ml; 95%CI, −810.93, −254.67), and procalcitonin (MD −0.67 ng/ml; 95%CI, −1.13, −0.22), while significantly increasing

lymphocyte counts (MD 360/μl; 95%CI, 0.18, 0.54).[61] In accordance with previous findings, we also found a substantial increase in lymphocyte count, IL-6 and D-dimer level, as well as a decrease in CRP.

The quality assessment of the studies included in our research, using AMSTAR 2, showed that most of the included studies had low and critically low quality. Similarly, an umbrella review which summarised the systematic reviews on the clinical presentations of COVID-19, diagnostic tools, therapeutic modalities and laboratory and radiologic findings, reported that all of the articles included had critically low ratings, based on AMSTAR 2.[154] Moreover, concordant findings were also made by studies reviewing the effectiveness of chloroquine, hydroxychloroquine and convalescent plasma for treating COVID-19.[144,155] Perhaps one explanation of these somewhat surprizing findings is that early in the COVID-19 pandemic, study quality was not adequately assessed during the peer-review process.[156]

To best of our knowledge, this is the first umbrella review on the efficacy of tocilizumab for treating COVID-19. This article consolidates the knowledge by providing a comprehensive summary of the most up-to-date evidence for one of the most promising options for treating COVID-19. Nevertheless, this study has several limitations which should be considered when interpreting the results and/or using this information in clinical practice. Firstly, we used AMSTAR 2 to assess the quality of the included articles, but this approach has some limitations. For instance, due to the pressing need for scientific papers during the COVID-19 crisis, several studies might not have reported some methodological details that are important for quality assessment. Secondly, several primary studies where included in more than one systematic review. We included all of these in our study, but the overlapping data were not included when calculating the pooled effect sizes. Thirdly, although we systematically searched the above-mentioned databases and conducted an extensive search for grey literature, there is still a chance that some articles were missed. Fourthly, we conducted subgroup analysis only by study design. Past medical history, geographical region or disease severity, which are important prognostic factors for COVID-19, were not included in the analysis.[157] Fifthly, most of the studies did not report the number of participants by sex and age group, so we were not able to perform subgroup on the effects of tocilizumab administration by age and sex. Sixthly, we included preprints in the study. Since preprints have not yet been peer-reviewed, this might lead to bias in the findings. Seventhly, some of the laboratory parameters, like creatinine kinase which can be used as a prognostic factor, were not included in the present study.[158] Eighthly, the protocol of the study was not registered in PROSPERO, although it was submitted to the relevant university committee.

5 | CONCLUSIONS

This umbrella review found that tocilizumab reduced the risk of intubation and mortality, lead to an earlier discharge from hospital and did not increase the risk of a super-imposed infection. Therefore, tocilizumab can be considered a successful treatment strategy and should be included in guidelines for treating COVID-19 patients. Nevertheless, the quality of the included articles was generally low and further high quality primary studies, in particular RCTs, are needed. Furthermore, a future umbrella review is needed to examine the safety of tocilizumab for treating COVID-19 patients in more detail.

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CONFLICT OF INTEREST

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS STATEMENT

The present study was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1401.316).

AUTHOR CONTRIBUTION

Maryam Noori, Seyed Aria Nejadghaderi, Saeid Safiri, Shahnam Arshi and Ali-Asghar Kolahi conceptualised the topic; Maryam Noori searched the databases; Mohammad Mahdi Rezaei Tolzali, Pourya Shokri and Shayan Rahmani performed screening and full-text review; Mohammad Mahdi Rezaei Tolzali, Pourya Shokri, Shayan Rahmani, Shokoufeh Khanzadeh, and Seyed Aria Nejadghaderi performed data extraction and quality assessment; Maryam Noori performed statistical analysis; Maryam Noori, Asra Fazlollahi, Seyed Aria Nejadghaderi, Kuljit Singh and Mark J. M. Sullman prepared the first draft of the manuscript; Saeid Safiri, Shahnam Arshi and Ali-Asghar Kolahi supervised this project. All authors reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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