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Tocilizumab administration for the treatment of hospitalized patients with COVID-19: A systematic review and meta-analysis

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Abstract

Tocilizumab has been repurposed against the 'cytokine storm' in the setting of coronavirus disease 2019 (COVID-19). Our aim was to evaluate the efficacy of tocilizumab in the management of hospitalized COVID-19 patients. We searched MEDLINE, CENTRAL and medRxiv for studies of tocilizumab in hospitalized COVID-19 patients. Primary objective was the effectiveness of tocilizumab on mortality. Secondary objectives included the need for invasive mechanical ventilation (IMV), composite endpoints of mortality or IMV and intensive care unit (ICU) admission or IMV, length of hospitalization and differences in mortality in subgroups (ICU and non-ICU patients and patients receiving or not receiving concomitant corticosteroids). We included 52 studies (nine randomized controlled trials [RCTs] and 43 observational) with a total of 27,004 patients. In both RCTs and observational studies, the use of tocilizumab was associated with a reduction in mortality; 11% in RCTs (risk ratio [RR] 0.89, 95% CI 0.82 to 0.96) and 31% in observational studies (RR 0.69, 95% CI 0.58 to 0.83). The need for IMV was reduced by 19% in RCTs (RR 0.81, 95% CI 0.71 to 0.93), while no significant reduction was observed in observational studies. Both RCTs and observational studies showed a benefit from tocilizumab on the composite endpoint of mortality or IMV. Tocilizumab improved mortality both in ICU and non-ICU patients. Reduction in mortality was evident in observational studies regardless of the use of systemic corticosteroids, while that was not the case in the RCTs. Tocilizumab was associated with lower mortality and other clinically relevant outcomes in hospitalized patients with moderate-to-critical COVID-19.

KEYWORDS
coronavirus disease, COVID-19, meta-analysis, mortality, SARS-CoV-2, tocilizumab

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is the coronavirus disease 2019 (COVID-19) causing agent, is a highly infectious viral pathogen that is accountable for the ongoing pandemic.[1] As of 30 April 2021, more than 151 million individuals have been infected with SARS-CoV-2 worldwide and 3,180,000 deaths globally have been attributed to COVID-19.[2] COVID-19 tends to appear with diversity in clinical manifestations ranging from asymptomatic infection to acute respiratory distress syndrome and death. Although the pathogenesis of COVID-19 is still imprecise, certain patients with severe or critical disease have laboratory evidence of a systemic inflammatory response resembling the cytokine release syndrome (CRS).[3] CRS is characterized by a sharp increase of many proinflammatory cytokines, such as IL-1β, IL-6, Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Tumor necrosis factor alpha (TNF-α), and elevated levels of D-dimers, ferritin and C-reactive protein (CRP).[4] Proposed immunomodulatory agents with potential use against the cytokine storm include glucocorticoids,[5] colchicine,[6] anakinra,[7] baricitinib[8] and sarilumab.[9] Antiviral drugs, such as remdesivir,[10] and monoclonal antibodies[11] are also used in selected cases.

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. Therapeutic indications include the treatment of severe, active and progressive rheumatoid arthritis[12]; active systemic juvenile idiopathic arthritis; and chimeric antigen receptor T cell-induced severe or life-threatening CRS in adults and paediatric patients of 2 years of age and older.[13] Recently (5 March 2021), the Food and Drug

Administration approved tocilizumab for adult patients with systemic sclerosis-associated interstitial lung disease. IL-6 plays a crucial role in CRS.[4] In COVID-19, the primary concept was that intercepting the IL-6 pathway might reduce the vigorous inflammatory response.[14] Several observational studies and randomized controlled trials (RCTs), with the RECOVERY trial being the largest,[15] have evaluated the administration of tocilizumab for the management of patients with moderate-to-severe COVID-19.[16–18] Nevertheless, tocilizumab should be used cautiously, as it results in increased risk of infection from all microorganisms, viral, bacterial, fungal and parasitic, with serious infections appearing in 2.7% of the treated patients (4.0–4.5/100 patient years of exposure).[19]

Data from studies so far have been contradictory regarding the efficacy and effectiveness of tocilizumab in the management of patients with moderate-to-critical COVID-19; this was due to different study designs, populations evaluated and the timing of tocilizumab administration.[20] Based on the available evidence, we performed a systematic review and meta-analysis of the available data from observational studies and RCTs in order to evaluate the overall effectiveness and efficacy of tocilizumab administration in patients with COVID-19 on mortality and need for intubation/mechanical ventilation, intensive care unit (ICU) admission and the length of hospitalization, both in usual clinical practice and in the controlled settings of RCTs.

METHODS

Literature search and inclusion criteria

We conducted a systematic literature search, from inception to 31 March 2021, to identify studies that assessed the efficacy of tocilizumab in COVID-19 in MEDLINE (through PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL); we also searched medRxiv (https://www.medrxiv.org) for unpublished RCTs. The search strategy algorithm and study selection are shown in detail in Appendix S1 in the Supporting Information. We prospectively submitted the systematic review protocol for registration on PROSPERO (CRD42021247188; Appendix S2 in the Supporting Information). We have followed PRISMA[21] and MOOSE[22] reporting guidelines. A study to be considered as eligible for registration would need to meet the following criteria:

1. Inclusion of subjects >18 years old hospitalized for COVID-19.
2. Randomized clinical trials, retrospective observational cohort studies, retrospective case–control studies and prospective case–control studies.
3. Intravenous or subcutaneous administration of tocilizumab for COVID-19 treatment.
4. The group of patients receiving tocilizumab was compared with a control arm (standard of care treatment or other approved drugs).

Objectives

Primary objective

The primary objective was to determine whether treatment with tocilizumab reduces mortality in patients hospitalized with COVID-19.

Secondary objectives

Secondary objectives included the evaluation of differences between the tocilizumab and control groups in:

- The need for intubation or invasive mechanical ventilation (IMV).
- A composite endpoint of mortality or IMV.
- A composite endpoint of ICU admission or IMV.
- The length of hospitalization.
- Mortality in non-ICU and ICU-treated patients.
- Mortality in patients according to the concomitant use of systemic corticosteroids.

Data extraction and risk of bias assessment

Two authors (CK and AG) reviewed concurrently all the eligible studies to perform data extraction. The reviewers worked independently during study data extraction; disagreements, if any, were resolved by discussion to obtain consensus, with unresolved conflicts decided by a third reviewer (KK). Obtained data were validated by a third independent author (GN). Studies published in languages other than English were excluded.

From each eligible study, we recorded information about the first author, publication year, journal, study design, follow-up time, population characteristics, total and tocilizumab-treated sample size, treatment indication, tocilizumab and comparator dose, ICU setting and use of corticosteroids. Moreover, we extracted information on mortality, intubation (or IMV) and days of hospitalization along with their effect estimates. Risk ratios (RRs) along with their CIs were calculated for mortality and intubation, assessed as binary outcomes, and median differences were calculated for days of hospitalization. Risk of bias of eligible trials was assessed by applying the Cochrane Collaboration's tool.[23]

Data analysis

We calculated RR and summary median differences, along with the corresponding 95% CI, by pooling the study-specific estimates using random-effects models.[24] Days of hospitalization, in most of the studies, were provided as medians and interquartile ranges (IQRs). Hence, in order to synthesize these estimates, we used a formula that converts medians and IQRs to mean and SDs.[25,26] The presence and

T A B L E 1 Characteristics of included studies and sample size for treatment (*n*) and total patients included (*N*)

Author, year	*n, N*	Study country	Centre	Study design
Albertini et al., 2021[31]	22, 44	France	Single centre	Prospective study
Biran et al., 2020[32]	210, 630	USA	Multicentre	Retrospective study
Campochiaro et al., 2020[33]	32, 65	Italy	Single centre	Retrospective study
Canziani et al., 2020[34]	64, 168	Italy	Multicentre	Retrospective study
Capra et al., 2020[35]	62, 85	Italy	Single centre	Retrospective study
Chachar et al., 2021[36]	33, 93	Pakistan	Single centre	Retrospective study
Chilimuri et al., 2020[37]	87, 1225	USA	Single centre	Retrospective study
Colaneri et al., 2020[38]	21, 112	Italy	Single centre	Retrospective study
De Rossi et al., 2020[39]	90, 158	Italy	Single centre	Retrospective study
Eimer et al., 2021[40]	29, 87	Sweden	Single centre	Retrospective study
Fisher et al., 2021[41]	45, 115	USA	Single centre	Retrospective study
Galván-Román et al., 2021[42]	58, 146	Spain	Single centre	Retrospective study
Gokhale et al., 2021[43]	70, 161	India	Single centre	Retrospective study
Gordon et al., 2021 (REMAP-CAP)[16]	353, 865	International[a]	Multicentre	RCT
Guaraldi et al., 2020[44]	179, 544	Italy	Multicentre	Retrospective study
Gupta et al., 2021[45]	433, 3924	USA	Multicentre	Retrospective study
Hermine et al., 2021 (CORIMUNO TOCI)[46]	63, 130	France	Multicentre	RCT
Hill et al., 2020[47]	43, 88	USA	Single centre	Retrospective study
Holt et al., 2020[48]	32, 62	USA	Single centre	Retrospective study
Horby et al., 2021 (RECOVERY)[15]	2022, 4113	UK	Multicentre	RCT
Ip et al., 2020[49]	134, 547	USA	Multicentre	Retrospective study
Kewan et al., 2020[50]	28, 51	USA	Single centre	Retrospective study
Klopfenstein et al., 2020[51]	30, 206	France	Single centre	Retrospective study
Lewis et al., 2020[52]	497, 994	USA	Multicentre	Retrospective study
Martínez-Sanz et al., 2021[53]	260, 1229	Spain	Multicentre	Retrospective study
Menzella et al., 2020[54]	41, 79	Italy	Single centre	Retrospective study
Mikulska et al., 2020[55]	130, 196	Italy	Single centre	Prospective study
Moiseev et al., 2020[56]	159, 328	Russia	Multicentre	Retrospective study
Narain et al., 2021[18]	527, 5776	USA	Multicentre	Retrospective study
Nasa et al., 2020[57]	22, 85	UAE	Multicentre	Retrospective study
Okoh et al., 2021[58]	20, 60	USA	Single centre	Retrospective study
Patel et al., 2021[59]	42, 83	USA	Single centre	Retrospective study
Potere et al., 2020[60]	10, 20	Italy	Single centre	Retrospective study
Quartuccio et al., 2020[61]	42, 111	Italy	Single centre	Retrospective study
Rajendram et al., 2021[62]	82, 164	USA	Multicentre	Retrospective study
Rodríguez-Baño et al., 2021[63]	239, 778	Spain	Multicentre	Retrospective study
Rodríguez-Molinero et al., 2021[64]	22, 44	Spain	Multicentre	Retrospective study
Rojas-Marte et al., 2020[65]	96, 193	USA	Single centre	Retrospective study
Rosas et al., 2021 (COVACTA)[66]	294, 438	Europe and North America	Multicentre	RCT
Rossi et al., 2020[67]	106, 246	France	Single centre	study
Rossotti et al., 2020[68]	74, 222	Italy	Single centre	Retrospective study
Roumier et al., 2021[69]	50, 96	France	Single centre	Prospective study
Ruiz-Antorán et al., 2021[70]	268, 506	Spain	Multicentre	Retrospective study
Salama et al., 2021 (EMPACTA)[17]	249, 377	International[b]	Multicentre	RCT
Salvarani et al., 2021 (RCT-TCZ-COVID-19)[71]	60, 126	Italy	Multicentre	RCT
Soin et al., 2021 (COVINTOC)[72]	91, 180	India	Multicentre	RCT
Somers et al., 2020[73]	78, 174	USA	Single centre	Retrospective study

Author, year	n, N	Study country	Centre	Study design
Stone et al., 2020 (BACC Bay)[74]	161, 243	USA	Multicentre	RCT
Tian et al., 2021[75]	65, 195	China	Multicentre	Retrospective study
Tsai et al., 2020[76]	66, 132	USA	Single centre	Retrospective study
Veiga et al., 2021 (TOCIBRAS)[77]	65, 129	Brazil	Multicentre	RCT
Zheng et al., 2020[78]	92, 181	China	Single centre	Retrospective study

Note: Sample sizes given for patients receiving intervention (*n*) alongside total patients included (*N*) in the study.
Abbreviations: COVID-19, coronavirus disease 2019; RCT, randomized controlled trial.
[a]UK, France, Netherlands, Australia, New Zealand, Canada, Spain and Ireland.
[b]USA, Peru, Brazil, Kenya, South Africa and Mexico.

the degree of heterogeneity were assessed with I^2 (ranging from 0% to 100%).[27] When more than three studies were included in the meta-analysis, prediction intervals (PI) were calculated to describe the uncertainty we expect in the summary effect if a new study is included in the meta-analysis.[28] Subgroup analysis was performed regarding the ICU setting and the use of corticosteroids. We further assessed the possible small study effects (an indication of publication bias) by visual inspection of funnel plots and Egger's test.[29] The presence of heterogeneity was estimated with the Cochran's Q statistic and it was quantified with I^2.[30] Finally, we accounted for the inter-study variability using a meta-regression approach. The covariates that were considered in the meta-regression model were age of participants, gender, the type of centres that the study engaged (single/multicentre) and the continent where the study was performed. All analyses were performed using Stata (version 14; StataCorp, College Station, TX, USA).

RESULTS

Study identification and selection

The search of the electronic databases (MEDLINE and CENTRAL) on 31 March 2021 identified a total of 873 studies, with further six RCTs identified through preprint servers; these six RCTs identified in medRxiv were subsequently identified in their final form in PubMed. Following removal of duplicates, screening and full-text review, 52 articles published worldwide were shortlisted for inclusion. Nine of them were RCTs and 43 were observational cohort studies involving a control arm (Table 1). Figure 1 shows the flow chart of the study selection process. The data from the RECOVERY trial were updated on 1 May when the study was published in its final form.[15]

Patients received tocilizumab either intravenously (8 mg/kg up to 800 mg, once or twice) or subcutaneously (324 mg). The total population of participants was 27,004, of whom 8048 (29.8%) received tocilizumab. The RCTs involved 6604 participants, of whom 3358 (50.8%) received tocilizumab, and observational cohort studies involved 20,400 participants, of whom 4690 (23%) received tocilizumab. In 39 studies, corticosteroids

were concomitantly administered; eight of them were RCTs and 31 observational studies (Table S1 in the Supporting Information).

Study outcomes

Mortality

Forty-seven studies with 25,385 participants, of whom 7814 patients were treated with tocilizumab, reported adjusted hazard ratios or crude results for overall mortality. Nine of the studies were RCTs with 6604 participants, of whom 3358 patients received tocilizumab, while 38 of the studies were observational studies with 18,781 participants, of whom 4456 patients were treated with tocilizumab. In both the RCTs and the observational studies, a meaningful survival benefit was observed in patients treated with tocilizumab. The benefit was 11% in the RCTs (RR 0.89, 95% CI 0.82 to 0.96, 95% PI 0.80 to 0.97) and 31% in observational studies (RR 0.69, 95% CI 0.58 to 0.83, 95% PI 0.28 to 1.73). RCTs presented small heterogeneity ($I^2 = 0.3\%$), whereas observational studies presented very large heterogeneity ($I^2 = 84.0\%$) (Figure 2). In order to assess the possible sources of heterogeneity, we performed a meta-regression of the mortality rates, including age of participants, gender, the type of centre that the study engaged (single/multicentre) and the continent where the study was performed. All the aforementioned factors were not significant.

Need for IMV

Fourteen studies with a total of 6713 participants, of whom 3285 patients were treated with tocilizumab, reported results for the need for IMV or intubation. Four of them were RCTs with a total of 4977 participants, of whom 2568 received tocilizumab. The need for IMV was reduced by 19% in patients treated with tocilizumab (RR 0.81, 95% CI 0.71 to 0.93, 95% PI 0.60 to 1.09); small heterogeneity was observed in the RCTs ($I^2 = 0.0\%$). In the 10 observational studies with a total of 1736 participants, of whom 717 were treated with tocilizumab, there was a numerical reduction in
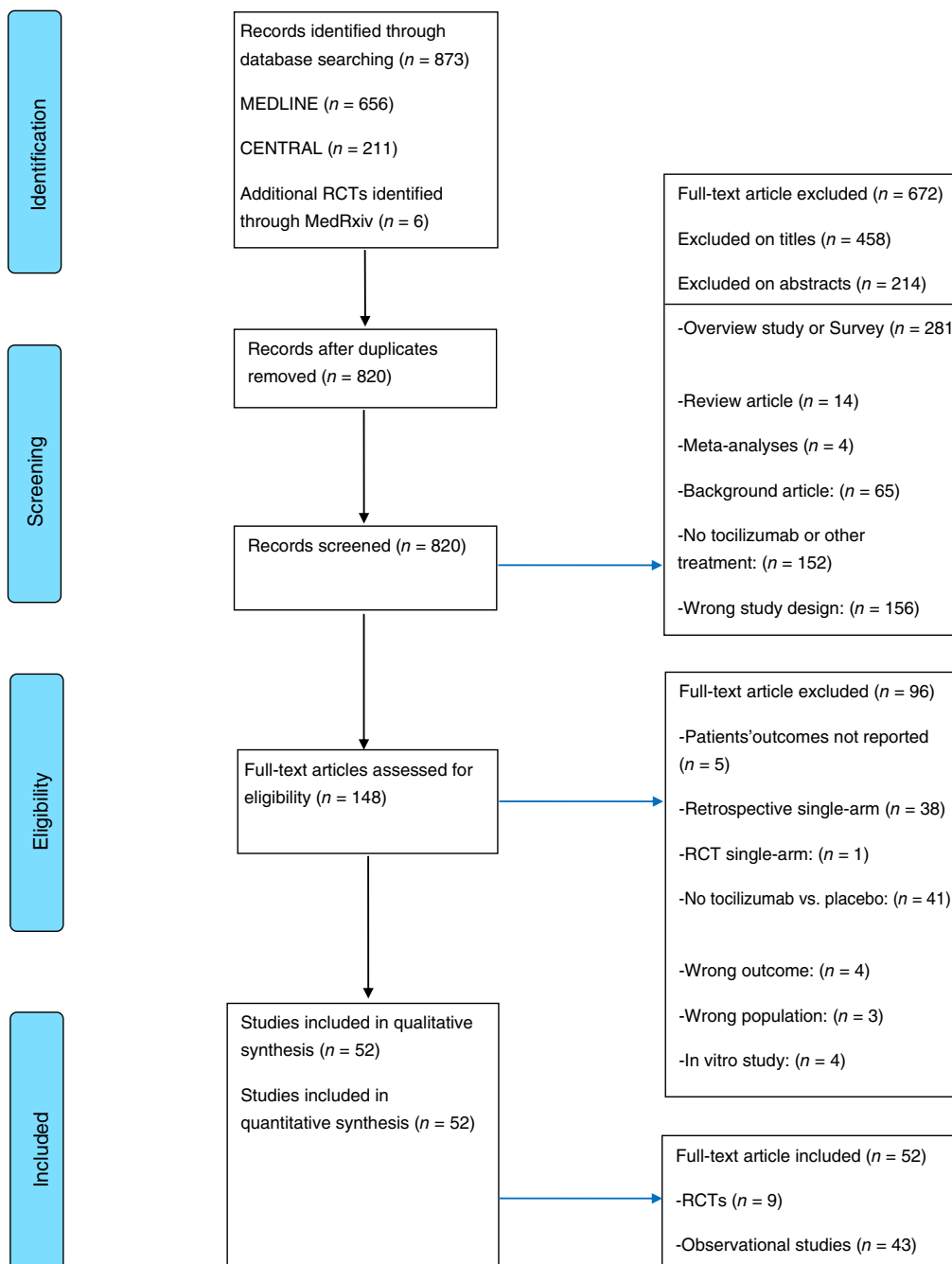
FIGURE 1 Meta-analysis flow diagram illustrating systematic search and screening strategy, including the number of studies meeting eligibility criteria and number of excluded studies

the need for IMV by 19%; however, this did not reach statistical significance (RR 0.81, 95% CI 0.57 to 1.14, 95% PI 0.28 to 2.29). The observational studies showed large heterogeneity ($I^2 = 70.2\%$) (Figure 3A).

Composite endpoint of mortality or IMV

Thirteen studies with a total of 9064 participants, of whom 3655 patients received tocilizumab, reported results on the composite outcome of mortality or IMV. In the seven RCTs (5986 participants; 2973 received tocilizumab), the composite adverse outcome was reduced by 17% in patients treated with tocilizumab (RR 0.83, 95% CI 0.77 to 0.89, 95% PI 0.76 to 0.92); small heterogeneity was observed ($I^2 = 0.0\%$, $p = 0.435$). In the six observational studies (3087 participants; 682 received tocilizumab), the composite adverse outcome was however reduced by 45% (RR 0.55, 95% CI 0.36 to 0.83, 95% PI 0.14 to 2.08), with large heterogeneity among studies ($I^2 = 73.2\%$) (Figure 3B).
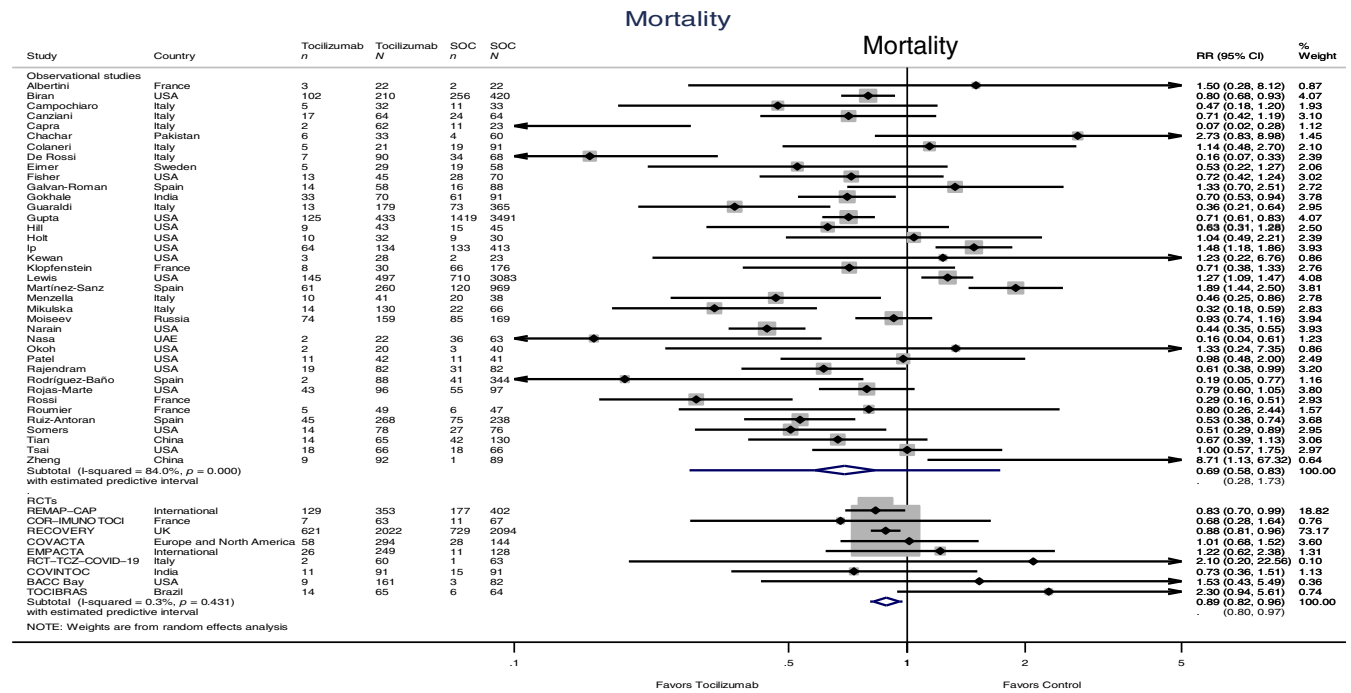
Mortality

FIGURE 2 Forest plot of mortality risk ratios (RRs) comparing tocilizumab and control treatment. Sample sizes are given for participants receiving intervention and participants receiving standard of care treatment (SOC), included in the study, when data were available. Summary estimates are presented separately for observational studies and randomized controlled trials (n, deaths; N, group size)

(A) Need for IMV/intubation
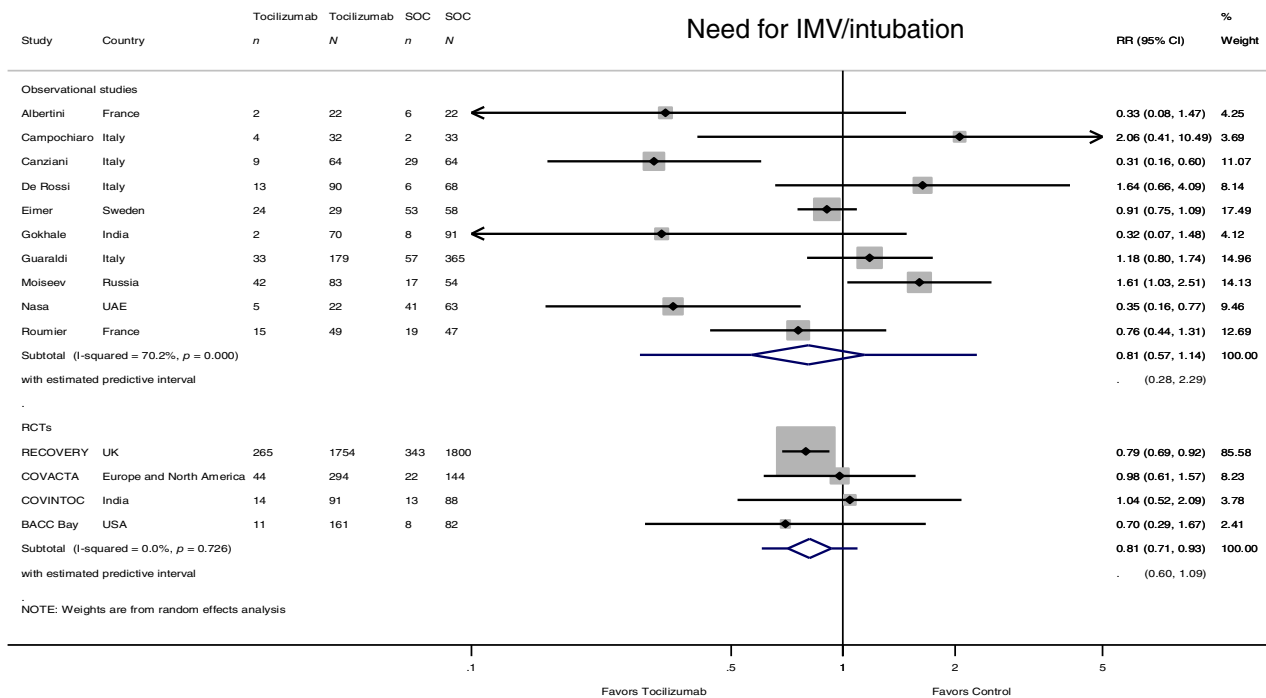
FIGURE 3 (A) Forest plot of risk ratios (RRs) for the need for invasive mechanical ventilation (IMV)/intubation comparing tocilizumab and control treatment (n, cases of need for IMV/intubation; N, group size). (B) Forest plot of the composite outcome of mortality or IMV/intubation RRs comparing tocilizumab and control treatment (n, cases of mortality or IMV/intubation; N, group size). (C) Forest plot of the composite outcome of intensive care unit (ICU) admission or IMV/intubation RRs comparing tocilizumab and control treatment (n, cases of ICU admission or IMV/intubation; N, group size). Sample sizes are given for participants receiving intervention and participants receiving standard of care treatment (SOC), included in the study, when data were available. Summary estimates are presented separately for observational studies and randomized controlled trials
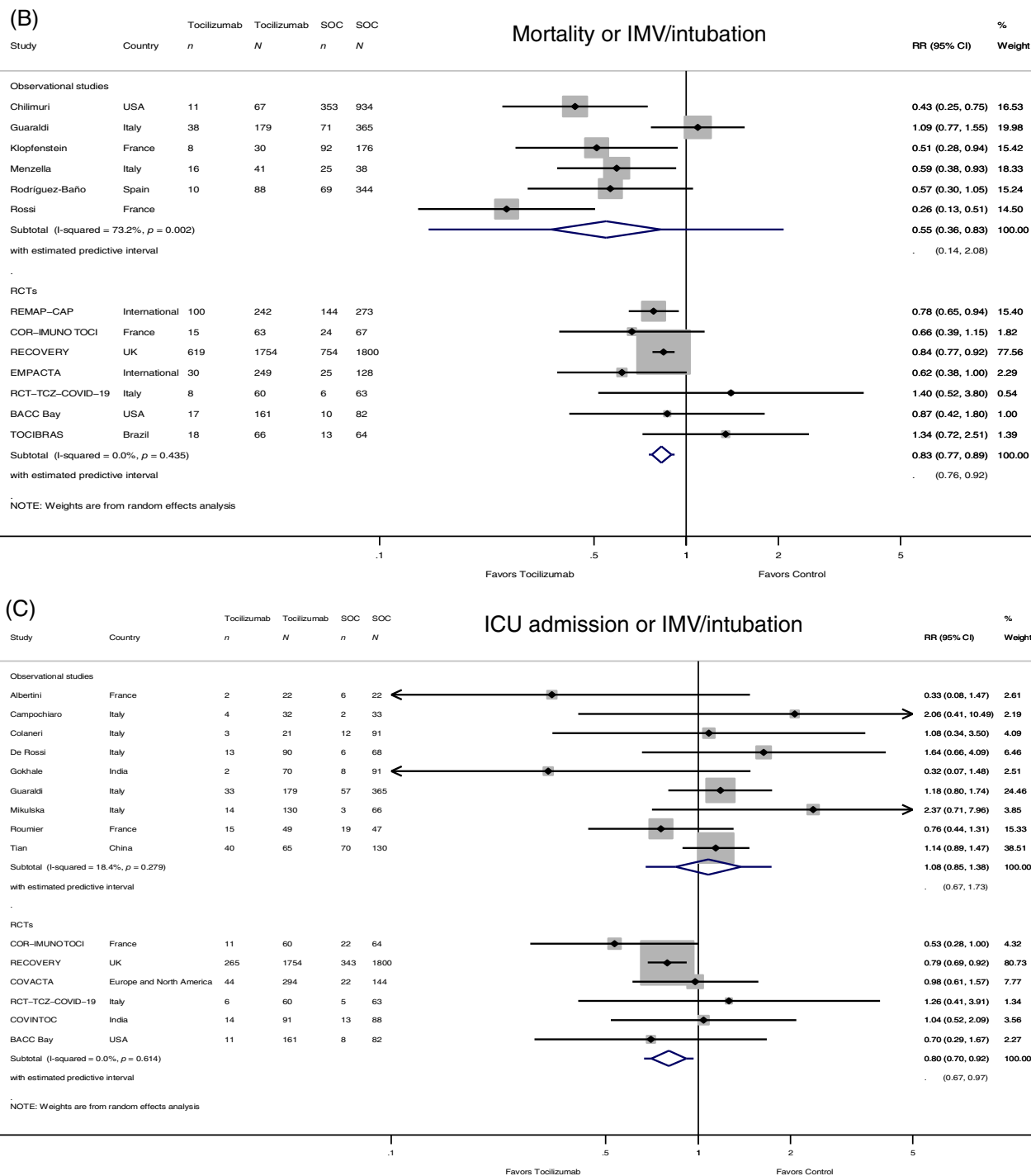
(B)

Forest plot: Mortality or IMV/intubation

Study	Country	Tocilizumab n	Tocilizumab N	SOC n	SOC N	RR (95% CI)	% Weight
Observational studies							
Chilimuri	USA	11	67	353	934	0.43 (0.25, 0.75)	16.53
Guaraldi	Italy	38	179	71	365	1.09 (0.77, 1.55)	19.98
Klopfenstein	France	8	30	92	176	0.51 (0.28, 0.94)	15.42
Menzella	Italy	16	41	25	38	0.59 (0.38, 0.93)	18.33
Rodríguez-Baño	Spain	10	88	69	344	0.57 (0.30, 1.05)	15.24
Rossi	France					0.26 (0.13, 0.51)	14.50
Subtotal (I-squared = 73.2%, p = 0.002)						0.55 (0.36, 0.83)	100.00
with estimated predictive interval						(0.14, 2.08)	
RCTs							
REMAP-CAP	International	100	242	144	273	0.78 (0.65, 0.94)	15.40
COR-IMUNO TOCI	France	15	63	24	67	0.66 (0.39, 1.15)	1.82
RECOVERY	UK	619	1754	754	1800	0.84 (0.77, 0.92)	77.56
EMPACTA	International	30	249	25	128	0.62 (0.38, 1.00)	2.29
RCT-TCZ-COVID-19	Italy	8	60	6	63	1.40 (0.52, 3.80)	0.54
BACC Bay	USA	17	161	10	82	0.87 (0.42, 1.80)	1.00
TOCIBRAS	Brazil	18	66	13	64	1.34 (0.72, 2.51)	1.39
Subtotal (I-squared = 0.0%, p = 0.435)						0.83 (0.77, 0.89)	100.00
with estimated predictive interval						(0.76, 0.92)	

NOTE: Weights are from random effects analysis

Favors Tocilizumab   Favors Control

(C)

Forest plot: ICU admission or IMV/intubation

Study	Country	Tocilizumab n	Tocilizumab N	SOC n	SOC N	RR (95% CI)	% Weight
Observational studies							
Albertini	France	2	22	6	22	0.33 (0.08, 1.47)	2.61
Campochiaro	Italy	4	32	2	33	2.06 (0.41, 10.49)	2.19
Colaneri	Italy	3	21	12	91	1.08 (0.34, 3.50)	4.09
De Rossi	Italy	13	90	6	68	1.64 (0.66, 4.09)	6.46
Gokhale	India	2	70	8	91	0.32 (0.07, 1.48)	2.51
Guaraldi	Italy	33	179	57	365	1.18 (0.80, 1.74)	24.46
Mikulska	Italy	14	130	3	66	2.37 (0.71, 7.96)	3.85
Roumier	France	15	49	19	47	0.76 (0.44, 1.31)	15.33
Tian	China	40	65	70	130	1.14 (0.89, 1.47)	38.51
Subtotal (I-squared = 18.4%, p = 0.279)						1.08 (0.85, 1.38)	100.00
with estimated predictive interval						(0.67, 1.73)	
RCTs							
COR-IMUNO TOCI	France	11	60	22	64	0.53 (0.28, 1.00)	4.32
RECOVERY	UK	265	1754	343	1800	0.79 (0.69, 0.92)	80.73
COVACTA	Europe and North America	44	294	22	144	0.98 (0.61, 1.57)	7.77
RCT-TCZ-COVID-19	Italy	6	60	5	63	1.26 (0.41, 3.91)	1.34
COVINTOC	India	14	91	13	88	1.04 (0.52, 2.09)	3.56
BACC Bay	USA	11	161	8	82	0.70 (0.29, 1.67)	2.27
Subtotal (I-squared = 0.0%, p = 0.614)						0.80 (0.70, 0.92)	100.00
with estimated predictive interval						(0.67, 0.97)	

NOTE: Weights are from random effects analysis

Favors Tocilizumab   Favors Control

FIGURE 3 (Continued)

Composite endpoint of ICU admission or IMV

Fifteen studies with a total of 6804 participants, of whom 3350 patients received tocilizumab, reported results on the composite endpoint of ICU admission or IMV. In the six RCTs (5233 participants; 2691 received tocilizumab), the adverse outcome was reduced by 20% in patients treated with tocilizumab (RR 0.80, 95% CI 0.70 to 0.92, 95% PI 0.67 to 0.97), with no heterogeneity ($I^2 = 0.0\%$). In the nine observational studies (1571 participants; 659 patients were treated with tocilizumab), there was no significant difference between the two treatment groups (RR 1.08, 95% CI 0.85 to 1.38, 95% PI 0.67 to 1.73) (Figure 3C).

Duration of hospitalization

Four RCTs and 14 observational studies reported results for the duration of hospitalization (in days) for a total of 4653

(A)

(B)
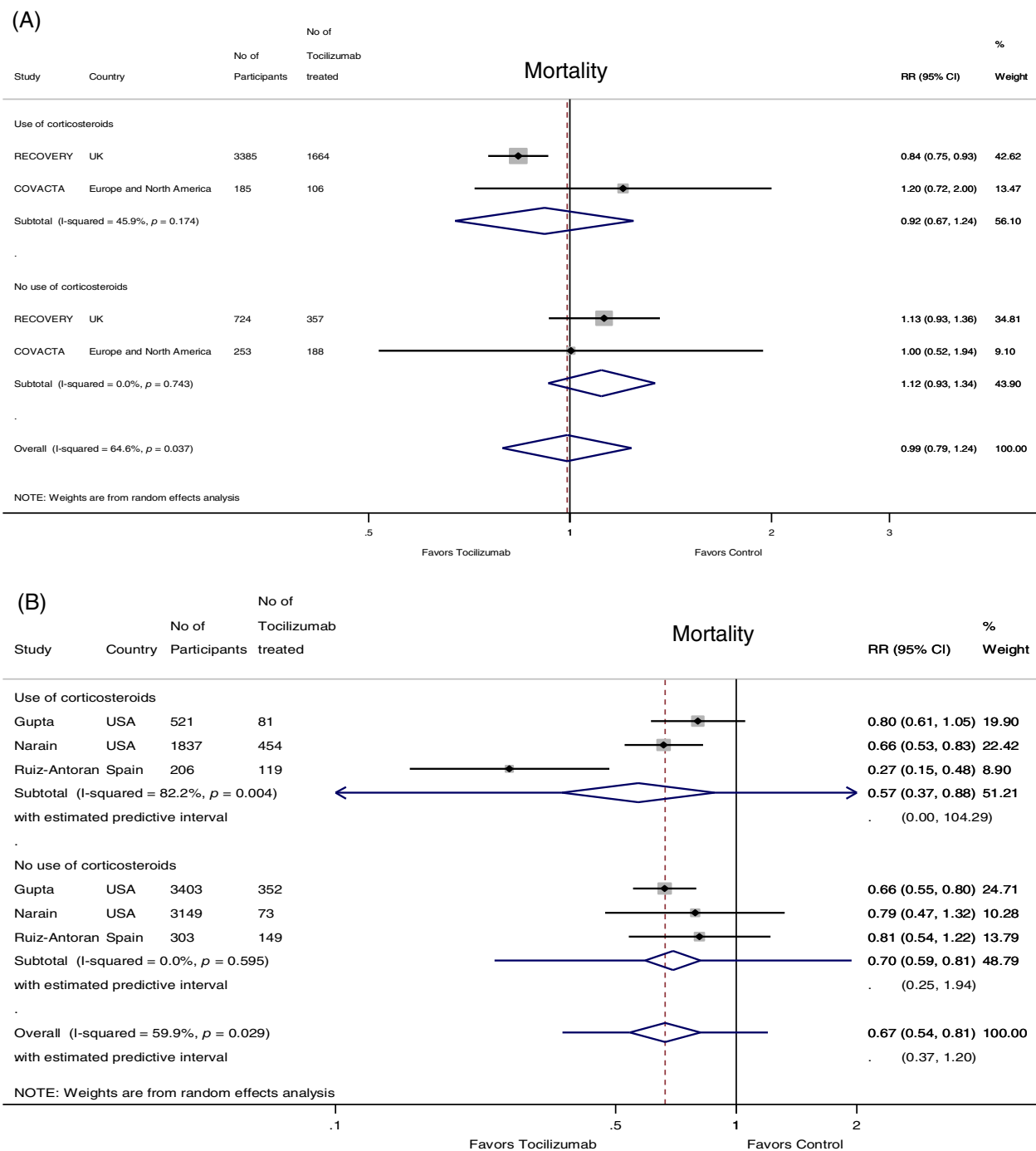
FIGURE 4 (A) Forest plot of mortality risk ratios (RRs) comparing the concomitant effect of tocilizumab versus control treatment in patients receiving or not receiving systemic corticosteroids in randomized controlled trials. (B) Forest plot of mortality RRs comparing the concomitant effect of tocilizumab versus control treatment in patients receiving or not receiving systemic corticosteroids in observational studies. Sample sizes are given for the total number of participants and the participants receiving intervention in the respective groups

participants, of whom 2202 patients received tocilizumab. From the studies reporting results for the median duration of hospitalization, in the three RCTs (1680 participants; 896 received tocilizumab), there was however a numerical reduction in the length of hospitalization between the two groups (−1.06 days, 95% CI −2.18 to 0.07, 95% PI −15.54 to 13.43) without reaching statistical significance, whereas in

the nine observational studies (2161 participants; 941 received tocilizumab) there was no significant difference between the two treatment groups (−0.15 days, 95% CI −0.80 to 0.50, 95% PI −2.65 to 2.34). In both types of studies, there was very large heterogeneity ($I^2 = 99.0\%$ and 97.5% for RCTs and observational studies, respectively) (Figure S1 in the Supporting Information).

Subgroup analysis

Differences in mortality in non-ICU and ICU-treated patients

Of the nine RCTs reporting mortality data, only one was performed in the ICU setting. Of the 38 observational studies reporting mortality, 24 with a total of 11,630 participants of whom 2681 received tocilizumab were conducted in non-ICU patients, whereas 14 studies with a total of 6956 participants of whom 1775 received tocilizumab were conducted in ICU patients. The use of tocilizumab was associated with an improvement in mortality, both in non-ICU and in ICU patients (RR 0.69 and 0.75, respectively) (Figure S2 in the Supporting Information). In the only RCT that was performed in the ICU setting (REMAP-CAP),[16] the survival benefit was significant (RR 0.83, 95% CI 0.70 to 0.99), with an effect comparable to that of all nine RCTs (RR 0.89) (Figure 2).

Differences in mortality in patients according to the concomitant use of systemic corticosteroids

Two RCTs and three observational studies reported mortality data separately in patients who received systemic corticosteroids as part of the standard of care regimen and those who did not receive corticosteroids.

In the two RCTs, there was no significant difference in mortality in the tocilizumab versus the control group (RR 0.99, 95% CI 0.79 to 1.24); this was evident both in patients who received corticosteroids (RR 0.92, 95% CI 0.67 to 1.24) and in those who did not receive corticosteroids (RR 1.12, 95% CI 0.93 to 1.34) (Figure 4A).

In the observational studies ($n = 3$), the use of tocilizumab was associated with a lower mortality risk (RR 0.67, 95% CI 0.54 to 0.81); this effect was evident both in the patients who received corticosteroids (RR 0.57, 95% 0.37 to 0.88) and in those who did not receive corticosteroids (RR 0.70, 95% CI 0.59 to 0.81), with a trend for a greater benefit in the group of patients who received systemic corticosteroids (Figure 4B).

Publication bias and small study effect

Egger's test was not statistically significant when mortality was assessed as outcome for both RCTs ($p = 0.155$) and observational studies ($p = 0.095$), suggesting no such bias (Figure S3 in the Supporting Information). When ICU admission or IMV and only IMV were assessed as outcomes, Egger's test was also not significant for both RCTs and observational studies ($p = 0.709$ and $p = 0.65$, respectively, for ICU admission or IMV; $p = 0.435$ and $p = 0.456$, respectively, for IMV) suggesting no such bias (Figures S4 and S5 in the Supporting Information). Egger's test was statistically significant when mortality or IMV was assessed as an outcome for observational studies ($p = 0.016$), suggestive of bias. No such bias was observed when RCTs were considered (Egger's test p-value $= 0.885$) (Figure S6 in the Supporting Information). Finally, no such bias was observed when median hospitalization days were assessed as outcome when observational studies (Egger's test p-value $= 0.676$) were considered (Figure S7 in the Supporting Information).

DISCUSSION

In this meta-analysis of 52 studies (nine RCTs and 43 observational studies that included 27,004 patients with COVID-19, of whom 8048 were treated with tocilizumab), a significant survival benefit of tocilizumab versus usual care in both RCTs and observational studies was shown. In secondary analyses, there was a benefit regarding tocilizumab use both in the ICU and non-ICU settings. In the studies providing data on the concomitant use of tocilizumab with systemic corticosteroids, there was no reduction in mortality with the concomitant use in the RCTs, while the reduction in mortality was evident in observational studies regardless of systemic corticosteroids use. Both RCTs and observational studies illustrated the positive effect of tocilizumab on the risk for intubation/IMV and in the composite outcome of mortality or IMV. Finally, we observed a benefit in favour of tocilizumab only in the RCTs providing data for the composite outcome of ICU admission or IMV.

The analysis of RCTs demonstrated an 11% reduction in mortality, despite some negative results from earlier small RCTs.[46,71] The mortality benefit was driven mainly by the large RECOVERY trial that included patients both in ICU and non-ICU settings with progressive COVID-19 (those with an oxygen saturation lower than 92% on room air or receiving oxygen therapy and evidence of systemic inflammation as expressed by CRP levels ≥75 mg/L),[15] and the REMAP-CAP trial that included critically ill patients receiving organ support in intensive care.[16] A plausible explanation for this disagreement is that the RECOVERY and REMAP-CAP trials involved more patients with severe or critical illness who were likely to have entered the CRS where anti-inflammatory therapy is likely to be more beneficial.[79] Interestingly, it seems that the positive result of tocilizumab on survival in RECOVERY is likely a synergistic effect with corticosteroids, as shown by the RRs of 0.84 and 1.13 in patients who received and did not receive corticosteroids, respectively. Moreover, in REMAP-CAP, steroids were used in 82% of participants (and 93.3% for patients enrolled post 17 June 2020). In contrast, in the early small RCTs, steroid use was likely less frequent. Based on this observation, we performed a secondary analysis of the concomitant steroid use in the RECOVERY[15] and COVACTA[66] trials that provided such data, where the observed trend for a benefit in favour of the combined treatment versus corticosteroids alone (RR 0.92) was driven mainly by the RECOVERY data. A similar effect was observed irrespective

of the use of systemic corticosteroids in the analysis of observational studies. As all patients in need of oxygen supplementation are receiving systemic corticosteroids as standard of care nowadays, the additional benefit shown with the use of tocilizumab in patients treated with corticosteroids is of importance.

Similar findings were demonstrated in a recent meta-analysis performed by the WHO of 27 RCTs (nine published and 18 unpublished) estimating the association between administration of IL-6 antagonists (tocilizumab, sarilumab and siltuximab) compared with usual care or placebo and 28-day all-cause mortality.[80] In our meta-analysis, we have additionally included 43 observational studies in support of the RCT data, and searched the utility of tocilizumab in the need for IMV, composite endpoints of mortality or IMV and ICU admission or IMV, length of hospitalization and differences in mortality in subgroups (ICU and non-ICU patients and patients receiving or not receiving concomitant corticosteroids).

Observational studies also showed a beneficial survival effect with 31% mortality reduction. These studies are characterized by significant heterogeneity regarding participants' characteristics, study protocols, drug dosage and route of administration, standard of care regimens and, most importantly, a plausible selection bias in the decision for administration of tocilizumab. Notably, a large proportion of patients received concomitant corticosteroids (up to 60% overall; Table S1 in the Supporting Information) in these studies, and possibly in some instances in higher doses as life-saving treatment.[81] In our secondary analysis, a reduction in mortality was observed irrespective of the use of systemic corticosteroids; however, combination therapy had a more pronounced effect on mortality (RR 0.57 in the corticosteroids group vs. 0.70 in the no-corticosteroids group). The data from observational studies, despite their significant heterogeneity, overall support the observation in RCTs for a beneficial effect of tocilizumab on mortality, which may be more prominent in addition to systemic corticosteroids that anyway represent the cornerstone of treatment of patients with COVID-19 and respiratory failure.

The beneficial effect of tocilizumab was also demonstrated by a significant reduction in the need for IMV by 19% in RCTs, with a similar trend in observational studies. The higher benefit in observational studies versus RCTs in the composite endpoint of mortality or IMV (45% vs. 17%) likely represents the higher mortality benefit in observational studies. Nevertheless, both these endpoints (mortality and the need for IMV) are relatively 'hard' endpoints, clearly reflecting the patients' needs. In contrast, we had contradictory results in the composite endpoint of the need for ICU admission or IMV, with a 20% reduction in the risk in RCTs and no beneficial effect in the observational studies. However, no difference was observed in hospitalization days in both types of studies. These contradictory results may reflect the setting of the studies, as ICU availability and admission criteria, as well as hospital discharge criteria, may

differ in different parts of the world, and this is also reflected in the expected heterogeneity in the observational trials data.

Our data provide further support to guidelines that recommend the use of tocilizumab in combination with corticosteroids in hospitalized COVID-19 patients recently admitted to the ICU or those outside ICU who are exhibiting rapid respiratory decompensation.[82] The aforementioned data were verified in the recent WHO meta-analysis, demonstrating that the effect of tocilizumab is amplified when synchronously administered with corticosteroids.[80] Tocilizumab is likely effective when inflammatory, rather than infectious, mechanisms are predominant, modulating the levels of proinflammatory IL-6 or its effects, thus reducing the duration and/or severity of COVID-19 illness. Although the mechanisms of hyper-inflammation and lung injury in COVID-19 are still not entirely clear, cytokine storm in severely ill patients includes, besides elevated IL-6, an increase in a wide spectrum of cytokines and inflammatory agents, including IL-1β, IP-10, TNF-α, interferon-γ, macrophage inflammatory protein 1α and 1β and Vascular Endothelial Growth Factor (VEGF).[83] Thus, it is plausible that combination therapy with corticosteroids will provide an effective anti-inflammatory treatment umbrella, with IL-6 blockade representing a central weapon, as higher IL-6 levels were strongly associated with shorter survival in patients with COVID-19.[84]

Our analysis cannot clearly support the optimal timing for tocilizumab administration, as we showed that the drug was beneficial both in moderate-to-severe patients treated in non-ICU settings, as well as in critical disease managed in the ICU. The latter finding is supported by the REMAP-CAP RCT,[16] as well as by observational studies showing a 25% survival benefit in ICU, compared to 31% in non-ICU patients. The cornerstone for the right timing for tocilizumab administration is the appropriate selection of the patients with moderate-to-severe disease, based on their clinical, radiological and inflammatory profile.

To the best of our knowledge, this is the first meta-analysis investigating the efficacy of tocilizumab on multiple outcomes in patients hospitalized with COVID-19, while previous analyses have reported only mortality events and ICU admissions.[85–87] This is also the largest meta-analysis on this topic so far, involving 8048 patients in the tocilizumab group and 18,956 patients in the control group, with data representing worldwide findings, providing diversity in ethnic background. An additional strength of our systematic review is that we evaluated both observational studies and RCTs, in order to evaluate the efficacy and effectiveness of tocilizumab on various outcomes, both in its use in settings of regular clinical care and in the controlled settings of clinical trials, further strengthening the generalizability of our results. Observational studies are not designed to replace or oppose RCTs but to complement them and provide new insights into the use and outcomes possible with available therapies when used in a non-RCT population and/or follow-up setting. Although observational studies are

not able to achieve the high internal validity of a registration RCT, when the analyses are performed in a wider population of everyday clinical practice, they can provide useful complementary data, helping to answer questions that RCTs do not or are unable to address. Small heterogeneity was observed in the outcomes of RCTs; however, large or very large heterogeneity was detected among observational studies, plausibly attributed to study design and time of randomization, disease severity, tocilizumab dosage and route of administration, the patients' inflammatory profile and the concomitant use of corticosteroids. Our study also has some limitations. First, we did not perform subgroup analyses according to the dosage and route of tocilizumab administration, due to the lack of specific data. Second, we did not analyse safety events from tocilizumab treatment, including thrombotic events or major bleeding, and bacterial or fungal infections, as this was not the aim of our study. Third, we decided not to include observational studies in preprint format from medRxiv. The methodological quality of COVID-19 clinical research has overall been lower than similar non-COVID-19 publications.[88] Therefore, results of the analyses of observational studies should be evaluated with caution, due to their heterogeneity and often retrospective design; however, they are overall in agreement with the more robust results from RCTs, thus they build on the body of evidence and further support current treatment guidelines. Fourth, despite the fact that Egger's tests suggested no evidence of small study effect, except from the analysis of ICU admission or IMV/intubation, for observational studies, we observed evidence of asymmetry in some of the funnel plots. The evident asymmetry could arise due to reasons other than small study effect, such as differences in methodological quality, heterogeneity in intervention effects, variability in clinical settings and different protocols of the trials. Lastly, we cannot comment on the optimal timing for the use of tocilizumab and the patients who are most likely to benefit from its use, as the data available would not allow us to perform such analyses.

In conclusion, this systematic review and meta-analysis of nine RCTs and 43 observational studies provides the most up-to-date and complete evidence for the role of tocilizumab in the management of COVID-19. We demonstrated that the use of tocilizumab is associated with lower mortality and risk of intubation or need for mechanical ventilation in hospitalized COVID-19 patients, with its benefit magnified when administered concomitantly with systemic corticosteroids. The optimal timing of administration and the patients who will benefit the most need to be evaluated in future appropriately designed trials.

CONFLICT OF INTEREST
None declared.

HUMAN ETHICS APPROVAL DECLARATION
Not applicable. The protocol for this systematic review was registered with PROSPERO (CRD42021247188 at https://www.crd.york.ac.uk/prospero/; for protocol details, see Appendix S2 in the Supporting Information).

AUTHOR CONTRIBUTIONS
Christos Kyriakopoulos: Conceptualization; investigation; methodology; project administration; validation; visualization; writing – original draft. **Georgios Ntritsos:** Data curation; formal analysis; investigation; methodology; resources; software; visualization; writing – original draft. **Athena Gogali:** Data curation; investigation; methodology; project administration; resources; validation; visualization; writing – original draft; writing – review and editing. **Charalampos Milionis:** Conceptualization; formal analysis; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Evangelos Evangelou:** Data curation; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – review and editing. **Konstantinos Kostikas:** Conceptualization; data curation; methodology; project administration; supervision; validation; writing – original draft; writing – review and editing.

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