Infect Dis Ther (2021) 10:1195–1213
https://doi.org/10.1007/s40121-021-00488-6

REVIEW

Systematic Review and Subgroup Meta-analysis of Randomized Trials to Determine Tocilizumab's Place in COVID-19 Pneumonia

Timothée Klopfenstein · Vincent Gendrin · Aurélie Gerazime · Thierry Conrozier · Jean-Charles Balblanc · Pierre-Yves Royer · Anne Lohse · Chaouki Mezher · Lynda Toko · Cerise Guillochon · Julio Badie · Alix Pierron · N.'dri Juliette Kadiane-Oussou · Marc Puyraveau · Souheil Zayet · For the HNF Hospital tocilizumab multidisciplinary team

Received: May 14, 2021 / Accepted: June 16, 2021 / Published online: July 11, 2021

ABSTRACT

Introduction: Tocilizumab randomized clinical trial results are heterogeneous because of the heterogenous population included in them.
Methods: We conducted a meta-analysis with subgroup meta-analysis (PRISMA guidelines) between severe and non-severe COVID-19.
Results: We included nine trials. Overall, the mortality rate was 24.5% (821/3357) in the tocilizumab group and 29.1% (908/3125) in the control group at day 28–30 (pooled OR, 0.85; 95% CI 0.76–0.96; $p = 0.006$). Considering the subgroup analysis, this benefit on mortality was confirmed and amplified in the severe COVID-19 group (pooled OR, 0.82; 95% CI 0.73–0.93; $p = 0.001$) but not in the non-severe COVID-19 group (pooled OR, 1.46; 95% CI 0.91–2.34; $p = 0.12$). For patients who were not mechanically ventilated at baseline (5523/6482), the pooled OR (0.74; 95% CI 0.64–0.85; $p < 0.0001$) for mechanical ventilation incidence at day 28–30 was in favor of tocilizumab (cumulative incidence of 14.8% versus 19.4% in tocilizumab and control arm, respectively). This benefit was confirmed in both subgroups, i.e., severe and non-severe COVID-19.
Conclusion: Tocilizumab is an effective treatment in hospitalized patients with COVID-19 and hypoxemia by improving survival and decreasing mechanical ventilation requirement. The greatest benefit is observed in severe COVID-19.

Keywords: Coronavirus disease 2019; Meta-analysis; Randomized clinical trial; Review; Tocilizumab

T. Klopfenstein (✉) · V. Gendrin · P.-Y. Royer · L. Toko · A. Pierron · N.'driJ. Kadiane-Oussou · S. Zayet (✉)
Infectious Disease Department, Nord Franche-Comté Hospital, 90400 Trevenans, France
e-mail: timothee.klopfenstein@hnfc.frS. Zayet
e-mail: souhail.zayet@gmail.com

A. Gerazime · M. Puyraveau
Methodology Unit, Clinical Investigation Center INSERM 1431, Jean-Minjoz University Hospital, Besançon, France

T. Conrozier · J.-C. Balblanc · A. Lohse · C. Guillochon
Rheumatology Department, Nord Franche-Comté Hospital, Trevenans, France

C. Mezher · J. Badie
Intensive Care Unit Department, Nord Franche-Comté Hospital, Trevenans, France

Key Summary Points
Tocilizumab reduces mortality and mechanical ventilation requirement in hospitalized patients with COVID-19 and hypoxemia.
Mortality benefit is confirmed and amplified in the severe COVID-19 group but not in the non-severe COVID-19 group.
Mechanical ventilation incidence benefit is confirmed in both groups (severe COVID-19 group and non-severe COVID-19 group).
Tocilizumab is effective in COVID-19 pneumonia. The greatest benefit is observed in severe COVID-19 pneumonia.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14791881.

INTRODUCTION

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread around the world infecting more than 150 million people and causing more than 3 million deaths [1]. Corticosteroids have proven to reduce mortality with strong evidence [2]. Tocilizumab is the second treatment which has also been shown to reduce mortality [3, 4]. However, randomized clinical trials (RCTs) results are heterogeneous [3–11]. Six randomized clinical trials [5–10] have not shown an impact on mortality at day 28–30 which is confirmed by meta-analysis on five of these six RCTs [12, 13]. The lack of positive results on mortality of these RCTs contrasts with results of cohort studies [13]. The heterogenous population in RCTs seems to explain that [14, 15]. A recent meta-analysis of these RCTs [16] has shown that the overall mortality varies widely across these RCTs (from 2% to 30%); this considerable variation is mainly explained by patient severity at baseline. Tocilizumab seems to be effective in severe patients and subgroup analysis is needed [14–17]. For example the only subgroup analysis on severe patients in RCT was performed by Soin et al. in COVINTOC [11] and it supports this assumption: among patients who had severe coronavirus disease 2019 (COVID-19) at baseline, 16% patients died in the tocilizumab group versus 34% in the standard care group ($p = 0.04$); in COVINTOC severe COVID-19 was defined as respiratory rate of at least 30/min or SpO_2 less than 90% or acute respiratory distress syndrome or septic shock. The last two main RCTs (REMAP-CAP [3] and RECOVERY [4]) showed mortality benefit of tocilizumab administration.

As a result of the heterogenous population in RCTs, we think that an updated meta-analysis with subgroup analysis in severe and non-severe COVID-19 is needed; for example, such as the subgroup analysis based on severe and non-severe COVID-19 that Soin et al. conducted in their RCT. We recently published a narrative review of these RCTs to assess an optimal group and timing for tocilizumab administration; in this review we performed a classification based on respiratory support at baseline which would be helpful for a subgroup meta-analysis [15]. However, as a result of the heterogenous description about respiratory support at baseline (different scales or clinical description were used in the RCTs) this classification cannot be used in a practical way. In these RCTs, the mortality increases in correlation with the severity of respiratory support at baseline [15]; furthermore, clinical severity at baseline is among the main risk factors associated with mortality in COVID-19 pneumonia [18–21]. So we chose to use the mortality in the control group to divide the RCTs into two groups: severe group (high mortality in the control group) and non-severe group (low mortality in the control group). The choice of the mortality rate to divide the RCTs depended on various factors:

the inclusion period (since the beginning of the pandemic) and the study site (country) are the main factors that influence the mortality in hospitalized patients with COVID-19 [22]. Most of these RCTs included patients in the beginning of the pandemic in wealthy countries (especially North America and Europe), so we chose a mortality rate of 17% which corresponds to the in-hospital mortality in the beginning of the pandemic among COVID-19 hospitalized adults in the USA [20]. Our analysis RCTs were divided into two groups: severe COVID-19 group (mortality rate in the control group at least 17%) and non-severe COVID-19 group (mortality rate in the control group less than 17%).

METHODS

This review was conducted in accordance with the *Cochrane Handbook for Systematic Reviews* (V6.1) [23] and is reported according to the PRISMA (preferred reporting items for systematic reviews and meta-analysis) statement [24]. The PICO method (population, intervention, comparison, outcome) was used before performing the literature search to formalize the objective of the study.

Search Strategy and Selection Criteria

We performed an electronic search of Medline, the Cochrane Library, and Embase on April 4, 2021, which was updated on April 27, 2021. A systematic search was done using PubMed to find MEDLINE indexed published articles and the preprint server MedRχiv to find unpublished manuscripts. As of March 27, 2021, the search was conducted by combining the MeSH words "COVID-19" AND "tocilizumab" AND "trial". In MedRχiv the search was conducted by combining "COVID-19" AND "tocilizumab" AND "trial" AND "randomized". We then screened citations on the basis of titles and abstracts. We selected all RCTs that compared the clinical outcome of patients with COVID-19 treated with tocilizumab versus standard of care or placebo. Irrelevant manuscripts were excluded. Our primary endpoint was the 28–30 day mortality. Secondary endpoints were mechanical ventilation incidence at day 28–30 and safety endpoint (serious adverse events).

Study Selection and Data Extraction

Two independent reviewers (TK, SZ) examined each title and abstract to identify potentially eligible articles. Records deemed eligible, and records that did not contain enough information to confirm their inclusion, underwent full text review. Disagreements were resolved through discussions, and by a third reviewer (TK, SZ, or VG) if required. Another independent reviewer (MP) verified all data extraction.

Risk of Bias Assessment

We excluded studies that were not written in English or French because of the language barrier. Risk of bias was independently assessed by two reviewers (TK and SZ). Studies were judged either as "low risk", "unclear", or "high risk" according to the *Cochrane Handbook for Systematic Reviews of Interventions* [25]. We considered the methodological quality for each study on the basis of the following categories: selection bias, performance bias, detection bias, potential for attrition bias, potential for reporting bias, and other potential bias.

Statistical Analysis

Where suitable statistical summary data were available, we combined selected outcome data in pooled meta-analyses using the Cochrane statistical software RevMan [26]. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated to estimate the impact of tocilizumab on mortality at 28–30 days, mechanical ventilation at 28–30 days, and serious adverse events. We conducted the meta-analysis using all of the trials and then we performed a subgroup meta-analysis in the two groups generated by the severity of the patients COVID-19. We assessed statistical heterogeneity using the I^2 test to determine whether fixed effects ($I^2 < 50\%$) or random effects ($I^2 \geq 50\%$) modelling should be used.

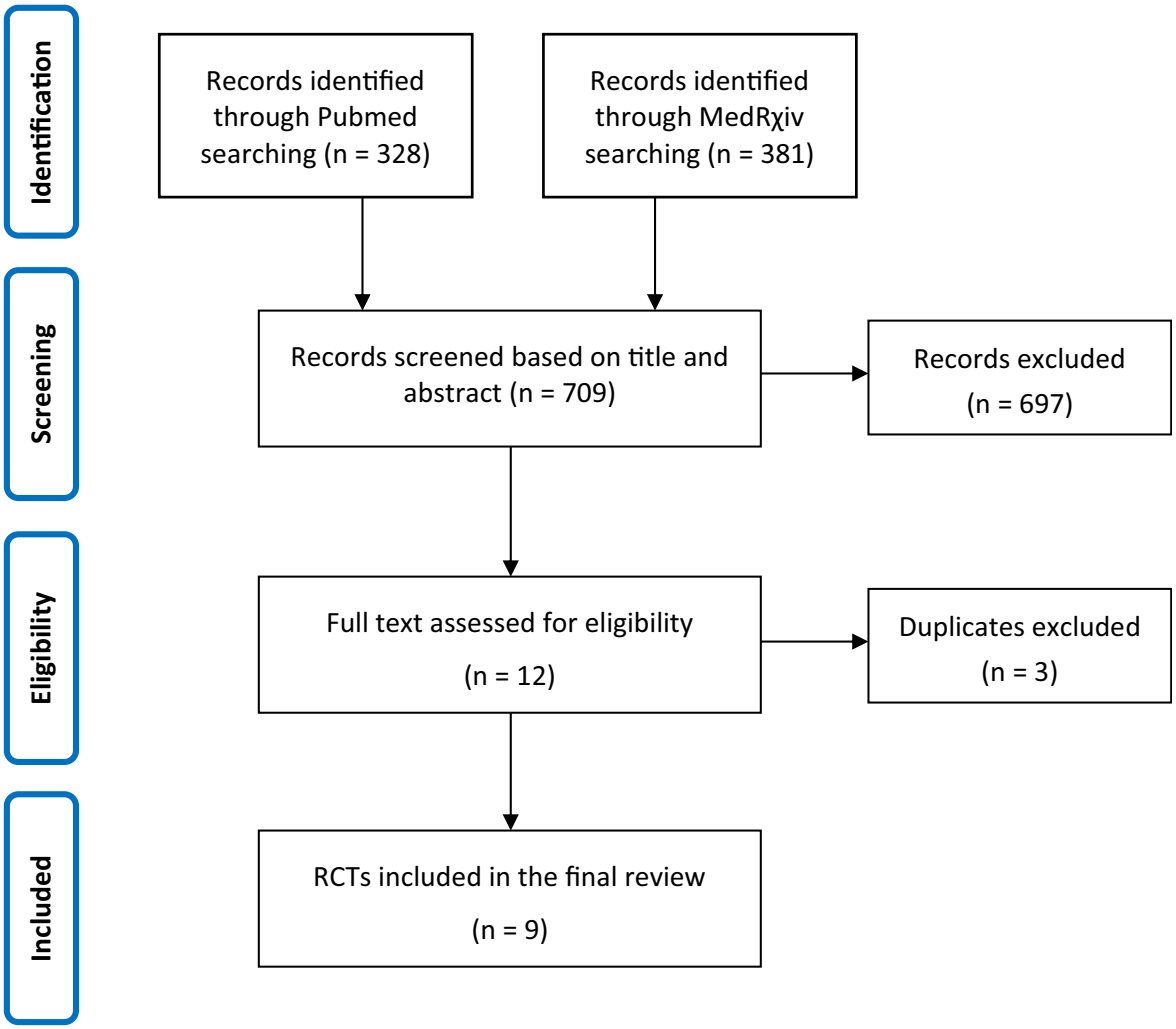

Fig. 1 PRISMA flowchart detailing the article selection process

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Study Selection and Characteristics

We included nine RCTs (Fig. 1: PRISMA flowchart); the general characteristics of the nine RCTs are summarized in Table 1. One RCT was still unpublished but we got its objectives and detailed results on the preprint server MedRχiv [4]. A total of 6482 patients were included: 3357 randomized to tocilizumab and 3125 to placebo. Concerning subgroup analysis, four RCTs had a mortality rate in the control group of at least 17% (from 18% to 36%) and were included in the severe COVID-19 group and five RCTs had a mortality rate in the control group of less than 17% (from 2% to 12%) and were included in the non-severe COVID-19 group (Table 2).

Mortality Analysis

Overall, the mortality rate was 24.5% (821/3357) in the tocilizumab group and 29.1% (908/3125) in the control group at day 28–30 (pooled OR, 0.85; 95% CI 0.76–0.96; $p = 0.006$; Fig. 2).

Table 1 Characteristics of tocilizumab randomized clinical trials in COVID-19

Studies	Study design	Country	Number of patients	TCZ regimen[a]
Salvarini et al. [5] (RCT-TCZ)	Open-label, controlled trial	Italy, 24 sites	126 patients (60 in TCZ arm)	Two doses (second dose 12 h later)
Stone et al. [6] (BACC-bay)	Double-blind, placebo-controlled trial	USA	243 patients (161 in TCZ arm)	Single dose
Salama et al. [7] (EMPACTA)	Double-blind, placebo-controlled trial	6 countries in America and Africa	389 patients (249 in TCZ arm)	Single dose. Possibility of a 2nd dose 8–24 h later
Hermine et al. [8] (CORIMUNO-TOCI)	Open-label, controlled trial	France, 9 sites	131 patients (63 in TCZ arm)	Single dose. Possibility of a 2nd dose 48 h later
Veiga et al. [9] (TOCIBRAS)	Open-label, controlled trial	Brazil, 9 sites	129 patients (65 in TCZ arm)	Single dose
Soin et al. [11] (COVINTOC)	Open-label, controlled trial	India, 12 sites	180 patients (90 in TCZ arm)	Single dose. Possibility of a 2nd dose 12–168 h later
Rosas et al. [10] (COVACTA)	Double-blind, placebo-controlled trial	9 countries in Europe and North America	444 patients (294 in TCZ arm)	Single dose
Horby et al. [4] (RECOVERY)	Open-label, controlled trial	UK	4116 patients (2022 in TCZ arm)	Single dose. Possibility of a 2nd dose 12–24 h later
Gordon et al. [3] (REMAP-CAP)	Open-label, controlled trial	Europe, Oceania, and North America	755 patients (353 in TCZ arm)	Single dose. Possibility of a 2nd dose 12–24 h later

TCZ tocilizumab

[a] All doses were an intravenous infusion of tocilizumab 8 mg/kg (maximum 800 mg), except for Soin et al. (6 mg/kg up to 480 mg for the first and second doses) and for the second dose of Hermine et al. (which was a fixed dose of 400 mg)

Considering the subgroup analysis this benefit was confirmed and amplified in the severe COVID-19 group (pooled OR, 0.82; 95% CI 0.73–0.93; $p = 0.001$) but not in the non-severe COVID-19 group (pooled OR, 1.46; 95% CI 0.91–2.34; $p = 0.12$) (Fig. 3). The funnel plot of the meta-analysis is available in Appendix 1.

Mechanical Ventilation Incidence Analysis

For patients who were not mechanically ventilated at baseline (5523/6482), the pooled OR (0.74; 95% CI 0.64–0.85; $p < 0.0001$) for mechanical ventilation incidence at day 28–30 was in favor of tocilizumab (cumulative incidence of 14.8% versus 19.4% in tocilizumab and control arm, respectively; Fig. 4). This benefit was confirmed in both subgroups: severe

Table 2 Main results of tocilizumab randomized controlled trials

		Salvarani et al. [5]	Stone et al. [6]	Salama et al. [7]	Veiga et al. [9]	Hermine et al. [8]	Soin et al. [11]	Rosas et al. [10]	Horby et al. [4]	Gordon et al. [3]
Respiratory support										
Respiratory support at baseline in TCZ arm		Not detailed but 72% of patients (43/60) had a $PaO_2/FiO_2 \geq 250$ mmHg (so a O_2 flow ≤ 3 L/min)	Ordinal scale score[a] 2: 14% (23/161) 3: 83% (133/161) 4: 3% (5/161)	Ordinal scale score[c] 2: 9% (24/249) 3: 65% (161/249) 4: 26% (64/249)	Ordinal scale score[b] 4: 60% (39/65) 5: 23% (15/65) 6: 17% (11/65)	WHO-CPS-Score (0–10)[e]: 5: 100% (63/63)	Respiratory support: supplemental O_2: 89% (81/91) NIV: 31% (28/91) IMV: 5% (5/91)	Ordinal scale score[d] 2: 3% (9/294) 3: 27% (78/294) 4: 32% (94/294) 5: 15% (45/294) 6: 23% (68/294)	Respiratory support: low flow O_2[f]: 46% (935/2022) NIV or HFNC: 41% (819/2022) IMV: 13% (268/2022)	Respiratory support:[g] HFNC: 29% (101/353) NIV: 42% (147/353) IMV: 29% (104/353)
Classification	$O_2 \leq 3$ L/min or no O_2	72%	97%	9%	0%	60%	64%	3%	46%	0.3%
	3 L/min $< O_2 \leq 6$ L/min	28%		65%	100%			27%		
	$O_2 > 6$ L/min	0%	3%							
	HFNC or NIV	0%	0%	26%	0%	23%	31%	32%	41%	70%
	IMV (IMV < 24 h)	0%	0%	0%	0%	17% (17%)	5%	38%	13%	29% (29%)

Table 2 continued

	Salvarani et al. [5]	Stone et al. [6]	Salama et al. [7]	Veiga et al. [9]	Hermine et al. [8]	Soin et al. [11]	Rosas et al. [10]	Horby et al. [4]	Gordon et al. [3]
CRP level at baseline									
CRP in TCZ arm, median (IQR) or *mean (SD)	105 (50–146)	116 (67–191)	125	*160 (104)	120 (75–220)	*111 (107)	*168 (101)	143 (107–203)	150 (85–221)
Significant results[h]									
Mortality at day 28	No	No	No	No	No	No (in favor of TCZ in severe COVID-19)	No	**In favor of TCZ**	**In favor of TCZ**
MV or ICU incidence	No	No	**In favor of TCZ**	No	**In favor of TCZ**	No	No	**In favor of TCZ**	**In favor of TCZ**
Hospitalization characteristics	No	No	**In favor of TCZ**	**In favor of TCZ**	**In favor of TCZ**	No	**In favor of TCZ**	**In favor of TCZ**	**In favor of TCZ**
Safety	No	**In favor of TCZ**	No	No	**In favor of TCZ**	No	No	No	No
RCT risk of bias[i]	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Mortality rate in RCTs									

Table 2 continued

	Salvarani et al. [5]	Stone et al. [6]	Salama et al. [7]	Veiga et al. [9]	Hermine et al. [8]	Soin et al. [11]	Rosas et al. [10]	Horby et al. [4]	Gordon et al. [3]
% of deaths in controlled arm (overall population)	2% (2%)	4% (5%)	9% (10%)	9% (15%)	12% (12%)	18% (15%)	19% (20%)	33% (31%)	36% (32%)

The ordinal scale score ranges from 1 to 7 for each study but was defined differently

Bold represents results with significant differences. There were no significant results in favor of control in any of these five categories

HFNC high flow nasal cannula, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *NA* not applicable, *NIV* non-invasive ventilation, *RCT* randomized clinical trial, *TCZ* tocilizumab

[a] 2, not receiving supplemental oxygen; 3, receiving supplemental oxygen ≤ 6 L/min; 4, receiving high flow oxygen > 6 and ≤ 10 L/min delivered by any device

[b] 4, receiving supplemental oxygen; 5, receiving NIV or high flow oxygen through a nasal cannula; 6, receiving IMV

[c] 2, not receiving supplemental oxygen; 3, receiving supplemental oxygen; 4, receiving NIV or high flow oxygen

[d] 2, not receiving supplemental oxygen; 3, receiving supplemental oxygen; 4, receiving NIV or high flow oxygen; 5, receiving IMV; 6, receiving ECMO or IMV and additional organ support

[e] Score 5 on the World Health Organization (WHO) clinical progression scale was defined by hospitalized; oxygen by mask or nasal prongs

[f] Fewer than 9 patients without respiratory O_2 support at baseline

[g] Only one patient was with supplemental O_2 only or no respiratory support at baseline

[h] We noticed a result in favor of TCZ or in favor of control if there was at least one statistically significant result for the category concerned. The "Hospitalization characteristics" category included clinical evolution on ordinal scale score, duration of hospitalization, and duration of ICU or IMV

[i] We used the RoB 2: the revised Cochrane risk-of-bias tool for randomized trials

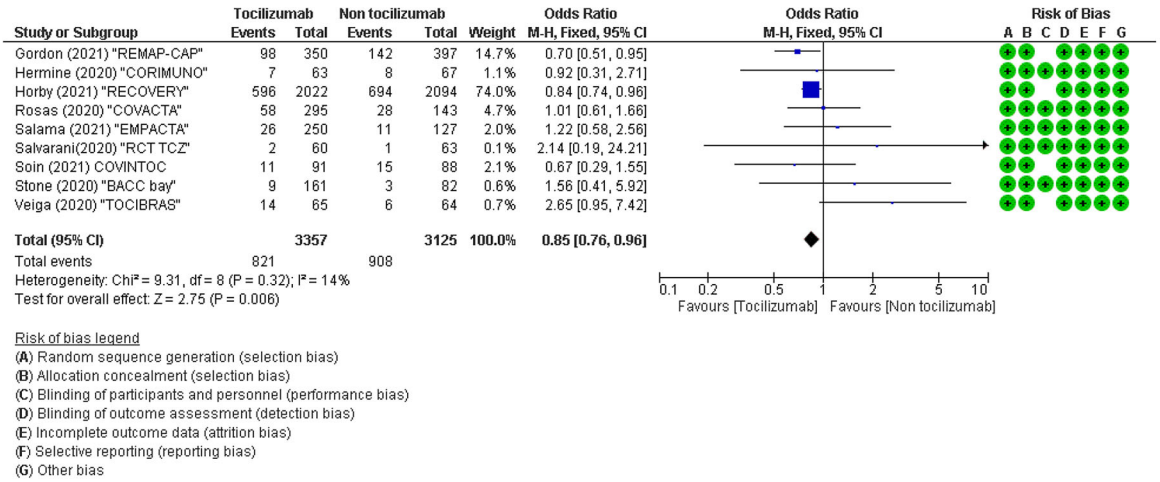

Fig. 2 Forest plot for the effect of tocilizumab on mortality at days 28–30 in randomized trials

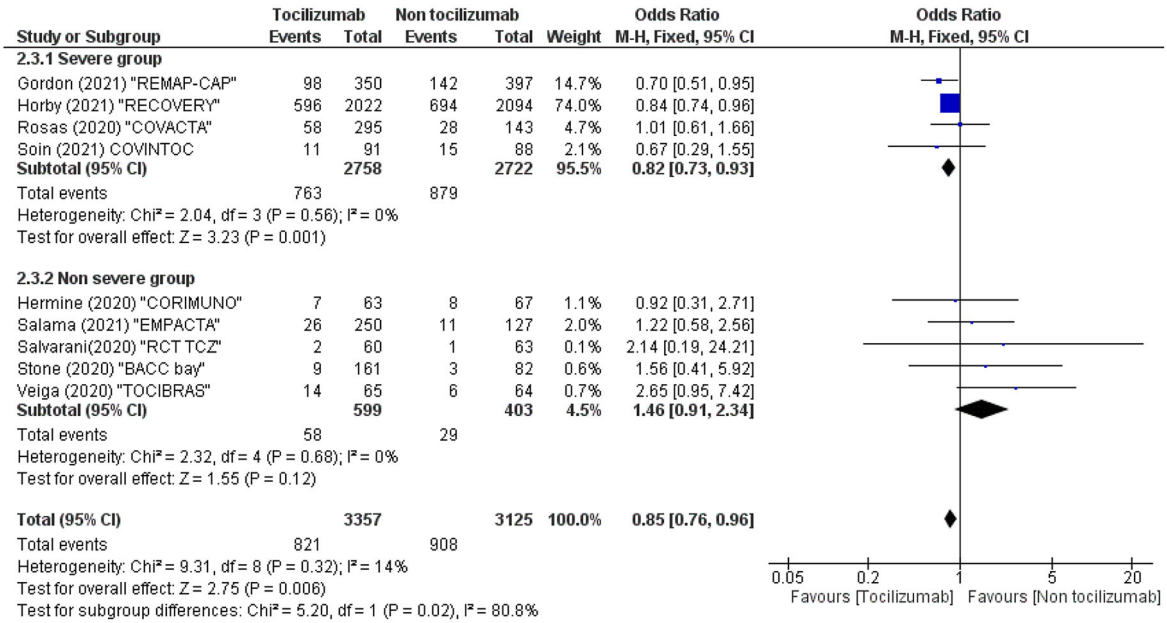

Fig. 3 Forest plot for the effect of tocilizumab on mortality at days 28–30 in randomized trials in severity event subgroup

COVID-19 group and non-severe COVID-19 group (Fig. 5).

Safety Analysis

There were no significant differences between the two arms about relative risk of serious adverse events (pooled OR, 0.87 in favor of tocilizumab; 95% CI 0.69–1.11; $p = 0.27$) (Fig. 6).

DISCUSSION

This meta-analysis shows that tocilizumab administration is an effective treatment in hospitalized patients with COVID-19 and hypoxemia by improving survival and decreasing mechanical ventilation requirement. Mortality benefit is confirmed and amplified in the severe COVID-19 group but not in the non-severe COVID-19 group. The benefit on

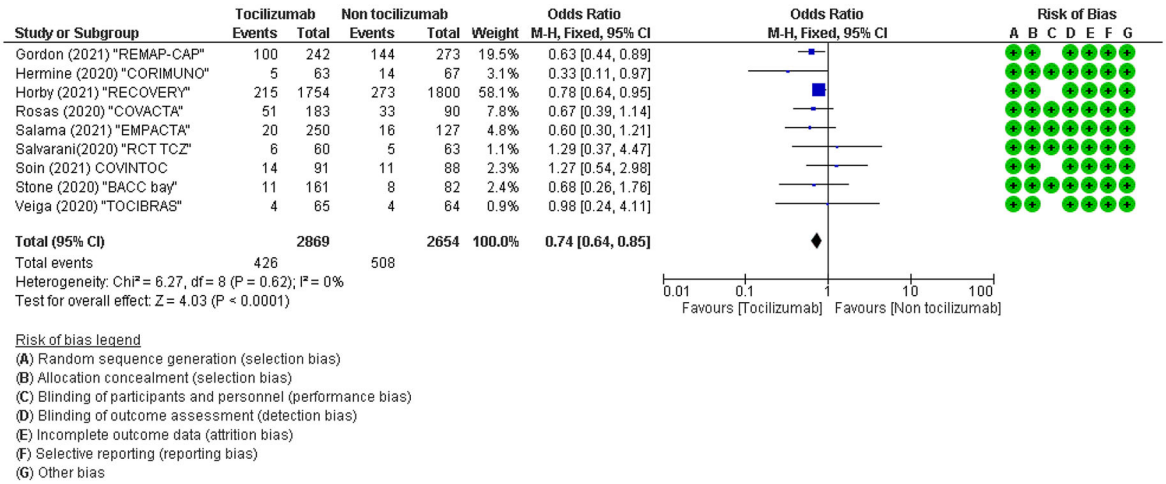

Fig. 4 Forest plot for the effect of tocilizumab on mechanical ventilation incidence at days 28–30 in randomized trials

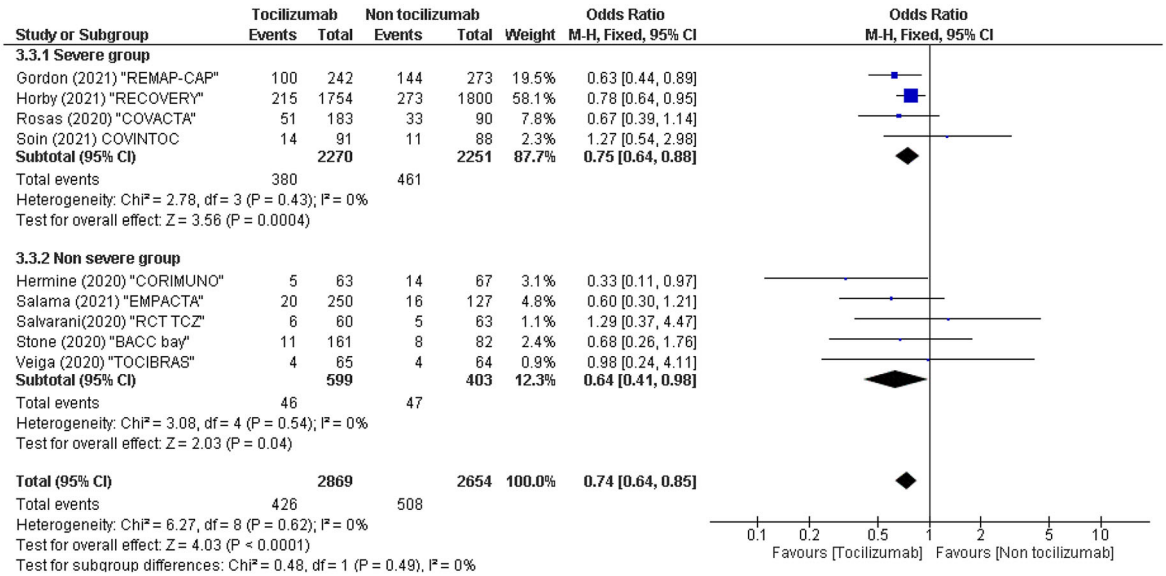

Fig. 5 Forest plot for the effect of tocilizumab on mechanical ventilation incidence at days 28–30 in randomized trials in severity event subgroup

mechanical ventilation incidence is confirmed in both subgroups: severe COVID-19 group and non-severe COVID-19 group.

Meta-Analysis Results

Mortality Analysis

Pooled OR in favor of tocilizumab shows a positive effect of tocilizumab administration on mortality at day 28–30 in hospitalized patients with COVID-19 and hypoxemia; these results are in accordance with REMAP-CAP [3] and RECOVERY [4] results. On the contrary, the seven other RCTs seemed to show no effect in favor or disfavor of tocilizumab [5–9, 11, 27]. Our main assumption to explain the lack of impact on mortality in these RCTs was they included heterogenous populations [14, 15, 17].

The subgroup analysis performed in our meta-analysis supports this assumption.

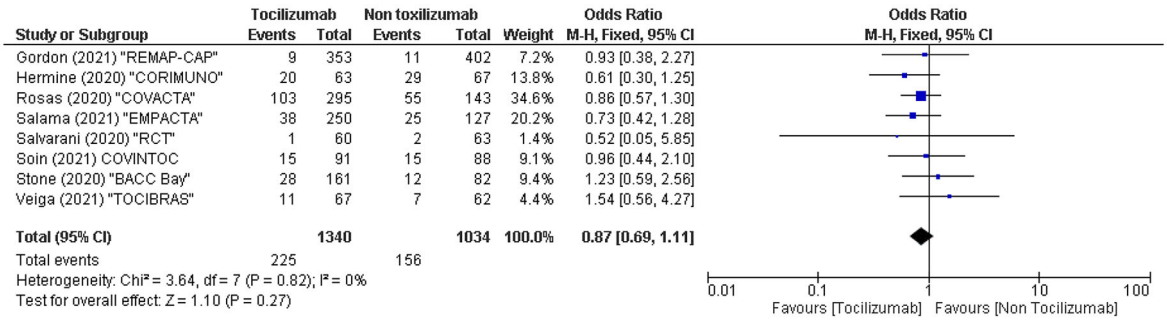

Fig. 6 Forest plot for relative risk of serious adverse events for tocilizumab versus control in randomized trials

(i) In the severe COVID-19 group, the pooled OR was clearly in favor of tocilizumab (0.82; 95% CI 0.73–0.93; $p = 0.001$) in contrast with the non-severe COVID-19 group. The test for subgroup differences suggests that there is a statistically significant subgroup effect ($p = 0.02$), meaning that severity statistically significantly modifies the effect of tocilizumab [28]. Concerning the four RCTs included in the severe COVID-19 group, results of REMAP-CAP and RECOVERY were clearly in favor of tocilizumab [2, 3] and tocilizumab benefits were in addition to dexamethasone among patients receiving corticosteroids [4]; in COVINTOC [11] the post hoc subgroup analysis only on patients with severe COVID-19 performed by Soin et al. showed a mortality rate at 16.0% in the tocilizumab arm versus 34.1% in the control arm ($p = 0.04$). COVACTA [10] had an OR of 1.01 [0.61; 1.66] without positive effect of tocilizumab administration on mortality at day 28 in the overall population; however, if we choose only patients with severe disease at an early stage (category 4 and 5 of the 7-category ordinal scale: respectively ICU (intensive care unit) or non-ICU hospital ward, requiring high-flow oxygen or noninvasive ventilation and ICU, requiring intubation and mechanical ventilation—but without extracorporeal membrane oxygenation or other organ support) the death rate is clearly lower in patients treated with tocilizumab than placebo (17% [24/139] versus 28% [15/54]). A mortality rate of 17% is extremely low in this ICU population and contrasts with medical literature, which usually reports around 30% [19] and reached 60% in the beginning of the pandemic [29].

(ii) Concerning the non-severe COVID-19 group, the pooled OR was 1.46 the for control arm but did not reach statistical significance (95% CI 0.91–2.34; $p = 0.12$). Veiga et al.'s trial [9] was stopped early in July 2020 after an increase in deaths [30] and is the only RCT which raised the question that tocilizumab may possibly harm by increasing the risk of death. If on the one hand tocilizumab could possibly increase the risk of death in a population with a majority (60%) of non-ICU patients [9] but on the other hand tocilizumab decreased the risk of death in the majority of ICU patients [3, 11] we would not see an impact on mortality in a heterogeneous population as it is in most RCTs [5–8, 10]. However, Veiga et al.'s [9] results must be viewed with caution because of the sample size of the trial and considering that there were no significant differences on mortality at day 28. Concerning the four other RCTs in the non-severe COVID-19 group: (a) on the one hand EMPACTA [7] and CORIMUNO [8] had an OR close to 1 without benefit for tocilizumab in terms mortality; however, they both met their primary endpoint (a composite criteria including mortality and ventilation requirement), Salama et al. (EMPACTA) [7] and Hermine et al. (CORIMUNO) [8] concluded that there is a potential benefit of tocilizumab in

COVID-19; (b) but on the other hand RCT-TCZ (Salvarini et al.) [5] and BACC Bay (Stone et al.) [6] had an OR greater than 1.5 in favor of the control arm but with a wide confidence interval. These two RCTs concern a selected population of moderate-to-mild COVID-19 pneumonia. In Stone et al.'s trial [6] more than 95% of patients had a level of O_2 below 6 L/min delivered by nasal cannula or no oxygen administration at baseline. In Salvarani et al.'s trial [5] we do not have the detailed description of respiratory support at baseline; however, the median PaO_2/FiO_2 was greater than 250 mmHg (at 264.5 mmHg). This selected population of moderate COVID-19 pneumonia at baseline is in line with the low mortality rate in the total population in these two trial ($\leq$ 5%), in contrast to a proportion of 10–12% of deaths in Salama et al.'s and Hermine et al.'s trials [7, 8]. Any conclusion about RCT-TCZ and BACC Bay might not be generalized to all COVID-19 pneumonia.

Mechanical Ventilation Analysis

This meta-analysis shows that tocilizumab decreased the incidence of mechanical ventilation in hospitalized patients with COVID-19. This benefit was confirmed in both subgroups: severe COVID-19 group and non-severe COVID-19 group. The nine RCTs were included in this analysis. The only one RCT with an OR greater than 1 in favor of the control arm was RCT-TCZ [5] with wide confidence intervals and benefit cannot be ruled out. As previously described in a meta-analysis including the first five RCTs [13], our meta-analysis confirms that tocilizumab decreases the incidence of mechanical ventilation in hospitalized patients with COVID-19. In countries facing a huge challenge in terms of ICU beds while dealing with this outbreak, tocilizumab may be helpful to manage the crisis epidemic context in terms of public health [31].

Strengths and Limitations

This review has strengths and limitations that should be taken into account when interpreting the results. The major limitation of the subgroup meta-analysis is that it was performed on the mortality rate in the control group and not based on patients' severity. We chose a mortality rate of 17% in the control group (to divide RCTs into severe and non-severe COVID-19) which corresponds to the in-hospital mortality in the beginning of the pandemic among hospitalized adults with COVID-19 in the USA. This number was based on data from the first COVID-19 wave in the USA and therefore may reflect imperfections in management during that early stage (e.g., lack of widespread adoption of steroids, different intubation practices) rather than being a valid cutoff point for measuring COVID-19 severity in a population, especially a population studied later in the pandemic. However most of the RCTs included patients in the beginning of the pandemic in wealthy countries (especially North America and Europe) which is why we chose this proportion and we do not think that this point compromises the differential findings of this subgroup meta-analysis. Another limitation of the subgroup meta-analysis is the proportion of patients with corticosteroids administration. Several lines of evidence suggest that tocilizumab is particularly effective when corticosteroids are used [4]. In the subgroup meta-analysis, concerning the proportion of corticosteroids administered in the tocilizumab arm, three RCTs out of five in the subgroup non-severe COVID-19 versus one RCT out of four in the subgroup severe COVID-19 had a rate of corticosteroid administration of less than 50%. This difference could possibly impact the result of the subgroup meta-analysis. The strengths were that we used the well-established PRISMA process and the studies were rigorously identified via a double search by two independents reviewers, with the support of experienced methodologists (MP) and a biostatistician (AG) to ensure the right search terms and high-quality databases were used. We also improved the validity of the search by using PubMed for published articles and MedRχiv for unpublished articles. Despite this detailed approach, some relevant papers may have been missed because of the search strategy, the choice of databases, inconsistent search terminology, indexing

problems, or the filters used. However, we identified the same nine RCTs for inclusion as the most recent meta-analysis on this subject [32].

Definition of Optimal Group and Timing for Tocilizumab Administration in COVID-19

We Must Learn from the Past!

Early in the COVID-19 pandemic retrospective cohort studies suggest an association between tocilizumab and lower mortality or mechanical ventilation requirement [33–36], and these data were confirmed by a well-conducted meta-analysis of these cohorts [13]. Methodological bias alone was not enough to explain the gap between tocilizumab efficacy shown in retrospective cohort studies and the first RCTs' conclusions [13, 14, 17]. In fact, tocilizumab was mainly used as an off-label rescue treatment in critically ill patients with COVID-19 in retrospective cohorts such as in Brescia (Italy) [36] or in Nord Franche-Comté (France) [37].

Primum Non Nocere!

Tocilizumab administration in patients with COVID-19 with a low level of oxygen seems to be ineffective according to conclusions drawn by Stone et al. [6] and Salvarini et al. [5]. However, as we discussed above, the mortality rates in these two studies were below 5% and any conclusions should be treated with caution. On the contrary, tocilizumab seems to be effective in the severe COVID-19 group and in two RCTs of the non-severe COVID-19 group (EMPACTA [7] and CORIMUNO [8]). In the discussion below, we try to assess the optimal group and timing for tocilizumab administration in COVID-19 on the basis of these six RCTs [3, 4, 7, 8, 10, 11].

Concerning Respiratory Stage (Respiratory Support at Baseline)

EMPACTA [7] and CORIMUNO [8] trials are the RCTs with positive results (in favor of tocilizumab) with the less severe COVID-19 (overall mortality around 10–12%); both concerned patients before intubation stage (mechanical ventilation was a criterion of exclusion). In Hermine et al.'s trial (CORIMUNO) [8] all patients had a pneumonia with a level above 3 L of O_2 but before ICU care (no patients on non-invasive ventilation or high flow oxygen). In Salama et al.'s trial (EMPACTA) [7], 65% of patients received supplemental oxygen (but we do not have the details about oxygen flow) and 25% received noninvasive ventilation or high flow oxygen. At the opposite end, REMAP-CAP [3] is an RCT with positive results (in favor of tocilizumab) with the more severe COVID-19 at baseline (overall mortality around 32%). In REMAP-CAP tocilizumab reduced mortality in patients, 29% of whom were at intubation stage and 71% were before intubation stage (29% high flow nasal cannula and 42% with non-invasive ventilation only). Note that patients had to be enrolled within 24 h after starting organ support; however, we do not have the detailed outcome according to baseline category to analyze if there is any difference of response between intubated patients or patients before intubation stage at baseline; this would have been interesting. In RECOVERY [4], in the subgroup of patients with mechanical ventilation, the efficacy remains unclear: the mortality rate at day 28 was 47% (125/268) for tocilizumab versus 48% (142/294) for placebo with a median adjusted OR at 0.94 (95% CI 0.73 to 1.19). As in RECOVERY, in COVACTA there was also no clear benefit of tocilizumab use for patients at intubation stage at baseline (category 5 and 6 of the 7-category ordinal scale with an OR at 0.89 [0.30–2.57] and 1.00 [0.50–2.02], respectively) [4].

Concerning Inflammation Stage (Biological Findings at Baseline)

Patients with evidence of inflammation have a greater benefit from tocilizumab administration than patients without or with a lower level of inflammation [38, 39]. In REMAP-CAP [38], a secondary analysis of primary outcome according to C-reactive protein (CRP) tercile subgroups shows that the optimal response was found in the highest CRP tercile (OR 1.92 [1.12–3.34] with a probability of superiority to control of 99.1%). In RECOVERY [4] all patients had a CRP level of at least 75 mg/L. In COVACTA in

patients with high ferritin levels, tocilizumab decreased the probability of death or mechanical ventilation compared with placebo [39].

Optimal Group and Timing for Tocilizumab Administration

Treating patients with severe COVID-19 pneumonia with evidence of inflammation early seems to be the optimal population and timing for tocilizumab administration. On the basis of the discussion above, we think that tocilizumab must be discussed in addition to corticosteroids in patients with hypoxemia and biological inflammation (especially at a CRP level of 75 mg/L or above; and a level of O_2 flow greater than 3 L/min) until early after intubation in patients on mechanical ventilation (especially during the first 24 h). ICU patients with O_2 flow of at least 6 L/min or noninvasive ventilation or high flow nasal cannula seem to have the greatest benefit from tocilizumab administration. The benefits of tocilizumab remain uncertain and it could cause harm at O_2 flow below 3 L/min and later after intubation.

CONCLUSION

This meta-analysis confirmed that tocilizumab is effective in hospitalized patients with COVID-19 and hypoxemia by improving survival and decreasing mechanical ventilation requirement. The greatest benefit is observed in patients with severe COVID-19.

ACKNOWLEDGEMENTS

The authors thank Mrs Charlotte Bourgoin and Elodie Bouvier for their strong implication in the present work. They also thank the management team of the Hospital Nord Franche-Comté and the pharmacists team for having made available tocilizumab outside its approved indication. Special acknowledgements to the whole HNFC tocilizumab multidisciplinary team and to all the physicians, caregivers (nurses and orderlies), and patients.

Funding. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The Journal's Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Timothée Klopfenstein, Souheil Zayet, and Vincent Gendrin drafted the manuscript. Aurélie Gerazime and Marc Puyraveau performed the statistical analysis. All authors revised the final manuscript.

Disclosures. All authors confirm that they have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The data presented are available on request from the corresponding author.

APPENDIX

Figures7, 8, 9, 10, and 11.

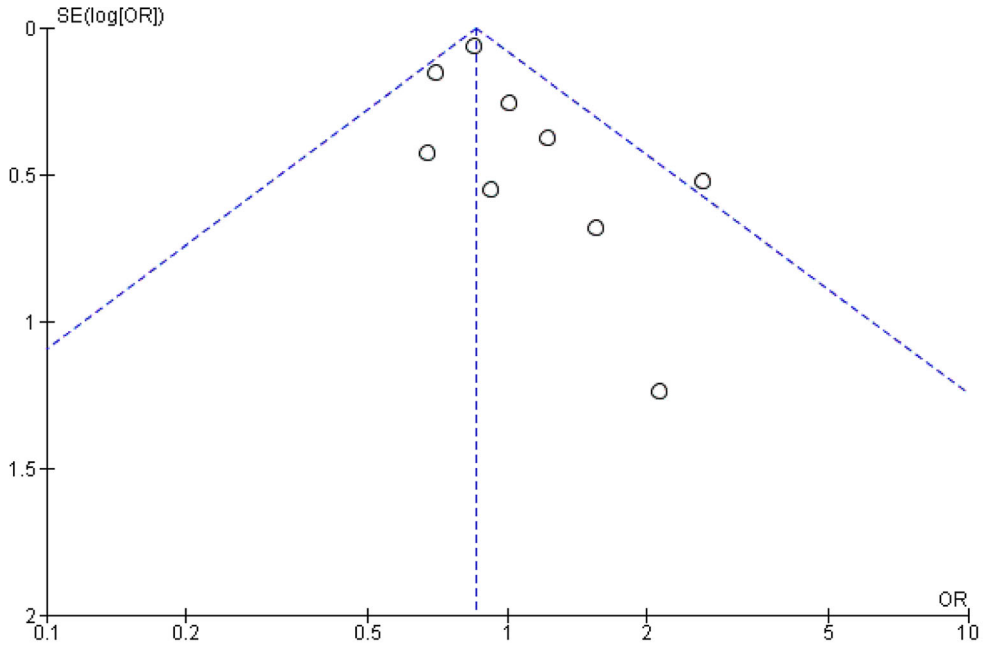

Fig. 7 Funnel plot for the effect of tocilizumab on mortality at days 28–30 in randomized trials

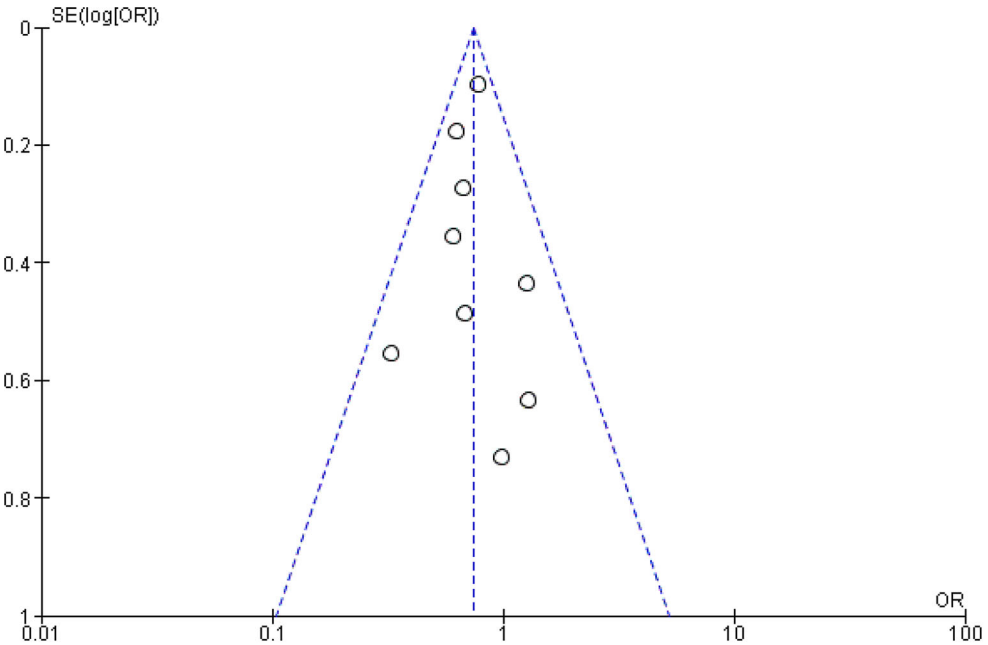

Fig. 8 Funnel plot for the effect of tocilizumab on mechanical ventilation incidence at days 28–30 in randomized trials

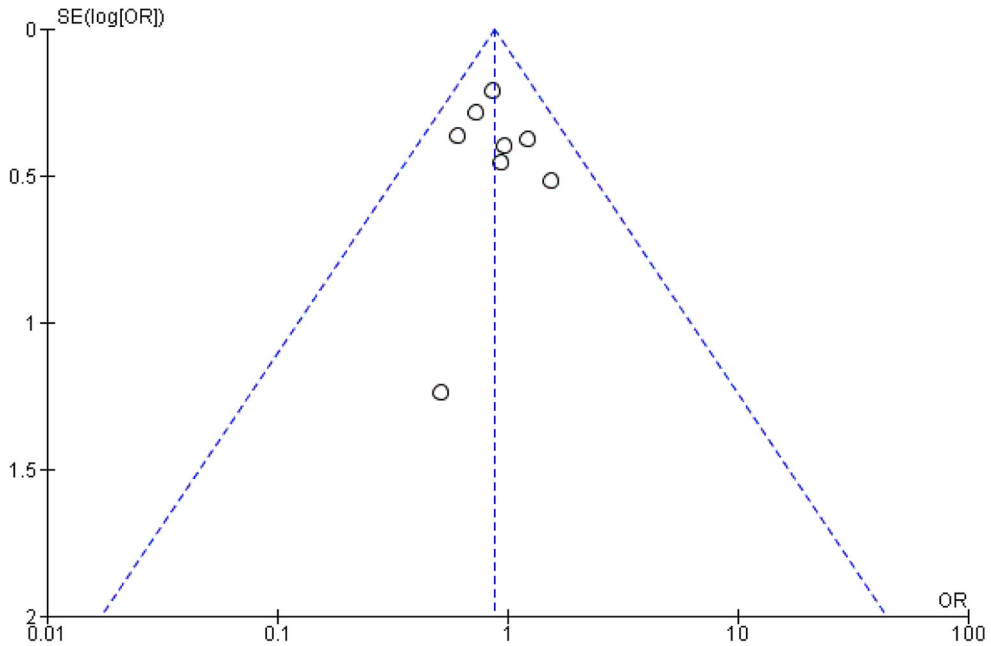

Fig. 9 Funnel plot for relative risk of serious adverse events for tocilizumab versus control in randomized trials

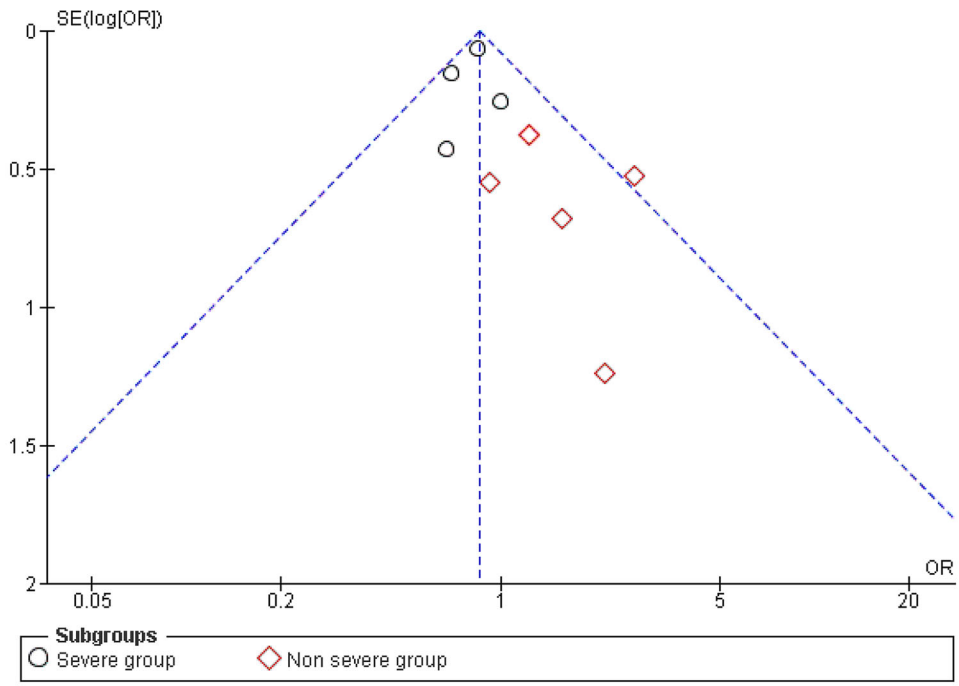

Fig. 10 Funnel plot for the effect of tocilizumab on mortality at days 28–30 in randomized trials in severity event subgroup

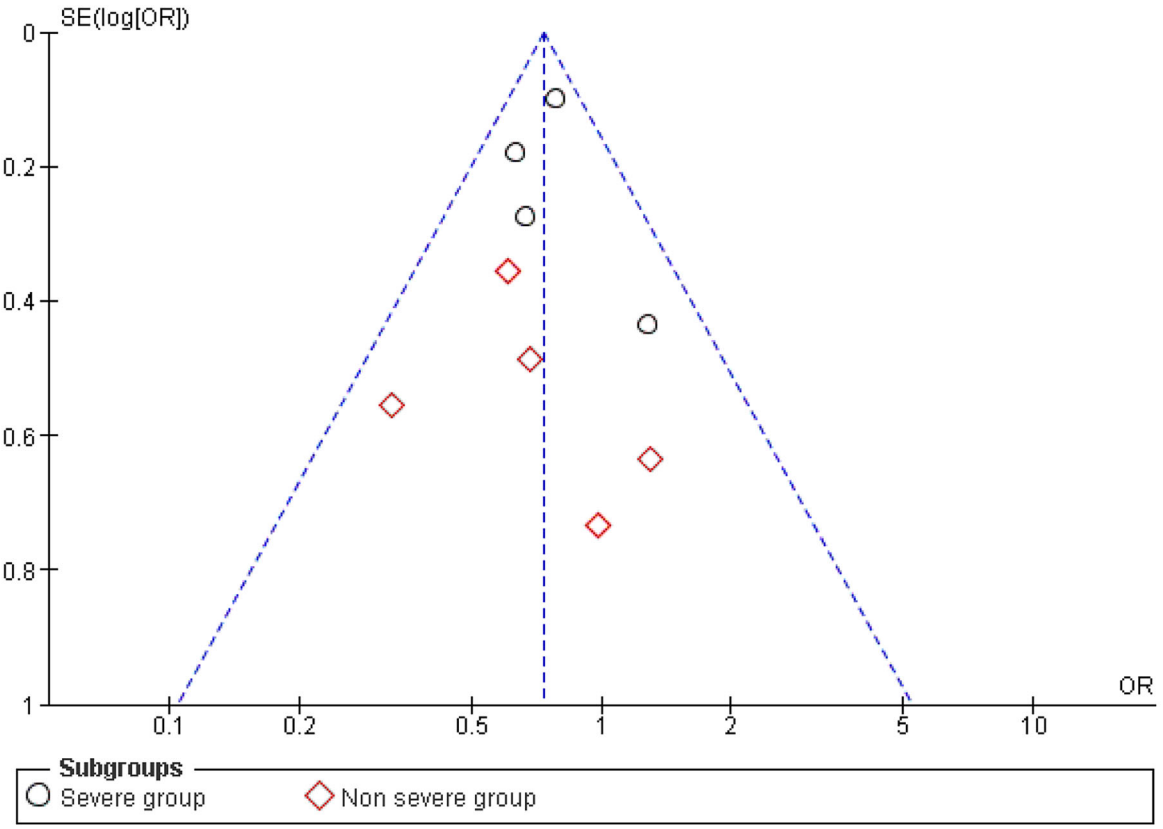

Fig. 11 Funnel plot for the effect of tocilizumab on mechanical ventilation incidence at days 28–30 in randomized trials in severity event subgroup

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