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REVIEW

Tocilizumab for treating COVID-19: a systemic review and meta-analysis of retrospective studies

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Abstract

Objectives COVID-19 has become a global epidemic, and effective therapies have not been discovered up to now. We conducted this study to explore the effectiveness and safety of tocilizumab recently used for treating COVID-19.

Method A comprehensive search was conducted (up to September 27, 2020), and 19 eligible records were identified according to the inclusion and exclusion criteria. The data of the studies were extracted by 2 independent reviewers and were analyzed to evaluate the safety and availability of tocilizumab for treating COVID-19.

Results Thirteen retrospective case-control studies ($n = 2285$ patients) and 6 retrospective single-armed studies ($n = 208$) were retrieved in this study. In the comparison of tocilizumab treatment group (TCZ) and standard treatment group (ST), significant associations with a lower risk of admission to ICU, use of ventilation, and mortality (OR, 95% CI: 0.53, 0.26~1.09; 0.66, 0.46~0.94; 0.44, 0.36~0.55) were found in the tocilizumab treatment group. What is more, patients treated with tocilizumab had better clinical improvement compared with the patients treated with ST (OR, 1.24; 95% CI, 0.96~1.62). After taking tocilizumab, the patients had lower C-reactive protein (CRP), white blood cell count (WBC), aspartate aminotransferase (AST) (WMD, 95% CI: − 99.66, − 156.24~− 43.09; − 0.95, − 1.8~− 0.11; − 12.58, − 18.88~−6.29) but higher troponin (WMD, 7.61; 95% CI, 3.06~12.15) than before. In addition, tocilizumab did not have significant influence on patients' neutrophil count (Neut), lymphocyte count (Lymp), platelet count (Plt), alanine aminotransferase (ALT), and creatine (WMD, 95% CI: − 0.29, − 2.91~2.33; 0.42, − 0.23~1.07; 5.2, − 2.85~13.25; 22.49, − 2.73~47.7; − 44.78, − 93.37~3.81).

Conclusion Tocilizumab may have potential effectiveness to treat COVID-19 according to the results of this study. However, more large-scale studies are needed for more accurate conclusions.

Keywords Tocilizumab · IL-6 blockade · COVID-19 · Meta-analysis

Introduction

Since December 2019, the global epidemic of novel coronavirus disease 2019 (COVID-19) had infected over 30,000,000 people worldwide up to September 27, 2020. COVID-19 can result in interstitial pneumonia with respiratory failure, which is the principal cause of death [1]. There is no widely approved medicine for treating this deadly infectious disease as yet.

In recent months, several case reports or case series [2–5] indicated that interleukin-6 receptor antagonist tocilizumab successfully improved the clinical manifestations of sever patients infected by COVID-19. There were also several retrospective case-control and single-armed studies that reported the outcomes of using tocilizumab for treating COVID-19. However, the results of those studies have not been systemically reviewed and analyzed. Thus, we collected and

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summarized those studies to explore the effectiveness and safety of tocilizumab recently used for treating COVID-19.

Materials and methods

Literature search

A comprehensive search using (tocilizumab) OR (anti-IL-6 monoclonal antibody) OR (IL-6 blockade) OR (IL-6 receptor antagonist) AND (COVID-19) OR (novel coronavirus disease) OR (SARS-CoV-2) was conducted by 2 authors using PubMed, Embase, Medline, and Cochrane (up to September 27, 2020), and the language was limited to English.

Selection criteria

The studies searched in three databases were included by the following criteria: (1) patients had a definite diagnosis of COVID-19 infection; (2) patients received tocilizumab treatment; and (3) sufficient data were provided for clinical outcomes. Additionally, unqualified studies were excluded by the following criteria: (1) case reports, reviews, editorials, and letters; (2) duplicate records; and (3) studies with insufficient data.

Data extraction and quality assessment

Two authors extracted necessary information from each included study: first author, publication year, sample size, gender, clinical outcomes of TCZ group, ST group, and pre-TCZ and post-TCZ. The quality of each study was not assessed because of the extremely insufficiency of data of the included studies.

Statistical analysis

In the retrospective case-control studies, odds ratios (ORs) of admission to ICU, use of ventilation, mortality, and clinical improvement were calculated to compare the effectiveness between tocilizumab treatment and standard treatment.

In the retrospective single-armed studies, weighted mean differences (WMDs) of CRP, procalcitonin, WBC count, AST, troponin, Neut count, Lymp count, Plt count, ALT, and creatine were compared between pre-TCZ and post-TCZ to assess the safety of tocilizumab on the blood system, inflammatory reaction, heart, liver, and kidney.

Formula SD ≈ Norm IQR = $(P_{75\text{-}} - P_{25}) \times 0.7413$ [6] was used to calculate the SD of the outcomes.

The heterogeneity of the results was estimated using the Q test and I^2 statistics. The fixed pooling model was used when $I^2 \leq 50\%$; otherwise, the random pooling model was selected. WMD < 0 suggested a decrease in indicator after taking tocilizumab. OR < 1 indicated favorable outcomes of admission to ICU, use of ventilation, and mortality but poor clinical improvement in TCZ group. These calculations were completed using Stata v.16.

Results

Characteristics of the included studies

The procedures used to screen eligible studies are shown in Fig. 1. Nineteen articles with 2493 patients were included. The details of the 19 included studies are summarized in Table 1, and all the calculated outcomes are shown in Table 2.

TCZ VS ST

Thirteen studies and 2285 patients were included to compare the outcomes between TCZ and ST groups. The ORs for admission to ICU, use of ventilation, mortality, and clinical improvement between TCZ and ST were shown in Fig. 2 and Fig. 3. Lower rate of admission to ICU, use of ventilation, and mortality and higher rate of clinical improvement were identified in the TCZ group.

Changes of clinical indicators after taking tocilizumab

After taking tocilizumab, the value of CRP significantly decreased (Fig. 4). In the blood system, the WBC count, Neut count, Lymp count, and Plt count were not obviously influenced by tocilizumab (Fig. 5). In addition, Fig. 6 showed that the value of AST significantly decreased and troponin increased after taking tocilizumab. However, the level of ALT and creatine were not significantly affected.

Sensitivity analysis

Sensitivity analysis of the OR for mortality between the TCZ and ST groups was calculated to evaluate the robustness of the results. Figure 7 indicates that the results would not be obviously changed by deleting any included study.

Discussion

Pneumonia is the most common clinical manifestation of COVID-19 infection, and 6–10% of the patients can evolve into respiratory failure, requiring mechanical ventilation or positive airway pressure therapy [26]. Dawei Wang [27] reported that the acute respiratory distress syndrome (ARDS) caused by COVID-19 may have associations with cytokine storm syndrome. Fei Zhou [28] also

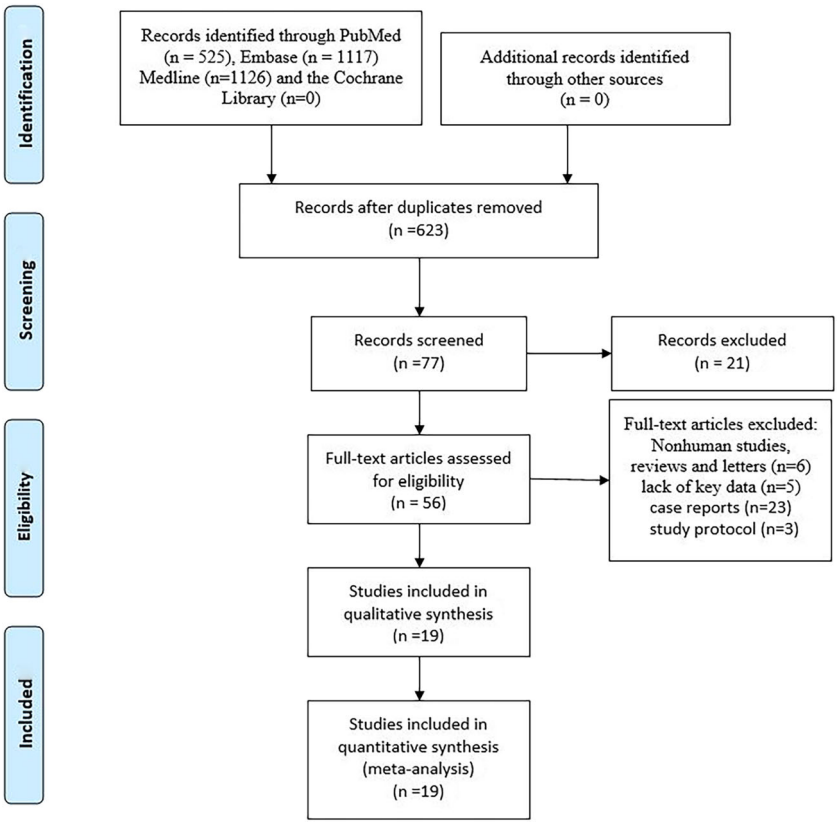

Fig. 1 PRISMA flow diagram of procedures used to screen eligible studies

reported that higher IL-6 was associated with more frequency mortality. Therefore, tocilizumab, as the IL-6 receptor antagonist, is used for treating COVID-19 in more and more therapeutic centers. Until now, studies

Table 1 Characteristics of the included studies

First author	Year	Sample size	Sex (male %)	Study type	Comparison
Corrado Campochiaro [7]	2020	65	86.15	Retrospective case-control study	TCZ group VS ST group
Ruggero Capra [8]	2020	85	75%	Retrospective case-control study	TCZ group VS ST group
Luca Quartuccio [9]	2020	111	78.60%	Retrospective case-control study	TCZ group VS ST group
Marta Colaneri [10]	2020	111	73.21%	Retrospective case-control study	TCZ group VS ST group
Timothée Klopfenstein [11]	2020	45	NA	Retrospective case-control study	TCZ group VS ST group
Mar Masia [12]	2020	138	61.6%	Retrospective case-control study	TCZ group VS ST group
Laetitia Albertini [13]	2020	44	70.5%	Retrospective case-control study	TCZ group VS ST group
Noa Biran [14]	2020	630	69.2%	Retrospective case-control study	TCZ group VS ST group
Giovanni Guaraldi [15]	2020	544	66%	Retrospective case-control study	TCZ group VS ST group
Tariq Kewan [16]	2020	65	61%	Retrospective case-control study	TCZ group VS ST group
Lorenzo M. Canziani [17]	2020	128	73%	Retrospective case-control study	TCZ group VS ST group
Yojana Gokhale [18]	2020	161	62.1%	Retrospective case-control study	TCZ group VS ST group
Nicola De Rossi [19]	2020	158	71.5	Retrospective case-control study	TCZ group VS ST group
Xiaoling Xu [20]	2020	21	85.70%	Retrospective single-armed study	Pre-TCZ VS post-TCZ
Nahéma Issa [21]	2020	10	NA	Retrospective single-armed study	Pre-TCZ VS post-TCZ
Rand Alattar [22]	2020	25	92%	Retrospective single-armed study	Pre-TCZ VS post-TCZ
Paola Toniati [23]	2020	100	88%	Retrospective single-armed study	Pre-TCZ VS post-TCZ
Betul Borku Uysal [24]	2020	12	50%	Retrospective single-armed study	Pre-TCZ VS post-TCZ
Muhammad Zain Mushtaq [25]	2020	40	82.5%	Retrospective single-armed study	Pre-TCZ VS post-TCZ

TCZ, tocilizumab; ST, standard treatment; NA, not accessible

Table 2 Clinical outcomes of using tocilizumab

TCZ group and ST group					
Outcomes	Numbers of included studies (sample size)	OR	95% CI	I^2	p value
Admission to ICU	3(295)	0.53	(0.26, 1.09)	65.5%	0.055
Use of ventilation*	6(911)	0.66	(0.46, 0.94)	73.1%	0.002
Mortality***	13(2227)	0.44	(0.36, 0.55)	69.1%	< 0.001
Clinical improvement	6(996)	1.24	(0.96, 1.62)	48.8%	0.082
Pre-TCZ and post-TCZ					
Outcomes	Numbers of included studies (sample size)	WMD	95% CI	I^2	p value
CRP (mg/L) ***	5(196)	− 99.66	(− 156.24, − 43.09)	96.2%	< 0.001
WBC count (10^9/L) *	3(57)	− 0.95	(− 1.8, − 0.11)	0%	0.027
Neut count (10^9/L)	3(137)	− 0.29	(− 2.91, 2.33)	93%	0.828
Lymp count (10^9/L)	3(137)	0.42	(− 0.23, 1.07)	92.20%	0.204
Plt count (10^10/L)	3(137)	5.2	(− 2.85, 13.25)	91.40%	0.206
ALT (U/L)	3(137)	22.49	(− 2.73, 47.7)	84.80%	0.08
AST (U/L) ***	3(137)	− 12.58	(− 18.88, − 6.29)	7.90%	< 0.001
Troponin (ng/L) **	2(112)	7.61	(3.06, 12.15)	0%	0.001
Creatine (umol/L)	3(137)	− 44.78	(− 93.37, 3.81)	79.90%	0.071

CI, confidence interval; WMD, weighted mean differences; OR, odds ratio; TCZ, tocilizumab; ST, standard treatment; ICU, intensive care unit; CRP, C-reactive protein; WBC, white blood cell; Neut, neutrophil; Lymp, lymphocyte; Plt, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

focused on the effectiveness and safety of tocilizumab for treating COVID-19 have not been systemically analyzed. Therefore, we reviewed and summarized these studies for more accurate conclusions.

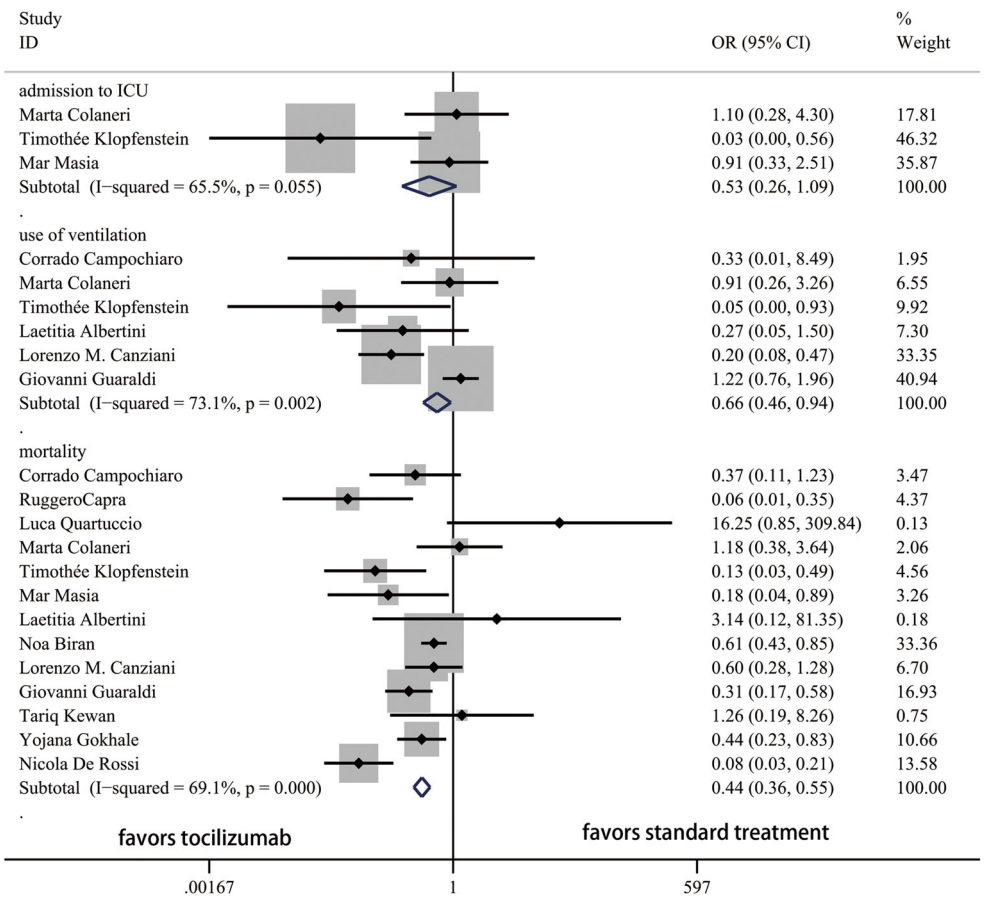

Fig. 2 Forest plot of ORs for admission to ICU, use of ventilation, and mortality between TCZ and ST. ICU, intensive care unit; OR, odds ratio; CI, confidence interval

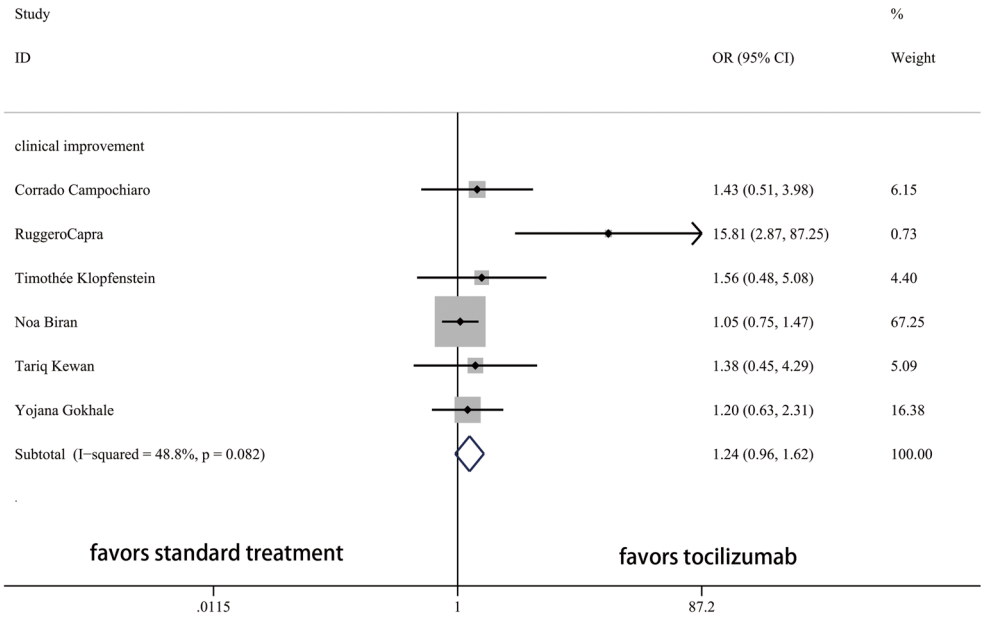

Fig. 3 Forest plot of ORs for clinical improvement between TCZ and ST. OR, odds ratio; CI, confidence interval

TCZ group have more favorable clinical outcomes compared with the ST group. Lower rate of admission to ICU, use of ventilation, and mortality and higher rate of clinical improvement were identified in this study, which is consistent with the conclusions from the case reports and case series [2–5]. By binding to human IL-6 receptor, tocilizumab competitively inhibits IL-6 signaling [29] and prevents the cytokine storm of patients infected COVID-19. After taking tocilizumab, the serum CRP significantly decreased, which is consistent with the outcomes of treating rheumatoid arthritis, Castleman disease, and Crohn disease [29].

In the blood system, tocilizumab does not have obvious influence on the neutrophil count, lymphocyte count, and platelet count. Despite a significant decrease of WBC was identified after taking tocilizumab, we cannot conclude that tocilizumab has effect on reducing WBC count because of the rarity of high WBC count in patients with COVID-19.

AST was apparently lower than before taking tocilizumab, and ALT was similar with before. A meta-analysis conducted by Mark C. Genovese indicated that transaminase elevations with tocilizumab were frequent [30], which is not consistent with the result of our study. More studies are needed to investigate the effect of tocilizumab on hepatic function. In addition, tocilizumab did not have significant influence on patients' creatine according to the result obtained from this study.

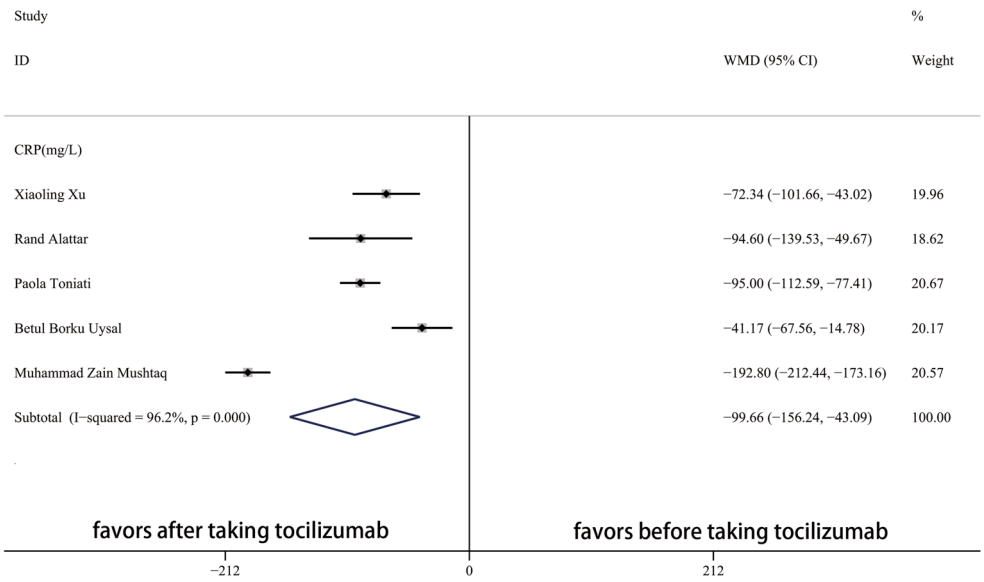

Fig. 4 Forest plot of WMDs for CRP between pre-TCZ and post-TCZ. CRP, C-reactive protein; WMD, weighted mean differences; CI, confidence interval

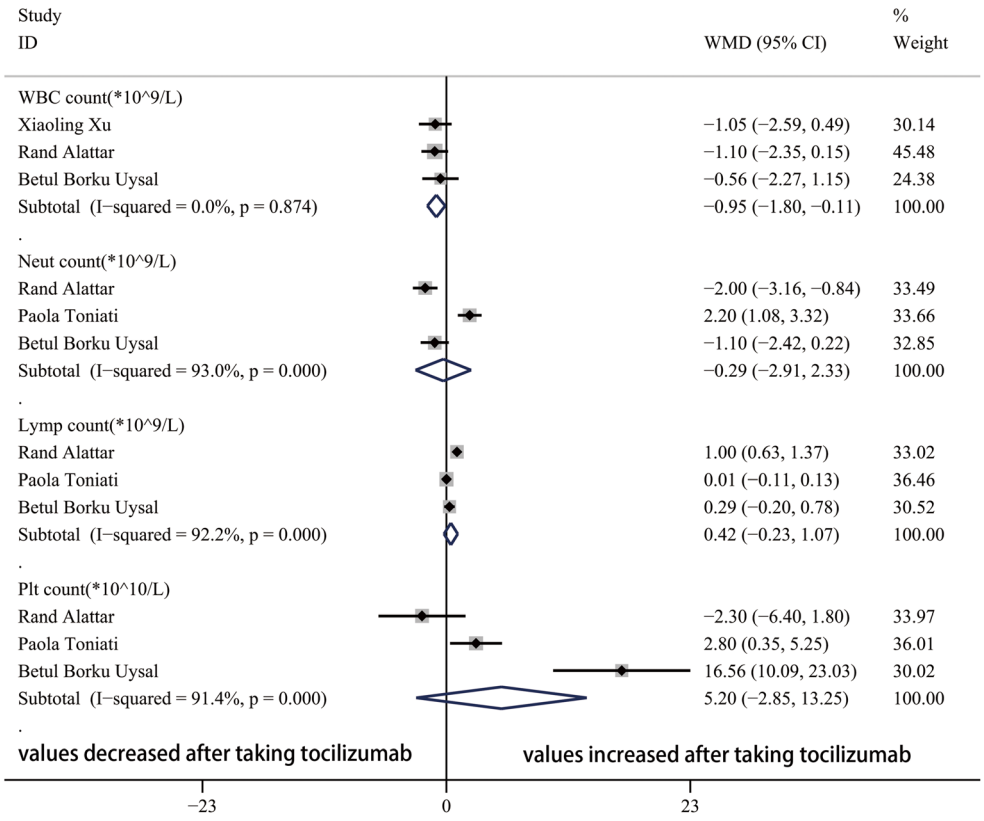

Fig. 5 Forest plot of WMDs for WBC count, Neut count, Lymp count, and Plt count between pre-TCZ and post-TCZ. WBC, white blood cell; Neut, neutrophil; Lymp, lymphocyte; Plt, platelet; WMD, weighted mean differences; CI, confidence interval

Cardiac injure is common (19.7%) among hospitalized patients with COVID-19 [31], and cardiac troponin I levels were significantly higher in those with severe COVID-19 infection compared with those with non-severe disease [32]. In this meta-analysis, troponin significantly increased after taking tocilizumab. Whether tocilizumab or the progression of the

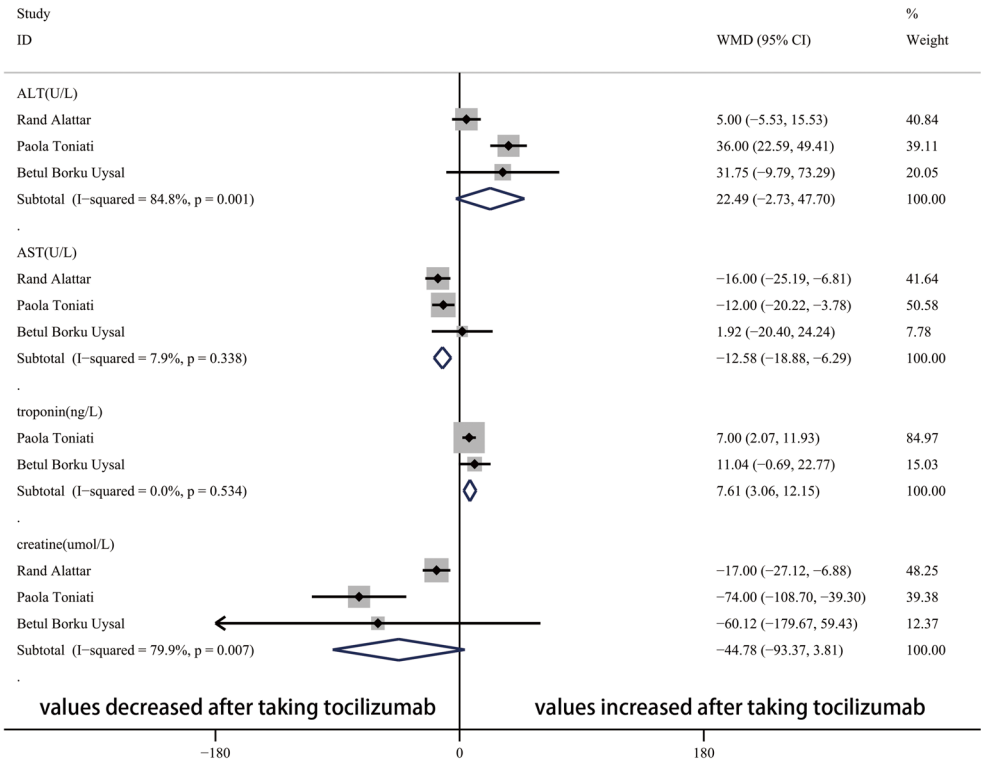

Fig. 6 Forest plot of WMDs for ALT, AST, troponin, and creatine between pre-TCZ and post-TCZ. ALT, alanine aminotransferase; AST, aspartate aminotransferase; WMD, weighted mean differences; CI, confidence interval

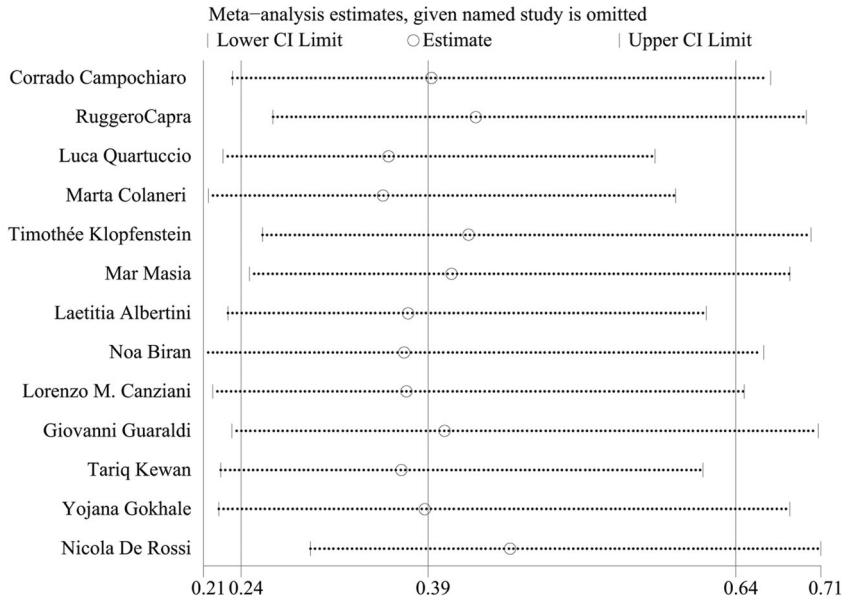

Fig. 7 Sensitivity analysis of studies on mortality between TCZ and ST

disease caused the elevated troponin remains unclear. More RCTs focused on the comparison of troponin between taking tocilizumab group and no-taking group are needed to figure out whether tocilizumab has cardiac toxicity.

No adverse events after taking tocilizumab were reported in the included studies. But toxic erythema, eosinophilia, and hypertriglyceridemia [33, 34] were reported by two case reports after taking tocilizumab. What is more, intestinal perforation should be noticed when using tocilizumab to treat COVID-19 [35].

Limitations

First, the sample size of this study was extremely small, which results in the high heterogeneities of several observational indicators, low robustness of the results, and low reliability of the conclusion. Second, all the included studies were retrospective observational studies. In retrospective case-control study, it is impossible to match the baseline characteristics of TCZ and ST groups, which may result in severe selection bias. In retrospective single-armed study, it is difficult to conclude that the improvement or deterioration of the laboratory indexes were caused by the effect of tocilizumab or the progression of the disease itself because of the absence of the control group. Third, in the situation of COVID-19 pandemic with no specific therapy drug available, studies with positive conclusions are more easily to be published, which may result in obvious publication bias. Although publication bias was not assessed because of the limited number of included studies, it does not mean there is no publication bias in this meta-analysis. Fourth, the data of each included study is insufficient.

Conclusion

Tocilizumab may have potential effectiveness to treat COVID-19 according to the results of this study. However, more large-scale studies are needed for more accurate conclusions because of the limited sample size of this study.

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Authors' contributions MZ and JYL collected and analyzed the data and wrote the paper; YHT and YWD collected and analyzed the data; JXZ and YHW revised the whole paper. All authors reviewed the final paper. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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