Decreased mortality in COVID-19 patients treated with Tocilizumab: a rapid systematic review and meta-analysis of observational studies

Jishnu Malgie[1], Jan W. Schoones[2], Bart G Pijls[1]

1) Department of Orthopaedics, Leiden University Medical Center, Leiden, The Netherlands. Albinusdreef 2; 2300 RC, Leiden, The Netherlands; P.O. Box 9600, Postzone J-11-S

2) Walaeus Library, Leiden University Medical Centre, Leiden, The Netherlands

Albinusdreef 2; 2300 RC, Leiden, The Netherlands; P.O. Box 9600

Corresponding author: Jishnu Malgie

E-mail corresponding author: jishnu.malgie@gmail.com

Main point:

Meta-analysis on 10 observational studies showed that mortality was 12% lower for COVID-19 patients treated with tocilizumab compared to COVID-19 patients not treated with tocilizumab. The number needed to treat was 11: for every 11 COVID-19 patients treated with tocilizumab 1 death appears to be

Abstract

Background: We systematically reviewed the literature to answer the following research questions: 1) does IL-6 (receptor) antagonist therapy reduce mortality in COVID-19 patients compared to patients not treated with IL-6 (receptor) antagonists and 2) is there an increased risk of side effects in COVID-19 patients treated with IL-6 (receptor) antagonists compared to patients not treated with IL-6 (receptor) antagonists?

Methods: We systematically searched PubMed, PMC PubMed Central, MEDLINE, WHO COVID-19 Database, Embase, Web-of-Science, COCHRANE LIBRARY, Emcare and Academic Search Premier (until June 30th2020). Random effects meta-analysis was used to pool the risk ratio and risk difference of individual studies. Risk of bias was appraised using the MINORS checklist

Results: The search strategy retrieved 743 unique titles of which 10 studies (all on tocilizumab) comprising 1358 patients were included. Nine out of ten studies were considered to be of high quality. Meta-analysis showed that the tocilizumab group had lower mortality than the control group. The risk ratio (RR) was 0.27 95%CI 0.12 to 0.59 and the risk difference (RD) was 12% 95%CI 4.6% to 20% in favour of the tocilizumab group. With only a few studies available there were no differences observed regarding side effects.

Conclusions: Our results showed that mortality was 12% lower for COVID-19 patients treated with tocilizumab compared to COVID-19 patients who were not treated with tocilizumab. The number needed to treat was 11, suggesting that for every 11 (severe) COVID-19 patients treated with tocilizumab 1 death is prevented. These results require confirmation by randomized controlled trials.

Keywords: COVID-19; mortality; IL-6 receptor antagonists; tocilizumab

Introduction

COVID-19 or the disease caused by the SARS-CoV-2 coronavirus has caused a pandemic with serious medical and economic consequences around the world. As of July 16th more than 13 million patients have been diagnosed with COVID-19 and more than 587.000 of them have died.[1] It is therefore paramount that treatments are discovered and become available to reduce disease severity and mortality caused by COVID-19.

Some reports have shown that immune response (inflammation) markers such as interleukin-6 (IL-6) are associated with disease severity and mortality in COVID-19 patients.[2, 3] Importantly, IL-6 can be antagonized by IL-6 receptor antagonists such as tocilizumab and sarilumab, or by IL-6 antagonists such as siltuximab. These compounds may therefore be considered as possible candidates for treatment of COVID-19 patients and early case-series are cautiously optimistic.[4, 5] Improvement of clinical and biochemical signs of hyper-inflammation and cytokine storm has been observed after treatment with tocilizumab resulting in a significant improvement in the levels of ferritin, C-reactive protein and D-dimer.[5] Given this proposed pathophysiological mechanism and early observations, a systematic review on the treatment effect and its possible side effects is required to establish the evidence-base for IL-6 (receptor) antagonists. We therefore systematically reviewed the literature to answer the following research questions: 1) does IL-6 (receptor) antagonist therapy reduce mortality in COVID-19 patients compared to patients not treated with IL-6 (receptor) antagonists and 2) is there an increased risk of side effects in COVID-19 patients treated with IL-6 (receptor) antagonists compared to patients not treated with IL-6 (receptor) antagonists?

Methods

The reporting of this meta-analysis is in accordance with the PRISMA statement.[6] We produced a short working protocol before the start of the study. However, due to the rapid review design this protocol was not registered at e.g the Prospero registry. We initially set out to search the literature on studies comparing either IL-6 receptor antagonists (tocilizumab, sarilumab), or IL-6 antagonists (siltuximab) to a control group, but only studies on tocilizumab were identified. Hence this review will focus on tocilizumab.

The population of interest consisted of COVID-19 patients treated with tocilizumab (TCZ, intervention group) ant patients not treated with tocilizumab as the control group. The primary outcome was mortality, expressed as the number of patients who died within the study period. The secondary outcomes were mortality after ICU admission, mortality after mechanical ventilation, days to recovery, days on ICU, days on mechanical ventilator support and possible side effect of the tocilizumab treatment such as secondary infection, neutropenia, intestinal perforation and impaired liver function.

Data sources and searches

The search strategy was composed in collaboration with a librarian (JS). The following databases were searched from their inception up to June 30th 2020: PubMed, PMC PubMed Central, MEDLINE, WHO COVID-19 Database, Embase, Web of Science, COCHRANE LIBRARY, Emcare and Academic Search Premier. The search strategy consisted of the following components, each defined by a combination of controlled vocabulary and free text terms:

1 anti-IL-6 treatment

2 COVID-19

The full search strategy is provided in the Appendix.

Study Selection

Studies identified by the search strategy were screened on title and abstract. This screening was performed by two reviewers (JM and BP) independently. Both reviewers recorded their findings in a pre-designed electronic database. Both databases were then compared and any disagreements were resolved by consensus. When the information in the abstract did not suffice, or if any doubt remained, the studies remained eligible.

The full text articles of eligible studies were independently evaluated by two reviewers (JM and BP). Both recorded their findings in a pre-designed electronic database. Any disagreements were resolved by consensus.

All bibliographic records identified through the electronic searches were collected in an electronic reference database and subjected to the following inclusion and exclusion criteria:

Inclusion criteria:

1) COVID-19 clinical patient study
2) Anti-IL-6 therapy versus non-anti-IL-6 therapy with a minimum of 5 patient in each treatment arm

Exclusion criteria:

1) No data on primary or secondary outcomes comparing anti-IL-6 therapy to non-anti-IL-6 therapy
2) anti-IL-6 therapy reserved for severe or cytokine storm patients (severe and apparent confounding by indication), while mild patients get standard therapy
3) Language not spoken by review team

Data extraction and Quality Assessment

Two reviewers (JM and BP) independently extracted data and appraised the risk of bias from included studies regarding the primary and secondary outcomes, patient demographics and study characteristics in a pre-defined electronic data sheet. The data sheet was designed during the extraction of trial data on a random sample of eligible studies. Any disagreements were resolved by consensus.

Risk of bias was appraised using the MINORS checklist.[7] MINORS is specifically designed to assess the methodological quality of non-randomized studies, as we did not expect to find any randomized controlled trials during the rapid review period.[7] An MINORS item scored 0 if not reported, 1 if reported but not adequate and 2 if reported and adequate. With 12 items this gives a maximal possible score of 24 points. We

considered a study of high quality if the total MINORS score was 17 or more and low quality if the total score was less than 17.[8]

Data Synthesis and Analysis

For the meta-analysis we used a random effects model to pool the risk ratio and risk difference of individual studies in order to estimate an overall risk ratio and risk difference (absolute risk difference) along with their associated confidence intervals.[9] The risk difference was included, because it is an appropriate solution for the empty cell problem and it allows calculation of the number needed to treat (NNT).[10, 11] The amount of statistical heterogeneity was assessed through visual inspection of the forest plots and by calculating I^2 statistics.[12] The I^2 statistic estimates how much of the total variability in the effect size estimates is due to heterogeneity among the true effects. In the presence of heterogeneity, and if the data allowed, we performed a random effects meta-regression on pre-defined factors (study level covariates). All analyses were performed using Metafor Package R statistics.[13]

We constructed a funnel plot for studies reporting the primary outcome to assess the amount of publication bias. In case the funnel plot was asymmetric, we used a trim-and-fill to explore the magnitude and direction of the publication bias.

Results

Study selection and study characteristics

The search strategy retrieved 1686 hits of which 743 were unique (no double entries for different databases). After selection 10 studies were included with a total of 554 patients (95 deaths) who received tocilizumab and 804 patients (222 deaths) in the control group who did not received tocilizumab.[14-23] Details of the study selection and the flowchart of the review are shown in Figure 1.

From the included studies four were from Italy, three from the USA, two from Spain and one from France. Details of included studies are shown in Table 1. On a study level, there were baseline differences between the TCZ group and control group regarding age, percentage of men, and percentage of comorbidities. However a

systematic difference between the TCZ and control groups regarding these baseline characteristics was not apparent. Based on the higher CRP and the lower PaO2-FiO2 ratio for the TCZ group, the TCZ group appeared to be more severely affected by COVID-19 at baseline than the control group, see Table 1.

Risk of bias

Details on the risk of bias are presented in Table 2. The mean MINORS score was 18.7 (range 13-21) out of 24 points. Nine studies were considered to be of high quality with a MINORS score of 17 or higher and one study was considered of low quality, which was mostly due to non-reporting.

Synthesis of the results and sensitivity analyses

Primary outcome: a summary of the data-synthesis is presented in Table 3. The TCZ group had lower mortality than the control group based on 10 studies with 1358 patients: the risk ratio (RR) was 0.27 95%CI 0.12 to 0.59 and the risk difference (RD) was 12% 95%CI 4.6% to 20% in favour of the TCZ group, see Figure 2. This risk difference for mortality translates into a number needed to treat (NNT) of 8 95%CI 5 to 22. There was substantial heterogeneity I^2 of 61%. Upon inspection of the forest plot this heterogeneity appeared to be caused by a single study [16], so a sensitivity (outlier) analysis was necessary. Leaving out this outlier gave low heterogeneity (I^2 of 19%) and gave similar results to the full analyses: RR 0.34 (95%CI 0.18 to 0.66) compared to 0.27 and RD 9.9% (95%CI 4.7% to 15%) compared to 12%. The outlier study did not use glucocorticoids while most other studies did use them, see Table 4 for details on co-medication use for each study.

The sensitivity analyses revealed that glucocorticoids and lopinavir and ritonavir were effect modifiers for risk of mortality between the TCZ and control group. In studies that used glucocorticoids the treatment effect of TCZ on mortality was smaller compared to studies that did not use glucocorticoids (I^2 =33%): the RD was 9.1% 95%CI 2.8% to 15% in favour of the TCZ group compared to a RD of 31% 95%CI 15% to 47% % in favour of the TCZ group. In studies that used lopinavir and ritonavir the treatment effect of TCZ on mortality was larger compared to studies that did not use lopinavir and ritonavir (I^2 =46%): the RD was 19% 95%CI 9.2% to 28% in favour of the TCZ group compared to a RD of 4.5% 95%CI 5.9% to 15% % in favour of the TCZ group. Since

there was overlap in the use of glucocorticoids and lopinavir and ritonavir, see Table 4, we created 3 co-medication groups. The results of this sub-group analysis are presented in Figure 3 (I^2 =17%) . For studies that used glucocorticoids without lopinavir and ritonavir there was no longer a difference in mortality between the TCZ and control group. For studies that used lopinavir and ritonavir either with or without glucocorticoids the TCZ group had lower mortality than the control group. Remdesivir, Azythromycin, anti-coagulation medication, and hydroxychloroquine were no effect modifiers.

The funnel plot showed some asymmetry so a trim and fill analysis was warranted, which revealed a minor influence of possible publication bias: RR 0.33 (95% CI 0.17 to 0.63) compared to 0.34 and RD 9.4% (95%CI 4.2% to 15%) compared to 9.9%. When restricting the analyses to high quality studies with a MINORS score of 20 points or more (6 studies), the risk difference was 15.7% (95%CI 5.7% to 25.7%) in favour of TCZ and the relative risk was 0.17 (95%CI 0.05 to 0.58) in favour of TCZ.

Three studies presented adjusted analyses for baseline imbalances regarding demographics and disease severity to account for differences at baseline. These analyses confirmed the lower mortality for the TCZ group: Hazard ratio 0.38[18], Hazard ratio 0.58[23] and Odds ratio 0.78[17].

Meta-regression on demographic variables showed that differences in age and sex did not influence the observed difference in treatment effects of TCZ on mortality for the included studies.

Secondary outcomes: a summary of the data-synthesis is presented in Table 3. There were no differences observed regarding mortality after mechanical ventilation, mechanical ventilation, ICU admission, secondary infection, neutropenia and impaired liver function. However, there were only a few studies (2 to 7) that reported these outcomes and there was considerable heterogeneity, see Table 3. Due to the low number of studies this heterogeneity could not be adequately explored. The following outcomes could not be assessed, because either no included studies reported them or the data presentation in the article did not allow for pooling of these outcomes: days to recovery, days on ICU, days on mechanical ventilator support and intestinal perforation.

Discussion

Summary of Evidence

In this systematic review and meta-analysis we evaluated the treatment effect of tocilizumab on mortality and possible side effects in COVID-19 patients compared to COVID-19 patients who did not receive tocilizumab. Our results showed that tocilizumab was associated with a 12% reduction in mortality for COVID-19 patients compared to the control group. . After rigorous sensitivity analyses - outlier analyses and taking into account the effect of possible publication bias – the most conservative estimate was 9.4% risk reduction which translates in a number needed to treat of 11. This analyses therefore suggests that for every 11 (severe) COVID-19 patients treated with tocilizumab 1 death is prevented. We are not aware of other meta-analysis on this topic. Results of high quality randomized controlled trials are needed to prove or refute our results regarding the positive effect of tocilizumab on mortality in COVID-19 patients.

Our analyses also suggested that use of co-medication is an important source of between-study variation. In studies that used glucocorticoids the treatment effect of TCZ on mortality was smaller compared to studies that did not use glucocorticoids. This finding implies that the treatment effect of TCZ is smaller when other immunosuppressive medication, such as glucocorticoids, are used. Importantly, for studies that used glucocorticoids without lopinavir and ritonavir there was no longer a difference in mortality between the TCZ and control group. However, a recent study by Ramiro et al has shown that a treatment strategy of high-dose methylprednisolone, followed by tocilizumab if needed, may accelerate respiratory recovery, lower hospital mortality and reduce the likelihood of invasive mechanical ventilation in COVID-19-associated cytokine storm syndrome.[24] Furthermore, Martinez-Urbistondo et al have shown that timing of this combination is very important.[25]

For studies that used lopinavir and ritonavir either with or without glucocorticoids the TCZ group had lower mortality than the control group. Remdesivir, Azythromycin, anti-coagulation medication, and hydroxychloroquine were no effect modifiers.

Regarding the secondary outcomes, there were no differences observed for mortality after mechanical ventilation, mechanical ventilation, ICU admission, secondary infection, neutropenia and impaired liver

function. However, there were only a few studies (2 to 7) in the analyses and there was considerable heterogeneity meaning that a possible effect for these outcomes could not reliably be determined (wide 95% confidence intervals). Therefore further research is necessary. Regarding secondary infections, concomitant treatments such as (prophylactic) antibiotics and corticosteroids could be contributing to the observed heterogeneity. Although we found no difference in neutropenia between the groups, it should be noted that in the 2 studies reporting neutropenia there were zero cases in the control group compared to 5 and 6 cases in the tocilizumab group, which raises concerns for this side effect. There were no intestinal perforations reported in the 10 included studies totalling 554 patients who received tocilizumab and 804 patients in the control group. In the field of rheumatology there is ample experience with tocilizumab in patients suffering from rheumatoid arthritis, who often use concomitant immunosuppressive medications.[26] A review on tocilizumab in treatment of rheumatoid arthritis patients reported that the overall rate of serious infections with tocilizumab was approximately 5 events per 100 person years of exposure and that the overall rate of intestinal perforation was 0.28 events per 100 person years of exposure.[26] However, it is unknown whether these adverse event rates are similar in COVID-19 patients.

Limitations and strengths

We should also consider some limitations. The most important one is the fact that all included studies were observational. Presently there are no published results of randomized controlled trials of tocilizumab versus control on mortality in COVID-19 patients. In theory observational studies overestimate the treatment effect of the interventions. However, this theory conflicts with empirical evidence especially when the methodological quality of included observational studies is high.[8, 27] Moreover, the patients, who received tocilizumab in the included studies were more severely affected by COVID-19 given their higher CRP values and lower PaO2-FiO2 ratio. This potential bias underestimates the observed effect of tocilizumab on mortality and may (partially) neutralize the overestimating effect of the observational study design. High quality randomized controlled trials are thus needed. When results from RCTs become available it is paramount to explore potential sources of heterogeneity when they are include in meta-analyses: differences between studies may not only arise from study design (e.g. RCT or observational) but may also arise from other study level factors

such as co-medication use.[28] RCTs may help in achieving balanced groups at baseline, but they do not guarantee balanced co-medication use after randomisation. Our results suggest that use of co-medication is particularly important as the effect of TCZ was no longer significant when glucocorticoids were used (without lopinavir and ritonavir).

The fact that we used crude risks for the calculation of RR and RD can be considered a limitation, as this does not allow control of baseline imbalances by treatment group. However, there were three studies that reported adjusted analyses for baseline imbalances and these analyses confirmed the lower mortality for the TCZ group: Hazard ratio 0.38[18], Hazard ratio 0.58[23] and Odds ratio 0.78[17].

Another limitation is the small number of studies for the secondary outcomes. These outcome could be addressed when more studies become available.

Our review has the following strengths. All phases of the review were performed independently by two reviewers independently in duplo. The methodological quality as reflected by the MINORS score was high in 9 out of 10 included articles and rigorous sensitivity analyses could not refute the conclusions. Restricting the analyses to studies with the highest methodological quality (MINORS score 20 or more), the results remained the same. The influence of publication bias was negligible as determined by funnel plots and trim-and-fill analyses. Sensitivity analyses on co-medication explained almost all heterogeneity.

Conclusion

Meta-analysis on 10 observational studies comprising 1358 patients showed that mortality was 12% lower for COVID-19 patients treated with tocilizumab compared to COVID-19 patients who were not treated with tocilizumab. The number needed to treat was 11, suggesting that for every 11 (severe) COVID-19 patients treated with tocilizumab 1 death is prevented. Given the observational design of the included studies, these results should be interpreted with caution and require confirmation by randomized controlled trials.

Funding:

There was no external funding for this work. Hence, no sponsor took part in the design or conduct of the study; nor in the collection, management, analysis, or interpretation of the data; nor in the preparation, review, or the approval of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Table 1 baseline study characteristics

Study	Group	n	Age	%men	%DM	%HT	%CV	CRP	Pao2-FiO2
Calleja-Rubio	TCZ	32							
	Control	60							
Campochiaro	TCZ	32	64	91	13	38	13	156	107
	Control	33	60	82	18	48	18	169	124
Capra	TCZ	62	63	73	13	45	13		
	Control	23	70	83	22	48	26		
Colaneri	TZC	21	62	90	10	38	10	214	
	Control	91	64	69	8,8	22	7,6	149	
Guaraldi	TCZ	179	64	71	13*	45*	11*		169
	Control	365	69	64	3*	14*	5*		277
Kewan	TCZ	28	63	71	39	68	7,1	161	148
	Control	23	70	47	35	74	30	51	207
Klopfenstein	TCZ	20	77		25	40	70	158	
	Control	25	71		32	44	68	105	
Martin-Moro	TZC	6	62	100					
	Control	11	83	45					
Rojas-Marte	TCZ	96	59	77	30	55		171	
	Control	97	62	65	39	53		146	
Somers	TZC	78	55	68	13	67	21	185	154
	Control	76	60	64	20	68	26	231	196

* = values are from Modena sub-cohort, not entire study population

TCZ = tocilizumab

DM = Diabetes mellitus

HT = Hypertension

CV = Cardiovascular disease

CRP = C-reactive protein in mg/L

PaO2-FiO2=ratio of arterial oxygen partial pressure to fractional inspired oxygen

Table 2 risk of bias assessment with MINORS score

Study	1*	2*	3*	4*	5*	6*	7*	8*	9*	10*	11*	12*	Total
Calleja-Rubio	2	1	1	2	2	1	0	0	2	0	0	2	13
Campochiaro	2	2	1	2	2	2	2	0	2	2	1	2	20
Capra	2	2	1	2	2	2	2	0	2	2	1	2	20
Colaneri	2	2	1	2	2	1	0	0	2	2	1	2	17
Guaraldi	2	2	1	2	2	2	2	0	2	2	1	2	20
Kewan	2	2	1	2	2	2	2	0	2	2	1	2	20
Klopfenstein	2	2	1	2	2	0	2	0	2	2	1	2	18
Martin-Moro	1	1	1	2	2	2	2	0	2	2	1	2	18
Rojas-Marte	2	2	1	2	2	2	2	0	2	2	1	2	20
Somers	2	2	2	2	2	2	2	0	2	2	1	2	21

*1. A stated aim of the study;

2. inclusion of consecutive patients;

3. prospective collection of data;

4. endpoints appropriate to study aim;

5. unbiased assessment of study endpoint;

6. Follow-up period appropriate to the major endpoint;

7. Less than 5% lost to follow-up;

8.; adequate control group

9. contemporary groups;

10. baseline equivalence of groups;

11. prospective calculation of study size;

12. adequate statistical analyses

Table 3: summary of data synthesis

	Outcome	Number of studies	Number of patients	Pooled estimate (RR) [95%CI]	Pooled estimate (RD) in % [95%CI]	Heterogeneity (I^2)
Treatment outcome	Mortality	10	1358	0.27 [0.12 to 0.59]	-12 [-20 to -4.6]	61%
	Mortality after mechanical ventilation	4	942	0.28 [0.21 to 1.32]	-4.1 [-11 to 3.1]	46%
	Mechanical Ventilation	7	889	1.7 [0.21 to 1.32]	1.8 [-15 to 11]	81%
	ICU admission	5	290	1.6 [0.81 to 3.12]	1.0 [-24 to 22]	85%
Side effect	Secondary infection	6	1092	1.9 [0.42 to 8.9]	3.8 [-6.4 to 14]	83%
	Neutropenia	2	609	NA	6.4 [-7.5 to 20]	77%
	Impaired liver function	2	609	1.7 [0.1 to 55]	0.7 [-0.7 to 2.1]	0%

RR = risk ratio; defined as: risk tocilizumab group / risk control group

RD = risk difference; defined as: risk tocilizumab group - risk control group

NA = not estimable due to empty cells (both studies had no cases of neutropenia in the control group)

95%CI = 95% confidence interval

Table 4 co-medication use on study level

Study	Glucocorticoids	Lopinavir and ritonavir	Remdesivir	Azythromycin	anti-coagulation	hydroxychloroquine
Calleja-Rubio	Yes	No	No	No	No	
Campochiaro	No	Yes	No	Yes	Yes	Yes
Capra	No	Yes	No	No	No	Yes
Colaneri	Yes	No	No	Yes	Yes	Yes
Guaraldi	Yes	Yes	No	Yes	Yes	Yes
Kewan	Yes	No	No	Yes	No	Yes
Klopfenstein	Yes	Yes	No	No	No	Yes
Martin-Moro	Yes	Yes	No	Yes	No	Yes
Rojas-Marte	Yes	Yes	Yes	Yes	Yes	Yes
Somers	Yes	No	Yes	No	Yes	Yes

Figure legends

Figure 1: Prisma flow chart

Figure 2: Forest plot showing the risk difference in mortality between patients treated with tocilizumab and patients not treated with tocilizumab. Meta-analysis on 10 observational studies comprising 1358 patients showed that mortality was 12% lower for COVID-19 patients treated with tocilizumab compared to COVID-19 patients who were not treated with tocilizumab.

Figure 3: Forest plot showing the risk difference in mortality between patients treated with tocilizumab and patients not treated with tocilizumab according to co-medication groups.

Figure 1

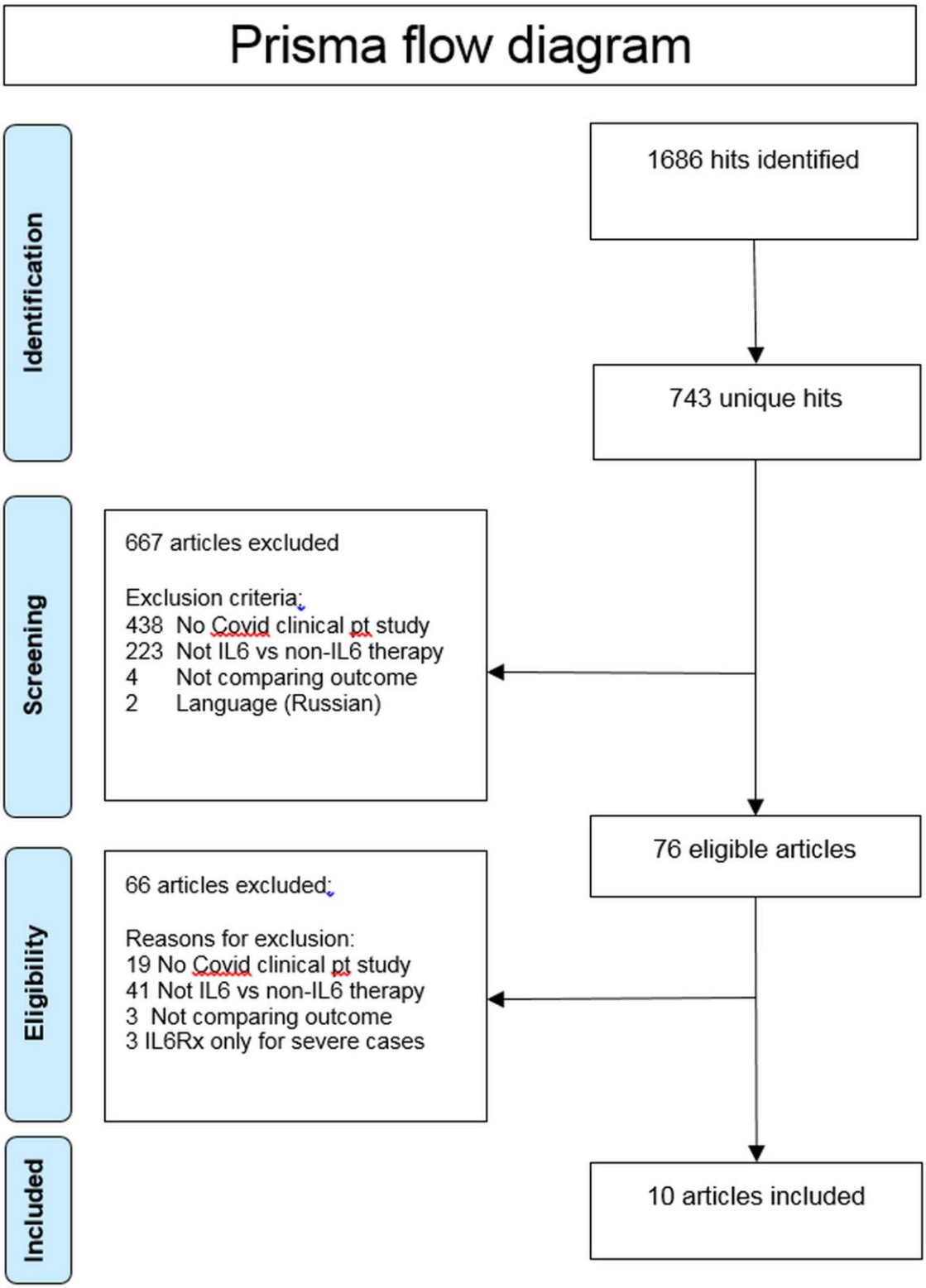

Figure 2

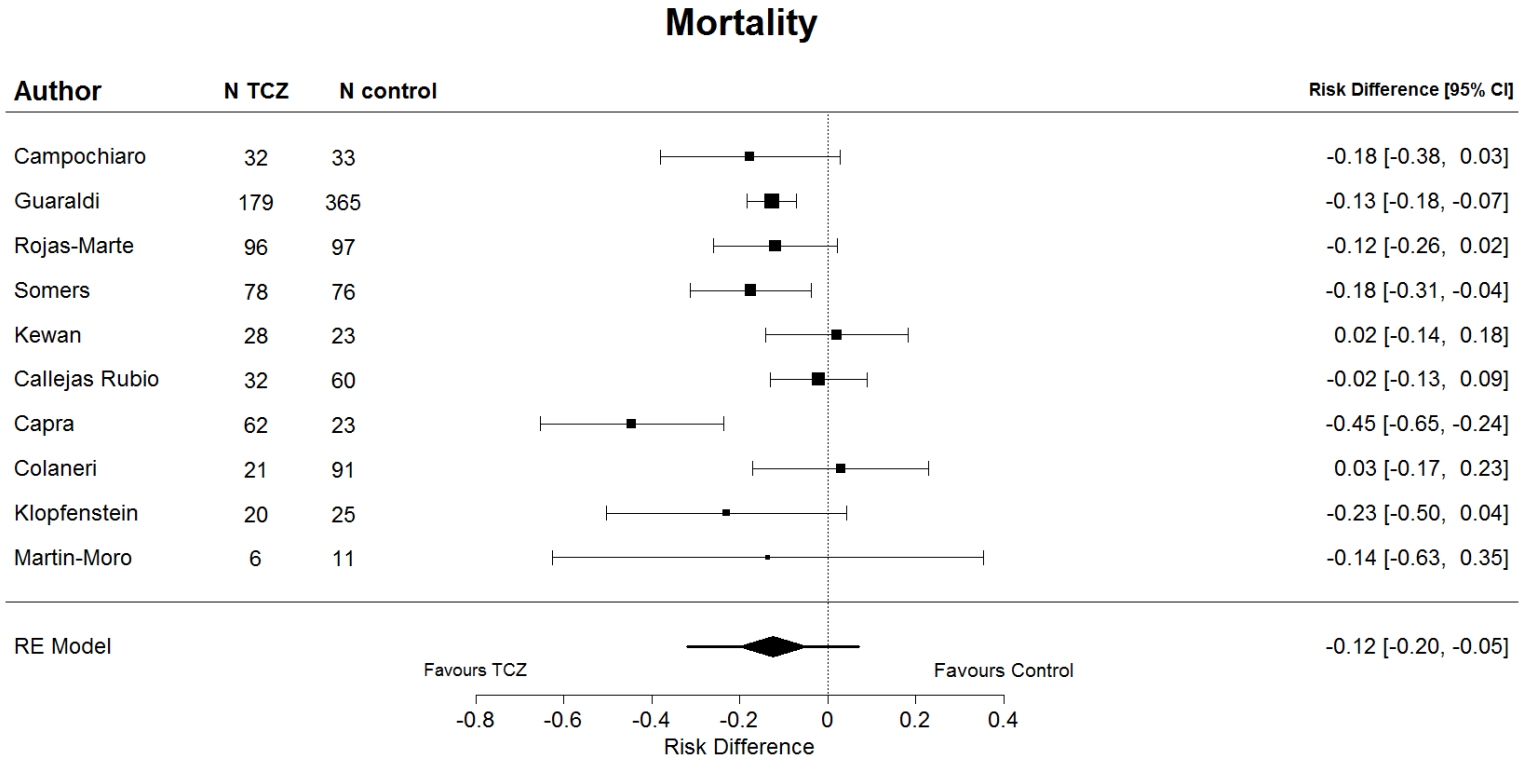

Figure 3