Placebo effects on all-cause mortality of patients with COVID-19 in randomized controlled trials of interleukin 6 antagonists: A systematic review and network meta-analysis

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Abstract

Aim: Many randomized controlled trials (RCTs) have investi- gated the use of interleukin 6 antagonists for the treatment of coronavirus disease 2019 (COVID-19), yielding inconsis- tent results. This network meta-analysis (NMA) aimed to identify the source of these inconsistent results by reassessing whether participants treated with standard of care (SoC) plus placebo have different all-cause mortality from those treated with SoC alone and to reevaluate the efficacy of interleukin 6 antagonists in the treatment of COVID-19.

Methods: We conducted a systematic search for relevant RCTs from the inception of electronic databases through 1 September 2022. The primary outcome was all-cause mor- tality. The secondary outcomes were the incidences of major medical events, secondary infections, all-cause discontinua- tion, and serious adverse events.

Results: The results of NMA of 33 RCTs showed that patients with COVID-19 treated with SoC plus placebo had

lower odds of all-cause mortality than those who received SoC alone (OR, 0.75 [95% confidence interval, 0.58–0.97]). This finding remained consistent after excluding studies with no incident deaths. In addition, when we consider the impact of the widely promoted COVID-19 vaccination and newly developed antiviral treatment strategy, the results from the analysis of the RCT published in 2021 and 2022 remained similar.

Conclusion: These findings suggest the potential influence of placebo effects on the treatment outcomes of COVID-19 in RCTs. When evaluating the efficacy of treatment strate- gies for COVID-19, it is crucial to consider the use of pla- cebo in the design of clinical trials.

Keywords: coronavirus disease 2019, COVID-19, interleukin 6, net- work meta-analysis, placebo effect.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused approximately 7.5 million deaths worldwide until February 20231 and continues to impact global public health and the economy.2 Numerous studies have been undertaken to identify potential treatments for COVID-19, with interleukin 6 (IL-6) antagonists among the most widely tested. The REACT (Rapid Evidence Appraisal for COVID-19 Therapies) group recently published a meta-analysis that investigated the efficacy of IL-6 antagonists in reducing all-cause mortality in patients with COVID-19.3 They concluded that the administration of IL-6 antago- nists (tocilizumab or siltuximab) was associated with a lower all-cause mortality than usual care or placebo. However, from the data provided in their Table 1 and Fig. 1, a higher all-cause mortality in patients treated with the standard of care (SoC) (about 28.0% on average) than that in patients treated with SoC plus placebo (about 17.5% on aver- age) is noted, suggesting a potential placebo effect. Several random- ized controlled trials (RCTs) with zero events in one arm were included in that meta-analysis, while RCTs with zero events in both arms were excluded.3

The placebo effect may play an important role in COVID-19 treatment. In RCTs that aim to treat severe disease, it would be unethical to assign the participants to control arms receiving no active treatment.4 Therefore, participants in most RCTs testing COVID-19 treatments received either SoC alone or SoC plus placebo. However, this may affect the confidence of evidence from RCTs.5 For example, a previous meta-analysis demonstrated that inhaled corticosteroids had a reduced probability of hospitalization in people with COVID-19.6 However, this association was only observed in open-label studies but not in other placebo-controlled trials, suggesting that the placebo effect might have contributed to the effectiveness of inhaled corticosteroids. Similarly, an RCT of heart failure revealed that people taking placebo had improved outcomes.7 A meta-analysis found that good adherence to a placebo was associated with lower mortality than poor adherence.8

The placebo effect can generally be defined narrowly or broadly. Narrowly speaking, the placebo effect refers to a phenome- non observed in clinical trials where patients receive an inert treat- ment, such as a placebo pill, yet still exhibit a reduction or improvement in their symptoms.9 This effect arises from patients' expectations, beliefs, and psychological factors, and it is distinct from other factors such as regression towards the mean, nature course of disease, time-related factors, and fluctuations in symp- toms.10 In a broader

context, placebo effects can manifest in various clinical scenarios, including treatment with an active agent during clinical practice, the informed consent process, the dissemination of positive information about medical treatments, and public health campaigns. The broader definition of placebo effects, also known as behavioral placebo effects, occurs due to verbal suggestions, classi- cal and nonclassical conditioning, empathic listening, and social interaction. These effects encompass additional factors, such as patients' trust in health care providers, emotional support, and the positive therapeutic encounters.11 As a result, enhanced expectations of treatment effectiveness can significantly impact treatment out- comes. Studies have linked heightened treatment expectations to increased response to various interventions, such as analgesics, psy- chotropics, deep brain stimulation, and surgical interventions.12

This study aimed to examine whether patients with COVID-19 treated with SoC plus placebo showed different major outcomes from those treated with SoC alone, exploring the placebo effects on major outcomes of COVID-19 treatment. We conducted a system- atic review and network meta-analysis (NMA) of RCTs that compared IL-6 antagonists with SoC alone or SoC plus placebo. Furthermore, we conducted sensitivity analysis to assess the robust- ness of our results by excluding RCTs with zero events in either one or both arms.

METHODS

General guidelines applied in the current study

The present NMA follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines (Table S1) and AMSTAR2 (Assessing the Methodological Quality of Systematic Reviews) guidelines. This study was approved by the institutional review board of the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (TSGHIRB No. B-109-29) and regis- tered in PROSPERO (CRD42022357488).

Search strategy and selection criteria

To examine our hypothesis that there might be significant differences in all-cause mortality between the placebo plus SoC and SoC only groups in IL-6 antagonist trials, we focused on RCTs of IL-6 antagonists in acute COVID-19 treatment. Strict inclusion/exclusion criteria should enhance the satisfaction of transitivity and the homogeneity assumptions. We con- ducted electronic searches on PubMed, Embase, ProQuest, ClinicalKey, Cochrane CENTRAL, ScienceDirect, Web of Science, and ClinicalTrials. gov databases from inception to 1 September 2022. We searched for RCTs that used IL-6 antagonists (i.e. tocilizumab, sarilumab, clazakizumab, siltuximab, or olokizumab) to treat patients with COVID-19, with either placebo-controlled or SoC controls. The detailed search strategies and key- words used in each database are listed in Table S2. We also conducted manual searches for potentially eligible articles from the reference lists of the review articles or meta-analyses.3,13–16

Inclusion and exclusion criteria

The PICO strategy applied was as follows: (i) participants: patients with a confirmed COVID-19 diagnosis by either serological or immu- nological testing; (ii) intervention: IL-6 antagonists; (iii) comparison: SoC plus placebo control (either injected or oral) or SoC only control; and (iv) outcome: all-cause mortality as the primary outcome, and major medical

events, secondary bacterial infections, all-cause discon- tinuation, and serious adverse events (AEs) as the secondary out- comes. To include as many RCTs as possible, we did not set restrictions on the age or underlying diseases of the participants. The definition of SoC could be either the standard antiviral treatments, symptomatic treatments, or other Food and Drug Administration– approved treatments for COVID-19. For ethical reasons, all RCTs administered other concurrent interventions to both groups to reduce the mortality of COVID-19. Therefore, the inclusion criteria were as follows:

1 Patients with COVID-19 randomly assigned to different treatment groups;

2 RCTs including one or two IL-6 antagonists for COVID-19 man- agement as the test group; and

3 using SoC plus placebo or SoC only as a control group.

The exclusion criteria were as follows:

1 Nonhuman studies;

2 observational studies in which patients were not randomly assigned

to different treatment groups;

3 case reports or case series; and

4 studies with no event in two of their treatment arms.

In cases of duplicate data (i.e. different articles based on the

same sample sources), we included the report with more information and a larger sample size.

Outcome definition

Following the rationale of a previous REACT Working Group meta- analysis,3 the primary outcome was defined as end-of-study all-cause mortality. This choice of end point was

based on the rationale that COVID-19 infection represents a course of disease (i.e. end of study) rather than a period of infection (i.e. 28 days). Secondary outcomes included: (i) major medical events (i.e. invasive mechanical ventilation, extracorporeal membrane oxygenation, or death); (ii) secondary bacte- rial infection; (iii) all-cause discontinuation; and (iv) serious AEs.

Data extraction

Two authors independently screened and extracted the relevant data from the included studies. If the original data were not available, we extracted the data from a previously published meta-analysis by the REACT Working Group addressing IL-6 antagonists for COVID-19.3 Discrepancies were adjudicated by a third author. We intended to extract intention-to-treat data as a first priority. When intention- to-treat data were not available, other types of data, such as per- protocol data, were extracted.

Cochrane risk-of-bias tool

Two independent authors evaluated the risk of bias (interrater reliability, 0.87) for each domain using the Cochrane risk-of-bias tool.17 Discrepancies were resolved by a third author.

Statistical analysis

For categorical data, the effect size was measured using an odds ratio (OR) with 95% confidence intervals, and if no event was observed in one of the treatment groups, we applied the continuity correction method by adding 0.5 event to both arms.18 However, if both the intervention and control arms of a study had no event, this correction method was not applied, and this study was excluded owing to the increased risk of bias.19 We used a frequents statistical approach to the NMA. A two-sided p-value <0.05 was considered statistically sig- nificant. We presented the results of the analyses using the SoC group as the reference group for all outcomes.20 Our NMA model is a linear mixed model that combines direct and indirect evidence to compare mul- tiple treatments. To be specific, the frequentist NMA used treatment con- trasts as the outcome, so effect size measures, such as OR or risk ratio are transformed into log OR or log risk ratio. These

transformed variables are considered continuous variables; therefore, a linear mixed model was used for data analysis. All analyses were undertaken using the network suite for Stata statistical software version 16.0 (StataCorp LLC),21 with the use of the restricted maximum likelihood estimation method to esti- mate between-study random effects.

To enhance the clinical application of our results, we used the ranking probabilities of treatments compared with the analysis of each outcome to calculate the surface under the cumulative ranking curve,22 ranging from 0 to 1, which is the percentage of the effect of each treatment relative to an imaginary treatment.

Evaluation of inconsistency assumption and subgroup analysis

We evaluated potential inconsistencies between the direct and indirect evidence for each pairwise comparison between treatments within the network using the loop-specific approach and the node-splitting method. Furthermore, we used the design-by-treatment interaction model to evaluate the global inconsistency in an NMA.23 We used comparison-adjusted funnel plots24 and Egger test to evaluate small study effects and publication bias within the direct evidence of the comparison between a pair of treatments.

Sensitivity analysis

To assess the potential bias by including studies with zero events in one treatment arm,25 we conducted a sensitivity analysis restricted to RCTs without any zero events, while our main analysis had already excluded studies with zero events in both arms. Furthermore, to assess the potential placebo effect, we conducted another sensitivity analysis restricted to RCTs with a placebo arm.

Evaluation of transitivity assumption

Because it is unlikely that any RCTs would directly compare the efficacy of SoC plus placebo with that of SoC alone, the compari- son between the two treatment arms would come from indirect evidence. Therefore, it is crucial to evaluate the transitivity assumption underlying the indirect comparison. Following a pre- vious NMA study,26 we evaluated the transitivity assumption by assessing the average effects of the common

reference treatment in RCTs comparing the reference treatment with SoC plus placebo and in RCTs comparing the reference treatment with SoC alone. This assessment was undertaken by using Comprehensive Meta- Analysis version 3 (Biostat Inc.).27 If there was no statistically significant difference, the assumption of transitivity was consid- ered robust.

In addition, since we recognized the fluctuation during the COVID-19 pandemic along with the development and wide promo- tion of the COVID-19 vaccine, we conducted subgroup analysis according to the publication year of the included RCTs. To be spe- cific, we arranged subgroup analyses for RCTs published in 2020 and for RCTs published in 2021 and 2022 because the development and wide promotion of COVID-19 vaccine occurred in late 2020.28

This study conforms to the provisions of the Declaration of Helsinki.

RESULTS

Eligibility of the retrieved studies and treatment arms

Figure 1 shows a flowchart of literature search and screening for the current NMA. After excluding eight articles due to various reasons (Table S3),29–36 a total of 33 RCTs were included.37–64 A total of 11,902 participants (mean age, 61.6 years [range, 51.9–74.8 years]; mean female proportion, 32.1% [range, 7.0%–52.0%]) were included (Table S4). The mean percentages of concomitant corticosteroid and antiviral agents usage were 56.6% (ranging from 0.0% to 100.0%) and 35.5% (ranging from 0.0% to 100.0%), respectively. All of the included RCTs recruited treatment-naive patients. In the subgroup of RCTs published in 2020, the mean percentages of concomitant c orticosteroid and antiviral agents usage were 65.0% and 32.0%, respectively; whereas, in RCTs published in 2021 and 2022, the usage rates were 51.0% and 32.0%, respectively.

Primary outcome: all-cause mortality

Compared with the SoC group, both the SoC plus placebo group (OR, 0.75 [95% CI, 0.58–0.97]) and some IL-6 antagonists (clazakizumab: OR, 0.44 [95% CI, 0.21–0.90]; tocilizumab: OR, 0.80 [95% CI, 0.72–0.89]) were associated with a lower risk of all-cause mortality (Figs 2 and 3, and the Table). According to the surface under the cumulative ranking curve (SUCRA), clazakizumab was ranked best among all interventions, whereas placebo was ranked sec- ond among all interventions (Table S5a). The meta-regression for the use of placebo revealed that there was no statistically significant change noted (P = 0.998).

Sensitivity analysis by excluding RCTs without zero events in any arm

Compared with the SoC group, SoC plus placebo (OR, 0.74 [95% CI, 0.57–0.96]) and some IL-6 antagonists (clazakizumab: OR, 0.43 [95% CI, 0.21–0.88; tocilizumab: OR, 0.80 [95% CI, 0.72–0.89]) were found to be associated with a lower risk of all-cause mortality (Figs S1a and S2a, and Table S6a). According to the SUCRA, clazakizumab was the best among all interventions, followed by placebo and tocilizumab (Table S5b).

Sensitivity analysis restricted to RCTs with a placebo control arm

None of the IL-6 antagonists included in the comparisons showed a significant reduction in the risk of all-cause mortality (Tables S5c and S6b, Figs S1b and S2b).

Assessment of transitivity assumption: comparing efficacy of IL-6 antagonists in the studies with placebo plus SoC or SoC as the control

The network plot of the primary outcome showed that the indirect comparison between SoC plus placebo and SoC mainly came from two indirect comparisons: (i) SoC plus placebo versus tocilizumab and tocilizumab vs SoC only (Fig. S1c); and (ii) SoC plus placebo versus sarilumab and sarilumab versus SoC only (Fig. S1d). There- fore, we evaluated the transitivity assumption for tocilizumab and sarilumab in these two indirect comparisons, respectively.

For tocilizumab, the all-cause mortality rate was 0.144 (95% CI, 0.097–0.210) in RCTs that compared tocilizumab with SoC plus placebo plus SoC and 0.148 (95% CI, 0.105–0.203) in RCTs that compared tocilizumab with SoC only. The difference between the two event rates was very small and nonsignificant (P = 0.928) (Fig. S2c).

For sarilumab, the all-cause mortality rate was 0.150 (95% CI, 0.086–0.250) in RCTs that compared sarilumab with SoC plus placebo and 0.197 (95% CI, 0.100–0.352) in RCTs that compared sarilumab with SoC only. The difference between the two event rates was also small and nonsignificant (P = 0.527) (Fig. S2d).

Subgroup analysis of 2020-published RCTs and 2021- and 2022-published RCTs

In the subgroup of RCTs published in 2020, none of the investigated treatments were associated with significantly different risks of all- cause mortality in comparison with the SoC group (Tables S5d and S6c; Figs S1e and S2e).

In the subgroup of RCTs published in 2021 and 2022, the results were similar to those of the main NMA. Compared with SoC alone, both SoC plus placebo (OR, 0.75 [95% CI, 0.58–0.98) and two IL-6 antagonists (clazakizumab: OR, 0.44 [95% CI, 0.21–0.90; tocilizumab: OR, 0.80 [95% CI, 0.72–0.89]) were associated with a lower risk of all-cause mortality (Figs S1f and S2f, and Table S6d). According to the SUCRA, clazakizumab was ranked best

among all interventions, whereas SoC plus placebo was ranked second among all interventions (Table S5e). In addition, there was no significant het- erogeneity in the subgroup analyses (Table S8c). Secondary outcome: major medical events (i.e. invasive mechanical ventilation, extracorporeal membrane oxygenation, or death)

Compared with SoC, only clazakizumab (OR, 0.38 [95% CI, 0.17–0.87) and tocilizumab (OR, 0.79 [95% CI, 0.71–0.88) were associated with a lower risk of major medical events (Figs S1g and S2g; Tables S5f and S6e).

Secondary outcome: secondary bacterial infection

Compared with SoC, SoC plus placebo group (OR, 1.71 [95% CI, 1.20–2.43]) and three IL-6 antagonists (tocilizumab: OR, 1.42 [95% CI, 1.05–1.91; sarilumab: OR, 1.76 [95% CI, 1.19–2.61]; siltuximab: OR, 3.22 [95% CI, 1.26–8.24]) were associated with a higher risk of secondary infection (Figs S1h and S2h; Tables S5g and S6f).

Secondary outcome: all-cause discontinuation

Compared with SoC, SoC plus placebo (OR, 1.54 [95% CI, 1.04–2.30]) and sarilumab (OR, 1.59 [95% CI, 1.03–2.47]) were associated with a higher risk of all-cause discontinuation (Figs S1i and S2i; Tables S5h and S6g).

Secondary outcome: serious AEs

None of the investigated treatments were associated with a signifi- cantly different risk of serious AEs compared with SoC (Tables S5i and S6h; Figs S1j and S2j).

Risk of bias, inconsistency, heterogeneity, publication bias, and GRADE

We found that 91.9% (182 of 198 items), 7.1% (14 of 198 items), and 1.0% (two of 198 items) of the included studies had low, unclear, and high risks of bias, respectively (Fig. S3). Funnel plots and Egger test across the included studies (Fig. S4a–j) revealed general symmetry and no evidence of small study effects. The three models for evaluating the consistency assumption showed no significant inconsistencies in the present NMA (Table S7). In addi- tion, there was no significant heterogeneity in our NMA for the primary outcome (Table S8a–c). According to the GRADE results (Table S9), the overall certainty

of evidence ranged from low to medium.

Discussion

Our NMA of RCTs found a significantly lower risk of all-cause mortality in patients with COVID-19 treated with SoC plus placebo compared with those treated with SoC alone, suggesting a placebo effect. When IL-6 antagonists were compared with SoC plus placebo, IL-6 antagonists did not show a significantly lower risk of all-cause mortality. While clazakizumab showed a nonsignificant reduction in the risk, the other three IL-6 antagonists were no better than SoC plus placebo. As SoC plus placebo showed a significantly lower all-cause mortality, these results suggest that part of the observed efficacy of IL-6 antagonists may be explained by a placebo effect. This is intriguing because all-cause mortality is considered an objective measure.

Although there has been some debate about the placebo effect in pain,65 psychiatric disorders,66 or other minor symptoms such as cough,67 few studies have examined the placebo effect on major or critical outcomes, such as mortality. To the best of our knowledge, the current study is the first NMA conducted in the COVID-19 set- ting to examine whether the use of a placebo may have a risk- reducing effect on mortality compared with SoC alone as a control. No violation of the transitivity and consistency assumptions was detected. In the subgroup analysis, we found that the placebo effect appeared to be present when the COVID-19 pandemic was gradually under control (i.e. in the 2021–2022 period).

In recent years, a number of neuropharmacologic studies have shown that the placebo effects were associated with a variety of neurobiological mechanisms across different diseases.9 For example, the placebo effects in pain have been associated with activation of endogenous opioids and cholecystokinin, while in Parkinson disease, they have been associated with dopamine release in the striatum. Neu- roimaging studies have also shown that these effects include reduced activity in brain areas associated with pain and negative emotions, and increased activity in the lateral and medial prefrontal cortex, ven- tral striatum, and brainstem. The neurobiological mechanisms are mediated by expectancies or anticipated future outcomes, including self-reinforcement. Unawareness

of the timing of analgesic use sub- stantially reduced the benefits compared with using an instruction such as ‘a potent painkiller is being used now.’ The way something is presented (framing effects) can enhance the placebo effects. As a result, significant placebo effects are likely to be achieved by a com- bination of belief in the placebo and previous experience of benefit from treatments, resulting in the activation of the brain learning mechanisms.68

We, therefore, propose two potential hypotheses to explain the placebo effect on mortality during the RCTs of COVID-19: (i) psychobehavioral impact by placebo administration; and (ii) immunomodulatory effect by placebo prescription.

Psychobehavioral impact of placebo administration

A previous meta-analysis by Simpson et al.8 found that good adherence to placebo was associated with significantly reduced mortality (OR, 0.56 [95% CI, 0.43–0.74]), and this effect size was similar to that of a beneficial drug therapy (OR, 0.55 [95% CI, 0.49–0.62]).8 A similar finding was also noted in another RCT of heart failure, which reported that the placebo effect on cardiac mortality was associated with good adherence.7 In the model pro- posed by Stetler et al.,69 the initial expectations, via the mediators of adherence and subsequent expectations, were considered to be one of the most important factors associated with the response to placebo. However, none of the included RCTs provided informa- tion on adherence and mortality in individual patients. Moreover, our NMA showed that the placebo group was associated with a higher risk of all-cause discontinuation than the SoC group. Therefore, this model does not seem to explain the placebo effect on the mortality of COVID-19.

Immunomodulatory effect of placebo prescription

Our hypothesis for the immunomodulatory effect of the placebo came from a previous observation in mucosal inflammatory diseases.70 Patients receiving placebo would enter the process of endogenous neu- rotransmitter release that could mimic the expected or conditioned pharmacologic effects.71 This neurobioimmunological network involves the collaboration between the prefrontal cortex, limbic system, and hypothalamus, which are

part of the neocortical-sympathetic-immune axis.71 This hypothesis is supported by the findings from studies of chronic immune-mediated pulmonary diseases, such as asthma72 and chronic cough.67 Similar findings were found in the trials of COVID-19, which is also considered to be an immune-mediated pulmonary disease. A previous meta-analysis of inhaled corticoste- roids for the treatment of patients with COVID-19 showed a reduced likelihood of hospitalization with active treatments only in open-label trials but not in placebo-controlled trials, reflecting the potential placebo effect.6 This hypothesis could also be supported by the results of the secondary outcome in our current NMA. Pla- cebo was associated with a significant increase in secondary bacte- rial infections, a finding similar to other active IL-6 antagonists. Therefore, the placebo itself might have an immunomodulating effect similar to IL-6 antagonists and thus may be associated with an increased risk of secondary bacterial infections.

The above mechanism was mainly derived from mild immuno- logical diseases, which may explain the differences in the results of our subgroup analyses of RCTs published in 2020 compared with those published in 2021 and 2022. In the early 2020, little was known about COVID-19 and very few strategies (such as vaccines and ant- iviral regimens) were available to combat it. Also, the original COVID-19 strains in 2020 were more virulent than the later COVID-19 variants (i.e. Omicron) that dominated in 2021–2022.1 In addition, many new strategies (such as widely promoted vaccines and newly developed antiviral treatments) against these weaker COVID-19 variants became available in 2021–2022. Therefore, COVID-19 in 2021–2022 was relatively different from that in 2020 and could be considered a less severe infectious disease.73 This the- ory of less severe COVID-19 infection in 2021–2022 was supported by the relatively lower proportion of concomitant corticosteroid use in RCTs published in 2021–2022 compared with those published in 2020 (51.0% vs 65.0%). The change in COVID-19 severity may explain the results of our subgroup analysis that only RCTs published in 2021–2022 showed a significant placebo effect.

Our NMA had several strengths. First, it distinguished between SoC only and SoC plus placebo, which could not be done in a tradi- tional pairwise meta-analysis. Second, we included only RCTs to reduce potential biases associated with observational studies. Third,

we first performed sensitivity analyses by excluding RCTs with zero events in any arm and then restricted our analysis to RCTs with a pla- cebo control arm to assess the potential placebo effect in patients treated with IL-6 antagonists. We assessed the transitivity assumption and found no evidence of intransitivity. The current NMA also has several limitations. First, some analyses were underpowered because of the heterogeneity in the characteristics of the participants (e.g., different concomitant medications or SoCs, a wide range of their age and trial duration) and the small number of trials for some treatment arms. Second, although most comparisons in this NMA did not show statistically significant inconsistencies, there was significant node-splitting inconsistency in the comparison between SoC only and sarilumab in the primary outcome. Also, in the subgroup analysis of RCTs published in 2020 versus in 2021 and 2022, we found that only RCTs published in 2021 and 2022 showed a significant placebo effect. This may reflect a higher vaccination coverage in the late pan- demic years (i.e. 2021 and 2022). However, because we did not have more information about the vaccination coverage in the included RCTs, we could not perform further analysis on this question. Third, because we specifically selected RCTs of IL-6 antagonists in COVID-19 man- agement, the results of significant placebo effects could not be extended to other medications in COVID-19 management. Finally, although our study distinguished between SoC plus placebo and SoC alone, we did not have direct evidence for their direct comparison. Thus, although the transitivity assumption was generally met, this finding of a placebo effect was not confirmed by direct evidence yet.

This NMA showed that the average all-cause mortality rate in the RCTs of IL-6 antagonists for the treatment of COVID-19 was sta- tistically lower in patients treated with SoC plus placebo than in those treated with SoC alone, suggesting a possible existence of a placebo effect. We also found that the all-cause mortality of patients treated with IL-6 antagonists investigated in this NMA was not different from those treated with SoC plus placebo. These findings suggest that part of the efficacy of IL-6 antagonists may be explained by the placebo effect. Therefore, when designing future trials on IL-6 antagonists for the treatment of COVID-19, researchers should consider including a placebo in the control group to provide more robust evidence.

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Disclosure statement

The authors report no financial interests or potential conflicts of inter- est. All of the data of the current study were available upon reason- able request to the corresponding authors. The institutional review board of the Tri-Service General Hospital has confirmed that no ethi- cal approval is required (TSGHIRB: B-109-29). The current study did not directly involve individual participants so that we did not have the opportunity to approach individual participants or explore individual participant's information. Therefore, it would be impossible to obtain consent to participate in the current study.

Author contribution

Ping-Tao Tseng and Bing-Syuan Zeng, who contributed equally as first authors, took the whole responsibility of literature search, data extraction, data analysis, and manuscript drafting. Trevor Thompson, Brendon Stubbs, Po-Ren Hsueh, Kuan-Pin Su, Yen-Wen Chen, Tien-Yu Chen, Yi-Cheng Wu, Pao-Yen Lin, Andre F. Carvalho, Chih-Wei Hsu, Dian-Jeng Li, Ta-Chuan Yeh, Cheuk-Kwan Sun, Yu-Shian Cheng, and Yow-Ling Shiue contributed to the study design, concept formation, and manuscript revision. Chih-Sung Liang and Yu-Kang Tu, who contributed equally as corresponding authors, took the whole responsibility of collection of information from the other authors, manuscript major revision, and manuscript submission.

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Supporting Information

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

Table 1. League table of all-cause mortality rate

Clazakizumab	0.58 (0.30–1.14)				
0.58 (0.30–1.13)	Placebo	0.99 (0.74–1.31)	0.81 (0.63–1.05)		
0.55 (0.27–1.11)	0.94 (0.74–1.20)	Tocilizumab	1.39 (0.67–2.90)	***0.78 (0.66–0.92)**	0.56 (0.24–1.35)
0.49 (0.24–1.00)	0.85 (0.67–1.06)	0.90 (0.68–1.19)	Sarilumab	0.87 (0.52–1.44)	
***0.44 (0.21–0.90)**	***0.75 (0.58–0.97)**	***0.80 (0.72–0.89)**	0.89 (0.67–1.18)	Standard of care	0.55 (0.23–1.36)
***0.27 (0.10–0.77)**	0.47 (0.22–1.03)	0.50 (0.24–1.06)	0.56 (0.25–1.23)	0.63 (0.30–1.32)	Siltuximab

Note: Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of all-cause mortality rate. Interventions are reported in order of mean ranking of all-cause mortality rate, and outcomes are expressed as odds ratios (ORs) (95% confidence intervals). For the pairwise meta-analyses, ORs <1 indicate that the treatment specified in the row got less all-cause mortality rate than that specified in the column. For the network meta-analysis (NMA), ORs <1 indicate that the treatment specified in the column got less all-cause mortality rate than that specified in the row. Bold results marked with * indicate statistical significance.

Figures

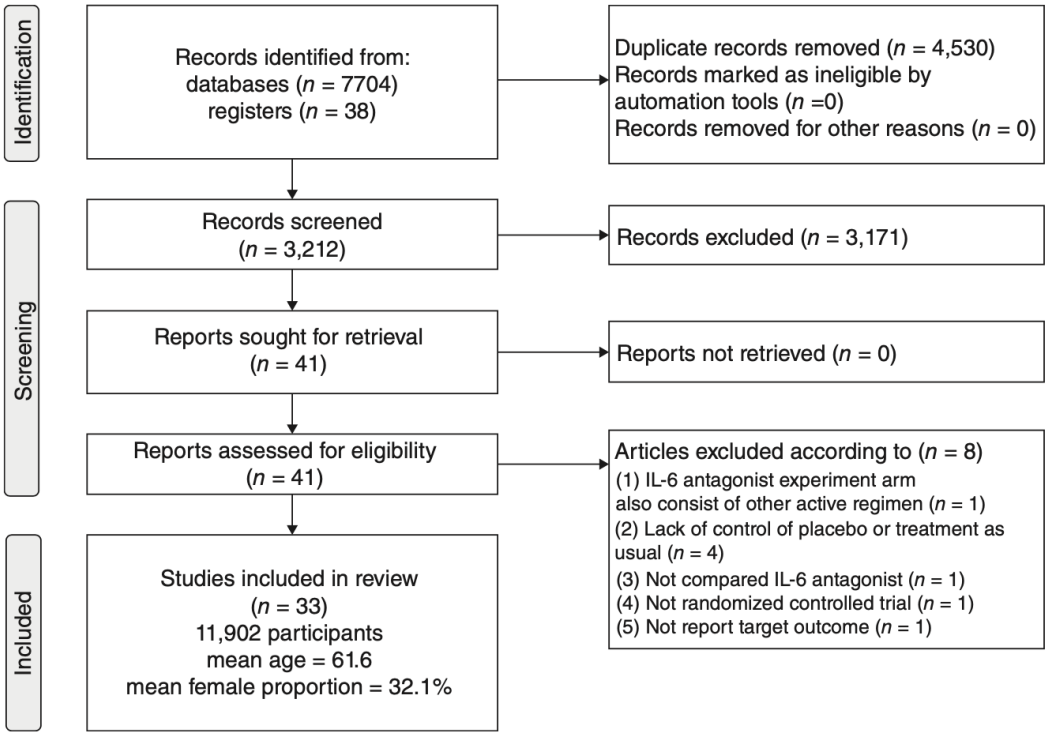

Figure 1: Flow diagram of the current network meta-analysis

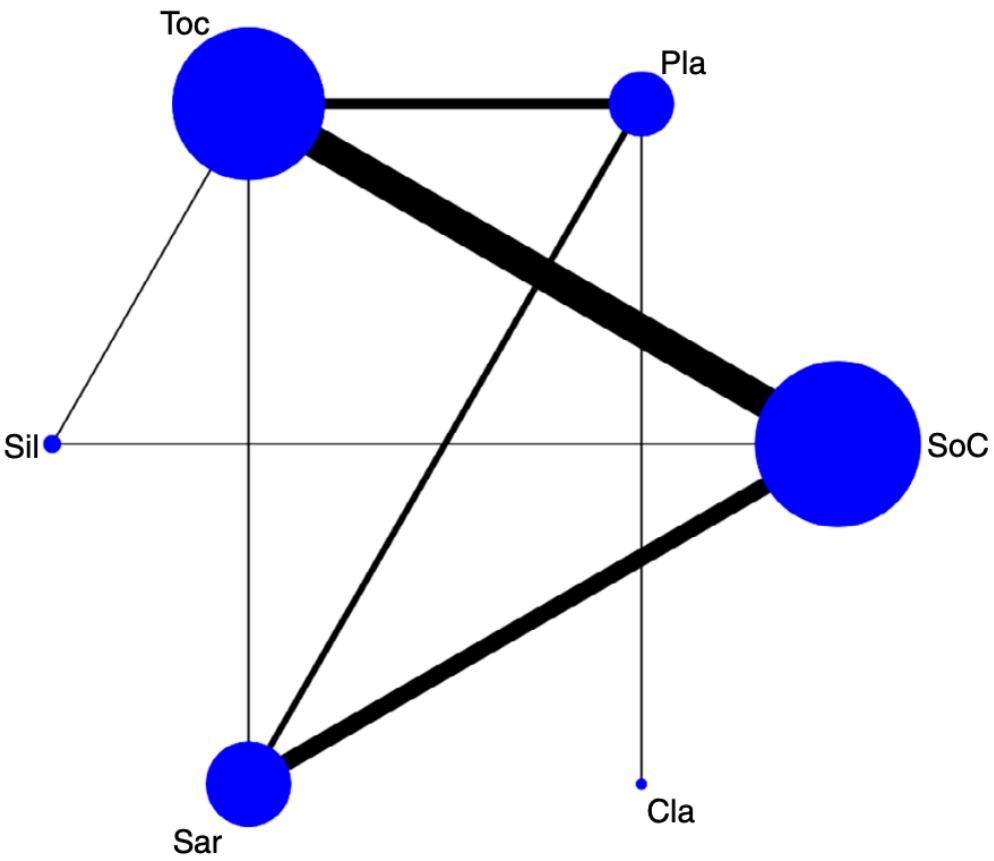

Figure 2: Network plot of the primary outcomes: all-cause mortality

Network plot of the primary outcomes: all-cause mortality. The lines between nodes represent direct comparisons in various trials, and the size of each note is proportional to the size of patients receiving each specific treatment. The thickness of the lines is proportional to the number of trials that compared the two treatments. Cla, clazakizumab; Pla, placebo; Sar, sarilumab; Sil, siltuximab; SoC, standard of care; Toc, tocilizumab.

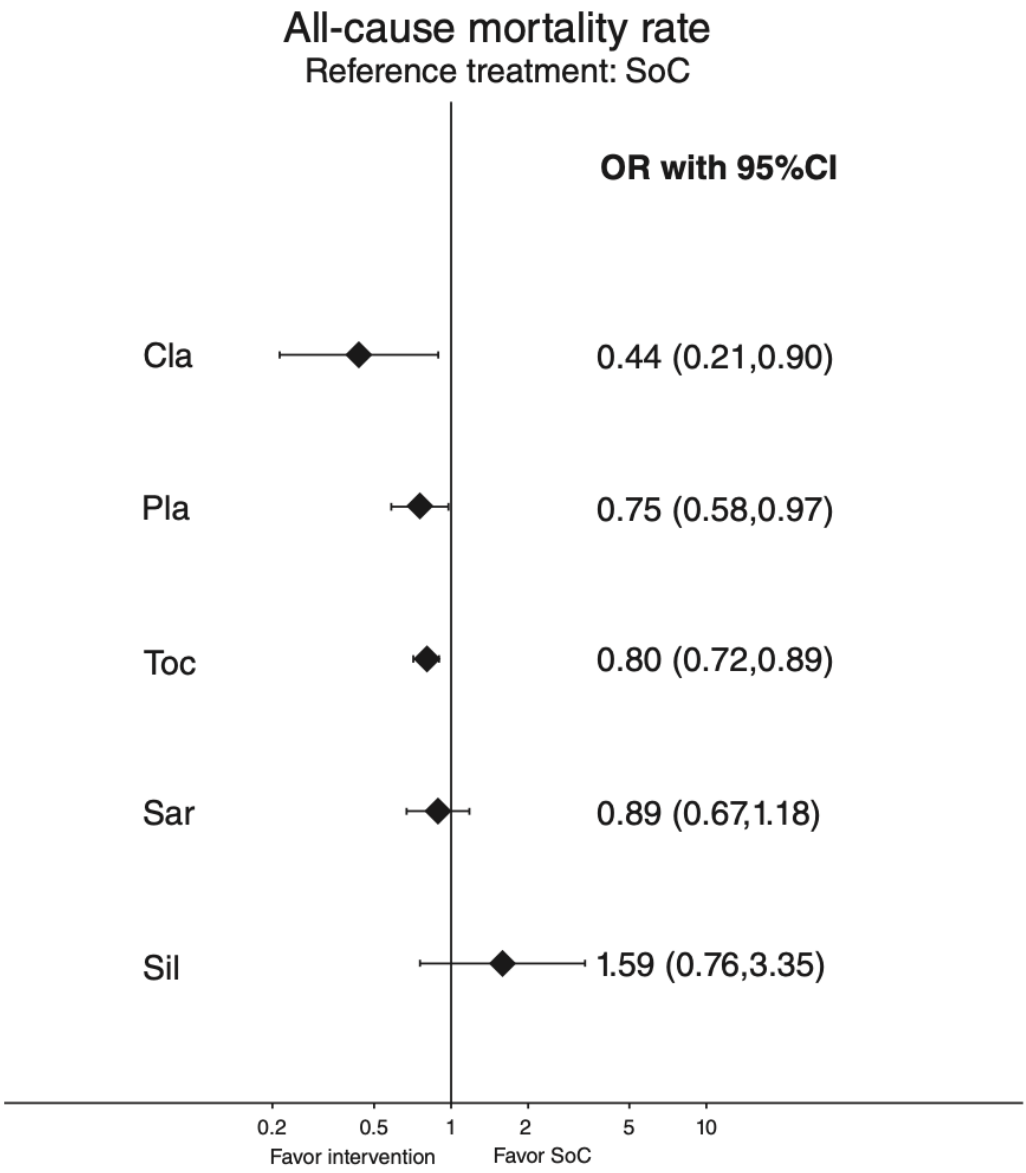

Figure 3: Forest plot of the all-cause mortality in reference to standard of care

Forest plot of the all-cause mortality (in reference to standard of care [SoC]). Specific treatments were associated with less all-cause mortality than the SoC if the odds ratio (OR) was <1. CI, confidence interval; Cla, clazakizumab; IL-6, interleukin-6; Pla, placebo; Sar, sarilumab; Sil, siltuximab; Toc, tocilizumab.