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Action Links	Jl-PH-D-22-00269	Persistent Neurological Manifestations in Long COVID-19 syndrome: A Systematic Review and Meta-Analysis	Other Author	Mar 11, 2022	Jun 21, 2022	Completed - Accept	Jun 21, 2022	Accept
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Interleukin-6 (IL-6) inhibitors as therapeutic agents for COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Preliminary study showed that coronavirus disease 2019 (COVID-19) disrupt body immune system including dysregulation of cytokine interleukin-6 (IL-6). IL-6 inhibitors agents have been used as treatment option for COVID-19, yet their benefit as therapeutic agent remain unclear .

Objective: We performed a systematic review and meta-analysis to synthesize the available data on the potential therapeutic effect of IL-6 inhibitor agents for the treatment of COVID-19.

Methods: Two authors initially screened and reviewed the relevant studies from available databases. The data extracted will be tabulated and analyzed for the outcomes. The primary outcome was mortality. Secondary outcomes included discharge from hospital, length of stay, and requirement for mechanical ventilation. Risk of bias was measured by Newcastle-Ottawa Scale. The quality of each study was assessed using OCEBM ratings.

Results: We reviewed 14 cohorts and 3 case controls with a total of 3061 subjects. Tocilizumab was the most commonly used in the studies (15 studies). Meta-analysis of included studies revealed significant reduction in mortality with tocilizumab and sarilumab (RR = 0,60, 95% CI 0.48–0,74). Other outcomes including hospital discharge (RR = 1.04, 95% CI 0.83–1.32), length of stay (mean difference –1.96 days, 95% CI –4.24 to 0.33) or requirement for mechanical ventilation (RR = 0,68, 95% CI 0.29–1,60) revealed no differences of IL-6 inhibitor agents compared to controls. Most included studies were low in risk of bias.

Conclusions: Available evidences suggests that IL-6 inhibitor agents do reduce the risk of mortality in COVID-19 especially in severe disease. Further well-designed trials are needed for assessing its efficacy and safety for COVID-19

Keywords: COVID-19, SARS-CoV-2, Interleukin-6, IL-6

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has set a major healthcare issues and economic burden worldwide. Since its outbreak in December 2019, researchers and physicians around the globe are working continuously through clinical trials and on-going research to find the cure and vaccine for COVID-19. Currently, treatments of COVID-19 are mainly repurposing drugs or symptomatic with no definitive treatment directed against the virus. (1)

In the absence of specific treatment or antiviral drugs been proven against SARS-CoV-2, researchers have proposed many therapeutics agents used as adjunctive treatments for COVID-19 patients apart from supplemental oxygen therapy or mechanical ventilation. Cytokine storm is one of the main mechanisms of the disease and is believed to trigger an exaggerated immune response in the host and has been observed more frequently in severe COVID-19 patients associated with complications, such as acute respiratory distress syndrome (ARDS) and other organ injuries. (2)

Monoclonal antibody against IL-6 receptors or IL-6 inhibitor has shown to be an effective agent in COVID-19 patients with severe illness. Initially, it is frequently used for the treatment of rheumatoid arthritis patients. These drugs targeting IL-6 as inflammatory mediators will decrease inflammatory response in cytokine storm, hence minimizing the incidence of jeopardize complications, such as ARDS. Tocilizumab and other anti-IL-6 receptors antagonist has been recommended as an immunotherapy in severely ill patients and improved the clinical outcomes as well as decrease in mortality rate. This review provides a summary of current evidences regarding interleukin-6 (IL-6) inhibitors drugs for treatment of COVID-19. (3,4,5)

Methods

This study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (6)

Search Strategy

A systematic literature search of the available studies was conducted on PubMed and medRxiv for articles published until November 2020. Additionally, we examined the bibliography of the selected articles for further potential studies. The search terms used were “interleukin 6,” OR “IL-6,” OR “tocilizumab,” OR "sarilumab," OR "siltuximab." AND “COVID-19,” OR “SARS-CoV-2” and their derivatives.

Inclusion and Exclusion Criteria

We included only studies that compared the effectiveness of the IL-6 inhibitors with placebo or other agents for treatment of COVID-19. The following inclusion criteria were utilized for article selection: (1) involve human patients with COVID-19; (2) be either a randomized controlled trial, prospective trial, retrospective analysis; (3) reported at least one clinical outcome, including hospital discharge, length of stay, mortality, and requirement for mechanical ventilation

The literature was restricted to English language articles only. The exclusion criteria were as follows: (i) non-original studies, such as meta-analyses, conference papers, comments, or consensus documents; (ii) case reports or case series; (iii) single-arm trials; (iii) studies that did not report outcomes for IL-6 inhibitor drugs in COVID-19, and studies that did not compare the outcomes with IL-6 inhibitor drugs compared to the placebo or control.

The primary outcome was mortality. Secondary outcomes included discharge from hospital, length of stay, and requirement for mechanical ventilation.

Study Selection and Data Extraction

Two authors (VOW and RBB) independently screened and examined the titles and abstract, followed by full-text review, using pre-defined criteria. In the event of disagreement between the two authors, consensus discussion would help to resolve the issue and make a final decision. Studies that entirely fulfilled our inclusion criteria were retrieved and additional articles were added based on the bibliography of the articles retrieved through the outlined search strategy. If the reviewers could not reach an agreement, the first author's will be consulted for the final decision.

We extracted and tabulated the following data: author(s), year of publication, study design, country, baseline characteristics, details of the regimen of IL-6 inhibitors and comparative agents, and clinical outcomes.

Risk of bias assessment

Two researchers (VOW and RBB) independently rated the potential bias for all included study. The Newcastle-Ottawa Scale (NOS) assessment tool was used for cohort or case control studies with maximum score was nine, whereas scores of seven or more was graded as high quality while less than seven scores as low quality. (7)

Data analysis

Statistical analysis was conducted using the software Review Manager v.5.3 (Cochrane Collaboration). The degree of heterogeneity was evaluated with the Q statistic generated from the χ^2 test. The proportion of statistical heterogeneity was assessed using the I² measure. Heterogeneity was defined as significant when the P-value was <0.05 or the I² > 50%. A random-effects model was applied when data were considered heterogeneous. The pooled risk ratio (RR) and 95% confidence interval (CI) were calculated for the outcomes of mortality, hospital discharge, and requirement for mechanical ventilation. In case of continuous variables, the mean difference for each study was calculated and plotted. P- value of <0.05 was considered statistically significant. (8)

Study Quality Assessment

We assessed the quality of evidence using The Oxford Center for Evidence-Based Medicine Quality ratings and classified the evidence ratings ranged from 1 to 5, with 1 representing high quality studies such as randomized controlled trial (RCT) and 5 representing case reports. (9)

Results

Study Characteristics

The search strategy initially generated 1213 articles. After removal of duplicates and abstract screening, 113 full-text articles were subsequently assessed for its eligibility. Finally, 17 articles were included in the final review including 14 cohorts and 3 case control. Figure 1. shows the PRISMA flow chart of study selection. Table 1. summarizes the baseline characteristics of all the 17 studies, including the study quality ratings and risk of bias. All included studies were retrospective observational trials, therefore the risk of bias was carried out using the Newcastle–Ottawa scale. All studies except for 1 were high quality in risk of bias (Supplementary Table 1).

Of the 17 non-randomized articles reported the use of IL-6 inhibitor and its comparator for COVID-19, 15 studies using tocilizumab (10-24), 1 using sarilumab (25), and 1 using siltuximab (26). The therapeutic interventions, drug dosing, IL-6 markers, and clinical outcomes are presented in Table 2. Most of the included studies were from Italy, with 7 studies (7,528 cases), followed by the United States (US) with 5 (2 cases), France with 2 (1 case), Spain with 1 (28 cases), Sweden with 1 (28 cases), and India with 1 (28 cases), respectively. Overall, this review included a total of 3061 patients, including 1104 in the tocilizumab group, 28 in the sarilumab group, 30 in the siltuximab group and 1899 in the control group. All the subjects in intervention group also received standard treatment in addition with IL-6 inhibitor drugs.

A single dose of 400 mg or 8 mg/kg intravenous was the most commonly reported regimen of tocilizumab, second dose may also be required as physician judgment. In one study, Della-Torre et al. (25) used intravenous injection of sarilumab of 400 mg. Gritti et al. (26) also used 11 mg/kg of intravenous injection of siltuximab. The use of hydroxychloroquine, antivirals, azithromycin, or anticoagulants were the most commonly reported regimen included in standard treatment.

Table 1. Baseline Characteristics of Patients in the Included Studies

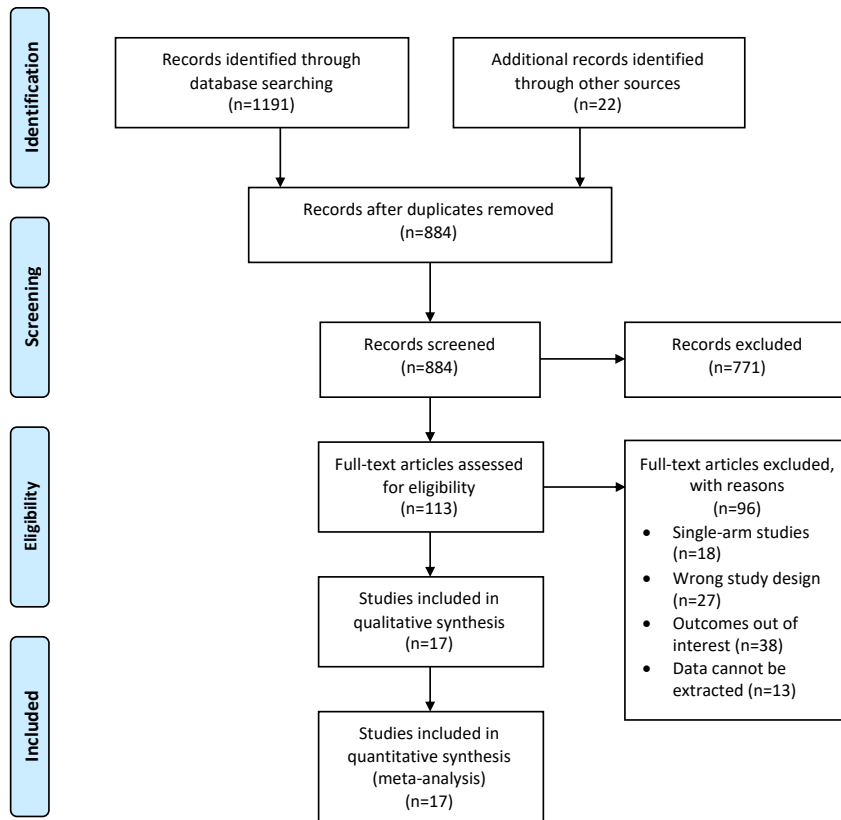


Figure 1. Flow diagram of included studies

Clinical Outcome

Hospital Discharge and Length of Stay

Analysis of the twelve included studies revealed that patients with COVID-19 had a similar risk to be discharged from hospital during study follow-up in the IL-6 treatment group compared with the control group (56.2% vs 57.7%; RR = 1.04, 95% CI 0.83–1.32; I₂ = 83%) (**Figure 2.**). The patients group and clinical outcomes are shown in Table 2. Evidence from 3 case control and 1 cohort studies in patients treated with tocilizumab suggested potential but uncertain effects on decreasing length of hospital stay (weighted MD –1.96, 95% CI –4.24 to 0.33) (Figure 3). A prospective cohort study reported longer duration of follow up in the siltuximab treatment group compared (33 days [7–58]) to standard care (22.9 days [2–45]). (26)

Table 2. Patients Group and Clinical Outcomes of COVID-19 Patients in the Included Studies

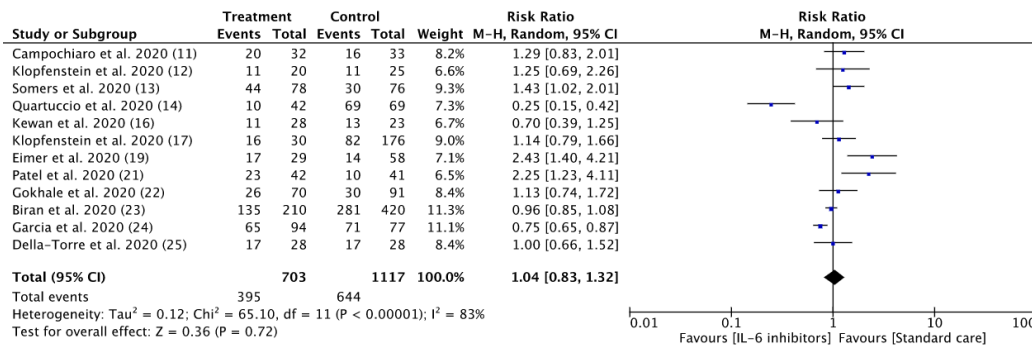


Figure 2. Risk of hospital discharge between IL-6 inhibitors and control groups. (Note= All of the studies were using Tocilizumab, except for Della-Torre et al. (25) with Sarilumab)

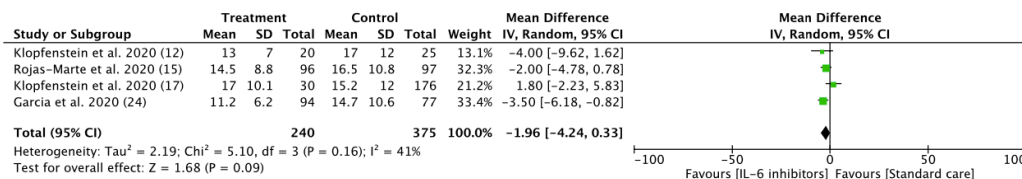


Figure 3. IL-6 inhibitors in reducing length of hospital stay. Weights are from random-effects analysis. (Note= All of the studies included were using Tocilizumab, Only studies reported the data in mean ± standard deviation [SD] were included in the analysis)

Mortality

Pooled analysis from twelve studies showed a lower risk of mortality in the IL-6 inhibitor treatment group compared to the control group, the difference also reach statistical significance (24,73 % vs 39,33 %; RR = 0,60, 95% CI 0.48–0,74; I² = 59% p < 0,00001) (**Figure 4.**). Two cohort studies reported (23, 26) the IL-6 inhibitor treatment group's decreased mortality rate. Prospective studies in Italy (25) reported that the sarilumab treatment group had a longer median time to death than the control group (19 days, IQR 13–26 vs four days, IQR 3–4; p=0.006). A prospective study of siltuximab treatment in COVID-19 reported a lower 30-day mortality rate than the control group (HR 0,462 , 95% [CI] 0.221–0.965; p=0.0399) (26).

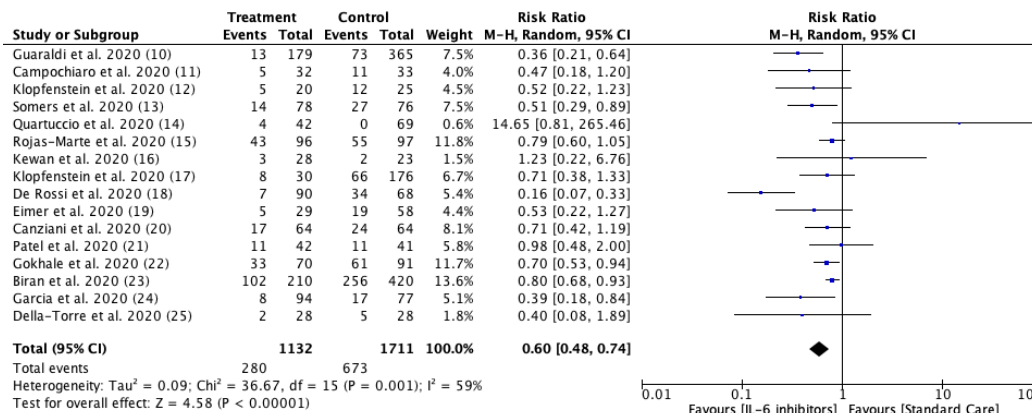


Figure 4. Risk of mortality between IL-6 inhibitors and control groups. (Note= All of the studies were using Tocilizumab, except for Della-Torre et al. (25) with Sarilumab)

Risk of Mechanical Ventilation

Pooled estimates from twelve studies showed a similar risk of mechanical ventilation between IL-6 Inhibitor treatment group and control group (16,53% vs 20,27%; RR = 0,68, 95% CI 0.29–1,60; I2 = 77%) (Figure 5.) A siltuximab treatment group in the prospective study showed the potential to reduced mechanical ventilation risk, although the results are not significant (HR 0.615; 95% CI 0.362–1.044) (26).

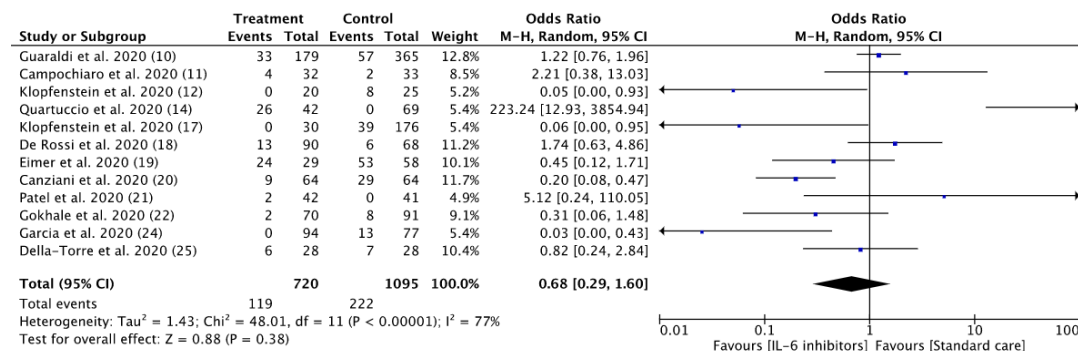


Figure 5. Risk of requirement for mechanical ventilation between IL-6 inhibitors and control groups. (Note= All of the studies were using Tocilizumab, except for Della-Torre et al. (25) with Sarilumab)

Discussion

COVID-19 primarily infects pneumocyte type II and cells expressing angiotensin-converting enzyme (ACE-2), which also serve as receptor and entry point for the virus (29). COVID-19 replication causing pyroptosis (apoptosis induced by inflammation) effects on its target cell, thus activating innate immunity and leading to the synthesis of pro-inflammatory cytokine by myeloid cells . COVID-19 also inhibits the synthesis of type I Interferon, which attenuates the body's immune response to the virus and provides a suitable environment for the virus to replicate rapidly. The Rapid increase of viral load and viral cytopathic effects induced a rapid progression of the inflammatory process, which lead to cytokine storm syndrome (29). CSS, marked by the uncontrolled release of the pro-inflammatory cytokine, may cause an increase of gas exchange, reducing pulmonary tissue oxygenation (31). Among those cytokines, several studies(32,33,34) suggest that IL-6 plays a crucial role in CSS's pathogenesis in COVID-19.

Monocytes and macrophages produce IL-6 after stimulated by Toll-like receptors and work through two different signal pathways. The first pathways are the classic pathway, in which IL-6 bind to transmembrane IL-6 (mIL-6R) and IL-6 soluble receptor (sIL-6R). The complex then binds to gp130 and triggered gene expression. The trans pathways are the second pathways, in which the complex of IL-6 and its receptors bind to signal transducer glycoprotein (gp130) and initiated intracellular signal transduction, thus initiated activation of

other pathways promoting cellular proliferation, differentiation, immune regulation, and oxidative stress (30).

The primary consideration of IL-6 inhibitors in the treatment of COVID-19 may be based on the ability to inhibit IL-6, which plays a central role in acute inflammation and cytokine release syndrome (27). At the time of writing this study, the Food and Drug Administration (FDA)-approved two classes of IL-6 Inhibitors; anti-IL-6 monoclonal antibodies (siltuximab) and anti-IL-6 receptor monoclonal antibodies (sarilumab, tocilizumab). Anti-IL-6 monoclonal antibodies (siltuximab) prevent IL-6 to binding to its receptors (both membranes bound and soluble receptors) and inhibit the formation between gp130 and hexameric signalling complex on the cell surface, thus hinder the activation of signal transducer and transcription signalling pathway (35). Anti-IL-6 receptor monoclonal antibodies (sarilumab and tocilizumab) bind to both transmembrane (mIL-6R) and soluble (sIL-6R) IL-6 receptor and inhibits both the classical and trans pathway of IL-6 signal transduction (36).

This study investigates the therapeutic effect of IL-6 Inhibitors based on four clinical outcomes; hospital discharge, length of stay, mortality rate, and mechanical ventilation risk. Based on an analysis of twelve studies, it was found that IL-6 inhibitors do not provide a beneficial effect on hospital discharge and length of stay. However, one retrospective study reported treatment of tocilizumab in critically ill COVID-19 patients might reduce the length of stay in ICU and hospital (19). A retrospective study in the USA also suggested an early administration of IL-6 Inhibitors (Sarilumab and tocilizumab) may help reduce the length of stay and needed mechanical ventilation(27).

The result of this study suggested the benefit of IL-6 inhibitors in reducing mortality rate based on an analysis of twelve studies. COVID-19 replication causing pyroptosis of the target cell, thus inducing synthesis of pro-inflammatory cytokine (28). The rapid increase of pro-inflammatory cytokine may lead to a cytokine storm, causing septic shock and multiple organ failure (29). IL-6 inhibitors may inhibit the pro-inflammatory cytokine, thus lower the disease's mortality. An observational study found that patient with rapid progressing COVID-19 respiratory failure may benefit from siltuximab treatment to reduce hyper inflammation driven by cytokine and mortality rate (26). A multicenter study in COVID-19 patient requiring ICU admission reported the favourable results of tocilizumab treatment to reduce hospital-related mortality, especially in patients required mechanical ventilator support and those younger than 65 years (23).

The analysis results of twelve studies in mechanical ventilation risk suggested that IL-6 inhibitors do not provide benefits to reducing mechanical ventilation risk in COVID-19 patients. A prospective study in Germany reported IL-6 as a strong predictor to mechanical ventilation (30), this results showed a potential of IL-6 inhibitors to lower the mechanical ventilation risk. Tocilizumab administered to non-critically ill COVID-19 patients in the early stage of inflammatory flare may reduce mechanical ventilation use (24). Two retrospective studies (20,21) reported a lower risk of mechanical ventilation initiation in patients receiving tocilizumab compared to those who do not receive anti-cytokine therapy.

There are some limitations regarding this review. First, the majority of included studies were using tocilizumab as treatment option, therefore lacking of another type of IL-6 drugs to be included in meta-analysis. In addition, most of the subjects were not homogenous in terms of baseline characteristics and most of the treatment group had more severe disease

at baseline compared with controls. Most of the studies included were retrospective studies with small sample size, which may result in low quality of evidence. Future well-designed randomized trials are needed for testing its efficacy to provide high-quality evidence to support the findings of this study.

Conclusion

IL-6 inhibitor agents have shown potential benefit in reducing risk of mortality in COVID-19 patients especially in severe disease. However, the appropriate dosage, drug administration, and the risk of serious adverse events remains unclear. Clinicians should consider the use of IL-6 inhibitor agents in well-established clinical trials to evaluating the benefit and risk of the drugs.

Conflict of Interests

The authors declare no conflict of interest regarding publication of this study.

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Abstract:	<p>Introduction</p> <p>Preliminary study showed that coronavirus disease 2019 (COVID-19) disrupt body immune system including dysregulation of cytokine interleukin-6 (IL-6). IL-6 inhibitors agents have been used as treatment option for COVID-19, yet their benefit as therapeutic agent remain unclear.</p> <p>Objective</p> <p>We performed a systematic review and meta-analysis to synthesize the available evidence on the potential therapeutic effect of IL-6 inhibitor agents for the treatment of COVID-19.</p> <p>Methods</p> <p>Two authors initially screened and reviewed the relevant studies from available databases. The data extracted will be tabulated and analyzed for the outcomes. The primary outcome was mortality. Secondary outcomes included discharge from hospital, length of stay, and requirement for mechanical ventilation. The quality of each study was assessed using OCEBM ratings.</p> <p>Results</p> <p>We reviewed 18 studies with a total of 3303 subjects. Tocilizumab was the most commonly used in the studies (15 studies). Meta-analysis of included studies revealed significant reduction in mortality with tocilizumab and sarilumab (RR = 0.61, 95% CI 0.49–0.76). Other outcomes including hospital discharge (RR = 1.04, 95% CI 0.86–1.24), length of stay (mean difference –1.96 days, 95% CI –4.24 to 0.33) or requirement for mechanical ventilation (RR = 0.68, 95% CI 0.32–1.45) revealed no differences of IL-6 inhibitor agents compared to controls.</p> <p>Conclusions</p> <p>Available evidences suggests that IL-6 inhibitor agents do reduce the risk of mortality in COVID-19 especially in severe disease. Further well-designed trials are needed for assessing its efficacy and safety for COVID-19</p>

Interleukin-6 (IL-6) inhibitors as therapeutic agents for COVID-19: A Systematic Review and Meta-Analysis

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Methods: Two authors initially screened and reviewed the relevant studies from available databases. The data extracted will be tabulated and analyzed for the outcomes. The primary outcome was mortality. Secondary outcomes included discharge from hospital, length of stay, and requirement for mechanical ventilation. Risk of bias was measured by Newcastle-Ottawa Scale. The quality of each study was assessed using OCEBM ratings.

Results: We reviewed 18 studies with a total of 3303 subjects. Tocilizumab was the most commonly used in the studies (15 studies). Meta-analysis of included studies revealed significant reduction in mortality with tocilizumab and sarilumab (RR = 0.61, 95% CI 0.49–0.76). Other outcomes including hospital discharge (RR = 1.04, 95% CI 0.86–1.24), length of stay (mean difference –1.96 days, 95% CI –4.24 to 0.33) or requirement for mechanical ventilation (RR = 0.68, 95% CI 0.32–1.45) revealed no differences of IL-6 inhibitor agents compared to controls.

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Keywords: COVID-19, SARS-CoV-2, Interleukin-6, IL-6

2. Review

Detailed Response to Reviewers

Interleukin-6 (IL-6) inhibitors as therapeutic agents for COVID-19: A Systematic Review and Meta-Analysis

Reviewers' Comments	Authors' Responses
List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	All the related variables and details can be found in the Table section at the end of the manuscript. We assessed the risk and quality of each evidence using The Oxford Center for Evidence-Based Medicine Quality ratings and classified the evidence ratings ranged from 1 to 5, with 1 representing high quality studies such as randomized controlled trial (RCT) and 5 representing case reports. (9) This rating was used to determine the evidence class of each included studies
Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	This study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (6)

3. Revisi

revision

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Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has set a major healthcare issues and economic burden worldwide. Since its outbreak in December 2019, researchers and physicians around the globe are working continuously through clinical trials and on-going research to find the cure and vaccine for COVID-19. Currently, treatments of COVID-19 are mainly repurposing drugs or symptomatic with no definitive treatment directed against the virus (1).

In the absence of specific treatment or antiviral drugs been proven against SARS-CoV-2, researchers have proposed many therapeutics agents used as adjunctive treatments for COVID-19 patients apart from supplemental oxygen therapy or mechanical ventilation. Cytokine storm is one of the main mechanisms of the disease and is believed to trigger an exaggerated immune response in the host and has been observed more frequently in severe COVID-19 patients. The dysregulation of inflammatory markers including IL-6 has been associated with COVID-19 complications, such as acute respiratory distress syndrome (ARDS) and other organ injuries, including neurological and cardiovascular diseases (2,3,4).

Monoclonal antibody against IL-6 receptors or IL-6 inhibitors has shown to be an effective agent in COVID-19 patients with severe illness (3,4). These drugs targeting IL-6 as inflammatory mediators will decrease inflammatory response in cytokine storm, minimizing the incidence of jeopardizing complications, such as ARDS, and improving clinical outcome and decrease in mortality rate (3,4). Tocilizumab and other IL-6 inhibitors have been approved by the Food and Drug Administration (FDA) for the management of severely ill patients with COVID-19 (4,5). This review provides a summary of current evidences regarding interleukin-6 (IL-6) inhibitors drugs for treatment of COVID-19.

Methods

This study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (6)

Search Strategy

A systematic literature search of the available studies was conducted on PubMed and medRxiv for articles published until November 2020. Additionally, we examined the bibliography of the selected articles for further potential studies. The search terms used were “interleukin 6,” OR “IL-6,” OR “tocilizumab,” OR "sarilumab," OR "siltuximab." AND “COVID-19,” OR “SARS-CoV-2” and their derivatives.

Inclusion and Exclusion Criteria

We included only studies that compared the effectiveness of the IL-6 inhibitors with placebo or other agents for treatment of COVID-19. The following inclusion criteria were utilized for article selection: (1) involve human patients with COVID-19; (2) be either a randomized controlled trial, prospective trial, retrospective analysis; (3) reported at least one clinical outcome, including hospital discharge, length of stay, mortality, and requirement for mechanical ventilation

1 The literatures were restricted to English language articles only. The exclusion criteria
2 were as follows: (i) non-original studies, such as meta-analyses, conference papers,
3 comments, or consensus documents; (ii) case reports or case series; (iii) single-arm trials; (iv)
4 studies that did not report outcomes for IL-6 inhibitor drugs in COVID-19, and studies that
5 did not compare the outcomes with IL-6 inhibitor drugs compared to the placebo or control.

6 The primary outcome was mortality. Secondary outcomes included discharge from
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9 ***Study Selection and Data Extraction***

10 Two authors (VOW and RBB) independently screened and examined the titles and
11 abstract, followed by full-text review, using pre-defined criteria. In the event of disagreement
12 between the two authors, consensus discussion would help to resolve the issue and make a
13 final decision. Studies that entirely fulfilled our inclusion criteria were retrieved and
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17 We extracted and tabulated the following data: author(s), year of publication, study
18 design, country, baseline characteristics, details of the regimen of IL-6 inhibitors and
19 comparative agents, and clinical outcomes.
20

21 ***Data analysis***

22 Statistical analysis was conducted using the software Review Manager v.5.3 (Cochrane
23 Collaboration). The degree of heterogeneity was evaluated with the Q statistic generated from
24 the χ^2 test. Heterogeneity was assessed using the I² measure. Heterogeneity was defined as
25 significant when the P-value was <0.05 or the I² > 50%. A random-effects model was
26 applied when data were considered heterogeneous. The pooled risk ratio (RR) and 95%
27 confidence interval (CI) were calculated for the outcomes of mortality, hospital discharge,
28 and requirement for mechanical ventilation. In case of continuous variables, the mean
29 difference for each study was calculated and plotted. P- value of <0.05 was considered
30 statistically significant. (7,8)

31 ***Study Quality Assessment***

32 We assessed the quality of evidence using The Oxford Center for Evidence-Based Medicine
33 Quality ratings and classified the evidence ratings ranged from 1 to 5, with 1 representing
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36 **Results**

37 ***Study Characteristics***

38 The search strategy initially generated 1213 articles. After removal of duplicates and
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40 18 articles were included in the final review including 1 RCT, 14 cohorts and 3 case control.
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Figure 1. Flow diagram of included studies

Table 2. Patients Group and Clinical Outcomes of COVID-19 Patients in the Included Studies

Study or Subgroup	Treatment		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Campochiaro et al. 2020 (11)	20	32	16	33	7.0%	1.29 [0.83, 2.01]	
Klopfenstein et al. 2020 (12)	11	20	11	25	5.2%	1.25 [0.69, 2.26]	
Somers et al. 2020 (13)	44	78	30	76	8.5%	1.43 [1.02, 2.01]	
Quartuccio et al. 2020 (14)	10	42	69	69	6.0%	0.25 [0.15, 0.42]	
Kewan et al. 2020 (16)	11	28	13	23	5.3%	0.70 [0.39, 1.25]	
Klopfenstein et al. 2020 (17)	16	30	82	176	8.0%	1.14 [0.79, 1.66]	
Eimer et al. 2020 (19)	17	29	14	58	5.7%	2.43 [1.40, 4.21]	
Patel et al. 2020 (21)	23	42	10	41	5.1%	2.25 [1.23, 4.11]	
Gokhale et al. 2020 (22)	26	70	30	91	7.3%	1.13 [0.74, 1.72]	
Biran et al. 2020 (23)	135	210	281	420	11.5%	0.96 [0.85, 1.08]	
Garcia et al. 2020 (24)	65	94	71	77	11.2%	0.75 [0.65, 0.87]	
Della-Torre et al. 2020 (25)	17	28	17	28	7.3%	1.00 [0.66, 1.52]	
Stone et al. 2020 (27)	147	161	72	81	11.8%	1.03 [0.94, 1.12]	
Total (95% CI)		864		1198	100.0%	1.04 [0.86, 1.24]	
Total events		542	716				
Heterogeneity: Tau ² = 0.07; Chi ² = 66.90, df = 12 (P < 0.00001); I ² = 82%							
Test for overall effect: Z = 0.38 (P = 0.71)							

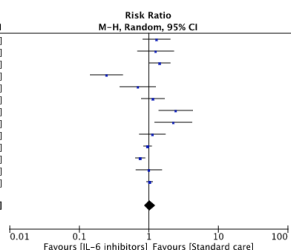


Figure 2. Risk of hospital discharge between IL-6 inhibitors and control groups. (Note= All of the studies were using Tocilizumab, except for Della-Torre et al. (25) with Sarilumab)

Study or Subgroup	Treatment		Control		Weight	Mean Difference		
	Mean	SD	Mean	SD		IV, Random, 95% CI	IV, Random, 95% CI	
Klopfenstein et al. 2020 (12)	13	7	20	17	12	25	13.1%	-4.00 [-9.62, 1.62]
Rojas-Martel et al. 2020 (15)	14.5	8.8	96	16.5	10.8	97	32.3%	-2.00 [-4.78, 0.78]
Klopfenstein et al. 2020 (17)	17	10.1	30	15.2	12	176	21.2%	1.80 [-2.23, 5.83]
Garcia et al. 2020 (24)	11.2	6.2	94	14.7	10.6	77	33.4%	-3.50 [-6.18, -0.82]
Total (95% CI)			240		375	100.0%	-1.96 [-4.24, 0.33]	
Heterogeneity: Tau ² = 2.19; Chi ² = 5.10, df = 3 (P = 0.16); I ² = 41%								
Test for overall effect: Z = 1.68 (P = 0.09)								

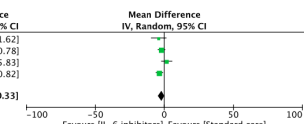


Figure 3. IL-6 inhibitors in reducing length of hospital stay. Weights are from random-effects analysis. (Note= All of the studies included were using Tocilizumab. Only studies reported the data in mean ± standard deviation [SD] were included in the analysis)

4. Accepted

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Interleukin-6 (IL-6) inhibitors as therapeutic agents for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis



Rizaldy Taslim Pinzon^{a,b,*}, Vincent Ongko Wijaya^{a,b}, Ranbebasa Bijak Buana^{a,b}

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Results: We reviewed 18 studies with a total of 3303 subjects. Tocilizumab was the most commonly used in the studies (15 studies). Meta-analysis of included studies revealed significant reduction in mortality with tocilizumab and sarilumab (RR = 0.61, 95% CI 0.49–0.76). Other outcomes including hospital discharge (RR = 1.04, 95% CI 0.86–1.24), length of stay (mean difference –1.96 days, 95% CI –4.24 to 0.33) or requirement for mechanical ventilation (RR = 0.68, 95% CI 0.32–1.45) revealed no differences of IL-6 inhibitor agents compared to controls.

Conclusions: Available evidence suggests that IL-6 inhibitor agents reduce the risk of mortality in COVID-19, especially in severe conditions. Further well-designed trials are needed for assessing its efficacy and safety for COVID-19.

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In the absence of specific treatment or antiviral drugs been proven against SARS-CoV-2, researchers have proposed many therapeutics agents used as adjunctive treatments for COVID-19

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Monoclonal antibody against IL-6 receptors or IL-6 inhibitors has shown to be an effective agent in COVID-19 patients with severe illness [34]. These drugs targeting IL-6 as inflammatory mediators will decrease inflammatory response in cytokine storm, minimizing the incidence of jeopardizing complications, such as ARDS, and improving clinical outcome and decrease in mortality rate [3,4]. Tocilizumab and other IL-6 inhibitors have been approved by the Food and Drug Administration (FDA) for the management of severely ill patients with COVID-19 [4,5]. This review summarizes

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current evidence regarding interleukin-6 (IL-6) inhibitors drugs for the treatment of COVID-19.

Methods

This study was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6].

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We included only studies that compared the effectiveness of the IL-6 inhibitors with placebo or other agents for treatment of COVID-19. The following inclusion criteria were utilized for article selection: [1] involve human patients with COVID-19 [2]; be either a randomized controlled trial, prospective trial, retrospective analysis [3]; reported at least one clinical outcome, including hospital discharge, length of stay, mortality, and requirement for mechanical ventilation

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We extracted and tabulated the following data: author(s), year of publication, study design, country, baseline characteristics, details of the regimen of IL-6 inhibitors and comparative agents, and clinical outcomes.

Data analysis

Statistical analysis was conducted using the software Review Manager v.5.3 (Cochrane Collaboration). The degree of heterogeneity was evaluated with the Q statistic generated from the χ^2 test. Heterogeneity was assessed using the I² measure. Heterogeneity was defined as significant when the P-value was <0.05 or the I² > 50%. A random-effects model was applied when data were considered heterogeneous. The pooled risk ratio (RR) and 95% confidence interval (CI) were calculated for the outcomes of mortality, hospital discharge, and requirement for mechanical ventilation. In case of

continuous variables, the mean difference for each study was calculated and plotted. P-value of <0.05 was considered statistically significant [7,8].

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Results

Study characteristics

The search strategy initially generated 1213 articles. After removal of duplicates and abstract screening, 113 full-text articles were subsequently assessed for its eligibility. Finally, 18 articles were included in the final review including 1 RCT, 14 cohorts and 3 case control. Fig. 1 shows the PRISMA flow chart of study selection. Table 1 summarizes the baseline characteristics of all the 18 studies, including the study quality ratings.

Of the 18 non-randomized articles reported the use of IL-6 inhibitor and its comparator for COVID-19, 16 studies using tocilizumab [10–24,27], 1 using sarilumab [25], and 1 using siltuximab [26]. The therapeutic interventions, drug dosing, IL-6 markers, and clinical outcomes are presented in Table 2. Most of the included studies were from Italy, with 7 studies, followed by the United States (US) with 6 studies, France with 2 studies, Spain with 1 study, Sweden with 1 study, and India with 1 study, respectively. Overall, this review included a total of 3303 patients, including 1265 in the tocilizumab group, 28 in the sarilumab group, 30 in the siltuximab group and 1980 in the control group. All the subjects in intervention group also received standard treatment in addition with IL-6 inhibitor drugs.

A single dose of 400 mg or 8 mg/kg intravenous was the most commonly reported regimen of Tocilizumab. In 8 out of 16 studies [10–12,17,20–24] suggested that the second dose of Tocilizumab may be administered based on physician judgment. In one study, Della-Torre et al. [25] used intravenous injection of sarilumab of 400 mg. Gritti et al. [26] also used 11 mg/kg of intravenous injection of siltuximab. The use of hydroxychloroquine, antivirals, azithromycin, or anticoagulants were the most commonly reported regimen included in standard treatment.

Clinical outcome

Hospital discharge and length of stay

Analysis of the thirteen included studies revealed that patients with COVID-19 had a similar risk to be discharged from hospital during study follow-up in the IL-6 treatment group compared with the control group (62.7% vs 59.8%; RR = 1.04, 95% CI 0.86–1.24; I² = 82%) (Fig. 2). The patient's group and clinical outcomes are shown in Table 2. Evidence from 3 case control and 1 cohort studies in patients treated with tocilizumab suggested potential but uncertain effects on decreasing length of hospital stay (weighted MD –1.96, 95% CI –4.24 to 0.33) (Fig. 3). A prospective cohort study reported longer duration of follow up in the siltuximab treatment group compared (33 days [7–58]) to standard care (22.9 days [2–45]). [26].

Mortality

Pooled analysis from thirteen studies showed a lower risk of mortality in the IL-6 inhibitor treatment group compared to the control group, the difference also reach statistical significance

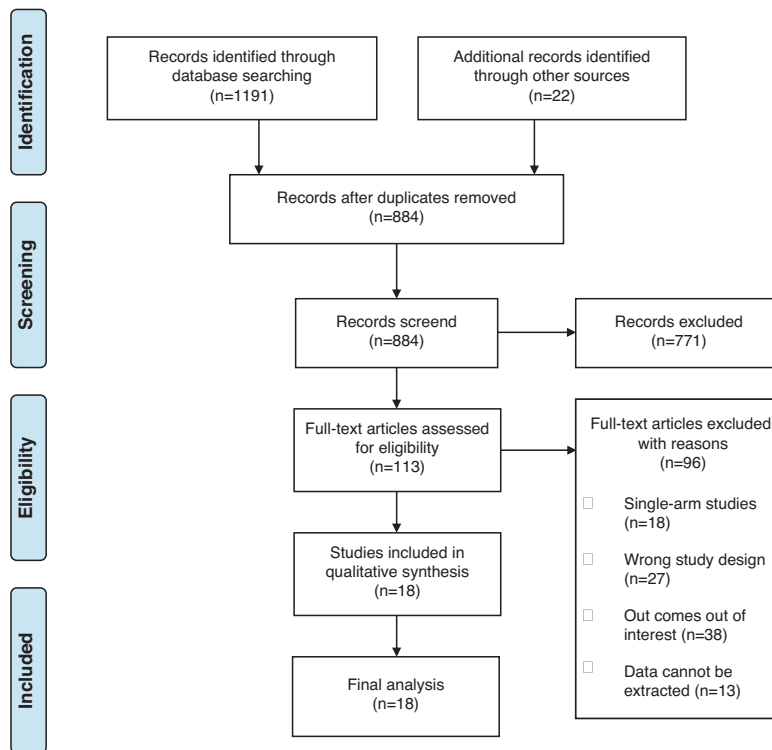


Fig. 1. Flow diagram of included studies.

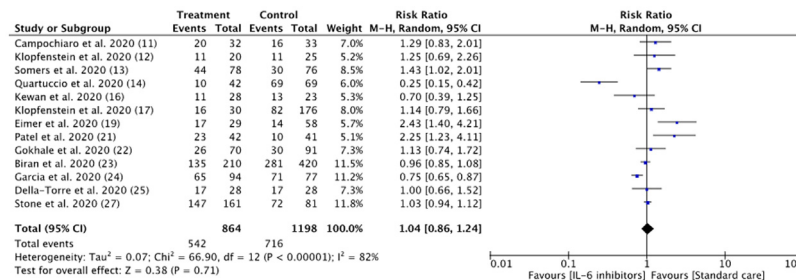


Fig. 2. Risk of hospital discharge between IL-6 inhibitors and control groups. (Note = All of the studies were using Tocilizumab, except for Della-Torre et al. [25] with Sarilumab).

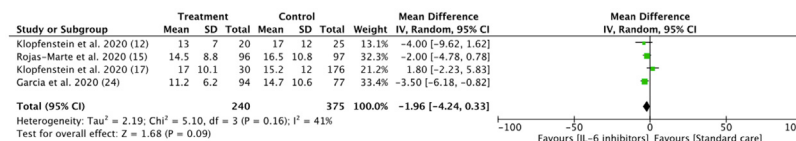


Fig. 3. IL-6 inhibitors in reducing length of hospital stay. Weights are from random-effects analysis. (Note = All of the studies included were using Tocilizumab, Only studies reported the data in mean ± standard deviation [SD] were included in the analysis).

(22.35% vs 37.72%; RR = 0.61, 95% CI 0.49–0.76; I² = 58% p < 0.00001) (Fig. 4). Two cohort studies reported [23,26] the IL-6 inhibitor treatment group's decreased mortality rate. Prospective studies in Italy [25] reported that the sarilumab treatment group had a longer median time to death than the control group (19 days, IQR 13–26 vs four days, IQR 3–4; p = 0.006). A prospective study of siltuximab treatment in COVID-19 reported a lower 30-day mortality rate than the control group (HR 0.462, 95% [CI] 0.221–0.965; p = 0.0399) [26].

Risk of mechanical ventilation

Pooled estimates from thirteen studies showed a similar risk of mechanical ventilation between IL-6 Inhibitor treatment group and control group (14.75% vs 19.55%; RR = 0.68, 95% CI 0.32–1.45;

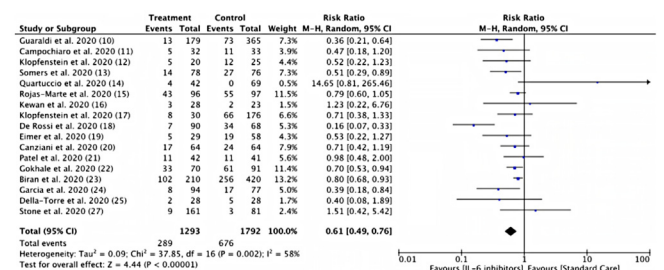


Fig. 4. Risk of mortality between IL-6 inhibitors and control groups. (Note = All of the studies were using Tocilizumab, except for Della-Torre et al. [25] with Sarilumab).

Table 1
Baseline characteristics of patients in the included studies.

Authors	Study Type	Country Location	No. of participants, n (%)	Severity, n (%)	Age, Median (IQR, y) or Mean ± SD	Study Quality Level
Guaraldi et al. 2020 [10]	Retrospective Cohort	Modena, Italy	544 COVID-19 patients	Severe, 544 (100%)	67 (56–77)	2
Campochiaro et al. 2020 [11]	Retrospective Cohort	Milan, Italy	65 COVID-19 patients	Severe, 65 (100%)	Treatment = 64 (53–75), Control = 60 (55–75.5)	2
Klopfenstein et al. 2020 [12]	Case Control	France	45 COVID-19 patients	Critical, 20 (44%)	Treatment = 76.8 (52–93), Control = 70.7 (33–96)	3
Somers et al. 2020 [13]	Retrospective Cohort	United States	154 COVID-19 patients	Severe, 154 (100%)	58 ± 14.9	2
Quartuccio et al. 2020 [14]	Retrospective Cohort	Udine, Italy	111 COVID-19 patients	NR	Treatment = 62.4 ± 11.8, Control = 56.2 ± 14.2	2
Rojas-Marte et al. 2020 [15]	Case Control	United States	193 COVID-19 patients	Critical, 121 (62.7%); Very Severe, 59 (30.6%)	60.4 ± 13.8	3
Kewan et al. 2020 [16]	Retrospective Cohort	United States	51 COVID-19 patients	Severe, 51 (100%)	65 (53–74)	2
Klopfenstein et al. 2020 [17]	Case Control	France	206 COVID-19 patients	Critical, 30 (14.6%)	Treatment = 75.6 ± 11.3, Control = 74.3 ± 11	3
De Rossi et al. 2020 [18]	Retrospective Cohort	Brescia, Italy	158 COVID-19 patients	NR	Treatment = 62.9 ± 12.5, Control = 71 ± 14.6	2
Eimer et al. 2020 [19]	Retrospective Cohort	Sweden	87 COVID-19 patients	Moderate, 11 (13%) Severe, 76 (87%)	Treatment = 58 (49–63), Control = 55 (52–64.8)	2
Canziani et al. 2020 [20]	Retrospective Cohort	Italy	128 COVID-19 patients	NR	63 ± 10	2
Patel et al. 2020 [21]	Retrospective Cohort	United States	83 COVID-19 patients	Severe, 42 (51%) Severe, 41 (49%)	Treatment = 68 (25–96), Control = 67 (20–91)	2
Gokhale et al. 2020 [22]	Retrospective Cohort	India	161 COVID-19 patients	Severe, 161 (100%)	Treatment = 52 (44–57), Control = 55 (48–65)	2
Biran et al. 2020 [23]	Retrospective Cohort	United States	630 COVID-19 patients	Severe, 630 (100%)	Treatment = 62 (53–71), Control = 65 (56–74)	2
Garcia et al. 2020 [24]	Retrospective Cohort	Spain	171 COVID-19 patients	NR	Treatment = 61.5 ± 12.4, Control = 61.4 ± 16	2
Della-Torre et al. 2020 [25]	Prospective Cohort	Milan, Italy	56 COVID-19 patients	Severe, 56 (100%)	Treatment = 56 (49–60), Control = 57 (52–60)	2
Gritti et al. 2020 [26]	Prospective Cohort	Italy	60 COVID-19 patients	Severe, 30 (100%)	Treatment = 64 (57–66), Control = 65.5 (56–70)	2
Stone et al. 2020 [27]	Randomized Controlled Trial	United States	242 COVID-19 patients	NR	Treatment = 61.6 (46.4–69.7), Control = 56.5 (44.7–67.8)	1

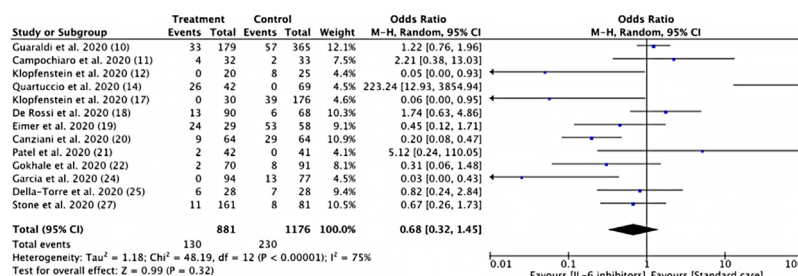


Fig. 5. Risk of requirement for mechanical ventilation between IL-6 inhibitors and control groups. (Note = All of the studies were using Tocilizumab, except for Della-Torre et al. [25] with Sarilumab).

I² = 75%) (Fig. 5). A siltuximab treatment group in the prospective study showed the potential to reduced mechanical ventilation risk, although the results are not significant (HR 0.615; 95% CI 0.362–1.044) [26].

Discussion

COVID-19 primarily infects pneumocyte type II and cells expressing angiotensin-converting enzyme (ACE-2), which also

Table 2
Patients group and clinical outcomes of COVID-19 patients in the included studies.

Authors	Treatment (no. of patients)	Control (no. of patients)	Baseline IL-6 level, pg/mL (Median [range] or Mean \pm SD)	Discharge, n (%)	Length of Stay, days (Median [range] or Mean \pm SD)		Death, n (%)	Mechanical Ventilation, n (%)	Other outcomes
					Treatment Group	Control Group			
Guaraldi et al. 2020 [10]	Tocilizumab 8 mg/kg i.v. repeated after 12 h (n = 88), 324 mg s.c. once (n = 91) + standard treatment	Standard treatment (hydroxychloroquine/azithromycin/antiretrovirals/low molecular weight heparin), (n = 365)	178.6 (67.6–402)	NR	12 (6–17)	8 (4–14)	86 (16%)	90 (17%)	
Campochiaro et al. 2020 [11]	Tocilizumab 400 mg i.v. once, repeated after 24 h in case of worsening + standard treatment (n = 32)	Standard treatment (hydroxychloroquine 400 mg daily, lopinavir/ritonavir 400/100 mg twice daily, ceftriaxone 2 g for 6 days, azithromycin 500 mg daily, enoxaparin 4000 UI once a day) (n = 33)	NR	36 (55%)	13.5 (10–16.7)	14 (12–15.5)	16 (25%)	1 (3%)	Patients with age <75 years had a higher survival (HR 1.46, 1.03–2.08, p = 0.03)
Klopfenstein et al. 2020 [12]	Tocilizumab 1 or 2 doses + standard treatment (n = 20)	Standard treatment (hydroxychloroquine/lopinavir-ritonavir and antibiotics,) (n = 25)	NR	22 (49%)	13 \pm 7	17 \pm 12	16 (36%)	8 (18%)	
Somers et al. 2020 [13]	Tocilizumab 8 mg/kg i.v. once + standard treatment (n = 78)	Standard treatment (n = 76)	NR	74 (48%)	20.4 (13.8–35.8)	22.9 (16.3–28.5)	41 (27%)	154 (100%) ^a	Rate of Superinfection, Treatment = 42 (54%); Control = 20 (26%)
Quartuccio et al. 2020 [14]	Tocilizumab 8 mg/kg i.v. once + standard treatment (n = 42)	Standard treatment (antivirals/antimalarials/glucocorticoids/antibiotics/anticoagulant) (n = 69)	Treatment = 63.5 (37–136), Control = 18.5 (10–33)	79 (72%)	NR	NR	4 (4%)	26 (23%)	Recovered or Improvement, Treatment = 30 (71%), Control = 69 (100%)
Rojas-Martel et al. 2020 [15]	Tocilizumab one dose + standard treatment (n = 96)	Standard treatment (hydroxychloroquine/remdesivir/corticosteroids/anticoagulants and azithromycin) (n = 97)	NR	NR	14.5 \pm 8.8	16.5 \pm 10.8	90 (50.8%)	121 (62.7%) ^a	Bacteremia was more commonly in the control group compared to tocilizumab group (23.7% vs. 12.5%, P = 0.04), whereas fungemia was similar in both groups (4% vs. 3% P = 0.7).
Kewan et al. 2020 [16]	Tocilizumab 8 mg/kg i.v. up to 400 mg once + standard treatment (n = 28)	Standard treatment (hydroxychloroquine/corticosteroids and azithromycin) (n = 23)	Treatment = 14 (8–59), Control = 35 (16–55)	24 (47%)	11 (6–22.25)	7(5–13.5)	5 (10%)	32 (63%) ^a	Among patients aged >65 years and required invasive ventilation, tocilizumab group had higher rate of clinical improvement [40% vs. 13%, p = 0.20], shorter median time to clinical improvement [8 days (5–14.5) vs. 12.5 (7.75–17.5), p = 0.53], and shorter median duration of vasopressor support [2.5 days (1.75–3.25) vs. 6.5 days (4.25–9.5), p = 0.011], compared to control

Table 2 (Continued)

Authors	Treatment (no. of patients)	Control (no. of patients)	Baseline IL-6 level, pg/mL (Median [range] or Mean \pm SD)	Discharge, n (%)	Length of Stay, days (Median [range] or Mean \pm SD)		Death, n (%)	Mechanical Ventilation, n (%)	Other outcomes
					Treatment Group	Control Group			
Klopfenstein et al. 2020 [17]	Tocilizumab 8 mg/kg i.v. one or two doses + standard treatment (n = 30)	Standard treatment (hydroxychloroquine/lopinavir-ritonavir/corticosteroids and antibiotics) (n = 176)	Treatment = 549 (3–4156), Control = 179 (66–399)	98 (48%)	17 \pm 10.1	15.2 \pm 12	74 (36%)	39 (22%)	
De Rossi et al. 2020 [18]	Tocilizumab 400 mg i.v (n = 43) or 324 mg s.c (n = 47) + standard treatment	Standard treatment (hydroxychloroquine 400 mg daily, lopinavir 800 mg plus ritonavir 200 mg per day) (n = 68)	NR	NR	NR	NR	41 (26%)	19 (12%)	Twelve patients in treatment group (13.3%) had pulmonary embolism, three reported died.
Eimer et al. 2020 [19]	Tocilizumab 8 mg/kg i.v. once + routine care (n = 29)	Routine care (n = 58)	Treatment = 351 (154–1193), Control = 180.5 (105.8–335.2)	31 (36%)	20.5 [16.5–30]	30 [21.5–30],	24 (28%)	77 (89%)	Treatment group had shorter length of stay (days) in ICU (12 [6.8–17.2] vs 20 [9.8–30], p = 0.04) and hospital (20.5 [16.5–30] vs 30 [21.5–30], p = 0.04), compared to control group Blood stream infection (17.2% vs. 24.1%, P = 0.65), ventilator-associated pneumonia(20.7% vs. 32.8%, P = 0.36), and pulmonary embolism(20.7% vs. 22.4%, P = 1.00) were more commonly in the control group compared to treatment group
Canziani et al. 2020 [20]	Tocilizumab 8 mg/kg i.v. repeated after 24 h + standard treatment (n = 64)	standard treatment (hydroxychloroquine/direct antivirals/antibiotics [ceftriaxone, azithromycin, piperacillin and tazobactam]/glucocorticoids [IV methylprednisolone 1–2 mg/kg/day]/prophylactic enoxaparin) (n = 64)	179 \pm 193	NR	NR	NR	41 (32%)	38/102 (34%)	The use of tocilizumab was not associated with the risk of thrombotic vascular events, bleeding, or infection (p > 0.05).
Patel et al. 2020 [21]	Tocilizumab 8 mg/kg i.v. repeated after 24 h + standard treatment (n = 42)	standard treatment (hydroxychloroquine/ antivirals/vitamin C) (n = 41)	Treatment; Severe = 61 \pm 107, Critical = 342 \pm 783	33 (40%)	NR	NR	22 (27%)	2 (2%)	At the time of last follow up (day 7), treatment group had lower rate of hospitalization (19% vs 48.8%) compared to control group
Gokhale et al. 2020 [22]	Tocilizumab 400 mg i.v + standard treatment once (n = 70)	standard treatment (antibiotics, hydroxychloroquine 400 mg once daily, ivermectin 12 mg once daily, oseltamivir 75 mg twice daily, low molecular weight heparin 1 mg/ kg s.c once daily, methylprednisolone 125500 mg i.v once daily) (n = 91)	NR	56 (35%)	14 (9–25.5)	6 (3–14)	94 (58%)	10 (6%)	

Table 2 (Continued)

Authors	Treatment (no. of patients)	Control (no. of patients)	Baseline IL-6 level, pg/mL (Median [range] or Mean \pm SD)	Discharge, n (%)	Length of Stay, days (Median [range] or Mean \pm SD)		Death, n (%)	Mechanical Ventilation, n (%)	Other outcomes
					Treatment Group	Control Group			
Biran et al. 2020 [23]	Tocilizumab 4 mg/kg i.v. one or two doses + standard treatment (n = 210)	Standard treatment (n = 420)	Treatment = 29 (9–96), Control = 18.5 (7–49.75)	416 (66%)	NR	NR	358 (57%)	587 (93%)	Among 286 patients with C-reactive protein levels of 15 mg/dL or higher, tocilizumab exposure was associated with decreased hospital-related mortality (HR 0.48, 95% CI 0.30–0.77; p = 0.0025)
Garcia et al. 2020 [24]	Tocilizumab 4–6 mg/kg/12 h i.v. up to three doses + standard treatment (n = 94)	Standard treatment (lopinavir/ritonavir 400/100 mg BID for 7–14 days + hydroxychloroquine 200–400 mg/12 h for 5 days + azithromycin 250–500 mg/24 h for 5 days) (n = 77)	NR	136 (79.5%)	11.2 \pm 6.2	14.7 \pm 10.6	25 (15%)	13 (8%)	Comorbidities, oxygen requirement upon admission, C-reactive protein level >16 mg/dl, and complications were significantly associated with mortality and ICU admission
Della-Torre et al. 2020 [25]	Sarilumab 400 mg i.v. once + standard treatment (n = 28)	Standard treatment (lopinavir/ritonavir, hydroxychloroquine and azithromycin) (n = 28)	Treatment = 67.5 (37.5–127), Control = 46 (34–117)	34 (61%)	12 (8–20)	13 (10–20)	7 (12.5%)	13 (23%)	Median time to death was significantly longer in the sarilumab group (19 days, IQR 13–26 vs 4 days, IQR 3–4; p = 0.006) compared to control. At 28-day follow-up, CRP returned to normal value in 86% patients treated with sarilumab and in 61% patients in the control group (p = 0.06) Adverse events were reported more frequently in the sarilumab group compared to the control group (43 vs 36%) Serum IL-6 level, PaO ₂ /FiO ₂ ratio, the percentage of lung consolidation and total volume of consolidated lung were associated with clinical improvement in patients treated with sarilumab
Gritti et al. 2020 [26]	Siltuximab 11 mg/kg i.v. one or two doses + standard treatment (n = 30)	Standard treatment (antivirals, hydroxychloroquine, and low molecular weight heparin) (n = 30)	Treatment = 129.86 (74.56–237.88)	16/30 (53%) ^a	33 (7–58)	22.9 (2–45)	10/30 (33%) ^a	5/30 (17%) ^a	Adverse events in Siltuximab group: cerebrovascular events, 1/30 (3%), infection 13/30 (43%) The 30-day mortality rate was significantly lower in the siltuximab-treated than the matched-control cohort patients (HR 0.462, 95% CI 0.221–0.965); p = 0.0399).
Stone et al. 2020 [27]	Tocilizumab 8 mg/kg i.v. single dose + standard treatment (n = 161)	Standard treatment (antivirals, hydroxychloroquine, and glucocorticoids) (n = 81)	Treatment = 23.6 (14–49.9), Control = 25.4 (14.6–40.3)	219 (90%)	6.0 (4.0–7.0)	6.0 (5.0–6.0)	12 (0.5%)	19 (0.8%)	Patients in tocilizumab treatment had fewer serious infections than patients who received standard care.

^a Study by Gritti et al [26] was not included in meta-analysis because its only reported the outcomes in treatment group.

serve as receptor and entry point for the virus [30]. COVID-19 replication causing pyroptosis (apoptosis induced by inflammation) effects on its target cell, thus activating innate immunity and leading to the synthesis of pro-inflammatory cytokine by myeloid cells. COVID-19 also inhibits the synthesis of type I Interferon, which attenuates the body's immune response to the virus and provides a suitable environment for the virus to replicate rapidly. The Rapid increase of viral load and viral cytopathic effects induced a rapid progression of the inflammatory process, which lead to cytokine storm syndrome [30]. CSS, marked by the uncontrolled release of the pro-inflammatory cytokine, may cause an increase of gas exchange, reducing pulmonary tissue oxygenation [32]. Among those cytokines, several studies [33–35] suggest that IL-6 plays a crucial role in CSS's pathogenesis in COVID-19.

Monocytes and macrophages produce IL-6 after stimulated by Toll-like receptors and work through two different signal pathways. The first pathways are the classic pathway, in which IL-6 bind to transmembrane IL-6 (mIL-6R) and IL-6 soluble receptor (sIL-6R). The complex then binds to gp130 and triggered gene expression. The trans pathways are the second pathways, in which the complex of IL-6 and its receptors bind to signal transducer glycoprotein (gp130) and initiated intracellular signal transduction, thus initiated activation of other pathways promoting cellular proliferation, differentiation, immune regulation, and oxidative stress [31].

The primary consideration of IL-6 inhibitors in the treatment of COVID-19 may be based on the ability to inhibit IL-6, which plays a central role in acute inflammation and cytokine release syndrome [28]. Anti-IL-6 monoclonal antibodies (siltuximab) prevent IL-6 to binding to its receptors (both membranes bound and soluble receptors) and inhibit the formation between gp130 and hexameric signalling complex on the cell surface, thus hinder the activation of signal transducer and transcription signalling pathway [36]. Anti-IL-6 receptor monoclonal antibodies (sarilumab and tocilizumab) bind to both transmembrane (mIL-6R) and soluble (sIL-6R) IL-6 receptor and inhibits both the classical and trans pathway of IL-6 signal transduction [37].

This study investigates the therapeutic effect of IL-6 Inhibitors based on four clinical outcomes; hospital discharge, length of stay, mortality rate, and mechanical ventilation risk. Based on an analysis of twelve studies, it was found that IL-6 inhibitors do not provide a beneficial effect on hospital discharge and length of stay. However, one retrospective study reported treatment of tocilizumab in critically ill COVID-19 patients might reduce the length of stay in ICU and hospital [19]. A retrospective study in the USA also suggested an early administration of IL-6 Inhibitors (Sarilumab and tocilizumab) may help reduce the length of stay and needed mechanical ventilation [28].

The result of this review suggested the benefit of IL-6 inhibitors in reducing mortality rate based on an analysis of thirteen studies. This result is in line with several recent systematic reviews that reported a lower mortality rate in the tocilizumab group than the control group [29,38–41]. COVID-19 replication causing pyroptosis of the target cell, thus inducing synthesis of pro-inflammatory cytokine [28]. The rapid increase of pro-inflammatory cytokine may lead to a cytokine storm, causing septic shock and multiple organ failure [30]. IL-6 inhibitors may inhibit the pro-inflammatory cytokine, thus lower the disease's mortality. An observational study found that patient with rapid progressing COVID-19 respiratory failure may benefit from siltuximab treatment to reduce hyper inflammation driven by cytokine and mortality rate [26]. A multicenter study in COVID-19 patient requiring ICU admission reported the favorable results of tocilizumab treatment to reduce hospital-related mortality, especially in patients required mechanical ventilator support and those younger than 65 years [23].

The analysis results of thirteen studies in mechanical ventilation risk suggested that IL-6 inhibitors do not provide benefits to reduc-

ing mechanical ventilation risk in COVID-19 patients. The recent RCT reported the Tocilizumab was not effective in preventing intubation in moderately ill COVID-19 patients, with a hazard ratio of 0.83 compared to the control group (95% confidence interval [CI], 0.38 to 1.81; $P = 0.64$), this study suggested the Tocilizumab failure to affect clinical outcome possibly because elevated Interleukins level represent host responses to infection rather than a self-amplifying inflammatory loop that would benefit from IL-6 inhibitors. [27] Unlike our study, a previous systematic review reported the benefit of tocilizumab to lower mechanical ventilation risk [39]. A prospective study in Germany reported IL-6 as a strong predictor of mechanical ventilation [31], these results showed the potential of IL-6 inhibitors to lower the mechanical ventilation risk. Tocilizumab administered to non-critically ill COVID-19 patients in the early stage of inflammatory flare may reduce mechanical ventilation use [24]. Two retrospective studies [20,21] reported a lower risk of mechanical ventilation initiation in patients receiving tocilizumab than those who do not receive anti-cytokine therapy.

Additionally, previous study shows that COVID-19-associated neurological diseases were linked with elevated levels of IL-6, and other inflammatory markers in the cerebrospinal fluid [42]. Conversely, increased serum levels of IL-6 was associated with an incidence of encephalopathy in a COVID-19 patient. Furthermore, the treatment with tocilizumab resolved the neuropsychiatric manifestations of the patient [42,43]. These findings may be indicative of IL-6 role in blood brain barrier disruption and the potential role of IL-6 inhibitor agents in treating COVID-19-related neurological diseases.

There are some limitations regarding this review. First, the majority of included studies were using tocilizumab as treatment option, therefore lacking of another type of IL-6 drugs to be included in meta-analysis. In addition, most of the subjects were not homogenous in terms of baseline characteristics and most of the treatment group had more severe disease at baseline compared with controls. Most of the studies included were retrospective studies with small sample size, which may result in low quality of evidence. Future well-designed randomized trials are needed for testing its efficacy to provide high-quality evidence to support the findings of this study.

Conclusion

IL-6 inhibitors agents have shown potential benefit in reducing risk of mortality in COVID-19 patients especially in severe disease. However, the appropriate dosage and drug administration remains unclear. Clinicians should consider the use of IL-6 inhibitor agents in well-established clinical trials to evaluating the benefit and risk of the drugs.

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Competing interests

None declared.

Ethical approval

Not required.

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