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Systematic Review

# A Contemporary Systematic Review of Systematic Reviews on the Safety and Efficacy of the Pharmacological Treatments of COVID-19

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## Abstract

**Introduction:** The 2019 Coronavirus infection caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has emerged as a significant public health emergency worldwide. The World Health Organization declared the outbreak as a pandemic on March 11th, 2020 and by September 16th, 2020, it had infected more than 29.6 million people and more than 936,000 deaths across nations. Many pharmacological drugs have been used to treat patients with COVID 19, including antimalarial, antivirals, monoclonal antibodies and corticosteroids, but the evidence of these therapeutics' safety efficacy remains unclear.

**Objective:** To systematically assess and compile the existing evidence from systematic reviews on existing pharmacological treatments' safety and efficacy for COVID-19 regarding mortality and RT-PCR conversion.

**Methods:** We conducted a comprehensive search of literature published in PubMed articles on systematic reviews of COVID-19 pharmacological treatments within the last one year as of July 25th, 2020. The quality of systematic reviews was performed by following AMSTAR-2.

**Results:** We identified 558 articles. After appropriate exclusion based on title and abstract, a full review was performed on 27 articles. A total of 9 systematic reviews were included in this article with a total population of 45101 patients; only 4 of them included meta-analysis. There were 6 systematic reviews with a moderate risk of bias, and only 3 reviews had a low risk of bias. The results of compiled reviews showed that the treatment of COVID-19 patients with CQ/HCQ had no benefit on viral clearance or decreased risk of death than standard care. Moreover, high dose CQ/HCQ regimens or combination with macrolides may induce harm by increasing the risk of prolonged QTc interval and ventricular arrhythmias. Evidence from RCTs showed no statistically significant difference in mortality rate between patients treated with lopinavir-ritonavir (LPV/r) or those receiving standard care or other antiviral drugs. The umifenovir showed good safety and tolerability but limited efficacy. Based on low-quality evidence, tocilizumab treatment lowered the mortality rate among treated patients compared to the control group, but this difference was not statistically significant. Moreover, the use of tocilizumab was associated with an increased risk for secondary infection. Meanwhile, the results of clinical studies on the role of corticosteroids in treatment of patients with COVID- 19 remain controversial.

**Conclusion:** To the authors' knowledge, this is the first systematic review of systematic reviews related to pharmacological medications used to treat patients with COVID-19. The existing evidence from systematic reviews on the safety and efficacy of the above-mentioned pharmacological treatments for COVID-19 remains insufficient. Most reviews had several limitations in the included studies such as: lack of an insufficient number of RCTs, combining evidence from RCT and non-RCT studies, heterogeneity in patient characteristics, measured outcomes and dosage of treatment regimens. High-quality evidence from RCTs is needed to provide more reliable insight on those therapeutics' efficacy and safety as a treatment option of current and future coronaviruses epidemics.

***Keywords:*** *COVID-19; SARS-COV 2; Treatment; Pharmacological; Efficacy; Safety*

## Introduction

Globally COVID-19 virus infection has emerged as a significant public health emergency that has unleashed human suffering, general anxiety, and economic disruption on an unprecedented scale. With a lack of definitive treatment for the 2019 coronavirus, the focus mainly lies in identifying and discovering the most effective treatment. Unfortunately, there is conflicting evidence on the most promising therapy for COVID-19, including mixed reviews regarding the safety and efficacy of advocated pharmacological interventions. The potential use of the two antimalarial drugs, Chloroquine and Hydroxychloroquine, increased globally as treatment options for coronavirus disease 2019 [1]. Initial studies found that both drugs inhibit SARS-CoV-2 effectively *in vitro* [2-4]. However, further evidence is needed. The anti-inflammatory effect of corticosteroids is often used as an additional treatment for viral pneumonia. Glucocorticoids inhibit many pro-inflammatory genes and restore homeostasis [5]. Mechanical ventilation, vasopressors and renal replacement therapy were most likely needed for patients who took corticosteroids in a study of MERS. Overall the results of clinical studies on its role on COVID-19 remain controversial [6]. Antivirals were associated with favorable outcomes when used to treat SARS and MERS in the past. Due to insufficient research, the effectiveness of these drugs in the treatment of patients with COVID-19 is still unclear. Monoclonal antibodies have immunosuppressive effects which call for using it with the most severe COVID-19 symptoms and hyperinflammatory syndrome [7]. They target IL-6 receptors. When comparing patients with mild and moderate disease, early serology analysis identified increased IL-6 serum levels in patients with severe Coronavirus disease (especially non-survivors) [8,9].

## Objective of the Study

The objective of this systematic review of systematic reviews is to compile and report on the safety and efficacy of currently used pharmacological drugs for the treatment of COVID-19 patients regarding mortality rate, RT-PCR conversion and some of the adverse events.

## Methods

Our systematic review's objective was to compile and report the evidence on the safety and efficacy of pharmacological drugs used to treat COVID -19 patients regarding reducing mortality, RT- PCR conversion, and other adverse events. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) as a guide for the completion of this systematic review [10]. Our study's eligibility criteria were determined using PICO (participants, interventions, comparison, outcomes and study designs) description model.

### Participants

Adult patients with confirmed COVID-19, at any clinical stage of the disease, thus mild, moderate, or severe/critical cases and with or without other comorbid conditions.

### Intervention

All currently known pharmacological treatments for COVID-19, specifically chloroquine, hydroxychloroquine, remdesivir, lopinavir, arbidol, oseltamivir, ribavirin, ritonavir, tocilizumab, azithromycin, ivermectin and corticosteroids.

### Comparator

Includes supportive care with or without one or more medications or placebo.

### Outcomes/endpoints

Mortality/death, RT-PCR negative results indicating negative seroconversion, and treatment-related adverse effects.

We searched MEDLINE/PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Google scholar databases for articles on systematic reviews of COVID-19 pharmacological treatments within the last one year as of July 25th, 2020. A comprehensive computerized search was conducted to search for studies focussing on the systematic review of COVID-19 treatments. The review used the search strategy consisting of the following keywords: (COVID-19) OR coronavirus) OR SARS-COV-2) AND "therapeutic*") AND Chloroquine) OR (hydroxychloroquine AND "last 1 years"[PDat])) OR remdesivir) OR Lopinavir) OR Arbidol) OR (oseltamivir AND "last 1 years"[PDat])) OR (ribavirin AND "last 1 years"[PDat])) OR (ritonavir AND "last 1 years"[PDat])) OR (tocilizumab AND "last 1 years"[PDat])) OR (azithromycin AND "last 1 years"[PDat])) OR (ivermectin AND "last 1 years"[PDat])) OR (corticosteroids AND "last 1 years"[PDat])) AND (systematic review[Title] AND "last 1 years"[PDat]) AND ("last 1 years"[PDat]).

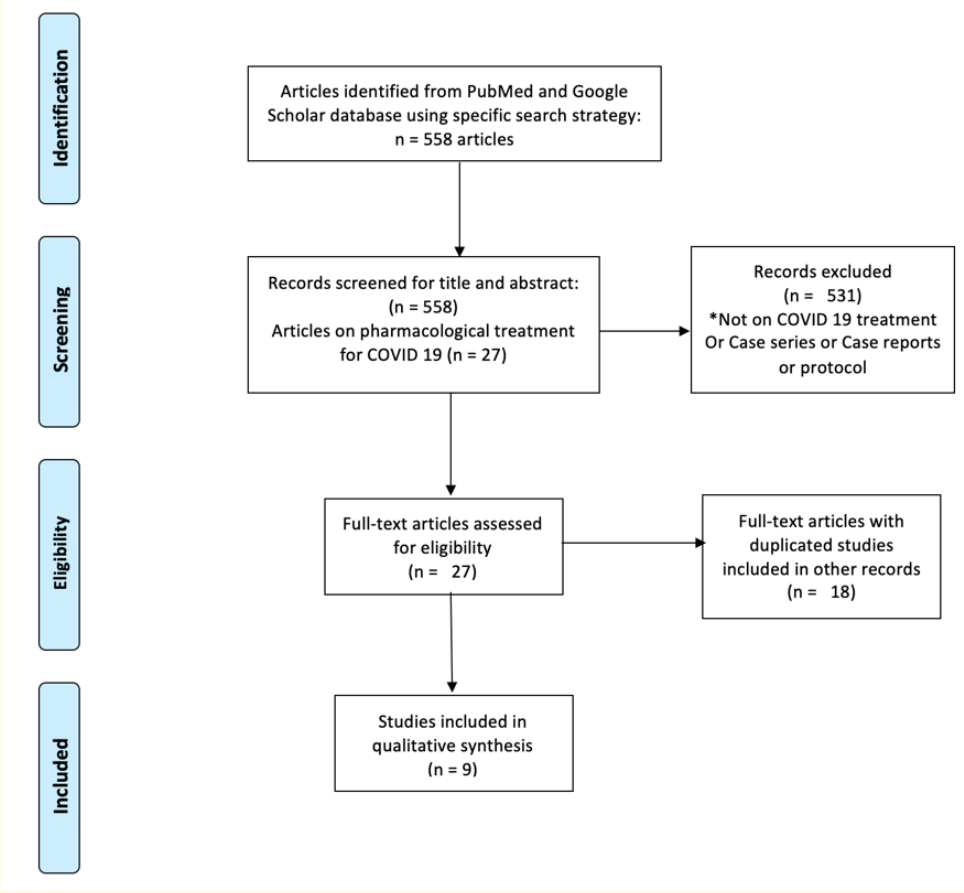


***Figure 1:*** *PRISMA flow diagram.*

The review included systematic reviews published within the last year reported in the English language that included studies on COVID 19 patients. We excluded systematic reviews that included studies on infections other than COVID-19 or comparing COVID 19 infection with other viral infections (SARS and MERS) along with reviews that were only analyzing case reports, case series, and conference papers. The initial step consisted of searching for studies based on the selected database (PubMed and Google Scholar). After removing the duplicates, the remaining reviews were then screened by applying inclusion criteria to the titles and abstracts. Studies highlighting prophylactic regimens, traditional medicine use, and convalescent plasma therapy were also excluded from our initial search results as the focus of this systematic review was only on pharmacological treatments for COVID-19. Based on the screening of titles and abstracts of 558 peer-reviewed publications, 27 potentially relevant systematic reviews were selected to examine further using full-text review. After reviewing the full text, only nine research studies were considered eligible for our qualitative synthesis, while others were excluded with an explanation as listed in supplementary appendix 1. The dual independent review was performed on titles and abstracts identified in the librarian search, with dual independent full-article review as necessary. Study inclusion disagreement was resolved by consensus among reviewers.

### Data extraction and quality

The paired, independent data extraction was performed, with disagreement resolved by consensus. A standardized data extraction form was developed to collect information from the included studies on the relevant treatment outcomes, besides the general and methodological aspects. Data were extracted on the number of studies included in the systematic review, year of publication, the number of patients, baseline characteristics (average age or sex proportion), specific intervention with types and doses, control intervention (placebo or specific control), study design or type of study (experimental and observational), type outcomes assessed, a risk-of-bias tool used to assess RCTs, risk of bias found, other quality issues, and findings (benefits and harms).

Five researchers (ShK, SA, SK, SL, and YS) independently extracted the data and assessed the studies' quality based on AMSTAR score, with disagreement resolved by consensus [11]. The studies selected in the review were divided into five treatment category groups, i.e. Antimalarial, Antiviral, Monoclonal antibodies, corticosteroids, and multiple drugs.

When considering the components of risk of bias assessment in the AMSTAR 2 tool, we included all the 16-factor questions that were considered relevant in assessing the Risk of Bias assessment.

For each systematic review, each component was scored as 1 (done appropriately), 0.5 (done partially), and 0 (unclear or not done), and individual scores were summed for a total score, with higher scores indicating lower risk of bias.

For Systematic review with meta-analysis (less than 6/16 meant higher risk, 7 - 11 meant moderate risk, and above 11/16 meant a low risk of bias).

For Systematic reviews without meta-analysis (less than 5/13 meant high risk, 6 - 9 meant moderate risk, and above 10/13 low risk of bias).

Risk-of-bias assessment was performed independently by reviewers, and disagreements were recorded and resolved by arriving at a consensus.

A descriptive analysis of the systematic reviews is presented in the form of tables. In reporting findings from systematic reviews, only four studies reported meta-analysis.

## Results

A total of 9 systematic reviews were included in the study, with a total population of 45101 participants, only 4 of them included meta-analysis. We identified three systematic reviews on chloroquine, and hydroxychloroquine's safety and efficacy, one on antiviral therapy, two systematic reviews were based on monoclonal antibodies tocilizumab, one on systemic corticosteroids used in COVID- 19 patients. In comparison, the other two systematic reviews commented on multiple drug categories. The reasons for excluding the articles that went for full review are presented in appendix 1. Typical studies in the systematic reviews were removed to avoid duplicate numbers. The leading causes of exclusion were systematic reviews compiling evidence from studies on COVID19 and non COVID19, reviews with incomplete data, or reviews that included only ongoing studies with no reported results. Table 1 shows the systematic reviews by treatment type, with a descriptive narrative analysis of the included systematic reviews.

| Author and Country | Study characteristics | Study Population characteristics | Reporting of outcomes of interest | | Other common adverse events | Results | |
|---|---|---|---|---|---|---|---|
| | | | mortality | RT PCR Negativity | | Interpretation using meta-analysis from actual data | Interpretation using narrative data |
| **Interventions using Antimalarials** | | | | | | | |
| Cortegiani.A., *et al*. 2020 Italy [12] | There are total 32 studies (6 RCTs, 26 non-randomized) in this SR | 29,192 participants<br><br>Mean age: NR<br>Male proportion: NR<br>Female proportion: NR | 7 studies assessed mortality as the primary outcome in both Intervention and Control groups. Two out of 7 studies had reported association of HCQ with significant decrease in mortality. | 2 out of 4 studies reported significant shorter time to viral clearance in HQ group versus the control group | All 10 studies reported significant prolonged QTc interval with varying time<br>**QTc Prolongation:** All 10 studies reported significant prolonged QTc interval with varying time | No meta-analysis was done in this SR | Although preliminary evidence suggests that treatment with CQ/HCQ may be associated with similar or even increased risk of death compared to standard care, these conclusions stem mostly from nonrandomized studies and the reasons of increased death remains not fully clarified. |
| Singh AK., *et al*. 2020 India [13] | There are total 10 studies (5 RCTs, 5 non-randomized) in this SR | 2042 participants<br><br>Mean age: 53.4<br>Male proportion: NR<br>Female proportion: NR | 3 studies assessed mortality as primary outcome and reported no significant difference in death among control and intervention groups | One study reported shortened recovery time in the HCQ group, remaining 6 studies reported no significant difference in negative seroconversion at 7 and 14 days. | None | Meta-analysis of 3 studies reported the rate of PCR negativity found no benefit with HCQ.<br>The meta-analysis of 3 trials reported the mortality outcome, showed a significant (2-fold) increase in death in HCQ arm compared to the control group. | While no benefit on viral clearance demonstrated by HCQ compared to the control in patients with COVID-19, a significant 2-fold increase in mortality with the HCQ warrants its use if at all, with an extreme caution, until the results from larger randomized controlled trials are available. |

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| Jankelson L., *et al*. 2020 USA [14] | There are total 11 studies (5 RCTs, 6 non-randomized) in this SR | 1515 participants<br>Mean age: 52.6<br>Male proportion: 65.4<br>Female proportion: 34.6 | None | None | 5 studies reported prolonged QTc interval varying from 60ms to 600 ms<br>Ventricular arrhythmias were reported in 2 studies. | No meta-analysis was done in this SR | Evidence of significant QT prolongation in patients with COVID-19 receiving hydroxychloroquine. Arrhythmia was documented during a short course of high dose chloroquine in critically ill COVID-19 patients. |
| **Interventions using Antivirals** | | | | | | | |
| Huang D., *et al*. 2020 China [15] | 7 studies | 501 participants<br>Mean age: 46.1 | none | 7 studies | none | Meta-analysis done.7 studies with 501 participants reported a negative rate of PCR.<br>6 studies reported a negative rate of PCR on day 7 and day 14 and 1 study reported negative PCR on day 7.<br>Umifenovir was not associated with a higher negative rate on day 7 (RR 1.09, 95% CI 0.91-1.31). However, umifenovir could increase the negative rate of PCR on day 14 (RR 1.27, 95% CI 1.04-1.55). | |
| **Interventions using corticosteroids** | | | | | | | |
| Veronese N., *et al*. 2020 China [16] | 3 observational Studies. | 405 participants<br>Mean age: 52<br>Male: 302,<br>Female: 240 | 1 study (Wu., *et al*.) | None | 2 studies (Wang., *et al*. Ling., *et al*.). | No meta -analysis was done for this SR. | Four included studies with 542 participants from China. Mainly males with mean age 52 years.<br>Only one study (Wu., *et al*.), carried out among 201 participants with different stages of pneumonia due to COVID-19, reported reduction in mortality in more severe forms of the condition such as ARDS, through the administration of standard doses of methylprednisolone which significantly reduced the risk of death by 62%.<br>Two of the included studies (Wang., *et al*. Ling., *et al*.) also reported possible adverse events of Corticosteroids in comparison with patients not given this intervention, which may include possible harm as it may aggravate the clinical course of disease or increase subsequent plasma viral load. |

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| Interventions using multiple drugs | | | | | | | |
| Tobaiqy., *et al*. 2020 KSA [17] | 41 studies Thirty-six studies were conducted in China (88%). | 783 Mean age 55.5,<br>M: 425<br>F 358 | retrospective observational studied (Chen., *et al*. 2020)<br>(Du., *et al*. 2020)<br>(Yang., *et al*. 2020) | 1etrospective observational studied (Chen., *et al*. 2020) | None | | Four studies included antiviral use one showed delayed Rt- PCR negativity among patients in ICU than those not in ICU. Reported rate of mortality among patients treated with antiviral agents ranged from 22% to 31%. Two studies reported that mortality rate among patients treated with steroids ranged from 18% -35% |
| Zhang J., *et al*. 2020 China, Singapore, South Korea and Hong Kong [18] | 42 nonrandomized, retrospective observational studies | 3765 participants<br>Mean age: 45<br>Male: 2797,<br>Female: 1406 | 23 studies: 4.3% of patients | None | 13 studies: ARDS (18.4%).<br>8 studies: Respiratory failure (16.2%)<br>8 studies: Shock (4.3%).<br>3 studies: Coagulopathy (3.3%).<br>7 studies: Acute Cardiac injury (7.8%).<br>11 studies: Acute Kidney injury (5.5%).<br>8 studies: Secondary infection (8.7%). | 8 studies reporting on 633 patients used the combination of lopinavir and ritonavir and 13 studies reporting on 2079 patients used other combinations of antivirals or did not specify the type of antiviral. Other combinations included oseltamivir, ganciclovir, ribavirin, and arbidol. Of these, 18 studies reported mortality rate and 12 studies reported the percentage of patients with ARDS.<br>Of all the patients who had been given antiviral intervention, the overall rate of mortality was 5.7% and ARDS was 20.2%.<br>The mortality rate was comparable between the lopinavir-ritonavir group and the "Others/Not specified" group (6.2% vs 5.5%, respectively; P = .93).<br>On subgroup analysis, the lopinavir-ritonavir treatment group had a lower rate of ARDS, although this difference was not statistically significant (15.6% vs 24.2%, P = .49).<br>Subgroup analysis was performed on studies using corticosteroids reported, sixteen studies with a total of 2407 patients, the pooled mortality rate in these patients was 7.2% (95% CI, 1.7–15.4%) and the pooled ARDS rate was 22.7% (95% CI, 9.9–38.6%). Meta-regression demonstrated a significant association between corticosteroid use and higher rate of ARDS (P = .0003) | |
| Interventions using monoclonal antibodies | | | | | | | |

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| Lana SH., *et al*. 2020 China [19] | 7 retrospective studies | 592 participants Mean age: TCZ 63.2 Control 65.9 | 7 studies | none | 1 study | Pooled analysis of 7 included studies showed that the mortality rate of patients with COVID-19 in the tocilizumab group was 16.3% (39/240) which was lower compared with the control group 24.1% (85/352), RR 0.62, 95%CI 0.31-1.22. One study reported adverse events. 42.9% (18/42) patients in the tocilizumab group had bacterial superinfection compared to none in the control group. | |
| A Cortegiani.,., *et al*. 2020 Israel, Italy [20] | Total 30 studies. 2 indirect preclinical studies. 28 clinical studies | 5755 participants | 26 studies | None | 14 Studies have reported several adverse events including Infection, inflammation Bacterial and fungal infection, Septic shock, Gastroesophageal perforation, Bacterial pneumonia and Abnormal laboratory tests (Bacteremia, increase hepatic enzyme, neutropenia and thrombocytopenia | None | Although preliminary evidence suggests that treatment with tocilizumab has no significant benefits in terms of mortality (3.3% -vs 2.3%) when treated with tocilizumab vs control groups. Also there are some safety concerns regarding secondary infection |

***Table 1:*** *Characteristics of included systematic reviews.*

**Chloroquine/hydroxychloroquine (CQ/HCQ):** The findings from three systematic reviews offers limited evidence on the role of these antimalarial drugs in the treatment of COVID-19 patients. Cortegiani and others (2020) reviewed 32 studies (6 RCTs, 26 nonrandomized) and concluded that the treatment of hospitalized COVID-19 patients with CQ/HCQ might not decrease mortality. Instead, a high dose of CQ/HCQ regimens or combination with macrolides may induce harm. Jankelson and others [12] reviewed ten studies to evaluate the risk of prolonged Q-T interval, ventricular arrhythmias, and sudden death among COVID -19 patients treated with CQ/HCQ [14]. They found that about 10% of patients treated with short CQ/HCQ courses had QT prolongation, and treatment with high dose CQ significantly increases the risk of ventricular arrhythmia in COVID 19 patients. Singh and others (2020) performed a meta-analysis to identify the effect of HCQ on viral clearance by RT- PCR and mortality outcome in patients with COVID-19 compared to the placebo [13]. The results suggested no benefit on viral clearance assessed by RT-PCR between treatment and control groups, while HCQ use showed a significant increase in death compared to the control in another meta-analysis of 3 studies without any heterogeneity.

### Antiviral

The Umifenovir administration could increase the negative rate of PCR on day 14 but was not associated with a higher negative rate of PCR on day 7. However, umifenovir was found to be safe in COVID-19 patients with no significant increased risk for side effects. The reason for the increased PCR negative rate on day 14 is not fully understood, but according to previous studies, the median seroconversion duration for antibodies was from 11 - 14 days. Hence, the possible effects of umifenovir on a negative conversion rate are only observed after two weeks after the disease onset [21].

The overall rate of mortality among COVID 19 patients received antiviral treatment including: LPV/r, oseltamivir, ganciclovir, ribavirin, and arbidol was 5.7%. Moreover, there were found no significant difference in mortality rate between patients received LPV/r (8 studies with 633 patients) and patients received other antiviral combinations or non-specific types of antivirals (13 studies with 2079 patients) [18].

### Monoclonal antibodies (antiIL6)

The results of observational studies suggest favorable outcomes in patients with severe or critical COVID - 19 treated with Tocilizumab compared to standard care. However, the evidence is still insufficient because of the lack of published RCT to assess this treatment's efficacy and safety [20]. Moreover, the analysis done by Lana and others (2020) reported that patients in the tocilizumab group had a lower all-cause mortality rate of 16.3% than that in the control group but this difference was not statistically significant [19]. However, these non-significant differences between the tocilizumab and control groups may explain that the tocilizumab group had more severe illness than the control group [19]. Moreover, Tocilizumab should be used cautiously during clinical trials with appropriate monitoring for the side effects because of higher secondary infection rate, hepatotoxic effects, neutro and thrombocytopenia, and intestinal perforation [20].

**Corticosteroids:** Corticosteroids were the most frequently reported therapeutic in the review done by Tobaiqy and others (2020) to report the evidence of therapeutics used for the management of COVID-19 patients in 25 out of 41 studies [17]. The pooled mortality rate among patients receiving corticosteroids was 7.2% (95% CI, 1.7 - 15.4%) by analysing data from16 studies with a total 2407 patients [18]. Veronese and others (2020) reviewed the literature to assess the use of corticosteroids in COVID-19 Pneumonia [16]. They included four studies with 542 Chinese participants. One study, including 201 patients, reported a reduced risk of death by 62% after methylprednisolone's administration. Another study reported no significant association between the use of corticosteroids and clinical outcomes. In contrast, two studies reported that patients treated with steroids had a double risk of being admitted to an ICU [22] or double duration of viral RNA detection in oropharyngeal swabs and feces [23] than control. However, there are several limitations to this review. The four included studies were retrospective and conducted in China. Moreover, there were heterogeneous data with variable doses and corticosteroids [16].

### Quality of systematic reviews (AMSTAR 2)

Quality of systematic reviews was done by following the AMSTAR-2 guide, which is designed to assess the quality of the reviews in 7 critical domains [11]:

- Protocol registered before commencement of the review
- Adequacy of the literature search

- Justification for excluding individual studies
- Risk of bias from individual studies being included in the review
- Appropriateness of meta-analytical methods
- Consideration of risk of bias when interpreting the results of the review
- Assessment of presence and likely impact of publication bias.

We found six systematic reviews with a moderate risk of bias, and only three reviews had a low risk of bias (Table 2). Two of the three systematic reviews on chloroquine/hydroxychloroquine safety and efficacy had a low risk of bias While the third review was done on the risk of arrhythmia and QT prolongation during CQ/HCQ treatment by Jankelson and others had a moderate risk of bias [14]. There is one systematic review with meta-analysis for antiviral treatments with a moderate risk of bias; on umifenovir by Huang and others. While the two systematic reviews for Tocilizumab had a moderate risk of bias, only one performed a meta-analysis. One review of corticosteroids used in Veronese's pneumonia patients and others had a moderate risk of bias. For the two reviews commented on multiple drug categories, the review done by Tobaiqy and others had a moderate risk of bias, while the meta-analysis and meta-regression review done by Zhang and others had a low risk of bias.

| Author, Year | Risk of Bias (RoB) | Author, Year | Risk of Bias (RoB) |
|---|---|---|---|
| **Systematic reviews with no meta-analysis** | | **Systematic reviews with meta-analysis** | |
| Cortegiani A., *et al*. 2020 [12] | Low (10/13) | Zhang J.J., *et al*. 2020 [18] | Low (13.5/16) |
| Jankelson L., *et al*. 2020 [14] | Moderate (8/13) | Singh.A.K., *et al*. 2020 [13] | Low (12.5/16) |
| Tobaiqy M., *et al*. 2020 [17] | Moderate (9/13) | Huang D., *et al*. 2020 [15] | Moderate (9/16) |
| Cortegiani A., *et al*. 2020 [20] | Moderate (9/13) | Lana S.H., *et al*. 2020 [19] | Moderate (11/16) |
| Veronese N., *et al*. 2020 [16] | Moderate (9/13) | | |

***Table 2:*** *Quality of evidence by AMSTAR-2.*

The detailed AMSTAR scoring using the mentioned criteria is presented as supplementary appendix 2.

## Discussion

Preliminary evidence suggests treatment with CQ/HCQ, but they were associated with increased risk of death. No beneficial effects were reported on patients hospitalized with COVID-19. These conclusions stem mostly from nonrandomized studies. No benefit on viral clearance is demonstrated by HCQ as compared to control. Guidelines on COVID-19 have warned against the potential risk associated with the use of CQ and HCQ (alone or in combination with azithromycin) and recommend the use of HCQ - azithromycin only in the context of clinical trials. Long QT syndrome and arrhythmia are significant concerns. Moreover, the accumulation of toxic levels of CQ and HCQ can be induced by acute kidney injury in COVID-19 patients. The use of corticosteroids in patients presenting with ARDS of different aetiologies remains controversial. Corticosteroids play a role in lowering the circulating levels of proinflammatory mediators. Recent evidence suggests that it may cause possible harm as it may aggravate the clinical course of the disease or increase subsequent plasma viral load. Methylprednisolone significantly decreased the risk of mortality in patients with ARDS owing to COVID-19 infection.

More research on this topic is needed before concrete recommendations can be made. Antivirals have been recommended for the treatment of COVID -19. The efficacy of antivirals for COVID -19 *in vivo* is unsatisfactory. There is no clear evidence on the effect of antivirals on mortality rate and RT-PCR negativity. One plausible explanation is that a higher dose is needed to achieve an equal suppression effect of SARS -CoV - 2 in patients with that *in vitro*. The variations in population, small sample size, the severity of illness, timing of treatment, dosage and co -treatments among included studies might lead to huge limitations. Moreover, low quality and certainty of evidence and enormous heterogeneity make it difficult to draw a clear conclusion about the advantages of antivirals for COVID -19 up until now. There is no clear evidence that Tocilizumab has a role in suppressing the virus's physiological inflammatory response. Indirect pre-clinical data and observational studies suggest a rationale for using Tocilizumab. It may be associated with more favorable outcomes in patients with severe or critical COVID-19, but there is no significant difference in mortality rates. Also, there are concerns regarding secondary infection associated with using this drug [25-40].

## Conclusion

To the authors' knowledge, this is the first systematic review of systematic reviews related to pharmacological medications used to treat patients with COVID-19. The existing evidence from systematic reviews on the safety and efficacy of the above-mentioned pharmacological treatments for COVID-19 remains insufficient. Most reviews had several limitations in the included studies such as: lack of an insufficient number of RCTs, combining evidence from RCT and non-RCT studies, heterogeneity in patient characteristics, measured outcomes, and dosage of treatment regimens. High-quality evidence from RCTs is needed to provide more reliable insight on those therapeutics' efficacy and safety as a treatment option of current and future coronaviruses epidemics.

## Appendix

| No. | Title | Author | Reason for exclusion |
|---|---|---|---|
| 1. | Efficacy and safety of current therapeutic options for COVID-19 - lessons to be learnt from SARS and MERS epidemic: A systematic review and meta-analysis | Zhong H., *et al*. 2020 | Include 7 studies on COVID 19 patients are all duplicated records |
| 2. | Vaccines and Drug Therapeutics to Lock Down Novel Coronavirus Disease 2019 (COVID-19): A Systematic Review of Clinical Trials | Bhagavathula A.S., 2020 | Ongoing trial on COVID 19 patients, No results |
| 3. | The potential of drug repositioning as a short-term strategy for the control and treatment of COVID-19 (SARS-CoV-2): a systematic review | Nima W.G., *et al*. 2020 | Includes 3 studies on COVID 19 patients all are duplicated records |
| 4. | Treatments Administered to the First 9152 Reported Cases of COVID-19: A Systematic Review | Fajgenbaum., *et al*. 2020 | Include 3 interventional clinical trials, couldn't be identified from supplementary table (incomplete data) |
| 5. | An Updated Systematic Review of the Therapeutic Role of Hydroxychloroquine in Coronavirus Disease-19 (COVID-19) | Das S., *et al*. 2020 | 12 clinical studies on COVID 19 patients which are duplicated records |
| 6. | A systematic review on use of aminoquinolines for the therapeutic management of COVID-19: Efficacy, safety and clinical trials | Patil V.M.*et al*, 2020 | Clinical trials on going on for use of chloroquine (CQ) and hydroxychloroquine (HCQ) in the treatment of COVID-19 infection. No results |

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| 7. | Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis | Sarma P., *et al*. 2020 | Includes 7 studies COVID 19 are all duplicated records |
| 8. | A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19 | Cortegiani A., *et al.* 2020 | Includes 23 ongoing clinical trials COVID 19 in China. No results |
| 9. | Clinical evidence for repurposing chloroquine and hydroxychloroquine as antiviral agents: a systematic review | Rodrigo C., *et al.* 2020 | Includes 6 studies on COVID 19 patients which are duplicated records |
| 10. | Assessment of Hydroxychloroquine and Chloroquine Safety Profiles - A Systematic Review and Meta-Analysis | Ren L., *et al.* 2020 | No studies on COVID 19 patients |
| 11. | Antiviral therapy in management of COVID-19: a systematic review on current evidence | Yousefifrad M., *et al*. 2020 | Include only one clinical trial COVID 19 which are duplicated records |
| 12. | Does Adding of Hydroxychloroquine to the Standard Care Provide any Benefit in Reducing the Mortality among COVID-19 Patients? a Systematic Review | Patel TK., *et al*. 2020 | Includes 6 studies COVID 19 which are duplicated records |
| 13. | Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review | Alzaghari SK and Acuna VS 2020 | Includes 6 studies COVID 19 which are duplicated records |
| 14. | Clinical Outcomes in COVID-19 Patients Treated with Tocilizumab: An Individual Patient Data Systematic Review | Antwi-Amoabeng D., *et al*. 2020 | Includes 11 studies COVID 19 which are duplicated records |
| 15 | A Rapid Systematic Review of Clinical Trials Utilizing Chloroquine and Hydroxychloroquine as a Treatment for COVID-19 | Chowdhury., *et al.* 2020 | Includes 7 studies, exclude 6, plus (Ga et. al excluded because no clear design, no results, no exclusion or inclusion criteria, no control) |
| 16 | The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis | Yang., *et al*. 2020 | Systematic review and meta-analysis included studies on patients of MERS, SARS and SARS-COV2 |
| 17 | Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis | Li., *et al*. 2020 | Systematic review and meta-analysis included studies on patients of MERS, SARS and SARS-COV2 |
| 18 | Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment | Cao., *et al*. 2020 | Systematic review and meta-analysis included studies on patients of MERS, SARS and SARS-COV2 |

***Supplementary Appendix 1:*** *Table of excluded studies.*

| Author, Year | Risk of Bias (RoB) | Research question specifying PICO | Review methods explained in protocol and justification for any deviation | Study selection and inclusion is explained | Comprehensive literature search | Dual screening | Dual extraction | Excluded studies with reason | Included studies characteristics | Risk of Bias assessment | Funding source | Meta Analysis based on Scientific method for combining results | Meta Analysis uses Risk of bias assessment for individual studies. | RoB in individual study is discussed in results | Explanation of Heterogeneity in results is discussed. | Publication Bias | Conflict of Interest |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Systematic reviews with no meta-analysis | | | | | | | | | | | | | | | | | |
| Cortegiani. A., *et al*. 2020 | Low (10/13) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | No meta analysis conducted | No meta analysis conducted | Yes | No | No meta analysis conducted | Yes |
| Jankelson L., *et al*. 2020 | Moderate (8/13) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No meta analysis conducted | No meta analysis conducted | No | No | No meta analysis conducted | No |
| Cortegiani A., *et al*. 2020 | Moderate (9/13) | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | No meta analysis conducted | No meta analysis conducted | Yes | No | No meta analysis conducted | Yes |
| Veronese N., *et al*. 2020 | Moderate (9/13) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No meta analysis conducted | No meta analysis conducted | No | No | No meta analysis conducted | Yes |
| Tobaiqy M., *et al*. 2020 | Moderate (9/13) | Yes | Partial Yes | No | Partial Yes | Yes | Yes | Yes | Partial Yes | Partial Yes | No | No meta analysis conducted | No meta analysis conducted | Yes | Yes | No meta analysis conducted | Yes |
| **Systematic reviews with meta-analysis** | | | | | | | | | | | | | | | | | |
| Zhang J.J., *et al*. 2020 | Low (13.5/16) | Yes | Yes | Yes | Yes | Yes | Yes | Partial Yes | Partial Yes | Partial Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Singh.A.K., *et al*. 2020 | Low (12.5/16) | Yes | Partial Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes |
| Huang D., *et al*. 2020 | Moderate (9/16) | Yes | Partial Yes | Yes | Partial Yes | Yes | Yes | Partial Yes | Partial Yes | No | No | Yes | No | No | Yes | No | Yes |
| Lana S.H., *et al*. 2020 | oderate (11/16) | Yes | Partial Yes | Yes | Partial Yes | Yes | Yes | Partial Yes | Partial Yes | No | No | Yes | Yes | Yes | Yes | No | Yes |

***Supplementary Appendix 2:*** *AMSTAR scoring.*

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**Volume 4 Issue 12 December 2020**