ORIGINAL ARTICLE

Evaluating the Efficacy and Safety of the Existing Repurposed Pharmacological Agents for Treating COVID-19: A Meta-analysis and Systematic Review of Clinical Trials

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Abstract

Purpose: The present study systematically searched important medical databases, assessed the quality of available pieces of evidence, and performed a meta-analysis to test the efficacy of different therapeutic options currently available for treating COVID-19.

Materials and methods: PubMed, CNKI, LILACS, Koreamed, WHO clinical trial registry, and medRxiv were searched since December 2019. Any observational or controlled study that tested the efficacy of any pharmacological intervention in COVID-19 patients either prospectively or retrospectively was included in the qualitative analysis. We assessed outcomes as dichotomous variables, i.e., a patient having a positive clinical outcome. Relative risks/risk ratios (RR) having a 95% confidence interval (CI) were derived. Studies conforming to inclusion criteria were pooled using the random-effect model.

Results: Nine trials on hydroxychloroquine (HCQ), six studies on antiviral, four studies on monoclonal antibodies, two on corticosteroids, two on convalescent plasma (CP), and one on interferon-α2b were included in the systematic review. Meta-analysis containing six scientific trials and analyzing 522 patients revealed that the relative risk of positive clinical outcomes with HCQ treatment was 1.042 (95% CI, 0.884 to 1.874) with a number needed to treat (NNT) of 12.6. A meta-analysis of two studies analyzing 285 patients showed that the relative risk of clinical resolution with lopinavir and ritonavir combination was 1.152 (95% CI 0.709 to 1.87). Out of various antiviral used, the only remdesivir showed a positive result in a case series. Monoclonal antibodies showed decreased C-reactive protein, decreased oxygen, and ventilator requirements. A corticosteroid may increase mortality with increased dose. Two small case series on CP showed some promising results.

Conclusion: The study showed slightly favorable results with HCQ, monoclonal antibodies, remdesivir, and CP in treating COVID-19 patients. Further research is warranted in establishing the efficacy of studied interventions.

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Keywords: Chloroquine, Convalescent plasma, Coronavirus, COVID-19, Hydroxychloroquine, Lopinavir, Ritonavir, SARS-CoV-2.

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Introduction

The outbreak of novel coronavirus (COVID-19 or 2019-CoV) infection has posed considerable threats to international health and the economy which was initially reported from Wuhan, the capital of Hubei, China.[1] Soon after, the number of cases soared exponentially, spreading across China and worldwide. As of April 2020, more than 30 million cases of the disease have been confirmed with over two lakhs deaths.[2] Unfortunately, the immediate end of this mayhem is not being expected very shortly.

The whole medical fraternity is racing against time to find a solution to tackle this deadly virus. Despite the feverish attempts across the world to search for an effective and viable therapeutic strategy for the treatment of the same, no consensus has been achieved as yet to suggest the ideal therapeutic agent or regimen for control of the same. Undeniably, therapeutic strategies are governed by strong literature support, existing local protocols, previous beneficial experiences in treated communities, and availability of the drugs. Considering the short duration since the disease has emerged and the aggressive pace with which it has afflicted all corners of the globe, collective efforts from different regions of the world have failed to zero down on the suitable therapeutic strategy and leaving us bereft of any superlative therapeutic agents or licensed vaccines. Thus, the perfect panacea for COVID-19 treatment remains elusive.

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Several clinical trials have been undertaken in this short duration of time to test the efficacy of certain drugs and therapeutic agents to treat patients COVID-19. Some commonly available drugs have been urgently repurposed to meet this unprecedented crisis which includes antiprotozoal [hydroxychloroquine (HCQ), chloroquine], antivirals (lopinavir/ritonavir/oseltamivir/remdesivir, ribavirin), antibiotics (azithromycin), anti-inflammatory (corticosteroid), immunomodulatory [interleukin 6 (IL-6) therapy with tocilizumab, eculizumab], etc.[3] These agents have all been tried with variable degrees of success in different regions. Interest has also been seen in Traditional Chinese Medicine which has been shown to reduce symptoms of fever and pulmonary infiltrates.[4] Although none of these options can be convincingly recommended at this moment and none of these modalities have established their individual superiority over others.

In the background of such therapeutic uncertainties, the present study attempts to systematically search important medical databases, assess the quality of available pieces of evidence (both published and unpublished), and perform a meta-analysis along with systematic review to test the usefulness of different therapeutic options currently available in treating COVID-19 patients.

Materials and Methods

The review strategy was decided before commencing the data search. The protocols underwent prospective registration at the National Institute for Health Research international prospective register of a systematic review (identifier CRD42020180979). We undertook and reported our search strategy and findings as recommended by the preferred reporting items for systematic reviews and meta-analyzes guidelines (http://www.prisma-statement.org).

The PICO statement which was used in the present study was as follows:

- P—Patients, problem, or population: Patients with confirmed SARS-CoV-2.
- I—Intervention: any pharmacological intervention that was used either before or after the diagnosis.
- C—Comparison: Compared with no treatment, placebo, or other active treatment.
- O—Outcomes assessment: Clinical or laboratory outcome.

Data Search

All publications that reported the usage of pharmacological intervention in patients infected with SARS-CoV-2 infection were reviewed up to April 26, 2020. We searched PubMed through MEDLINE. To search for non-English publications, we examined CNKI, KoreaMed, and LILACS. To retrieve unpublished work and ongoing studies we went through WHO Clinical Trial Registry (who.int/ictrp) and medrxiv. The bibliographies contained in the retrieved articles were analyzed further and additional suitable studies were checked. Whenever confusion arose about the data, the article's authors were contacted for elucidation. Other languages were translated into English using Google Translate (https://translate.google.com/). The search strategy details are depicted in the Appendix.

Selection of Studies

An observational or controlled study which tested the efficacy of any pharmacological intervention in COVID-19 patient either prospectively or retrospectively was selected for inclusion in the qualitative analysis. Criteria for inclusion in the meta-analysis were:

- The studies that compared a pharmacological intervention with no active treatment, placebo, or active treatment.
- The studies that were conducted on living humans.
- The studies which reported appropriate data or studies whose data could be extracted for performing a meta-analysis.
- A case report of a single patient was excluded.

Data Extraction

A table for data extraction was used to extract equivalent information from the included studies which consisted of the publication year, country of origin, the study design, its sample size, active intervention, comparator, outcome assessment, and side effects if any. Three authors (SKD, NSC, RH) reviewed the articles independently, to assess its quality and ascertaining the criteria for inclusion in the analysis of the pooled data. A fourth reviewer (HS) blinded to the assessment of the primary reviewers, independently checked the selection of the article, data extraction, and assessed the risk of bias. The mutual consensus was resorted to resolve any disagreement. Publications from the same author were cautiously checked to avoid replication of studies.

Measurement of Treatment Effect

We assessed the following outcomes of treatment effects: the resolution of symptoms, clearance of virus, survival, percentage of people not requiring intensive care unit admission, percentage of the patient not requiring ventilator support, and adverse effects if any. However, to perform a meta-analysis, we grouped the above outcomes as "positive clinical outcome" and assessed what percentage of patients showed positive clinical outcomes.

Risk of Bias Analysis

"Review of the development of the risk of bias tool for nonrandomized studies for interventions—ROBINS-I" was used for nonrandomized trials and case series.[5] Review of the development of the risk of bias tool for nonrandomized studies for interventions interprets every study as an effort to replicate an ideal randomized trial that is expected to answer a particular clinical problem. Seven domains in three categories are analyzed for potential risk of introducing bias t which are refereed based on signaling questions. Detailed methods of risk of bias assessment are described in the Supplement.

Data Synthesis

We assessed outcomes as dichotomous variables, i.e., a patient having a positive clinical outcome. Relative risks or risk ratios (RR) having a confidence interval (CI) of 95% were calculated. Relative risks or risk ratios more than 1.0 favored the intervention group, indicating that the effect of the intervention is favored.

Data Analysis

When multiple trials were available related to a particular therapeutic agent, reporting "positive clinical outcomes", the meta-analysis was performed. If the trials related to a particular drug, demonstrated very high degrees of clinical diversity, they were not pooled. However, in the trials which demonstrated adequate clinical similarity to be combined, their statistical heterogeneity was investigated. Based on the results of our heterogeneity assessment, the fixed-effect model was used for a low degree of heterogeneity (whenever the I^2 statistic reached 40%), and random-effects analysis

was used when there was more than moderate heterogeneity (whenever the I^2 statistic exceeded 50%). A *p* value for heterogeneity <0.01, indicated significant heterogeneity. All calculations were done and figures were plotted using "OpenMetaAnalyst" software.[6]

Results

The process of review and study selection is represented in Flowchart 1

Twenty-four studies were involved in this systematic review (Table 1). Nine trials on HCQ, six studies on various antiviral, four studies on monoclonal antibodies, two on corticosteroids, two on convalescent plasma (CP), and one on interferon-α2b were included. Meta-analysis was performed with the six controlled trials on HCQ and two trials on lopinavir and ritonavir (Lpv/r).

HCQ and Chloroquine

Six controlled trials and three case series were identified that described the use of HCQ in patients of COVID-19.[7–15] Most of these trials were conducted in China and had small sample sizes. They used HCQ in different doses and assessed the following outcomes: viral clearance, need for ICU care, need for ventilator support, clinical and radiological resolution of pneumonia, clinical improvement, and mortality, although the outcome assessment was not uniform across the studies. The studies yielded a mixed result. A meta-analysis of six controlled trials consisting of 522 patients showed a pooled risk ratio of positive clinical outcome: 1.042 (95% CI 0.884 to 1.874) and a number needed to treat (NNT): 12.6[7–12] (Fig. 1). Sensitivity analysis of studies that looked at the influence of HCQ on viral clearance revealed a risk ratio: 1.09 (95% CI 0.786 to 1.514)[8,9,11] (Fig. 2). Four controlled trials reported side effects associated with HCQ use. Common side effects were diarrhea, ECG abnormalities, rash, etc. A meta-analysis of these four studies reported that the pooled risk ratio of having side effects with HCQ was 2.964 (95% CI 1.432 to 6.135) and the number needed to harm (NNH) was 7.4 (Fig. 3).

In the three case series, one case series did not provide adequate data.[14] One case series of 80 patients showed favorable outcomes in 65 patients and viral clearance of 93% on the 8th day.[13] Another small series of 11 patient, found that 8 patients remained positive for SARS-CoV-2 on the 6th day despite being treated with HCQ.[15]

Combination of HCQ and Azithromycin

One case series comprising of 11 patients treated with HCQ and azithromycin, found virus clearance only in 20% of patients after 5 to 6 days of treatment initiation.[15] In another study, where 6 patients got HCQ and azithromycin combination reported 100% virus clearance as compared to 52% in patients treated with HCQ alone.[13]

Antivirals

The literature search found that the following antiviral drugs were tested to treat COVID-19 patients: lopinavir, lopinavir and ritonavir combination (Lpv/r), remdesivir, atazanavir, favipiravir, nelfinavir, ribavirin, peramivir, and umifenovir (Arbidol).

In an open-label randomized trial of 199 patients, they received either Lpv/r (400 and 100 mg, respectively) twice daily for 14 days, along with standard care, or standard care alone. Treatment with Lpv/r was not seen to lower the time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% CI 0.95 to 1.80) as compared to the control group. But mortality at 28 days (19.2 vs 25.0%; difference, −5.8 percentage points; 95% CI −17.3 to 5.7) was lower in Lpv/r group.[16]

The ELACOLI trial enrolled 86 patients in three groups: Lpv/r, arbidol monotherapy, and standard therapy without antiviral. The average time needed for conversion of positive-to-negative SARS-CoV-2 nucleic acid and clinical resolution on the 7th and 14th days was similar between groups.[17]

Flowchart 1: The review process and included studies

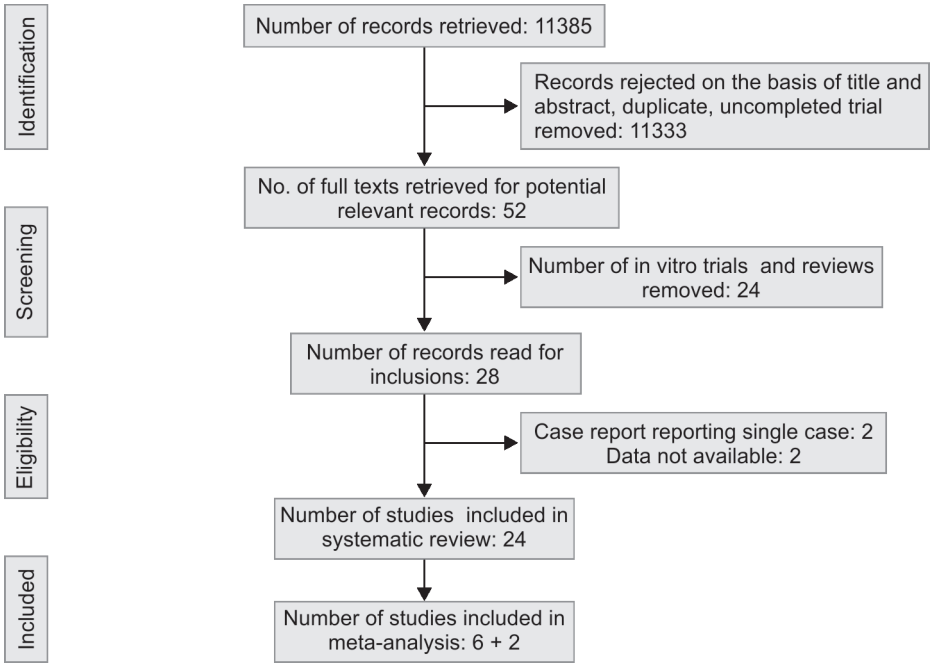

Table 1: Characteristics of individual studies

Study ID	*Country*	*Intervention*	*Sample size*	*Study type*	*Outcome assessed*	*Effect of intervention*	*Adverse effect*
Chen[7]	China	HCQ	62	RCT	CR	Favorable	Mild rash, headache
Chen[8]	China	HCQ	30	RCT	VC	Favorable	Diarrhea
Gautret[9]	Italy	HCQ	30	CT	VC, CR	Favorable	–
Barbosa[10]	USA	HCQ	63	CT	Need for respiratory support, lymphocyte count	Not favorable	–
Tang[11]	China	HCQ	150	RCT	VC	No difference	Blurred vision, diarrhea
Mahévas[12]	France	HCQ	181	CT	Need of ICU, death	Not favorable	ECG abnormalities
Gautret[13]	Italy	HCQ	80	CS	Viral clearance	Favorable	–
Gao[14]	China	HCQ	100	CS	Resolution of pneumonia, viral clearance	Favorable	–
Molina[15]	France	HCQ	11	CS	Viral clearance	Not favorable	–
Cao[16]	China	Lpv/r	199	RCT	Time to clinical improvement, 28-day mortality	Not favorable	GI symptoms
Li[17]	China	Lpv/r, arbidol	86	RCT	VC, CR	No difference	–
Cai[18]	China	Lpv, favipiravir	299	CS	Viral clearance	No difference	–
Hu[19]	China	Lpv/r	323 (28)*	CS	CR	Not favorable	–
Chen[20]	China	Favipiravir, arbidol	240	RCT	Clinical recovery	No difference in groups	Increased uric acid with favipiravir
Grein[21]	USA, Canada, Japan	Remdesivir	61 (53)*	CS	Ventilator support, mortality	Favorable	Hepatic renal dysfunction, diarrhea, rash, hypotension
Xu[22]	China	Tocilizumab	20	CS	CR	Favorable	–
Luo[23]	China	Tocilizumab	15	CS	IL-6 level	Favorable	–
Gritti[24]	Italy	Siltuximab	21	CS	CPR level, ventilator requirement	Favorable	–
Bian[25]	China	Meplazumab	28	CT	Viral clearance, clinical recovery	Favorable	–
Wang[26]	China	Corticosteroid	46	CT	Oxygenation, CT chest	Favorable	–
Lu[27]	China	Corticosteroid	244	CT	28-day mortality	Favorable	–
Duan[28]	China	Convalescent plasma	10	CS	Safety of transfusion, clinical improvement	Favorable	Evanescent facial red spot in two patients
Shen[29]	China	Convalescent plasma	5	CS	Viral clearance, clinical recovery	Favorable	–
Zhou[30]	China	Interferon-α2b, arbidol	77	CS	VC	Favorable	–

HCQ, hydroxychloroquine; Lpv/r, lopinavir and ritonavir combination; RCT, randomized controlled trial; CT, controlled trial; CS, case series ()* actual number of patients who received the study drugs; VC, viral clearance; CR, clinical recovery

A meta-analysis of both the studies showed a relative risk of clinical resolution on day 14 was 1.152 (95% CI 0.709 to 1.87) (Fig. 4).

In one case series involving 298 hospitalized patients, 229 received lopinavir, 30 received favipiravir and the rest did not receive any antiviral. There was no difference in the clearance of virus was observed between the three groups.[18]

Another retrospective review of 323 hospitalized patients found that 28 patients who received Lpv/r had a higher percentage of unfavorable outcomes than 295 patients who did not receive any antivirals.[19]

A randomized control trial (RCT) having a sample size of 240 COVID-19 patients, compared the clinical efficacy umifenovir (Arbidol) with favipiravir (1600 mg twice/first day followed by 600 mg twice/day) for 10 days. The study did not find any difference in rates of clinical recovery on the 7th day between the two groups.[20]

Another case series involving 53 patients with severe COVID-19 pneumonia receiving remdesivir under a compassionate-use protocol showed improvement in clinical status of 68% of patients after a median follow-up of 18 days. Thirty-six patients (68%) had a reduction in oxygen support and 17 of 30 patients (57%) who were receiving mechanical ventilation could be extubated. Twenty-five

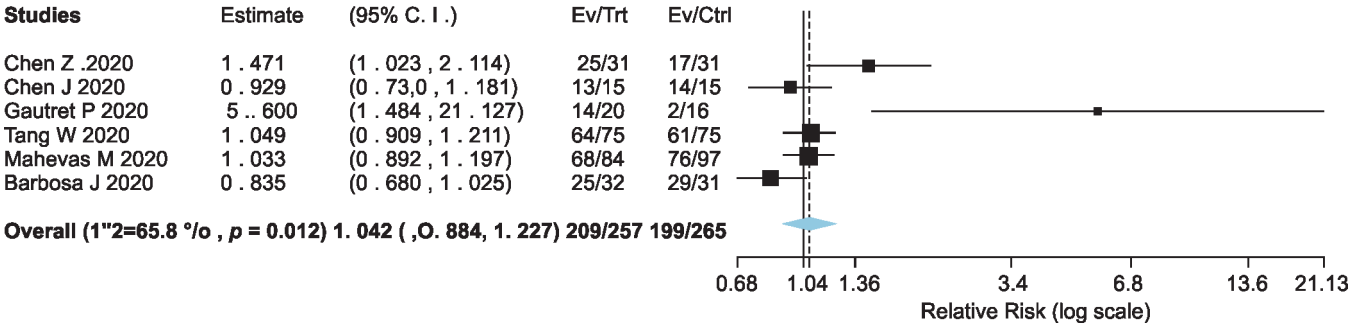

Fig. 1: Pooled risk ratio of positive clinical outcome in patients treated with hydroxychloroquine

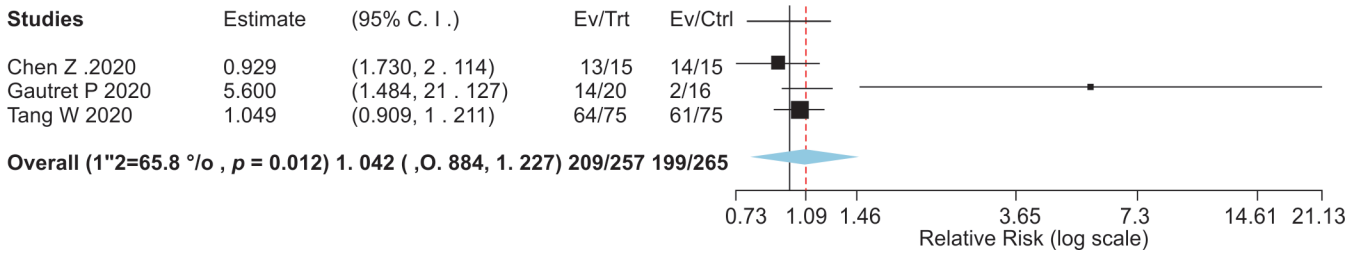

Fig. 2: Pooled risk ratio of viral clearance of patients treated with hydroxychloroquine

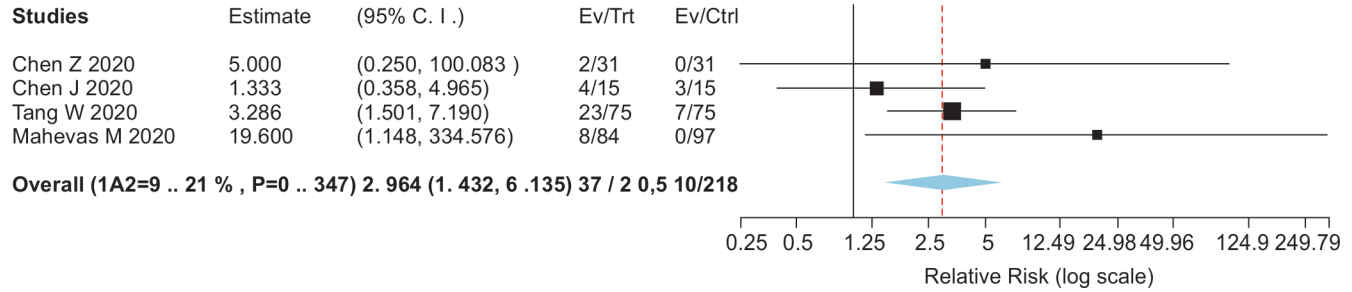

Fig. 3: Pooled risk ratio of the adverse effect of patients treated with hydroxychloroquine

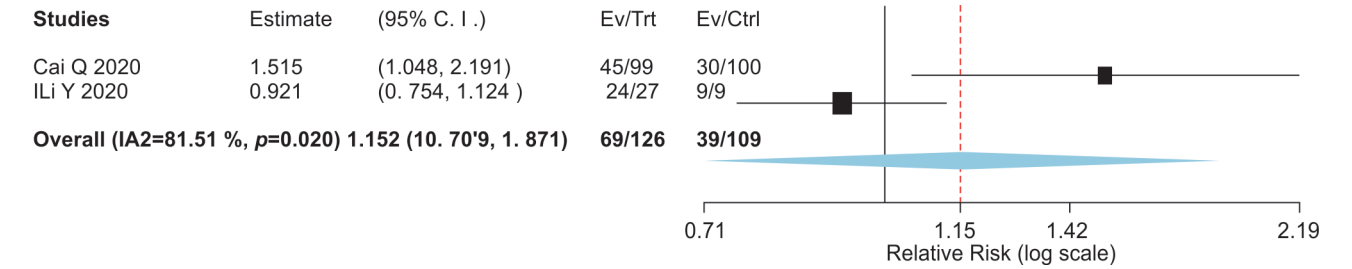

Fig. 4: Pooled risk ratio of clinical recovery on day 14 of patients treated with lopinavir and ritonavir combination

patients (47%) were discharged, and 7 (13%) died; mortality was 18% (6 of 34) among patients who were receiving invasive ventilation and 5% (1 of 19) among those who were not undergoing invasive ventilation.[21]

Monoclonal Antibodies

Till the time of writing this manuscript, the following monoclonal antibodies were used in patients with COVID-19: tocilizumab, siltuximab, and meplazumab.

Two case series of using tocilizumab were identified. One series of 20 patients who received tocilizumab showed a reduced need for oxygen supplement in 80% of patients and resolution of pneumonia in CT scan in 90.5%.[22] In another series, 15 seriously ill COVID patients received either tocilizumab alone or in combination with methylprednisolone. Three patients died. Interleukin 6 level decreased after treatment with tocilizumab in 10 patients.[23]

Twenty-one patients of COVID-19 pneumonia and acute respiratory distress syndrome (ARDS) received siltuximab at a dose of 700 to 1,200 mg. Clinical condition improved in 33% (7/21) of patients, the clinical condition remains unchanged in 43% (9/21) of patients, and the clinical condition worsened in 24% (5/21) patients.[24]

Mepolizumab has been tried in a controlled trial where 17 patients got the study drugs and 11 hospitalized patients served as control. Virology clearance and clinical outcome were significantly better in the treatment group on day 7 and 14.[25]

Corticosteroids

Two retrospective studies evaluated the effect of corticosteroid in patients suffering from COVID pneumonia. In one study, enrolling 46 patients, 26 received methylprednisolone. The patient who received methylprednisolone had faster radiological improvement and in oxygenation as well.[26]

Another study assessing the effects of adjuvant corticosteroid on the clinical outcome of 244 critically ill COVID patients, where 151 received steroids and 93 controlled.

One hundred and forty-seven (60%) patients experienced dyspnea and 87 (36%) developed ARDS, and subgroup analyzes, where multivariate analysis after adjustment was performed, revealed no mortality difference. The author also conducted a propensity-matched case-control study where the 28-day mortality rate was 39% (12 out of 31) in patients receiving steroids and 16% (5 out of 31) among control subjects. The study observed that increased corticosteroid dosage had a significant association with elevated mortality risk.[27]

Convalescent Plasma

Convalescent plasma has appeared as one of the promising therapies in moderate to severe COVID patients. Ten patients with severe COVID-19 (six males and four females) were enrolled and they received CP transfusion. Nine patients also received arbidol monotherapy or combination therapy using remdesivir or ribavirin, or peramivir, while one patient received ribavirin as monotherapy. Symptoms like fever, cough, shortness of breath, and chest pain disappeared or largely improved within 1–3 days upon CP transfusion in 10 patients. All patients demonstrated some degrees of resolution of lung infiltrates as evaluated by CT chest. SARS-CoV-2 RNA as assessed by RT-PCR was positive in seven patients and negative in three cases before CP transfusion. SARS-CoV-2 RNA was not detectable or decreased in five patients after 3 days and one patient after 6 days of CP therapy.[28]

In another study, five critically ill patients of COVID-19 and who had rapidly progressing severe pneumonia and ARDS and high viral load despite antiviral treatment and were administered CP, methylprednisolone, antiviral, and other supportive measures. Following plasma transfusion, normalization of body temperatures occurred within 3 days in four of five patients, a decrease in the sequential organ failure assessment (SOFA) score occurred and the PO_2/FiO_2 rose within 12 days. Viral loads also reduced and turned negative within 12 days following transfusion, and an increase in SARS-CoV-2-specific enzyme linked immunoabsorbent assay (ELISA) and neutralizing antibody titers occurred following transfusion. The resolution of ARDS was observed in four patients at 12 days post-transfusion, and three patients could be weaned from mechanical ventilation within 2 weeks of treatment. The authors informed that three out of the five patients had been discharged from the hospital, and the remaining two patients' condition remained stable at 37 days following transfusion.[29]

Interferon-α2b

Seventy-seven patients of COVID-19 were administered either nebulized IFN-α2b, arbidol, or a combination of both. Treatment with IFN-α2b with or without arbidol significantly enhanced viral clearance and concurrently lowered the duration of raised blood levels for the inflammatory markers IL-6 and CRP.[30]

Risk of Bias Assessment

Most studies that are included in this systematic review and meta-analysis had moderate to severe risk of bias. Twelve trials were found to have an overall severe risk of bias. Rest had either low or moderate risk of boas. Table 2 depicts the details of the risk of bias assessment.

Discussion

The present analysis systematically reviewed 24 studies on various pharmacological agents used for the treatment of COVID-19 infection which yielded mixed results. Maximum studies were in their preprint version and had a serious risk of bias. A meta-analysis of six studies revealed that the relative risk of positive clinical outcomes with HCQ treatment was 1.042 (95% CI 0.884 to 1.874) with an NNT of 12.6. However, this treatment is not devoid of side effects. The relative risk of side effects with HCQ was 2.964 (95% CI 1.432 to 6.135) with an NNH of 7.4. Out of various antiviral used, the only remdesivir showed some positive results in a case series. Four small studies using monoclonal antibodies showed decreased C-reactive protein, decreased oxygen, and ventilator requirements. A large study on the use of steroids in COVID pneumonia did not reveal any benefit, rather a possibility of increased mortality with the increased dose of steroids. Two small case series on CP showed some promising results in terms of viral clearance, pneumonia resolution, decreased need for ventilator support, and mortality.

SARS-CoV-2, which is a single-stranded RNA-enveloped virus, enters the human cells through the viral structural spike (S) protein which binds itself to the angiotensin-converting enzyme 2 (ACE2) receptors facilitated by type II transmembrane serine protease, TMPRSS2.[31] After gaining entry inside the cell, the virus synthesizes RNA via its RNA-dependent RNA polymerase. Synthesis of structural proteins occurs leading to the completion of assembly and then the viral particles are released.[32–34] The understanding of the viral lifecycle provides potential targets for pharmacological intervention. Hydroxychloroquine/chloroquine prevents the entry of the virus into host cells by receptor glycosylation, inhibition of proteolysis, decrease acidification of lysosomes, and exert immunomodulatory effects.[35–37] Antiviral acts on 3C protease, S protein/ACE2, and RNA polymerase and inhibits membrane fusion.[3,38] Monoclonal antibodies act by inhibiting IL-6 and thereby reducing cytochrome storm.[22] Convalescent plasma obtained from patients who have recovered from COVID-19 patients and developed humoral immunity against the virus, contains neutralizing antibodies in large quantities of. These antibodies are expected to neutralize SARS-CoV-2 and halt disease progression.[39]

This systematic review is one of the first of its kind which did an extensive systematic literature search to find all pieces of evidence in regards to the use of pharmacotherapy in COVID-19. It assessed the quality and risk of bias of the available pieces of evidence. It gives a comprehensive summary of pieces of evidence regarding the efficacy of pharmacological interventions used to date. The review has several limitations. It lacks good quality RCTs. Most studies are either case-control studies or case series. There exist a lot of statistical and clinical heterogeneity between the studies in term of drug dose and outcome assessment. We excluded certain studies that evaluated the efficacy of traditional Chinese medicine on COVID-19 as safety and mechanism of action such as therapy were not studied in detail and beyond our scope of knowledge and training. The study also did not evaluate the effects of the dose and timing of various medications on clinical outcomes.

The quest for a benign and efficacious medication for COVID-19 has just begun. One thousand one hundred and thirty-six trial protocols have been registered with the WHO clinical registry so far and the number will increase with each passing day. A large

Table 2: Risk of bias assessment using "Review of the development of the risk of bias tool for nonrandomized studies for interventions—ROBINS-I" tool

Study	*Preintervention*		*At intervention*	*Postintervention*				*Overall bias*
Author	*Bias due to confounding*	*Bias in the selection of participants*	*Bias in the classification of intervention*	*Bias from deviation from intended intervention*	*Bias due to missing data*	*Bias due to measurement of outcome*	*Bias in selection of reported result*	*Low, moderate, serious, critical*
Chen[7]	M	L	L	L	M	M	M	Moderate
Chen[8]	L	M	L	L	M	M	M	Moderate
Gautret[9]	S	S	L	M	S	M	M	Moderate
Barbosa[10]	S	M	M	L	L	S	M	Moderate
Tang[11]	S	S	M	M	M	M	M	Moderate
Mahévas[12]	S	S	M	M	S	M	L	Serious
Gautret[13]	S	S	S	M	M	M	S	Serious
Gao[14]	?	?	?	?	?	?	?	Serious
Molina[15]	S	S	M	S	M	M	S	Serious
Cao[16]	L	L	L	M	M	L	L	Low
Li[17]	M	L	L	L	M	M	L	Low
Cai[18]	S	S	S	S	?	?	?	Serious
Hu[19]	S	S	S	?	?	S	?	Serious
Chen[20]	L	M	M	L	M	L	L	Low
Grein[21]	S	S	M	S	M	M	S	Serious
Xu[22]	S	M	S	S	S	M	M	Serious
Luo[23]	S	S	M	M	M	S	S	Serious
Gritti[24]	S	S	M	S	M	S	M	Serious
Bian[25]	M	M	M	M	M	M	M	Moderate
Wang[26]	L	M	M	M	L	S	M	Moderate
Lu[27]	M	M	S	M	M	M	s	Moderate
Duan[28]	S	S	?	?	M	?	L	Serious
Shen[29]	S	S	S	M	M	L	M	Serious
Zhou[30]	S	S	M	S	S	?	?	Serious

L, low risk of bias; M, moderate risk of bias; S, severe risk of bias; C, critical risk of bias, ?, data not reported

multicenter, adaptive, randomized, open clinical trial for evaluating the safety and efficacy of HCQ, remdesivir, and standard of care in adult hospitalized patients of COVID-19 underway has already started to recruit patients from 100 countries. This "Solidarity Trial" aims to have a sample size of 700 adult COVID patients and its result can be expected to be published very soon.[40]

This systemic review of 24 studies and two meta-analyzes of 6 and 2 studies showed some favorable results with HCQ, monoclonal antibodies, remdesivir, and CP for treating patients of COVID-19. Corticosteroids showed no beneficial effect on a patient with COVID pneumonia. Currently, the available pieces of evidence are not methodologically robust and have a high risk of bias. Further RCT is needed to establish the efficacy of studied pharmacological interventions.

Author Contributions

Saurabh Kumar Das, Nang Sujali Choupoo, Rudrashish Haldar are responsible for the integrity of this work from inception to manuscript preparation. They contributed to study design, study selection, quality assessment, record review, data synthesis, and manuscript composition. Hillol Sarkar, Reshma Tewari, and Sumit Ray contributed to the review process by searching the literature and reviewing the search records and manuscript. All authors read the final manuscript.

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