Development of Evidence-Based COVID-19 Management Guidelines for Local Context: The Methodological Challenges

Sarah Nadeem,1,2 Salima Saleem Aamdani,1 Bushra Ayub,1 Nashia Ali Rizvi,1 Fatima Safi Arslan,3 Russell Seth Martins,3 Maria Khan,3 and Syed Faisal Mahmood2

1CITRIC Centre for Clinical Best Practices, Aga Khan University, Karachi, Pakistan
2Department of Medicine, Aga Khan University, Karachi, Pakistan
3Aga Khan University, Karachi, Pakistan

Correspondence should be addressed to Sarah Nadeem; sarah.nadeem@aku.edu

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Background. The coronavirus disease 2019 (COVID-19) pandemic has presented as a therapeutic challenge for clinicians worldwide due to its rapid spread along with evolving evidence and understanding of the disease. Internationally, recommendations to guide the management of COVID-19 have been created and updated continuously by the WHO and CDC, which have been locally adapted by different countries. Similarly, Pakistan’s National Command Operation Center (NCOC), in its national COVID-19 management strategy, generated guidelines for national implementation. Keeping the guidelines updated has proved challenging globally and locally. Here, we present a summary of the process to assess the evidence, including a time-restricted systematic review based on NCOC Clinical Management Guidelines for COVID-19 Infections v4 published on 11th December 2020 version, correlating it with current recommendations and with input one of the guidelines authors, particularly noting the methodological challenges.

Methods. We conducted a systematic review synthesizing global research on treatment options for COVID-19 hospitalized patients, limiting it to pharmacological interventions for hospitalized COVID-19 patients included in Pakistan’s NCOC’s national guidelines v4 published on 11th December 2020. Each treatment recommendation’s strength and quality of evidence was assessed based on the grading of recommendations assessment, development, and evaluation (GRADE) methodology. We conducted a systematic review synthesizing global research on treatment options for COVID-19 hospitalized patients, limiting it to pharmacological interventions for hospitalized COVID-19 patients included in Pakistan’s NCOC’s national guidelines v4 published on 11th December 2020. Each treatment recommendation’s strength and quality of evidence was assessed based on the grading of recommendations assessment, development, and evaluation (GRADE) methodology. These were then compared to the most current living WHO COVID-19 pharmacological treatment guidelines v7.1. One of the authors of the NCOC guidelines reviewed and commented on the findings as well. Results. We note that the data from our systematic review strongly supports corticosteroids use in treating severe and critically ill COVID-19 hospitalized patients correlating with WHO v7.1 guidelines 24 September 2021. However, evidence from our review and WHO v7.1 for the use of tocilizumab had some conflicting evidence, with data from our review until December 2020 supporting only a weak recommendation for its use, compared to the strong recommendation by the WHO for the use of tocilizumab in patients with severe or critical COVID-19 infection. Regarding the use of antibiotics and ivermectin use in treating COVID-19 hospitalized patients, data from our review and WHO v 7.1 recommend against their use. Conclusion. Research data about the efficacy and safety of pharmacological interventions to treat hospitalized patients with COVID-19 are rapidly evolving, and based on it, the evidence for or against recommendations changes accordingly. Our study illustrates the challenges of keeping up with the evidence; the recommendations were based on studies up till December 2021, and we have compared our recommendations with the WHO v7.1, which showed some significant changes in the use of pharmacological treatment options.
1. Introduction

Pakistan, like other countries worldwide, has seen many cases of coronavirus disease 2019 (COVID-19) since the pandemic began [1]. The national government-led response included the creation of a central National Command Operation Center (NCOC), setting up designated hospitals, isolation testing facilities, and following dedicated treatment guidelines based on WHO recommendations. National guidelines were created, 2nd April 2020 (v1), with most recent version (v4) currently in use, “Clinical Management Guidelines for COVID-19 Infections” published by the Government of Pakistan on 11th December 2020 [2]. These have been formulated by national experts incorporating international guidelines and adapting them to local contexts.

2. Methods

Here, we present a summary of the process to assess the evidence, including a time-restricted systematic review based on NCOC version, correlating it with current recommendations specifically looking at it from a local perspective; along with input from NCOC guidelines.

We describe the methodological challenges that exist in the developing evidence-based guidelines for an evolving pandemic. We performed a systematic review to evaluate the interventions noted in the NCOC guidelines v4 and to GRADE recommendations for pharmacological interventions for hospitalized patients. Then, we compared our recommendations to WHO v7.1 COVID-19 therapeutics guidelines and subsequently invited an expert narrative review by NCOC experts specifically looking at it from a local perspective.

This study was conducted at the Center for Clinical Best Practices (CCBP), Clinical and Translational Research Incubator (CITRIC), Aga Khan University, Karachi, Pakistan, after approval from the institutional ethical review committee.

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [3]. We aimed to review the effectiveness of pharmacological interventions included in the NCOC guidelines on mortality and length of stay in hospitalized patients with COVID-19 including evidence available until 11th December 2020. The WHO clinical progression scale for clinical improvement (ordinal scale) was used to categorize the disease severity for each study.

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria were used to evaluate and formulate recommendations for or against and strength by considering the quality of evidence and balance between benefits and harms [4] (Table 1 and Supplementary Figure 1).

Studies in English published from 1st November 2019 to 31st December 2020 were included in the review. Data extraction and synthesis data extraction were performed by two independent investigators using a structured data extraction form to ensure consistency. Any disagreements were noted and resolved by further discussion with a third investigator. The extracted data are given in Tables 2–5). The quality of the final included studies was assessed according to each study design. Observational studies were assessed by the National Institute of Health Study Quality Assessment Tool [5]. Randomized control trials were evaluated by Cochrane Risk of Bias (RoB) [6]. Quasiexperimental studies were assessed by the Cochrane Effective Practice and Organization of Care (EPOC) risk of bias tool [7] (Supplementary Figures 2–9).

3. Results

In our systematic review, a total of 122 studies were included (Supplementary Figure 1). Data extracted from these final studies are given in Table 2 (cohort and cross-sectional studies), Table 3 (case-control studies), Table 4 (interventional studies), and Table 5 (quasiexperimental studies).

All drugs in the NCOC v4 guidelines were included, and their efficacy was assessed by evaluating length of hospitalization, mortality, and ordinal scores, and a recommendation was made based on GRADE methodology. As per the NCOC panel recommendation, we additionally included colchicine in the review and comparison of WHO, NCOC v4, and our review between drugs, as given in Table 6.

3.1. Corticosteroids. Multiple studies have evaluated the efficacy of corticosteroids in the management of COVID-19 (Tables 2 and 5). We gave strong recommendation for the use of corticosteroids because the studies were showing early recovery in severe and critical patients; however, we gave weak recommendation for its use in noncritical patients as it did not show any positive outcomes. Most of the studies in our systematic review were observational; hence, we gave a moderate quality of evidence.

As per our systematic review, we recommend

(i) For the use of corticosteroids in severe and critical patients, hospitalized COVID-19 patients. Strong recommendation, moderate-quality evidence.

(ii) Against the use of corticosteroids in nonsevere patients, hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence.

WHO v7.1 dated 24/9/2021 recommended for the use of systematic corticosteroid rather than no corticosteroids in severe and critical COVID-19 patients.

3.2. Tocilizumab. In our systematic review, mortality rates with tocilizumab therapy ranged from 6.98% to 60% (depending on patient inclusion criteria), with many studies showing a protective effect of tocilizumab with regards to mortality, especially if given intravenously (as compared to subcutaneously) and within 12 days of admission [8–28]. Patients treated with tocilizumab alone were more likely to show improvement on the WHO ordinal scale (63.9% vs. 36.1%) and less likely to require ICU care (40.4% vs. 59.6%) as compared to those treated with corticosteroids in addition to tocilizumab [29]. We gave weak recommendation as the studies were showing controversial results on managing COVID-19 hospitalized adults with tocilizumab. Many of
the studies were showing inconsistent results; therefore, we gave moderate certainty.

As per our systematic review, we recommend

(i) For the use of tocilizumab in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence.

WHO v7.1 recommended for the use of tocilizumab in patients with severe or critical COVID-19 infection.

3.3. Ivermectin Therapy. Due to its effectiveness in various other viral infections, ivermectin was assessed as a therapeutic agent for COVID-19 infection (Tables 2 and 4). As studies showed no major difference in mortality, we gave weak recommendation for the use of ivermectin and low quality of evidence because of insufficient evidence.

As per our systematic review, we recommend

(i) Against the use of ivermectin therapy in the use of COVID-19 hospitalized patients. Weak recommendation, low-quality evidence.

WHO v7.1 recommended against the use of ivermectin in patients with COVID-19.

3.4. Antibiotics. The macrolide azithromycin has demonstrated antiviral activity, especially in human bronchial epithelial cells where it reduces viral cell replication and causes an increase in viral-induced pattern recognition receptors. It has exhibited a synergistic effect with the drug hydroxychloroquine, and together, they decrease the production of inflammatory cytokines such as IL-1 and IL-6 [30]. We gave weak recommendation for the

### Table 1: Selection criteria and search strategy.

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>Exclusion criteria</th>
<th>Search string</th>
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<tr>
<td>Interventions</td>
<td>Observational and interventional studies describing the use of the following pharmacologic interventions for the treatment of COVID-19: (i) Steroids (dexamethasone, hydrocortisone, and prednisone methylprednisolone) (ii) Anticoagulation (iii) Remdesivir (iv) Antibiotics (v) Colchicine (vi) Tocilizumab (vii) Other investigational therapies (convalescent plasma, intravenous immunoglobulin, plasmapheresis, ivermectin, and famotidine).</td>
<td>Pharmacologic or nonpharmacologic treatment interventions other than those specified in inclusion criteria.</td>
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<tr>
<td>Outcomes</td>
<td>Studies describing at least one of the following primary or secondary outcome measures: (a) Primary outcomes: (i) In-hospital mortality (ii) Length of hospital stay. (b) Secondary outcomes: (i) Progression of disease (ii) Treatment of adverse effects</td>
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<tr>
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<td>Title</td>
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<td>Stessel et al., Belgium</td>
<td>Impact of implementation of an individualized thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study.</td>
<td>52</td>
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<td>2</td>
<td>Jonmarker et al., Sweden</td>
<td>Dosing of thromboprophylaxis and mortality in critically ill COVID-19 patients</td>
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<td>3</td>
<td>Salton et al., Italy</td>
<td>Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia</td>
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<td>4</td>
<td>Mutair et al., Saudi Arabia</td>
<td>Hydroxychloroquine in hospitalized patients with COVID-19: An observational cohort study</td>
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<td>Annie et al., the United States</td>
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<td>6</td>
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<td>Clinical characteristics, treatment regimen, and duration of hospitalization among COVID-19 patients in Ghana: A retrospective cohort study</td>
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<td>Ashinyo et al., Ghana</td>
<td>The association between treatment with hydroxychloroquine and hospital mortality in COVID-19 patients</td>
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<td>9</td>
<td>Ayerbe et al., Spain</td>
<td>The association between treatment with hydroxychloroquine and hospital mortality in COVID-19 patients</td>
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<td>Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: A multicentre study</td>
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<td>Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients</td>
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<td>Canoglu et al., Turkey</td>
<td>Therapeutic dosing of low-molecular-weight heparin may decrease mortality in patients with severe COVID-19 infection</td>
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<td>Catteau et al., Belgium</td>
<td>A retrospective controlled cohort study of the impact of glucocorticoid treatment in SARS-CoV-2 infection mortality</td>
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<td>Ana Fernández-Cruz, Spain</td>
<td>Low-dose hydroxychloroquine therapy and mortality in hospitalized patients with COVID-19: A nationwide observational study of 8075 participants</td>
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<td>Freedberg et al., the United States</td>
<td>Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study</td>
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<td>16</td>
<td>Geleris et al., United States</td>
<td>Observational study of hydroxychloroquine in hospitalized patients with COVID-19</td>
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<table>
<thead>
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<th>S. no.</th>
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<th>Concomitant group</th>
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<td>17</td>
<td>Berry et al., United States</td>
<td>Hydroxychloroquine and tocilizumab therapy in COVID-19 patients: An observational study</td>
<td>66</td>
<td>(i) Hydroxychloroquine 800 mg on day 1 and 400 mg on days 2–5, followed by 200 mg TID&lt;br&gt;(ii) Hydroxychloroquine in combination with azithromycin&lt;br&gt;(iii) Tocilizumab first dose 400 mg, followed by 800 mg</td>
<td>(i) Neither hydroxychloroquine/azithromycin&lt;br&gt;(ii) Azithromycin alone&lt;br&gt;(iii) No tocilizumab</td>
<td>For patients in tocilizumab/no tocilizumab group: (i) Steroid&lt;br&gt;(ii) Hydroxychloroquine alone&lt;br&gt;(iii) Azithromycin alone&lt;br&gt;(iv) Azithromycin plus hydroxychloroquine</td>
<td>(i) Mortality&lt;br&gt;(ii) Adverse drug events&lt;br&gt;(i) Mortality&lt;br&gt;(ii) Adverse drug events</td>
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<td>18</td>
<td>Karolyi et al., Austria</td>
<td>Hydroxychloroquine versus lopinavir/ritonavir in severe COVID-19 patients</td>
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<td>Hydroxychloroquine loading dose of 400 mg twice on the first day, followed by 200 mg twice daily</td>
<td>Lopinavir/ritonavir 400 mg/100 mg administered twice daily</td>
<td>Concomitant antibiotic (i) Antibiotics (azithromycin, ampicillin/clavulanic acid, and amoxicillin/ clavulanic acid)&lt;br&gt;(ii) Vitamin C</td>
<td>(i) In-hospital mortality&lt;br&gt;(ii) Intensive care unit (ICU) admission&lt;br&gt;(iii) Length of stay&lt;br&gt;(iv) PCR (polymerase chain reaction) negativity&lt;br&gt;(v) Side effects of treatment&lt;br&gt;(i) Admission to ICU&lt;br&gt;(ii) Mechanical ventilation&lt;br&gt;(iii) Length of stay&lt;br&gt;(iv) PCR (polymerase chain reaction) negativity&lt;br&gt;(v) Side effects of treatment</td>
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<td>Kirenga et al., Uganda</td>
<td>Characteristics and outcomes of admitted patients infected with SARS-CoV-2 in Uganda</td>
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<td>Hydroxychloroquine</td>
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<td>(i) Antibiotics (azithromycin, ampicillin/clavulanic acid, and amoxicillin/clavulanic acid)&lt;br&gt;(ii) Vitamin C</td>
<td>(i) Death&lt;br&gt;(ii) Negative reverse transcriptase PCR (RT-PCR) tests&lt;br&gt;(iii) Length of hospitalization&lt;br&gt;(iv) Length of hospitalization</td>
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<td>20</td>
<td>Lagier et al., France</td>
<td>Outcomes of 3737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis</td>
<td>56</td>
<td>(i) Azithromycin + hydroxychloroquine &gt;3 days&lt;br&gt;(hydroxychloroquine 200 mg of oral hydroxychloroquine, 3 times daily for 10 days and 500 mg of oral azithromycin on day 1 followed by 250 mg, daily for the next 4 days)&lt;br&gt;(ii) Other treatment (azithromycin + hydroxychloroquine for at least 3 days)&lt;br&gt;(iii) Azithromycin + hydroxychloroquine &lt;3 days&lt;br&gt;(iv) Hydroxychloroquine alone&lt;br&gt;(v) Azithromycin alone&lt;br&gt;(vi) No azithromycin and hydroxychloroquine</td>
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<td>(i) Death&lt;br&gt;(ii) Transfer to the intensive care unit (ICU)&lt;br&gt;(iii) ≥10 days of hospitalization&lt;br&gt;(iv) Viral shedding</td>
<td>(i) Death&lt;br&gt;(ii) Transfer to the intensive care unit (ICU)&lt;br&gt;(iii) ≥10 days of hospitalization&lt;br&gt;(iv) Viral shedding</td>
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<td>Albertini et al., France</td>
<td>Observational study on off-label use of tocilizumab in patients with severe COVID-19</td>
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<td>Tocilizumab 8 mg/kg</td>
<td>No tocilizumab</td>
<td>(i) Hydroxychloroquine&lt;br&gt;(ii) Azithromycin</td>
<td>(i) Mortality&lt;br&gt;(ii) Mechanical ventilation&lt;br&gt;(iii) Length of stay&lt;br&gt;(iv) Adverse events</td>
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<td>Billet et al., the United States</td>
<td>Anticoagulation in COVID-19 effect of enoxaparin, heparin, and apixaban on mortality</td>
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<td>Standard care (i) Apixaban prophylaxis (ii) Apixaban full therapy (iii) Enoxaparin prophylaxis (iv) Enoxaparin full therapy</td>
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<td>Capra et al., Italy</td>
<td>Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia</td>
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<td>Tocilizumab</td>
<td>No tocilizumab</td>
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<td>26</td>
<td>Gupta et al., the United States</td>
<td>Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19</td>
<td>122</td>
<td>Tocilizumab patients received tocilizumab within 2 days of ICU admission</td>
<td>Tocilizumab patients did not receive tocilizumab within 2 days of ICU admission</td>
<td>Standard care (i) Hydroxychloroquine 400mg (ii) Lopinavir 800 mg (iii) Ritonavir 200 mg</td>
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<td>Kaminski et al., the United States</td>
<td>Tocilizumab therapy for COVID-19: A comparison of subcutaneous and intravenous therapies</td>
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<td>Tocilizumab, 400 mg IV</td>
<td>Tocilizumab, subcutaneous dose of 324 mg (given as two simultaneous doses of 162 mg)</td>
<td>Standard care (i) Hydroxychloroquine (ii) Azithromycin (iii) Corticosteroids</td>
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<td>Kim et al., Korea</td>
<td>Lopinavir-ritonavir versus hydroxychloroquine for viral clearance and clinical improvement in patients with mild-to-moderate coronavirus disease 2019 Early hydroxychloroquine but not chloroquine use reduces ICU admission in COVID-19 patients</td>
<td>44</td>
<td>Lopinavir-ritonavir 400 and 100 mg twice daily</td>
<td>Hydroxychloroquine 400 mg once daily</td>
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<td>Lammers et al., Netherlands</td>
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<td>Hydroxychloroquine on day 1, 400 mg, and 400 mg after 12 hours, 200 mg BID on days 2-5</td>
<td>Chloroquine on 1st day 600 mg and 300 mg after 12h, 300 mg BID on days 2-5</td>
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Table 2: Continued.

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<td>Lauriola et al., Italy</td>
<td>Effect of combination therapy of hydroxychloroquine and azithromycin on mortality in patients with COVID-19</td>
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<td>Remdesivir 200mg loading dose on day 1, followed by a 100mg dose daily on day 2-5</td>
<td>No treatment (standard care not specified)</td>
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<td>Lee et al., the United States</td>
<td>Remdesivir for the treatment of severe COVID-19: A community hospital’s experience</td>
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<td>Remdesivir 200mg loading dose on day 1, followed by a 100mg daily on days 2–5</td>
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<td>Yiming Li et al., China</td>
<td>Corticosteroid therapy in critically ill patients with COVID-19: A multicenter, retrospective study</td>
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<td>Corticosteroids</td>
<td>No corticosteroids</td>
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<td>33</td>
<td>Liu et al., China</td>
<td>Clinical characteristics and corticosteroids application of different clinical types in patients with coronavirus disease 2019</td>
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<td>Corticosteroids (ii) Methylprednisolone (1-2)mg/kg day general type, 1–5mg/kg day severe type, and 1–4mg/kg day critical type</td>
<td>No corticosteroids</td>
<td>(i) Interferon-α (IFN-α)(ii) Lopinavir/ritonavir (iii) Dexamethasone (iv) Antiretrovirals (v) Low-molecular-weight heparin</td>
<td>(i) 90 days mortality (ii) Viral clearance</td>
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<td>Gautret et al., France</td>
<td>Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in patients with COVID-19: A multicenter, retrospective study</td>
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<td>Hydroxychloroquine (200mg of oral TID for 10 days) and azithromycin (500mg on day 1 followed by 250mg per day for 4 days)</td>
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<td>Yu et al., China</td>
<td>Low dose of hydroxychloroquine reduces mortality of critically ill patients with COVID-19: An observational study</td>
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<td>Hydroxychloroquine oral 200mg BID for 7–10 days</td>
<td>Nonhydroxychloroquine</td>
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<td>36</td>
<td>Guaraldi et al., Italy</td>
<td>Tocilizumab in patients with severe COVID-19: A retrospective cohort study</td>
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<td>Tocilizumab 8mg/kg IV (up to a maximum of 800mg) in two infusions, 12 h apart, or subcutaneously at 162mg administered in two simultaneous doses, one in each thigh (i.e., 324mg in total)</td>
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<td>Grein et al., United States</td>
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<td>Remdesivir 8mg/kg IV (maximum 800mg/dose)</td>
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<td>Alexis K. Okoh et al., the United States</td>
<td>Tocilizumab use in COVID-19 associated pneumonia</td>
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<td>Tocilizumab 8mg/kg IV (maximum 800mg/dose)</td>
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<td>(i) Improvement in the respiratory status (ii) Discharged alive from ICU by study day 28 (iv) Viral clearance</td>
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<td>No tocilizumab</td>
<td>—</td>
<td>(i) Hydroxychloroquine (ii) Lopinavir/ritonavir (iii) Azithromycin (iv) Remdesivir (v) Interferon (vi) Steroids</td>
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<tr>
<td>82</td>
<td>Tortajada et al., Spain</td>
<td>59</td>
<td>Corticosteroids (ii) Methylprednisolone 250mg IV once and 40mg BBQ for 4 days (iii) Dexamethasone 20mg IV QD for 5 days, followed by 10mg QD for 5 more days</td>
<td>No corticosteroids</td>
<td>—</td>
<td>—</td>
<td>(i) Hydroxychloroquine (ii) Azithromycin (iii) Lopinavir/ritonavir (iv) Tocilizumab (v) Interferon beta</td>
<td>(i) WHO ordinal scale (ii) Admission to ICU (iii) Clinical improvement</td>
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Table 2: Continued.
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<th>S. no.</th>
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<th>Study duration in days</th>
<th>Intervention group</th>
<th>Comparator group</th>
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<th>Outcome measures applicable to this review</th>
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<tr>
<td>83</td>
<td>Magagnoli et al., the United States</td>
<td>Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19</td>
<td>21</td>
<td>(i) Hydroxychloroquine  (ii) Hydroxychloroquine + azithromycin  (iii) No hydroxychloroquine</td>
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<td>—</td>
<td>(i) Mortality  (ii) Use of mechanical ventilation</td>
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<td>84</td>
<td>Joyner et al., United States</td>
<td>Early safety indicators of COVID-19 convalescent plasma in 5000 patients</td>
<td>39</td>
<td>Convalescent plasma</td>
<td>—</td>
<td>—</td>
<td>The safety of transfusion of COVID-19 convalescent plasma assessed as the incidence and relatedness of severe adverse events including death.</td>
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<td>85</td>
<td>Rajfer et al., South Florida, the United States</td>
<td>Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The ivermectin in COVID-19 study</td>
<td>58</td>
<td>Ivermectin 200 μg/kg</td>
<td>No ivermectin</td>
<td>(i) Corticosteroid  (ii) Hydroxychloroquine  (iii) Azithromycin</td>
<td>(i) Mortality  (ii) Successful extubation (iii) Length of hospital stay</td>
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<tr>
<td>86</td>
<td>Hanif et al., the United States</td>
<td>Thrombotic complications and anticoagulation in COVID-19 pneumonia: A New York City hospital experience</td>
<td>31</td>
<td>(i) Therapeutic anticoagulation prior to admission  (ii) Therapeutic anticoagulation during the admission  (iii) Prophylactic anticoagulation only during the hospital stay  (iv) No anticoagulation</td>
<td>—</td>
<td>—</td>
<td>(i) Mortality  (ii) Length of stay  (iii) Intubation  (iv) Successful extubation</td>
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<tr>
<td>87</td>
<td>Duan et al., China</td>
<td>Effectiveness of convalescent plasma therapy in severe COVID-19 patients</td>
<td>30</td>
<td>Convalescent plasma: one dose of 200 ml of inactivated CP with neutralization activity of &gt;1:640 was transfused into the patients within 4h following the WHO blood transfusion protocol</td>
<td>—</td>
<td>—</td>
<td>(i) Antiviral therapy  (ii) Other supportive care  (iii) Antibiotic treatment  (iv) Antifungal treatment  (v) Glucocorticoid  (vi) Oxygen support at the appropriate situation</td>
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</table>

Note: The table continues with similar entries for additional studies.
<table>
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<th>S. no.</th>
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<th>Title</th>
<th>Study duration in days</th>
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<th>Outcome measures applicable to this review</th>
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<tbody>
<tr>
<td>1</td>
<td>Klopfenstein et al., France</td>
<td>Impact of tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort of 206 COVID-19 patients</td>
<td>72</td>
<td>Tocilizumab 8mg/kg per dose, 1 or 2 doses</td>
<td>(i) Standard treatment (ii) Hydroxychloroquine (iii) Lopinavir-ritonavir therapy (iv) Antibiotics (v) Corticosteroids</td>
<td>(i) Hydroxychloroquine (ii) Lopinavir-ritonavir therapy (iii) Antibiotics (iv) Corticosteroids</td>
<td>(i) Mortality (ii) Intensive mechanical ventilation (iii) Duration to hospitalization (iv) Death (v) ICU admission (vi) Invasive mechanical ventilation (vii) Duration of hospitalization</td>
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<td>2</td>
<td>Klopfenstein et al., France</td>
<td>Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients</td>
<td>24</td>
<td>Tocilizumab 8mg/kg per dose, 1 or 2 doses</td>
<td>(i) Standard treatment (ii) Hydroxychloroquine (iii) Lopinavir-ritonavir therapy (iv) Antibiotics (v) Corticosteroids</td>
<td>(i) Hydroxychloroquine (ii) Lopinavir-ritonavir therapy (iii) Antibiotics (iv) Corticosteroids</td>
<td>(i) Azithromycin (ii) Hydroxychloroquine (iii) Broad-spectrum antibiotics (iv) Therapeutic dose anticoagulation (v) Corticosteroids (vi) Remdesivir (vii) Mesenchymal stem cells and interleukin (IL)-1 and IL-6 inhibitors</td>
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<td>3</td>
<td>Sean et al., the United States</td>
<td>Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study</td>
<td>16</td>
<td>Convalescent plasma therapy —</td>
<td>—</td>
<td>—</td>
<td>(i) Survival (ii) Oxygen requirement</td>
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<td>4</td>
<td>Abolghasemi et al., Iran</td>
<td>Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study</td>
<td>61</td>
<td>Convalescent plasma 500 cc (one unit)</td>
<td>No convalescent plasma</td>
<td>(i) Lopinavir/ritonavir (ii) Hydroxychloroquine</td>
<td>(i) Mortality (ii) Intubation (iii) Length of stay (iv) Length of stay</td>
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<td>S. no.</td>
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<td>Outcome measures applicable to this review</td>
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<td>7</td>
<td>Perrone et al., Italy</td>
<td>Tocilizumab for patients with COVID-19 pneumonia: The single-arm TOCIVID-19 prospective trial</td>
<td>34</td>
<td>Tocilizumab 8 mg/kg up to a maximum of 800 mg per dose</td>
<td>—</td>
<td>(i) Azithromycin (ii) Hydroxychloroquine (iii) Antibiotics (iv) Steroids (v) Low-molecular-weight heparin</td>
<td>Lethality rate Lethality rate</td>
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<td>9</td>
<td>Scarsi et al., Italy</td>
<td>Association between treatment with colchicine and improved survival in a single-center cohort of adult hospitalized patients with COVID-19 pneumonia and acute respiratory distress syndrome</td>
<td>32</td>
<td>(i) Cokhicine 1 mg/day (ii) Standard of care (hydroxychloroquine, lopinavir/ritonavir, and intravenous dexamethasone)</td>
<td>Standard of care (hydroxychloroquine, lopinavir/ritonavir, and intravenous dexamethasone)</td>
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<td>Survival rate Survival rate</td>
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<tr>
<td>10</td>
<td>Keller et al., The Bronx</td>
<td>Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19</td>
<td>34 Early glucocorticoid first 48 hours</td>
<td>No glucocorticoid</td>
<td>—</td>
<td>(i) In-hospital mortality (ii) In-hospital mechanical ventilation (iii) Mortality in mechanical ventilation</td>
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<td>11</td>
<td>Yu et al., China</td>
<td>Lopinavir/ritonavir is associated with pneumonia resolution in COVID-19 patients with influenza coinfection: A retrospective matched-pair cohort study</td>
<td>30 Lopinavir/ritonavir treatment</td>
<td>No lopinavir/ritonavir treatment</td>
<td>(i) Glucocorticoid treatment (ii) Ribavirin treatment (iii) Lopinavir/ritonavir treatment (iv) Oseltamivir (v) Arbidol</td>
<td>(i) Dead or deteriorated (ii) Cured (i) Dead or deteriorated (i) Cured</td>
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<tr>
<td>12</td>
<td>Qu et al., not mentioned</td>
<td>Comparative effectiveness of lopinavir/ritonavir-based regimens in COVID-19</td>
<td>—</td>
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</table>

(i) Lopinavir/ritonavir (LPV/r) alone (ii) Lopinavir/ritonavir (LPV/r) + Novaferon (iii) Lopinavir/ritonavir (LPV/r) + interferon (iv) Lopinavir/ritonavir (LPV/r) + interferon + Novaferon (v) Lopinavir/ritonavir (LPV/r) + interferon + Arbidol (LPV/r: PO 500 mg (400 mg lopinavir + 100 mg ritonavir) BID; Novaferon: aerosol 20 microgram BID; Arbidol: PO 0.2 g TID; interferon: aerosol 500 × 10^4 IU · BID) | (i) Time of negative nucleic acid conversion. (ii) Length of hospitalization. (iii) The rate of adverse reaction (iv) Transferring to ICU and clinical mechanical therapy (i) Time of negative nucleic acid conversion. (ii) Length of hospitalization. (iii) The rate of adverse reaction (iii) Transferring to ICU and clinical mechanical therapy |
<table>
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<th>Concomitant drugs</th>
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<tr>
<td>1</td>
<td>NCT04353336</td>
<td>Abd-Elsalam et al., Egypt</td>
<td>Hydroxychloroquine in the treatment of COVID-19: A multicenter randomized controlled study</td>
<td>122</td>
<td>2</td>
<td>Hydroxychloroquine</td>
<td>(i) Paracetamol (ii) Oxygen (iii) Fluids (iv) Empiric antibiotic (cephalosporins) (v) Oseltamivir (vi) Invasive mechanical ventilation with hydrocortisone</td>
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<td>(i) Death (ii) Duration of hospital stay</td>
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<td>2</td>
<td>Trial registration not specified.</td>
<td>Antinori et al., Italy</td>
<td>Compassionate remdesivir treatment of severe COVID-19 pneumonia in intensive care unit (ICU) and non-ICU patients: clinical outcome and differences in posttreatment hospitalization status</td>
<td>27</td>
<td>1</td>
<td>Remdesivir (ICU and ward setting)</td>
<td>None</td>
<td>—</td>
<td>(i) WHO ordinal scale (ii) Hospitalization status (iii) Adverse events</td>
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<tr>
<td>3</td>
<td>NCT04323527</td>
<td>Borba et al., Brazil</td>
<td>Effect of high vs. low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection</td>
<td>—</td>
<td>2</td>
<td>High-dose chloroquine (600 mg CQ; 4 x 150 mg tablets twice daily for 10 days; total dose 12 g)</td>
<td>Low-dose chloroquine (450 mg CQ twice daily on the first day and 450mg once daily for 4 days)</td>
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<td>(i) WHO ordinal scale (ii) Hospitalization status (iii) Clinical status (iv) Laboratory examinations (v) Electrocardiogram results</td>
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<td>4</td>
<td>ChiCTR2000029308</td>
<td>Cao et al., China</td>
<td>A trial of lopinavir-ritonavir in adult hospitalized with severe COVID-19</td>
<td>17</td>
<td>2</td>
<td>Lopinavir-ritonavir (400 mg and 100 mg twice daily)</td>
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<td>—</td>
<td>(i) WHO ordinal scale (ii) Time to clinical improvement (iii) Day 28 mortality (iv) ICU length of stay</td>
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<td>5</td>
<td>IRCT20200501047259N1</td>
<td>Gharebaghi et al., Iran</td>
<td>The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: A randomized placebo-controlled double-blind clinical trial</td>
<td>—</td>
<td>2</td>
<td>Intravenous immunoglobulin (IVIG). Four vials of 5 g IVIG daily</td>
<td>Placebo and standard of care</td>
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<td>(i) WHO ordinal scale (ii) Clinical status at 30 days (iii) 30 days mortality</td>
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<tr>
<td>6</td>
<td>NCT04383535</td>
<td>Simonovich et al., Italy</td>
<td>A randomized trial of convalescent plasma in COVID-19 severe pneumonia</td>
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<td>2</td>
<td>Convalescent plasma</td>
<td>Placebo and standard of care</td>
<td>—</td>
<td>(i) WHO ordinal scale (ii) Clinical status at 30 days (iii) 30 days mortality</td>
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<td>7</td>
<td>NCT04375098</td>
<td>Balcells et al., Chile</td>
<td>Early anti-SARS-CoV-2 convalescent Plasma in patients admitted for COVID-19: A randomized phase II clinical trial</td>
<td>70</td>
<td>2</td>
<td>Deferred plasma, 400 ml plasma</td>
<td>Deferred plasma, 400 ml plasma</td>
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<td>(i) Mechanical ventilation (ii) Hospitalization &gt;14 days (iii) Death (iv) Oxygen requirement</td>
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Table 4: Continued.

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<tr>
<th>S. No.</th>
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<th>Title</th>
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<th>Study arm</th>
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<th>Control group</th>
<th>Concomitant drugs</th>
<th>Outcome measures applicable to this review</th>
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<tbody>
<tr>
<td>8</td>
<td>IRCT20150303021315</td>
<td>Malekzadeh et al., Iran Subcutaneous tocilizumab in adults with severe and critical COVID-19: A prospective open-label uncontrolled multicenter trial</td>
<td>100</td>
<td>2</td>
<td>Tocilizumab at a dose of 324mg (i) Antiviral agents (ii) Hydroxychloroquine (iii) Interferon beta-1a (iv) Antibiotic agents</td>
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<tr>
<td>9</td>
<td>NCT04654655</td>
<td>Salvarani et al., Italy Effect of tocilizumab vs. standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial</td>
<td>73</td>
<td>2</td>
<td>Tocilizumab at a dose of 8mg/kg up to a maximum of 800mg (i) Tocilizumab IV+steroids (ii) Steroids (iii) Canakinumab</td>
<td>(i) Hydroxychloroquine (ii) Heparin (iii) LMWH (iv) Antiretroviral (v) Azithromycin</td>
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<td>10</td>
<td>NCT04566057</td>
<td>Stone et al., the United States Efficacy of tocilizumab in patients hospitalized with COVID-19</td>
<td>57</td>
<td>2</td>
<td>Tocilizumab, 8mg per kilogram of bodyweight administered intravenously not to exceed 800mg</td>
<td>Placebo and standard of care</td>
<td>(i) Remdesivir (ii) Dexamethasone (iii) Hydroxychloroquine (iv) Glucocorticoids</td>
<td>(i) Clinical worsening (ii) At 14 days: admissions to ICU (iii) At 14 days: deaths (iv) At 14 days: discharges</td>
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<td>11</td>
<td>NCT0455655</td>
<td>Wang et al., China Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled multicenter trial</td>
<td>36</td>
<td>2</td>
<td>Remdesivir, 200mg on day 1 followed by 100mg on days 2–10 in single daily infusions</td>
<td>Placebo and standard of care</td>
<td>(i) Lopinavir-ritonavir (ii) Interferon</td>
<td>(i) Time to clinical improvement within 28 days (ii) Mortality at day 28 (iii) Safety outcomes included adverse events, emergent adverse events, and premature discontinuation of study drugs</td>
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<tr>
<td>12</td>
<td>NCT04585843</td>
<td>Medina et al., Colombia Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: A randomized double-blind, placebo-controlled multicenter trial</td>
<td>17</td>
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<td>Placebo and standard care</td>
<td>Placebo and standard care</td>
<td>(i) NSAIDS (ii) Macrolides (iii) Antipyretics (iv) Antibiotics (v) Glucocorticoids (vi) Immunomodulating agents (vii) Anticoagulants</td>
<td>(i) WHO ordinal scale (ii) Deaths (iii) Clinical deterioration (iv) Adverse events</td>
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<td>13</td>
<td>NCT04612157</td>
<td>Hung et al., Hong Kong Triple combination of interferon beta-1b, lopinavir-ritonavir and ribavirin in the treatment of patients admitted to hospital with COVID-19: An open-label, randomized, phase 2 trial</td>
<td>40</td>
<td>2</td>
<td>Double-blind, placebo-controlled</td>
<td>Placebo and standard care</td>
<td>(i) Interferon Beta-1b (ii) Lopinavir-Ritonavir (iii) Ribavirin</td>
<td>(i) Mortality (ii) Length of hospital stay (iii) Negative RT-PCR result</td>
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<td>No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild-to-moderate coronavirus disease 2019: results of a randomized, open-labelled prospective study</td>
<td>28</td>
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<td>(i) Ribavirin</td>
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<td>Remdesivir for severe coronavirus disease 2019 (COVID-19) versus a cohort receiving standard of care</td>
<td>33</td>
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<td>Remdesivir</td>
<td>No remdesivir</td>
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<td>Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial</td>
<td>48</td>
<td>2</td>
<td>Convalescent plasma</td>
<td>Standard of care</td>
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<td>Mortality reduction in 46 severe COVID-19 patients treated with hyperimmune plasma: A proof-of-concept single arm multicenter interventional trial</td>
<td>32</td>
<td>1</td>
<td>Plasma infusion</td>
<td>None</td>
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<td>Convalescent plasma in the management of moderate COVID-19 in adults in India: open-label phase II multicenter randomized controlled trial (PLACID trial)</td>
<td>84</td>
<td>2</td>
<td>Convalescent plasma (two doses of 200 ml) + best standard of care</td>
<td>Standard of care</td>
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**Table 4: Continued.**
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<td>1</td>
<td>NCT04374071</td>
<td>Fadel et al., United States</td>
<td>Early short-course corticosteroids in hospitalized</td>
<td>8</td>
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<td>Corticosteroid methylprednisolone 0.5–1 mg/kg/day divided in 2 intravenous doses for 3 days</td>
<td>(i) Standard care (ii) Lopinavir-ritonavir (iii) Ribavirin (iv) Hydroxychloroquine (v) Steroid</td>
<td>(i) Lopinavir-ribavirin (ii) Hydroxychloroquine (iii) Tocilizumab (iv) Methylprednisolone (v) Oral prednisone</td>
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<td>NCT04374071</td>
<td>Fatima et al., Pakistan</td>
<td>Comparison of efficacy of dexamethasone and methylprednisolone in moderate to severe COVID-19 disease.</td>
<td>30</td>
<td>2</td>
<td>Intravenous methylprednisolone 1 mg/kg/day in 2 divided</td>
<td>Intravenous dexamethasone 8 mg/day given for 5 days</td>
<td>(i) Plasma therapy (ii) Antibiotics (iii) Tocilizumab</td>
<td>(i) Mortality (ii) ICU transfer (iii) Ventilator needed</td>
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<td>3</td>
<td>NCT4357106</td>
<td>Olivares-Gazca et al., Mexico</td>
<td>Infusion of convalescent plasma is associated with clinical improvement in critically ill patients with COVID-19: A pilot study</td>
<td>22</td>
<td>1</td>
<td>Convalescent plasma</td>
<td>—</td>
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<td>Mortality</td>
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<td>2020-000890-25</td>
<td>Philippe Gautret et al., France</td>
<td>Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial</td>
<td>—</td>
<td>2</td>
<td>Hydroxychloroquine 200 mg, 3 times per day for 10 days</td>
<td>No hydroxychloroquine</td>
<td>(i) Azithromycin 500 mg on day 1 and 250 mg per day for the next four days (hydroxychloroquine-treated patients) (ii) Combination of hydroxychloroquine and azithromycin (iii) Occurrence of side effects</td>
<td>(i) Virological clearance at day 6 (ii) Virological clearance over the time (iii) Occurrence of side effects</td>
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<td>(i) For the use of corticosteroids in severe and critical patients, hospitalized COVID-19 patients. Strong recommendation, moderate-quality evidence (ii) Against the use of corticosteroids in nonsevere patients, hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence</td>
<td>Recommended the use of systematic corticosteroid rather than no corticosteroids in severe and critical COVID-19 patients.</td>
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<td>1</td>
<td>Corticosteroids</td>
<td>(i) To use in severe or critical patients (ii) Not to use in nonsevere or asymptomatic</td>
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<td>(i) To use in patients who have worsened despite the initial 24-48 hours of steroids (ii) Not to use in patients who have not received a trial of steroids or with elevated markers only</td>
<td>For the use of tocilizumab in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence</td>
<td>Recommended the use of tocilizumab in patients with severe or critical COVID-19 infection.</td>
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<td>2</td>
<td>Tocilizumab</td>
<td>This is not recommended in the national guidelines</td>
<td>Against the use of ivermectin therapy in the use of COVID-19 hospitalized patients. Weak recommendation, low-quality evidence</td>
<td>Recommended against the use of ivermectin in patients with COVID-19</td>
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<td>3</td>
<td>Ivermectin therapy</td>
<td>There is no role for prophylactic chloroquine and hydroxychloroquine to prevent COVID-19 infection after exposure (i) To use in proven or strong suspicion of secondary infection</td>
<td>Against the use of hydroxychloroquine alone or in combination with other antibiotics in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence</td>
<td>Recommended against the use of hydroxychloroquine or chloroquine for treatment of COVID-19</td>
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<td>4</td>
<td>Hydroxychloroquine/ chloroquine</td>
<td>(i) To use in proven or strong suspicion of secondary infection (ii) To not use for “prevention” of secondary infections or in patients with no clear evidence of bacterial infection Prophylactic anticoagulation (i) To use in all hospitalized patients (ii) To not use in nonsevere or asymptomatic patients</td>
<td>No evidence available</td>
<td>No evidence available</td>
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<td>5</td>
<td>Antibiotics</td>
<td>(i) For the use of anticoagulant therapeutic doses. Therapeutic: strong recommendation, moderate-quality evidence (ii) For the use of prophylactic dose anticoagulants to treat COVID-19 hospitalized patients. Prophylactic: strong recommendation, moderate-quality evidence</td>
<td>No evidence available</td>
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<td>6</td>
<td>Anticoagulation therapy</td>
<td>Therapeutic anticoagulation (i) To use in proven or high suspicion of VTE (ii) To not use in patients with isolated elevated D-dimers or no evidence of VTE (i) To use in severe patients with less than 10 days of symptoms (ii) To use in nonsevere, asymptomatic, or critical patients or in whom symptoms are longer than 10 days (i) To use in severe patients with less than 10 days of symptoms</td>
<td>For the use of remdesivir in hospitalized COVID-19 patients. Recommendation, high-quality evidence</td>
<td>Conditional recommendation against administering remdesivir in addition to usual care.</td>
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<td>7</td>
<td>Remdesivir</td>
<td>(i) To use in severe patients with less than 10 days of symptoms (ii) To not use in nonsevere, asymptomatic, or critical patients or in whom symptoms are longer than 10 days</td>
<td>Against the use of ritonavir/lopinavir in hospitalized COVID-19 patients. No recommendation, moderate-quality evidence</td>
<td>Recommended against administering lopinavir/ritonavir for treatment of COVID-19.</td>
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<td>8</td>
<td>Lopinavir/ritonavir</td>
<td>(ii) To not use in nonsevere, asymptomatic, or critical patients or in whom symptoms are longer than 10 days</td>
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<td>Intervention</td>
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<td>9</td>
<td>Convalescent plasma</td>
<td>No evidence available</td>
<td>Against the use of convalescent plasma in the management of hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence</td>
<td>No evidence available</td>
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<td>10</td>
<td>Famotidine</td>
<td>Not recommended in the national guidelines</td>
<td>For the use of famotidine in hospitalized COVID-19 patients. Weak recommendation, low-quality evidence</td>
<td>No evidence available</td>
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<td>11</td>
<td>Immunoglobulin therapy</td>
<td>No evidence available</td>
<td>For the use of immunoglobulin therapy in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence</td>
<td>No evidence available</td>
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<td>12</td>
<td>Colchicine</td>
<td>No evidence available</td>
<td>Against the use of colchicine in hospitalized COVID-19 patients. No recommendation, low-quality evidence</td>
<td>No evidence available</td>
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management of COVID-19 hospitalized adults with hydroxychloroquine alone or in combination with other antibiotics because the studies were not showing positive outcomes on mortality and length of stay. We gave moderate certainty of evidence as most of the studies in our systematic review were cohort and case-control studies.

As per our systematic review, we recommend

(i) Against the use of antibiotics, including hydroxychloroquine alone or in combination with other antibiotics in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence.

WHO v7.1 recommended against the use of hydroxychloroquine or chloroquine for treatment of COVID-19.

3.5. Anticoagulation Therapy. As per our systematic review, the therapeutic doses of anticoagulation, i.e., nadroparin calcium (2850IU) reduced mortality as compared to the prophylactic doses in the majority of studies [31–34]. While few studies found no difference, Billet et al. reported mortality reduction for prophylactic doses of both apixaban and enoxaparin and therapeutic doses of apixaban but not enoxaparin [35–38]. Therapeutic doses of apixaban did not provide an additional mortality reduction compared to prophylactic doses. Therapeutic doses of anticoagulation were shown to reduce the incidence of a venous thromboembolic event; however, both therapeutic and prophylactic doses of anticoagulation reduce in-hospital mortality compared to patients not receiving anticoagulation [31, 33, 35, 39]. We gave strong recommendation to both therapeutic and prophylactic doses of anticoagulants, as in several studies, it has shown to reduce mortality. Many studies in our systematic review were observational, so we rated the evidence as moderate.

As per our systematic review, we recommend

(i) For the use of anticoagulant therapeutic doses. Therapeutic: strong recommendation, moderate-quality evidence.


No evidence available as per WHO v7.1.

3.6. Antivirals. Remdesivir, an antiviral agent, has been associated with lower mortality, with one study reporting 62% lower odds of mortality and greater clinical improvement [40, 41]. However, the results of other studies have not been as conclusive. Studies using the WHO ordinal scale have found weak associations between remdesivir use and improved patient outcomes [42]. With regards to other antivirals, there are conflicting data from studies. Varying WHO ordinal scale results were found for antivirals lopinavir-ritonavir. Multiple studies found no difference in mortality with the combination of ritonavir/lopinavir and remdesivir [43, 44]. We gave weak recommendation for the use of remdesivir because of the inconsistent results of the studies. However, we recommend against the use of ritonavir/lopinavir due to conflicting research evidence. Most of the studies on remdesivir were randomized controlled trials; therefore, we rated it as high quality of evidence, while studies on ritonavir/lopinavir were mostly observational, so it has moderate certainty.

As per our systematic review, we recommend

(i) For the use of remdesivir in hospitalized COVID-19 patients. Weak recommendation, high-quality evidence.

(ii) Against the use of ritonavir/lopinavir in hospitalized COVID-19 patients. No recommendation, moderate-quality evidence.

WHO v7.1: conditional recommendation against administering remdesivir in addition to usual care.


3.7. Convalescent Plasma. Convalescent plasma initially was looked at as a possible therapy for COVID-19 infection due to its prior usefulness in other epidemic viruses. Some initial observational studies suggested the use of convalescent plasma in improving pulmonary function, decreasing adverse effects, increasing survival, and shortening hospital stay [45–47]. While most observational studies reported positive outcomes, RCTs have not supported convalescent plasma use. We gave weak recommendation for convalescent plasma use because RCTs have not shown significant improvement in patients’ health status. As many of the studies were observational, therefore, we gave it a moderate quality of evidence.

As per our systematic review, we recommend

(i) Against the use of convalescent plasma in the management of hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence.

There are no available evidence as per WHO v7.1.

3.8. Famotidine. While famotidine is conventionally used as an H2 receptor blocker, it also has antiviral properties [48]. Freedberg et al., in a single-centered retrospective cohort study, reported reduced mortality with famotidine use [49]. Similarly, when comparing a treatment regimen of HCQ, azathioprine, remdesivir, and corticosteroids with famotidine, and those without famotidine, Mather et al. reported lower mortality in the famotidine arm (14% in the famotidine group vs. 26% in the nonfamotidine group) [50]. Despite these results, larger studies and RCTs have not yet established the role of famotidine, and therefore, we gave it low certainty. Given the minimal side effect profile of famotidine, our judgement based on data available at the time was for its use but with weak recommendation.

As per our systematic review, we recommend

(i) For the use of famotidine in hospitalized COVID-19 patients. Weak recommendation, low-quality evidence.
3.9. Immunoglobulin Therapy. Based on the limited number of studies, a retrospective cohort study conducted by Shao et al. found IVIG therapy to reduce the 28-day mortality in critically ill patients (27% in the IVIG group vs. 53% in the non-IVIG group) [51]. Similarly, a randomized trial by Gherebaghi et al. also proved that IVIGs reduced mortality [52]. Studies have shown lower mortality; therefore, we supported its use with weak recommendation. As no significant interventional studies are supporting its use, we gave it moderate certainty.

As per our systematic review, we recommend

(i) Against the use of immunoglobulin therapy in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence.

There are no available evidence as per WHO v7.1.

3.10. Colchicine. Colchicine works by inhibiting the assembly of microtubules during mitosis by binding to tubulin inside cells and forming tight tubulin-colchicine complexes. This is its major anti-inflammatory mechanism of action [53]. In our review, only 1 single-center cohort of adult hospitalized patients with COVID-19 pneumonia and acute respiratory distress syndrome was found using colchicine 1 mg/day, investigating the association between colchicine use and improved survival in adult hospitalized patients with COVID-19 pneumonia and acute respiratory distress syndrome and found a 20.8% decrease in mortality amongst patients treated with colchicine along with other standards of care drugs [54]. Because of the insufficient research evidence, we are not recommending colchicine use and gave it a low quality of evidence.

As per our systematic review, we recommend

(i) Against the use of colchicine in hospitalized COVID-19 patients. No recommendation, low-quality evidence.

There are no available evidence as per the WHO v7.1.

4. Discussion

A great breadth of literature exists on the therapeutic management of hospitalized adults with COVID-19 based on disease severity, much of which have been analyzed and appraised systematically [55]. Currently, living systematic reviews provide information to guide clinical practice [56, 57]. However, this approach assumes that all treatment options are available or approved in each country or region, which is not the case. In Pakistan, the Government of Pakistan has released Clinical Management Guidelines for COVID-19 Infections v4, and several other systematic reviews have been conducted to assess the efficacy of drugs used in the treatment of COVID-19, with the WHO living guidelines for pharmacological management including the most up to date data. It was thus imperative that our findings be compared and assessed against broader literature that has been published.

Our review found the lack of randomized trials to be a limitation for evidence regarding less extensively studied agents, while the more extensively investigated agents had been studied by randomized trials. Since then, newer studies, that have been conducted and included in our synthesis. To consolidate the pool of information to assess the effectiveness of currently approved therapeutic options for COVID-19 infection in Pakistan, we have synthesized data relating to only those treatments that are recommended in our country’s guidelines using global data from 1st November 2019 to December 31st, 2020 [2].

Of all the drug classes analyzed, corticosteroids were found to have the most consistent effect on mortality and length of stay. The WHO clinical progression (ordinal) scale showed a reduction in mortality among patients being treated with corticosteroids. All but a few studies support the use of corticosteroids in patients hospitalized with COVID-19 [58, 59]. Trials that assessed anticoagulation (especially therapeutic vs. prophylactic dosages) were also predominantly found to improve thromboembolic outcomes and mortality. However, variations in the type of anticoagulant used make it hard to recommend a single drug. Nadroparin, tinzaparin, dalteparin (LMWH), heparin, apixaban, and enoxaparin were all found to have reduced mortality [31, 33, 38]. Trials assessing tocilizumab supported its use to limit mortality and length of stay [13, 28, 29, 60]. One study found that the addition of corticosteroids to tocilizumab was a significant protective factor against mortality [61].

Studies assessing remdesivir failed to show any conclusive difference in mortality and length of stays of patients with COVID-19 [42]. Of the antivirals that are being used for COVID-19, lopinavir and ritonavir have predominantly been assessed by various observational studies as well as clinical trials, both of which have been uncertain. Ribavirin alone and in combination with other antivirals (lopinavir/ritonavir + interferon-alpha) was also shown to have minimal efficacy [62]. Data from RCTs led to recommendation against the use of convalescent plasma [63–66], which in the early days of COVID-19 was looked at as a major intervention.

Very few studies have been conducted on famotidine (an H2 receptor blocker) and IVIG. Studies have reported a significantly reduced mortality in patients being treated by famotidine or IVIG compared to control groups; however, further randomized trials and data are needed to make a concrete recommendation. Studies assessing ivermectin also report divided results and highlight the need for further studies. One of the studies assessing colchicine has reported better outcomes in adult hospitalized patients with COVID-19 pneumonia [30].

Our review is the first one to systematically review the drugs specified by the Government of Pakistan’s Clinical Management Guidelines for COVID-19 Infections v4, and several other systematic reviews have been conducted to assess the efficacy of drugs used in the treatment of COVID-19, with the WHO living guidelines for pharmacological management including the most up to date data. It was thus imperative that our findings be compared and assessed against broader literature that has been published.
review, have shown tocilizumab, IVIGs, and colchicine to be effective as well. Larger trials, such as the solidarity trials, have since proven that remdesivir is not effective [67].

The urgency of information about COVID-19 infection treatment has resulted in poorly organized studies that use a variety of different outcome measures, which deter meaningful comparison between different therapeutic agents. Indeed, our review reported a wide range of outcome measures, resulting in difficulty synthesizing data.

To standardize outcome measures across studies, several international bodies worked in union and formulated a set of outcome measures, which included the WHO clinical progression scale. This is an ordinal scale, ranging from 0 (no infection) to 10 (mortality) that is especially useful in widespread diseases. The lower scores (for mild disease, which may or may not require assistance) are more subjective, and the higher scores (of severe disease requiring different levels of intervention) are likely to change based on regional practices. However, the scale is quick to use because the data required are readily available in medical records. Despite its usefulness in standardizing clinical research, the uptake of this scale has not been encouraging [68]. Our systematic review reports only 13 studies that have used this scale to report clinical progression. Gaps in reporting, with different studies grouping or failing to mention the number of patients for each score, undermines the use of a standardized scale to make sound accurate comparisons of clinical data. We recommend the use of the WHO clinical progression scale as a standard practice for studies on COVID-19 infection, with full reporting of all scores to enable comparison of study outcome measures and optimize the systematic analysis of clinical data.

There are several limitations to this systematic review, mostly stemming from considerable heterogeneity between articles. These include variations in participant inclusion criteria of studies, variations in outcome measures, variations in drugs used across the same class, variations in drug dosages, and variations in geographic locations and patient populations across studies. In addition, the retrospective nature of many studies, the limited sample sizes, and inadequate statistical adjustment for reported associations also adversely impact interpretability.

5. Conclusion

Data on pharmacological interventions to treat COVID-19 are rapidly evolving, and based on it, the recommendations have also been changed. In our systematic review, the recommendations were based on studies up till December 2021, and we have compared our recommendations with the WHO v7.1, which showed significant changes in recent treatment modalities of COVID-19 infection. Our understanding regarding the management of COVID-19 has evolved rapidly over the last two years and continues to do so. Given the urgent need to offer any therapeutic option, interim recommendations were often made based on the best available data at the time. These data were, however, often from studies that were exploratory or not as rigorously done. This is apparent in the disparate recommendation between the 2 guidelines and the systematic review (which is only looking at studies published during the early part of the pandemic). This also brings to light the need to continually assess the literature and be able to ready to change (previously established) therapeutic recommendations.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Supplementary Figure 1. PRISMA flow diagram reporting various studies assessed for further evaluation and included in the review. Supplementary Figure 2. Risk of bias graph for quasiexperimental studies. Supplementary Figure 3. Risk of bias summary for quasiexperimental studies. Supplementary Figure 4. Risk of bias graph for randomized control trials. Supplementary Figure 5. Risk of bias summary for randomized control trials. Supplementary Figure 6. Risk of bias graph for case-control studies. Supplementary Figure 7. Risk of bias summary for case-control studies. Supplementary Figure 8. Risk of bias graph for observational cohort and cross-sectional Studies. Supplementary Figure 9. Risk of bias summary for observational cohort and cross-sectional studies. (Supplementary Materials)

References


[39] G. N. Nadkarni, A. Lala, E. Bagiella et al., “Anticoagulation, mortality, bleeding and pathology among patients...


