Review Article

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

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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 of 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 recommendation for pharmacological 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).

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 showed a 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 2: Description of study characteristics: cross-sectional and cohort studies.

| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|--------|-----------------|-------|------------------------|-------------------|-----------------|------------------|-------------------------------------------|
| 1      | Stessel et al., Belgium | Impact of implementation of an individualized thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study. | 52 | Nadroparin calcium 2850 IU (preimplementation of protocol) | Nadroparin calcium 2850 IU (postimplementation of protocol) | — | (i) One-month mortality (ii) Two-week and three-week mortality (iii) Hospital length of stay |
| 2      | Jonmarker et al., Sweden | Dosing of thromboprophylaxis and mortality in critically ill COVID-19 patients | 56 | (i) Tinzaparin or dalteparin low (2500–4500 IU tinzaparin or 2500–5000 IU dalteparin) (ii) Tinzaparin or dalteparin medium (> 4500 IU but < 175 IU/kg, kg, of bodyweight tinzaparin or > 5000 IU but < 200 IU/kg of bodyweight dalteparin) (iii) High dose (≥ 175 IU/kg of bodyweight tinzaparin or ≥ 200 IU/kg of bodyweight dalteparin) | — | (i) 28 days mortality (ii) ICU stay (iii) Thromboembolic events | | |
| 3      | Salton et al., Italy | Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia | 58 | Methylprednisolone loading dose of 80mg intravenously, followed by an infusion of 80mg/d in 240ml of normal saline at 10ml/h for at least 8 days | — | Standard of care (antibiotics, antivirals, vasopressors, and renal replacement therapy) | (i) Mortality (ii) Transfer to intensive care unit (iii) Invasive mechanical ventilation |
| 4      | Mutair et al., Saudi Arabia | Hydroxychloroquine in mild cases | 31 | Hydroxychloroquine in moderate cases | Hydroxychloroquine in moderate cases | — | (i) Hydroxychloroquine (ii) Azithromycin (iii) Vitamin C (iv) Vitamin E (v) Ceftriaxone (vi) Enoxaparin |
| 5      | Annie et al., the United States | Hydroxychloroquine in hospitalized patients with COVID-19: real-world experience assessing mortality | 116 | (i) Hydroxychloroquine alone (ii) Hydroxychloroquine plus azithromycin | — | Mortality | Mortality |
| 6      | Arshad et al., the United States | Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19 | 230 | (i) Hydroxychloroquine alone (ii) Azithromycin alone 500mg once daily on day 1 followed by 250mg once daily for the next 4 days. (iii) Hydroxychloroquine plus azithromycin | Neither treatment | (i) Steroid (ii) Tocilizumab | (i) Mortality (ii) Hospital length of stay in days (iii) Hospital length of stay in days |
| 7      | Ashinyo et al., Ghana | Clinical characteristics, treatment regimen, and duration of hospitalization among COVID-19 patients in Ghana: A retrospective cohort study | 93 | (i) Chloroquine + hydroxychloroquine (ii) Hydroxychloroquine + azithromycin (iii) Hydroxychloroquine only (iv) Azithromycin only (v) Supportive treatment | — | Duration of hospitalization | Duration of hospitalization |
| 8      | Ayerbe et al., Spain | The association between treatment with heparin and survival in patients with COVID-19 | 55 | (i) Heparin | — | — | |
| 9      | Ayerbe et al., Spain | The association of treatment with hydroxychloroquine and hospital mortality in COVID-19 patients | 55 | Hydroxychloroquine was dosed as 400mg twice daily the first day, followed by 200mg twice daily for 4–6 days. | — | — | |

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| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|-------|----------------|-------|------------------------|--------------------|-----------------|------------------|---------------------------------------------|
| 10    | Bartoletti et al., Italy | Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: A multicentre study | 130 | Corticosteroid ≥0.5 mg/kg of prednisone | — | (i) Hydroxychloroquine (ii) Lopinavir/ritonavir (iii) Darunavir/ritonavir (iv) Low-molecular-weight heparin (v) Other standard of care (vi) Tocilizumab (vii) Steroids (viii) Anakinra (ix) Azithromycin (x) Other | — |
| 11    | Camprubi et al., Spain | Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients | 21 | Ivermectin 200 μg/kg for 8–18 days | No ivermectin | (i) Tocilizumab (ii) Steroids (iii) Anakinra (iv) Remdesivir (v) Lopinavir/ritonavir (vi) Hydroxychloroquine (vii) Azithromycin (viii) Beta-interferon (ix) Hydroxychloroquine (x) Azithromycin | — |
| 12    | Canoglu et al., Turkey | Therapeutic dosing of low-molecular-weight heparin may decrease mortality in patients with severe COVID-19 infection | 51 | Heparin prophylactic dose LMWH (0.5 mg/kg twice daily) | Heparin therapeutic dose LMWH (1 mg/kg twice daily) | (i) Favipiravir (ii) Lopinavir/ritonavir (iii) Supportive treatment | — |
| 13    | Catteau et al., Belgium | A retrospective controlled cohort study of the impact of hydroxychloroquine therapy and mortality in hospitalized patients with COVID-19: A nationwide observational study of 8075 participants | 72 | Hydroxychloroquine 2400 mg over 5 days | No hydroxychloroquine | (i) Lopinavir/ritonavir (ii) Hydroxychloroquine (iii) Tocilizumab (iv) Remdesivir (v) Macrolides (vi) Anakinra | — |
| 14    | Ana Fernández-Cruz, Spain | Low-dose hydroxychloroquine therapy and mortality in hospitalized patients with COVID-19: A nationwide observational study of 8075 participants | 35 | Steroid | No steroid | (i) Hydroxychloroquine (ii) Lopinavir/ritonavir (iii) Azithromycin (iv) Interferon (v) Tocilizumab (vi) Anakinra | — |
| 15    | Freedberg et al., the United States | Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study | 56 | Famotidine | No famotidine | — | — |
| 16    | Geleris et al., United States | Observational study of hydroxychloroquine in hospitalized patients with COVID-19 | 50 | Hydroxychloroquine 600 mg twice on day 1 and then 400 mg daily for a median of 5 days | No hydroxychloroquine | (i) Systemic glucocorticoid (ii) Antibiotic agent (iii) Azithromycin (iv) Tocilizumab (v) Remdesivir | Intubation or death |

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| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures | Outcome measures applicable to this review |
|-------|----------------|-------|------------------------|--------------------|-----------------|------------------|-----------------|------------------------------------------|
| 17    | Berry et al., United States | Hydroxychloroquine and tocilizumab therapy in COVID-19 patients: An observational study | 66 | (i) Hydroxychloroquine 800 mg on day 1 and 400 mg on days 2–5, followed by 200 mg TID (ii) Hydroxychloroquine in combination with azithromycin (iii) Tocilizumab first dose 400 mg, followed by 800 mg | (i) Neither hydroxychloroquine/azithromycin (ii) Azithromycin alone (iii) No tocilizumab | For patients in tocilizumab/no tocilizumab group: (i) Steroid (ii) Hydroxychloroquine alone (iii) Azithromycin alone (iv) Azithromycin plus hydroxychloroquine | (i) Mortality (ii) Adverse drug events | (i) Mortality (ii) Adverse drug events |
| 18    | Karolyi et al., Austria | Hydroxychloroquine versus lopinavir/ritonavir in severe COVID-19 patients | 57 | Hydroxychloroquine loading dose of 400 mg twice on the first day, followed by 200 mg twice daily | Lopinavir/ritonavir 400 mg/100 mg administered twice daily | Concomitant antibiotic (i) Antibiotics (azithromycin, amoxicillin/ cloxacillin combination, and augmentin) (ii) Vitamin C | (i) In-hospital mortality (ii) Intensive care unit (ICU) admission (iii) Length of stay (iv) PCR (polymerase chain reaction) negativity (v) Side effects of treatment (i) Admission to ICU (ii) Mechanical ventilation | (i) In-hospital mortality (ii) Intensive care unit (ICU) admission (iii) Length of stay (iv) PCR (polymerase chain reaction) negativity (v) Side effects of treatment |
| 19    | Kirenga et al., Uganda | Characteristics and outcomes of admitted patients infected with SARS-CoV-2 in Uganda | — | Hydroxychloroquine | No hydroxychloroquine | — | (i) Death (ii) Negative reverse transcriptase PCR (RT-PCR) tests (v) Length of hospitalization | (i) Death (ii) Negative reverse transcriptase PCR (RT-PCR) tests |
| 20    | Lagier et al., France | Outcomes of 3737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis | 56 | (i) Azithromycin + hydroxychloroquine >3 days (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) (ii) Other treatment (azithromycin + hydroxychloroquine for at least 3 days) (iii) Azithromycin + hydroxychloroquine <3 days (iv) Hydroxychloroquine alone (v) Azithromycin alone (vi) No azithromycin and hydroxychloroquine | — | — | (i) Death (ii) Transfer to the intensive care unit (ICU) (iii) ≥10 days of hospitalization (iv) Viral shedding | (i) Death (ii) Transfer to the intensive care unit (ICU) (iii) ≥10 days of hospitalization (iv) Viral shedding |
| 21    | Albertini et al., France | Observational study on off-label use of tocilizumab in patients with severe COVID-19 | 16 | Tocilizumab 8 mg/kg | No tocilizumab | (i) Hydroxychloroquine (ii) Azithromycin | (i) Mortality (ii) Mechanical ventilation (iii) Length of stay (iv) Adverse events | (i) Mortality (ii) Mechanical ventilation (iii) Length of stay (iv) Adverse events |
### Table 2: Continued.

| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|--------|-----------------|-------|------------------------|--------------------|------------------|-------------------|--------------------------------------------|
| 22     | Almazrou et al., Saudi Arabia | Comparing the impact of hydroxychloroquine-based regimens and standard treatment on COVID-19 patient outcomes: A retrospective cohort study | 20 | Hydroxychloroquine | — | — | (i) Hospital length of stay (ii) Time in ICU, days (iii) ICU admission (iv) Mechanical ventilation |
| 23     | Billet et al., the United States | Anticoagulation in COVID-19: effect of enoxaparin, heparin, and apixaban on mortality | 30 | (i) Apixaban prophylaxis (ii) Apixaban full therapy (iii) Enoxaparin prophylaxis (iv) Enoxaparin full therapy (v) Unfractionated Heparin standard prophylaxis (vi) Unfractionated Heparin high prophylaxis (vii) Unfractionated Heparin full therapy | — | — | (i) Mortality (ii) Respiratory support |
| 24     | Capra et al., Italy | Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia | — | Tocilizumab | No tocilizumab | — | |
| 25     | Mario Fernández-Ruiz et al., Spain | Tocilizumab for the treatment of adult patients with severe COVID-19 pneumonia: A single-center cohort study | — | Tocilizumab | — | — | |
| 26     | Gupta et al., the United States | Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19 | 122 | Tocilizumab patients received tocilizumab within 2 days of ICU admission | Tocilizumab patients did not receive tocilizumab within 2 days of ICU admission | — | (i) Survival rate (ii) Ventilatory status |
| 27     | Kaminski et al., the United States | Tocilizumab therapy for COVID-19: A comparison of subcutaneous and intravenous therapies | 54 | Tocilizumab, 400 mg IV | Tocilizumab, subcutaneous dose of 324 mg (given as two simultaneous doses of 162 mg) plus azithromycin 500 mg once, followed by 250 mg oral once daily for additional 4 days. (ii) Tocilizumab therapy (iii) Corticosteroids for 3–5 days | — | (i) Survival rate (ii) Ventilatory status |
| 28     | Kim et al., Korea | 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 | 44 | Lopinavir-ritonavir 400 and 100 mg twice daily | Hydroxychloroquine 400 mg once daily | — | (i) Time to negative conversion of viral RNA (ii) Time to clinical improvement (iii) Adverse events |
| 29     | Lammers et al., Netherlands | — | Hydroxychloroquine on day 1, 400 mg, and 400 mg after 12 hours, 200 mg BID on days 2–5 | Chloroquine on 1st day 600 mg and 300 mg after 12h, 300 mg BID on days 2–5 | — | (i) Death (ii) Transfer to the intensive care unit (ICU) |
| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|-------|----------------|-------|------------------------|--------------------|------------------|-------------------|------------------------------------------|
| 30    | Lauriola et al., Italy | Effect of combination therapy of hydroxychloroquine and azithromycin on mortality in patients with COVID-19 | — | (i) Azithromycin and hydroxychloroquine (hydroxychloroquine dose of 200 mg TID (alone or in combination) and azithromycin 500 mg QD for 10 days) (ii) Hydroxychloroquine 200 mg TID | No treatment (standard care not specified) | — | Mortality |
| 31    | Lee et al., the United States | Remdesivir for the treatment of severe COVID-19: A community hospital’s experience | 111 Remdesivir 200mg loading dose on day 1, followed by a 100 mg daily on days 2-5 | — | (i) Antibiotics (ii) Convalescent plasma (iii) Dexamethasone | — | (i) Mortality (ii) Length of stay (iii) ICU admission |
| 32    | Yiming Li et al., China | Corticosteroids | 62 | Corticosteroids | No corticosteroids | — | (i) 90 days mortality (ii) Viral clearance |
| 33    | Liu et al., China | Clinical characteristics and corticosteroids application of different clinical types in patients with coronavirus disease 2019 | 121 | (i) Corticosteroid (ii) Methylprednisolone (1-2)mg/kg day general type, 1-5mg/kg day severe type, and 1-4mg/kg day critical type | No corticosteroids | (i) Interferon-α (IFN-α) (ii) Lopinavir/ritonavir | (i) Mortality (ii) Length of stay (iii) ICU admission |
| 34    | Gautret et al., France | Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19 | — | Hydroxychloroquine (200mg of oral TID for 10 days) and azithromycin (500mg on day 1 followed by 250mg per day for 4 days) | — | — |
| 35    | Yu et al., China | Tocilizumab use in COVID-19 associated pneumonia | 61 | Tocilizumab 8mg/kg IV (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (i.e., 324 mg in total) (ii) Hydroxychloroquine (iii) Azithromycin (iv) Fingerprick test for SARS-CoV-2 (v) Low-molecular-weight heparin | Nonhydroxychloroquine | (i) Lopinavir and ritonavir (ii) Ribavirin (iii) Intravenous immunoglobulin | (i) Mortality (ii) Length of stay |
| 36    | Guaraldi et al., Italy | Tocilizumab in patients with severe COVID-19: A retrospective cohort study | — | Tocilizumab 8mg/kg IV (up to a maximum of 800 mg) in two infusions, 12 h apart, or subcutaneously at 162 mg administered in two simultaneous doses, one in each thigh (i.e., 324 mg in total) (ii) Hydroxychloroquine (iii) Azithromycin (iv) Fingerprick test for SARS-CoV-2 (v) Low-molecular-weight heparin | — | — |
| 37    | Grein et al., multicenter | Compassionate use of remdesivir for patients with severe COVID-19 | — | Remdesivir loading dose of 200 mg intravenously on day 1 plus 100mg daily for the following 9 days | — | Supportive care |
| 38    | Alexis K. Okoh et al., the United States | Tocilizumab use in COVID-19 associated pneumonia | 61 | Tocilizumab 8mg/kg IV (maximum 800mg/dose) | No tocilizumab | Standard of care | (i) Clinical improvement (ii) Changes in oxygen support requirements (iii) Adverse events (iv) Death (v) Decoilation in oxygen therapy (vi) In-hospital death (vii) Septic shock (viii) Acute kidney injury (AKI) requiring hemodialysis |
| S. no. | Author, country      | Title                                                                 | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures                                                                 |
|-------|----------------------|----------------------------------------------------------------------|------------------------|---------------------|------------------|--------------------|----------------------------------------------------------------------------------|
| 39    | Shao et al., China   | Clinical efficacy of intravenous immunoglobulin therapy in critical ill patients with COVID-19: A multicenter retrospective cohort study | 122                    | IVIG 0.1-0.5g/kg per day | Non-IVIG         | —                  | (i) 28 days mortality (ii) 60 days mortality (iii) In-hospital days (iv) Total course of disease |
| 40    | Kansas et al., United States | Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study | 61                     | Tocilizumab 8mg/kg and received 400 mg tocilizumab as a 60 min single intravenous infusion | No tocilizumab   | —                  | (i) Hydroxychloroquine with a loading dose of 400mg twice daily followed by 200mg BID for 5 days (ii) Azithromycin 500 mg per day for 5 days (iii) Steroid (iv) Noninvasive oxygen support improvement in oxygen support (v) Clinical improvement among patients required mechanical ventilation (vi) Length of stay in hospital (vii) Mortality (viii) Noninvasive oxygen support improvement in oxygen support (ix) Noninvasive oxygen support improvement in hospital |
| 41    | Ramos et al., Netherlands | Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19 associated cytokine storm syndrome: results of the CHIC study | 92                     | (i) Methylprednisolone 250mg intravenously on day 1, followed by MP 80mg intravenously on days 2-5 (ii) Tocilizumab single dose 8mg/kg bodyweight intravenous, maximum 800mg between day 2 and day 5 | —                | —                  | (i) Gatifloxin 2g every 24 hours for 7 days (ii) Chloroquine 300mg every 12 hours following a loading dose of 600mg (iii) Clinical improvement (iv) WHO ordinal scale (v) Hospital mortality (vi) Mechanical ventilation (vii) Duration of hospitalization |
| 42    | Colaneri et al., Italy | Tocilizumab for treatment of severe COVID-19: patients preliminary results from SMAHET-COVID-19 Registry (SMACORE) | 14                     | Tocilizumab 8mg/kg (up to a maximum 800mg per dose) IV repeated 12 hours plus standard of care | Standard of care | —                  | (i) Hydroxychloroquine 200mg BID (ii) Azithromycin 500mg once (iii) Propylenic dose of low weight heparin (iv) Methylprednisolone (a tapered dose of 1mg/kg up to a maximum of 80mg) for 10 days (v) ICU admission (vi) 7 days mortality rate (vii) Clinical and laboratory data (viii) Days of hospitalization |
| 43    | Mather et al., United States | Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19: Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1008 cases in Marseille, France | 80                     | (i) Famotidine 80mg (range 40-160mg) was received over a median of 4 days (ii) Hydroxychloroquine 600mg/day | (i) No famotidine | —                  | (i) Hydroxychloroquine, 600mg/day (ii) Azithromycin 500mg once (iii) Remdesivir (iv) Corticosteroids (v) Death (vi) Disease severity (vii) Mechanical ventilation |
| 44    | Million et al., France | Hydroxychloroquine + azithromycin: a combination of 200mg of oral HCQ, 3 times daily for 10 days combined with 5 of AZ (500mg on day 1 followed by 250 mg daily for the next 4 days) | 29                     | Hydroxychloroquine + azithromycin early treatment, as standard care. | —                | —                  | (i) Length of hospitalization (ii) Death (iii) Contagiousness as assessed by PCR and culture. |
| 45    | Morrison et al., United States | Clinical characteristics and predictors of survival in adults with coronavirus disease 2019 receiving tocilizumab | 34                     | Tocilizumab was administered as a 8mg/kg IV dose using actual bodyweight with a maximum dose of 800mg. Doses were rounded to 400mg, 600mg, or 800mg. (ii) Hydroxychloroquine (iii) Lopinavir/ritonavir with ribavirin (iv) Remdesivir | —                | —                  | (i) Lopinavir/ritonavir with ribavirin, received as supportive care (ii) Hydroxychloroquine, received as supportive care (iii) Remdesivir (iv) WHO ordinal scale (v) 28 day in-hospital survival (vi) 28 day in hospital survival (vii) Duration of hospitalization (viii) Duration of hospitalization |
Table 2: Continued.

| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|--------|-----------------|-------|------------------------|--------------------|-----------------|-------------------|------------------------------------------|
| 46     | Pasquini et al., Italy | Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU | 21 | Remdesivir, first dose of 200 mg IV on day 1 plus 100 mg daily from day 2 on. | No remdesivir | (i) Tocilizumab<br>(ii) Hydroxychloroquine<br>(iii) Lopinavir/ritonavir with ribavirin | Mortality<br>Mortality |
| 47     | Patel et al., India | Safety and efficacy of tocilizumab in the treatment of severe acute respiratory syndrome coronavirus 2 pneumonia: A retrospective cohort study | 31 | Tocilizumab dosed at 8 mg/kg, up to a maximum dose of 800 mg | — | (i) ARB<br>(ii) Metformin<br>(iii) Aspirin<br>(iv) Beta-blockers<br>(v) Insulin<br>(vi) Corticosteroids<br>(vii) Hydroxychloroquine<br>(viii) Immunosuppressants<br>(ix) NSAIDs<br>(x) Methotrexate<br>(xi) ACEI<br>(xii) Azathioprine<br>(xiii) Sulfasalazine | (i) Mortality<br>(ii) Admission to the intensive care unit (ICU) with invasive mechanical ventilation or death<br>(iii) Hospital stay |
| 48     | Rahmani et al., Iran | Comparing outcomes of hospitalized patients with moderate and severe COVID-19 following treatment with hydroxychloroquine plus atazanavir/ritonavir | 58 | Hydroxychloroquine + atazanavir/ritonavir has 400 mg BD on the first day and then 200 mg, 300/100 mg daily was started within 24 h of the hospital admission for all patients | — | (i) IFN<br>(ii) Ribavirin<br>(iii) Corticosteroid<br>(iv) IVIG<br>(v) Vitamin C<br>(vi) Antibiotics | (i) 28 days mortality<br>(ii) Hospital stay<br>(iii) ICU stays<br>(iv) Rate of ICU admissions and intubation<br>(v) ECG findings (defined as arrhythmia or prolonged QT fraction) |
| 49     | Rodríguez-Molina et al., Spain | Observational study of azithromycin in hospitalized patients with COVID-19 | 52 | Azithromycin prescribed at a dose of 500 mg on the first day (oral or intravenous), followed by 250 mg daily, until completing 5 days of treatment. | Standard of care | (i) Azithromycin<br>(ii) Tocilizumab<br>(iii) Methylprednisolone<br>(iv) Dexamethasone | (i) Hospital stays<br>(ii) Mortality<br>(iii) Oxygen requirement<br>(iv) In-hospital mortality<br>(v) Cardiac arrest and abnormal ECG findings (defined as arrhythmia or prolonged QT fraction) |
| 50     | Rosenberg et al., the United States | Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State | 19 | (i) Hydroxychloroquine with or without azithromycin<br>(ii) Azithromycin | — | (i) Hospital stays<br>(ii) Mortality<br>(iii) Length of stay | (i) Hospital stays<br>(ii) Mortality<br>(iii) Length of stay |
| S.no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|-------|----------------|-------|------------------------|-------------------|----------------|-----------------|------------------------------------------|
| 51    | Rubio-Rivasa et al., Spain | Beneficial effect of corticosteroids in preventing mortality in patients receiving tocilizumab to treat severe COVID-19 illness | 22 | Tocilizumab as a single IV infusion at a dose of 400 mg (weight <80kg) or 600 mg (weight ≥80 kg) or using methylprednisolone at doses ranging from 0.5 mg/kg/d to 250 mg IV in 3 pulses | — | (i) Hydroxychloroquine (ii) Azithromycin (iii) Lopinavir/ritonavir (iv) Remdesivir (v) Prophylactic anticoagulation therapy (vi) Subcutaneous interferon beta-1b 0.25 mg/48h. | (i) In-hospital mortality (ii) In-hospital mortality |
| 52    | Shi et al., China | Evaluation of antiviral therapies for coronavirus disease 2019 pneumonia in Shanghai, China | 19 | (i) Arbidol group 200 mg, three times/day (ii) Lopinavir/ritonavir group two tablets, two times/day (iii) Arbidol + lopinavir/ritonavir group (iv) Interferon group 100 000 U/kg, two times/day (v) Interferon + lopinavir/ritonavir group (vi) Interferon + darunavir group one tablet, one time/day. | — | — | (i) Improvements in pulmonary involvement (ii) Length of hospital stay (iii) Length of hospital stay |
| 53    | Tang et al., China | Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy | 34 | Unfractionated heparin or low-molecular-weight heparin (LMWH) for 7 days or longer. | No heparin or less than 7 days | — | — |
| 54    | Tong et al., China | Ribavirin therapy for severe COVID-19: a retrospective cohort study | 60 | Intravenous ribavirin 500 mg every 12h | — | — | — |
| 55    | Toniati et al., Italy | Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single-center study of 100 patients in Brescia, Italy | 12 | Tocilizumab at a dosage of 8 mg/kg (max 800 mg) by two consecutive intravenous infusions 12h apart (ii) Lopinavir + ritonavir 400 mg and 100 mg twice a day. (iii) Remdesivir (iv) Azithromycin (v) Ceftriaxone (vi) Piperacillin/tazobactam (vii) Hydroxychloroquine 400 mg/day (viii) Dexamethasone 20 mg/day | — | — | Improvement in acute respiratory failure Improvement in acute respiratory failure |
| 56    | Tsai et al., China | Successful treatment of 28 patients with coronavirus disease 2019 at a medical center in Taiwan | 154 | — | — | None | None |
| 57    | Vu et al., Florida | Effects of tocilizumab in COVID-19 patients: A cohort study | 19 | Tocilizumab 400 mg (30-100 kg) and 600 mg (> 100 kg) | — | (i) Hydroxychloroquine (ii) Methylprednisolone (iii) Intravenous immunoglobulin (iv) Convalescent plasma | (i) WHO ordinal scale (ii) Mortality (iii) Length of stay |
| 58    | Wu et al., China | Systemic corticosteroids and mortality in severe and critical COVID-19 patients in Wuhan, China | 81 | — | No corticosteroid | — | (i) Mortality (ii) Hospital stays (iii) Hospital stays |
| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|-------|-----------------|-------|------------------------|--------------------|-----------------|------------------|-------------------------------------------|
| 59    | Yan et al., China | Factors associated with prolonged viral shedding and impact of lopinavir/ritonavir treatment in hospitalized noncritically ill patients with SARS-CoV-2 infection | 39 | (i) Lopinavir/ritonavir 400 mg and 100 mg, orally twice daily (ii) Corticosteroid therapy 75 mg, orally twice daily (iii) Antibiotics (iv) High-flow nasal cannula oxygen therapy (v) Noninvasive mechanical ventilation (vi) Invasive mechanical ventilation | — | — | (i) Length of stay (ii) Viral shedding days (iii) Length of stay (iv) Viral shedding days |
| 60    | Yang et al., China | The role of methylprednisolone on preventing disease progression for hospitalized patients with severe COVID-19 | 67 Methylprednisolone 50–80 mg/d | (i) Nonmethylprednisolone (ii) Oseltamivir (iii) Arbidol hydrochloride (iv) Lopinavir/ritonavir (v) Darunavir and cobicistat | — | — | (i) Progression to critical illness (ii) Deaths |
| 61    | You et al., China | The use of methylprednisolone in COVID-19 patients: A propensity score matched retrospective cohort study | 60 Methylprednisolone 40 mg once or twice per day within 48 hours of admission for one week. Nonmethylprednisolone | — | — | (i) Progressed to severe cases (ii) Secondary infection (iii) Hospital stays (iv) Length of hospital stay (v) Oxygen requirement (vi) Fever time (vii) Mortality (viii) Length of hospital stay | (i) Mortality (ii) Length of hospital stay |
| 62    | Yuan et al., China | Effects of corticosteroid treatment for nonsevere COVID-19 pneumonia: A propensity score-based analysis | 37 | (i) Corticosteroid (ii) Methylprednisolone | Noncorticosteroid group | — | (i) Progressed to severe cases (ii) Secondary infection (iii) Hospital stays (iv) Length of hospital stay (v) Oxygen requirement (vi) Fever time (vii) Mortality (viii) Length of hospital stay |
| 63    | Mushtaq et al., Pakistan | Outcome of COVID-19 patients with use of tocilizumab: A single-center experience | 62 Tocilizumab 4–8 mg/kg. | — | — | (i) Azithromycin (ii) Ceftriaxone or piperacillin/tazobactam (iii) Methylprednisolone (iv) Hydroxychloroquine | (i) Mortality (ii) Length of hospital stay (iii) Improvement in laboratory parameters |
| 64    | Yan Zuo et al., China | Lopinavir/ritonavir and interferon combination therapy may help shorten the duration of viral shedding in patients with COVID-19: A retrospective study in two designated hospitals in Anhui, China | 56 | (i) Corticosteroid (ii) Lopinavir/ritonavir (iii) Chloroquine (iv) Ribavirin (v) IFN-a (vi) Arbidol (vii) Intravenous immunoglobulin (viii) Traditional Chinese medicine | — | — | Length of stay | Length of stay |
| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|-------|----------------|-------|------------------------|--------------------|-----------------|------------------|-------------------------------------------|
| 65    | Yu et al., China | COVID-19 patients benefit from early antiviral treatment: A comparative, retrospective study | 27 | (i) Arbidol (ii) Interferon (iii) Oseltamivir (iv) Ribavirin (v) Ganciclovir (vi) Antibiotic treatment (vii) Antifungal treatment (viii) Oxygen therapy (ix) Glucocorticoids (x) Immunotherapy | — | — | (i) Time from illness onset to confirmed by SARS-CoV-2 RNA detection (ii) Time from illness onset to initiation of antiviral treatment (iii) Duration of total antiviral medication during the illness (iv) Time from illness onset to SARS-CoV-2 negative (v) Acute respiratory distress syndrome (vi) Acute kidney injury (vii) Liver dysfunction (viii) Death |
| 66    | Llitjos et al., France | High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients | 9 | Prophylactic anticoagulation | Therapeutic anticoagulation 0.3–0.7 U/ml | — | (i) Lopinavir-ritonavir (ii) Hydroxychloroquine (iii) Ivermectin, 12–15 mg (iv) Remdesivir (v) Thrombosis prophylaxis with LMWH From February 15 to March 27, 2020 | (i) Death (ii) Invasive mechanical ventilation requirement within 15 days |
| 67    | Borie et al., France | Glucocorticoids with low-dose anti-IL1 anakinra rescue in severe non-ICU COVID-19 infection: A cohort study | 42 | (i) Corticosteroid + anakinra (ii) Methylprednisolone 120 mg (daily dose) on three consecutive days (iii) Glucocorticoid | Thrombosis prophylaxis with LMWH | — | (i) Lopinavir-ritonavir (ii) Hydroxychloroquine (iii) Ivermectin, 12–15 mg (iv) Remdesivir (v) Thrombosis prophylaxis with LMWH | (i) Death (ii) Invasive mechanical ventilation requirement within 15 days |
| 68    | Majmundar et al., the United States | Efficacy of corticosteroids in non-intensive care unit patients with COVID-19 pneumonia from the New York metropolitan region | 57 | (i) Corticosteroids (ii) Methylprednisolone (iii) Prednisone (iv) Dexamethasone | Noncorticosteroids | (i) Intensive care unit (ICU) transfer (ii) ICU transfer (iii) Intubation (iv) Death (v) Discharge (vi) Length of stay (i) Non-ICU length of stay (days) (ii) ICU admission (iii) ICU length of stay (days) (iv) Overall mortality (v) ICU mortality (vi) Non-ICU mortality (vii) ICU or mortality | (i) Intensive care unit (ICU) transfer (ii) ICU transfer (iii) Intubation (iv) Death (v) Discharge (vi) Length of stay (i) Non-ICU length of stay (days) (ii) ICU admission (iii) ICU length of stay (days) (iv) Overall mortality (v) ICU mortality (vi) Non-ICU mortality (vii) ICU or mortality |
| 69    | Martinez-Sanz et al., Spain | Effects of tocilizumab on mortality in hospitalized patients with COVID-19: A multicenter cohort study | 24 | Tocilizumab | Standard of care | (i) Corticosteroids (ii) Hydroxychloroquine (iii) Azithromycin (iv) Lopinavir/ritonavir | (i) Hydroxychloroquine (ii) Tocilizumab (iii) Enoxaparin therapeutic dose (i) Hydroxychloroquine (ii) Tocilizumab (iii) Enoxaparin therapeutic dose | (i) Intensive care unit (ICU) transfer (ii) ICU transfer (iii) Intubation (iv) Death (v) Discharge (vi) Length of stay (i) Non-ICU length of stay (days) (ii) ICU admission (iii) ICU length of stay (days) (iv) Overall mortality (v) ICU mortality (vi) Non-ICU mortality (vii) ICU or mortality |
| 70    | Memella et al., Italy | Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing non-invasive ventilation | 70 | (i) Tocilizumab + standard therapy (ii) Hydroxychloroquine (iii) Antivirals (lopinavir/ritonavir or darunavir/ cobicistat) (iv) Anticoagulants (full dosage) (v) Steroids (methylprednisolone 0.5–1 mg/kg/die) | Standard therapy | (i) Standard therapy | (i) Intubation/death (ii) Death | (i) Intubation/death (ii) Death |
| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|--------|----------------|-------|------------------------|--------------------|-----------------|------------------|---------------------------------------------|
| 71     | Mikulska et al, Italy | Tocilizumab and steroid treatment in patients with COVID-19 pneumonia | — | (i) Tocilizumab. 8 mg/kg (maximum 800 mg)  
(ii) Methylprednisolone. 1 mg/kg for 5 days intravenously, then 0.5 mg/kg for 5 days  
(iii) Standard of care | Standard of care | — | (i) Time to failure, defined as intubation and mechanical ventilation or death  
(ii) Overall survival  
(iii) Time of hospitalization for the comparison between tocilizumab/ methylprednisolone/ SOC  
(i) Mortality  
(ii) A combined variable of need for mechanical or noninvasive MV and death  
(iii) The development of severe ARDS, according to the Berlin definition  
(i) All-cause mortality (either in-hospital or after discharge) and associated factors.  
(ii) The impact of an early clinical response to tocilizumab in hospital and ICU stay.  
(iii) Evaluate safety of tocilizumab therapy.  
(i) Mortality  
(ii) Intubation and major bleeding  
(iii) WHO ordinal scale |
| 72     | Monreal et al., Spain | High versus standard doses of corticosteroids in severe COVID-19: A retrospective cohort study | 61 | High doses of corticosteroids: short-term pulse therapy of methylprednisolone-equivalent dosages from 250 to 1000 mg/day during one or more consecutive days. | — | — | (i) Mortality  
(ii) Mortality  
(iii) All-cause mortality (either in-hospital or after discharge) and associated factors.  
(iv) The impact of an early clinical response to tocilizumab in hospital and ICU stay.  
(v) Evaluate safety of tocilizumab therapy.  
(v) Mortality  
(vi) WHO ordinal scale |
| 73     | Pérez et al., Spain | Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: A retrospective cohort study | 52 | Tocilizumab: initial 600 mg, with a second or third dose (400 mg) in case of persistent or progressive disease | Not received tocilizumab | — | (i) Mortality  
(ii) Intubation and major bleeding  
(iii) WHO ordinal scale |
| 74     | Nadkarni et al., the United States | Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19 | 61 | (i) Therapeutic anticoagulation  
(ii) Prophylactic anticoagulation | — | — | (i) WHO ordinal scale  
(ii) Mortality  
(iii) Length of stay  
(iv) Development of nosocomial infection during hospitalization  
(v) WHO ordinal scale |
| 75     | Nazir et al., Pakistan | Convalescent plasma for COVID-19 acute respiratory distress syndrome: outcomes assessment using the WHO ordinal scale | 121 | Before tocilizumab | After tocilizumab | Concomitant steroids | (i) WHO ordinal scale  
(ii) Mortality  
(iii) Length of stay  
(iv) Development of nosocomial infection during hospitalization  
(v) WHO ordinal scale  
(vi) WHO ordinal scale |
| 76     | Omri et al., Qatar | Convalescent plasma for the treatment of patients with severe coronavirus disease 2019: A preliminary report | 62 | Convalescent plasma | Standard of care | — | (i) WHO ordinal scale  
(ii) Mortality  
(iii) Length of stay  
(iv) Improvement in the respiratory status  
(v) Discharged alive from ICU by study day 28  
(vi) Viral clearance  
(vii) Viral clearance |
Table 2: Continued.

| S. no. | Author, country | Title | Study duration in days | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|--------|-----------------|-------|------------------------|--------------------|------------------|-------------------|---------------------------------------------|
| 77     | Paccoud et al., France | Compassionate use of hydroxychloroquine in clinical practice for patients with mild to severe COVID-19 in a French university hospital | 79 Hydroxychloroquine, 200 mg 3 times daily for 10 days | (i) Oxygen therapy to maintain an oxygen saturation >96% (ii) Intravenous or oral acetaminophen (iii) Antibiotics | — | — | (i) Death (ii) Admission to an ICU (iii) Time to death (iv) Time to hospital discharge for a return home or in an aftercare and rehabilitation (v) Adverse events recorded in patients receiving hydroxychloroquine treatment |
| 78     | Price et al., the United States | Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019: survival and clinical outcomes | 22 (i) Hydroxychloroquine (ii) Glucocorticoids (iii) Tocilizumab, 8 mg/kg intravenously, not to exceed 800 mg | — | — | (i) Survival (ii) 14 days survival (iii) Mechanical ventilation (iv) Days mechanically ventilated (v) Days of symptoms prior to hospitalization (vi) Days hospitalized (vii) Hospitalized at day 14 |
| 79     | Rodriguez-Batio et al., Spain | Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: A multicenter cohort study (SAM-COVID-19) | 59 (i) Tocilizumab (ii) Corticosteroid pulse dose (iii) Corticosteroids intermediate-high dose (iv) Combination therapy | No treatment | — | (i) WHO ordinal scale (ii) Death or intubation (iii) Mortality (iv) Dialysis |
| 80     | Rosmi et al., United States | Combination of tocilizumab and steroids to improve mortality in patients with severe COVID-19 infection: A Spanish multicenter, cohort study of patients with COVID-19 requiring oxygen support | 91 (i) Hydroxychloroquine (ii) Tocilizumab | (i) No hydroxychloroquine (ii) No tocilizumab | (i) Steroids (ii) Anticoagulation | (i) Invasive mechanical ventilation (ii) Mortality (iii) Discharge |
| 81     | Antorán et al., Spain | Efficacy of hydroxychloroquine and tocilizumab in patients with COVID-19: single-center retrospective chart review | 49 Tocilizumab | No tocilizumab | — | — |
| 82     | Tortajada et al., Spain | Corticosteroids for COVID-19 patients requiring oxygen support? Yes, but not for everyone: effect of corticosteroids on mortality and intensive care unit admission in patients with COVID-19 according to patients’ oxygen requirements | 59 (i) Corticosteroids (ii) Methylprednisolone 250 mg iv once and 40 mg, BBQ for 4 days (iii) Dexamethasone 20 mg iv QD for 5 days, followed by 10 mg QD for 5 more days | No corticosteroids | — | — |

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| S. no. | Author, country | Study duration in days | Title | Intervention group | Comparator group | Concomitant group | Outcome measures applicable to this review |
|--------|----------------|------------------------|-------|--------------------|------------------|-------------------|--------------------------------------------|
| 83     | Magagnoli et al., the United States | 21 | Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19 | (ii) Hydroxychloroquine | (i) Hydroxychloroquine | — | — |
|        |                 |                        |       | (iii) Hydroxychloroquine + azithromycin | (ii) Hydroxychloroquine + azithromycin | — | (i) Mortality |
|        |                 |                        |       | (iii) No hydroxychloroquine | (iii) No hydroxychloroquine | — | (ii) Use of mechanical ventilation |
| 84     | Joyner et al., United States | 39 | Early safety indicators of COVID-19 convalescent plasma in 5000 patients | Convalescent plasma | — | — | The safety of transfusion of COVID-19 convalescent plasma |
| 85     | Rajfer et al., South Florida, the United States | 58 | Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The ivermectin in COVID-19 study | Ivermectin 200 μg/kg | No ivermectin | — | — |
|        |                 |                        |       | (i) Corticosteroid | (i) Corticosteroid | — | (i) Mortality |
|        |                 |                        |       | (ii) Hydroxychloroquine | (ii) Hydroxychloroquine | — | (ii) Successful extubation |
|        |                 |                        |       | (iii) Azithromycin | (iii) Azithromycin | — | (iii) Length of hospital stay |
| 86     | Hanif et al., the United States | 31 | Thrombotic complications and anticoagulation in COVID-19 pneumonia: A New York City hospital experience | — | — | — | — |
|        |                 |                        |       | (i) Therapeutic anticoagulation prior to admission | (i) Therapeutic anticoagulation prior to admission | (i) Mortality | — |
|        |                 |                        |       | (ii) Prophylactic anticoagulation only during the hospital stay | (ii) Prophylactic anticoagulation only during the hospital stay | — | (ii) Length of stay |
|        |                 |                        |       | (iii) No anticoagulation | (iii) No anticoagulation | (iii) Intubation | (iii) Intubation |
| 87     | Duan et al., China | 30 | Effectiveness of convalescent plasma therapy in severe COVID-19 patients | Convalescent plasma: one dose of 200 ml of inactivated CP with neutralization activity of >1:640 was transfused into the patients within 4h following the WHO blood transfusion protocol | — | — | — |
|        |                 |                        |       | (i) Antiviral therapy | (i) Antiviral therapy | (i) The safety of convalescent plasma transfusion | — |
|        |                 |                        |       | (ii) Other supportive care | (ii) Other supportive care | (ii) The improvement of clinical symptoms and laboratory and radiological parameters within 3 days after convalescent plasma transfusion | — |
|        |                 |                        |       | (iii) Antibiotic treatment | (iii) Antibiotic treatment | (iii) Improvement of clinical symptoms and laboratory and radiological parameters within 3 days after convalescent plasma transfusion | (iv) Glucocorticoid |
|        |                 |                        |       | (iv) Antifungal treatment | (iv) Antifungal treatment | (iv) Successful extubation | (v) Oxygen support at the appropriate situation |
|        |                 |                        |       | (v) Glucocorticoid | (v) Glucocorticoid | (v) The improvement of clinical symptoms and laboratory and radiological parameters within 3 days after convalescent plasma transfusion | — |
|        |                 |                        |       | (vi) Oxygen support at the appropriate situation | (vi) Oxygen support at the appropriate situation | (vi) The improvement of clinical symptoms and laboratory and radiological parameters within 3 days after convalescent plasma transfusion | — |
|        |                 |                        |       | (vii) Convalescent plasma transfusion | (vii) Convalescent plasma transfusion | (vii) Convalescent plasma transfusion | — |
Table 3: Description of study characteristics: case-control studies.

| S. no. | Author, country | Title | Study duration in days | Intervention group | Control group | Concomitant intervention | Outcome measures applicable to this review |
|--------|-----------------|-------|------------------------|--------------------|---------------|--------------------------|--------------------------------------------|
| 1      | Klopfenstein et al., France | Impact of tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort of 206 COVID-19 patients | 72 | Tocilizumab 8mg/kg per dose, 1 or 2 doses | (i) Standard treatment (ii) Hydroxychloroquine (iii) Lopinavir-ritonavir therapy (iv) Antibiotics (v) Corticosteroids | (i) Mortality (ii) Intensive mechanical ventilation (iii) Duration to hospitalization (iv) Death (v) ICU admission (vi) Invasive mechanical ventilation (vii) Duration of hospitalization |
| 2      | Klopfenstein et al., France | Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients | 24 | Tocilizumab 8mg/kg per dose, 1 or 2 doses | (i) Standard treatment (ii) Hydroxychloroquine (iii) Lopinavir-ritonavir therapy (iv) Antibiotics (v) Corticosteroids | (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 |
| 3      | Sean et al., the United States | Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study | 16 | Convalescent plasma therapy | — | (i) Survival (ii) Oxygen requirement |
| 4      | Abolghasemi et al., Iran | Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study | 61 | Convalescent plasma 500cc (one unit) | No convalescent plasma | (i) Lopinavir/ritonavir (ii) Hydroxychloroquine | (i) Mortality (ii) Intubation (iii) Length of stay (iv) Improvements in clinical symptoms (v) Adverse events from treatment |

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| S. no. | Author, country | Title | Study duration in days | Intervention group | Control group | Concomitant intervention | Outcome measures | Outcome measures applicable to this review |
|-------|----------------|-------|------------------------|-------------------|---------------|------------------------|----------------|------------------------------------------|
| 5     | Rosotti et al., Italy | Safety and efficacy of anti-IL-6 receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: A comparative analysis Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data Tocilizumab for patients with COVID-19 pneumonia: The single-arm TOCIVID-19 prospective trial | — | Tocilizumab | (i) Hydroxychloroquine plus lopinavir/ritonavir (ii) Remdesivir | (i) Azithromycin (ii) Amoxicillin (iii) Tocilizumab (iv) Lopinavir-ritonavir (v) Remdesivir | (i) Survival (ii) Length of stay | (i) Survival (ii) Length of stay |
| 6     | Matthieu et al., France | Hydroxychloroquine No hydroxychloroquine | 43 | Hydroxychloroquine | — | (i) Azithromycin (ii) Amoxicillin (iii) Tocilizumab (iv) Remdesivir (v) Lopinavir-ritonavir (vi) Remdesivir (vii) Low-molecular-weight heparin | (i) Survival (ii) Weaning from oxygen | (i) Survival (ii) Weaning from oxygen |
| 7     | Perrone et al., Italy | Tocilizumab 8 mg/kg up to a maximum of 800 mg per dose | 34 | Tocilizumab | — | (i) Hydroxychloroquine (ii) Azithromycin (iii) Corticosteroids (iv) Anticoagulation (v) Remdesivir (vi) Antibiotics (vii) Vasopressors | (i) Overall mortality rate (ii) Mortality in nonintubated patients only (iii) Mortality in intubated patients (iv) Length of stay | (i) Overall mortality rate (ii) Mortality in nonintubated patients only (iii) Mortality in intubated patients (iv) Length of stay |
| 8     | G. Rojas-Marté et al, the United States | Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case-controlled study | 49 | Tocilizumab | — | (i) Hydroxychloroquine (ii) Azithromycin (iii) Corticosteroids (iv) Anticoagulation (v) Remdesivir (vi) Antibiotics (vii) Vasopressors | (i) Overall mortality rate (ii) Mortality in nonintubated patients only (iii) Mortality in intubated patients (iv) Length of stay | (i) Overall mortality rate (ii) Mortality in nonintubated patients only (iii) Mortality in intubated patients (iv) Length of stay |
| 9     | Scarsi et al., Italy | 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 | 32 | (i) Colchicine 1 mg/day (ii) Standard of care (hydroxychloroquine, lopinavir/ritonavir, and intravenous dexamethasone) | Standard of care (hydroxychloroquine, lopinavir/ritonavir, and intravenous dexamethasone) | — | Survival rate | Survival rate |
| S. no. | Author, country | Title | Study duration in days | Intervention group | Control group | Concomitant intervention | Outcome measures applicable to this review |
|-------|----------------|-------|------------------------|-------------------|---------------|------------------------|--------------------------------------------|
| 10    | Keller et al., The Bronx | Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19 | 34 Early glucocorticoid first 48 hours | No glucocorticoid | — | (i) In-hospital mortality (ii) In-hospital mechanical ventilation. (iii) Mortality in mechanical ventilation |
| 11    | Yu et al., China | Lopinavir/ritonavir is associated with pneumonia resolution in COVID-19 patients with influenza coinfection: A retrospective matched-pair cohort study | 30 Lopinavir/ritonavir treatment | No lopinavir/ritonavir treatment | (i) Glucocorticoid treatment (ii) Ribavirin treatment (iii) Lopinavir/ritonavir treatment (iv) Oseltamivir (v) Arbidol | (i) Dead or deteriorated (ii) Cured |
| 12    | Qu et al., not mentioned | Comparative effectiveness of lopinavir/ritonavir-based regimens in COVID-19 | — | — | | (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 (v) Transferring to ICU and clinical mechanical therapy |
| S. no. | Trial registration number | Author, country | Title | Study duration in days | Study arm | Intervention group | Control group | Concomitant drugs | Outcome measures | Outcome measures applicable to this review |
|-------|--------------------------|-----------------|-------|------------------------|-----------|--------------------|---------------|------------------|----------------|------------------------------------------|
| 1     | NCT04353336             | Abd-Elsalam et al., Egypt | Hydroxychloroquine in the treatment of COVID-19: A multicenter randomized controlled study | 122 | 2 | Hydroxychloroquine (i) Paracetamol (ii) Oxygen (iii) Fluids (iv) Empiric antibiotic (cephalosporins) (v) Oseltamivir (vi) Invasive mechanical ventilation with hydrocortisone | — | — | (i) Death (ii) Duration of hospital stay | (i) Death (ii) Duration of hospital stay |
| 2     | Trial registration not specified. | Antinori et al., Italy | 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 | 27 | 1 | Remdesivir (ICU and ward setting) None | — | — | (i) WHO ordinal scale (ii) Hospitalization status (iii) Adverse events | (i) WHO ordinal scale (ii) Hospitalization status (iii) Adverse events |
| 3     | NCT04323527             | Borba et al., Brazil | 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 | — | 2 | High-dose chloroquine (600 mg CQ: 4 × 150 mg tablets twice daily for 10 days; total dose 12 g) Low-dose chloroquine (400 mg CQ twice daily on the first day and 450 mg once daily for 4 days) | — | — | (i) Supplemental oxygen (ii) Noninvasive ventilation (iii) Invasive ventilation (iv) Antibiotic agents (v) Vasopressor support (vi) Renal replacement therapy (vii) Extracorporeal membrane oxygenation (ECMO) | (i) Safety (ii) Lethality (iii) Clinical status (iv) Laboratory examinations (v) Electrocardiogram results |
| 4     | ChiCTR2000029308        | Cao et al., China | A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19 | 17 | 2 | Lopinavir-ritonavir (400 mg and 100 mg twice daily) | — | — | (i) WHO ordinal scale (ii) Time to clinical improvement (iii) Day 28 mortality (iv) ICU length of stay | (i) WHO ordinal scale (ii) Time to clinical improvement (iii) Day 28 mortality (iv) ICU length of stay |
| 5     | IRCT2020050104725N1     | Gharebaghi et al., Iran | The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019. A randomized placebo-controlled double-blind clinical trial | — | 2 | Intravenous immunoglobulin (IVIG). Four vials of 5 g IVIG daily | Placebo and standard of care | — | Mortality | Mortality |
| 6     | NCT04383535             | Simonovich et al., Italy | A randomized trial of convalescent plasma in COVID-19 severe pneumonia | — | 2 | Convalescent plasma | Placebo and standard of care | (i) Antiviral agents (ii) Glucocorticoids (iii) Steroids (iv) Tocilizumab (v) Hydroxychloroquine (vi) Lopinavir/ritonavir (v) Thromboprophylaxis (vi) Anticoagulation | — | — | (i) WHO ordinal scale (ii) Clinical status at 30 days (iii) 30 days mortality | (i) WHO ordinal scale (ii) Clinical status at 30 days (iii) 30 days mortality |
| 7     | NCT04375098             | Balcells et al., Chile | Early anti-SARS-CoV-2 convalescent Plasma in patients admitted for COVID-19: A randomized phase II clinical trial | 70 | 2 | Early plasma, 400 ml of ABO compatible convalescent plasma Deferred plasma, 400 ml plasma | — | — | (i) Mechanical ventilation (ii) Hospitalization >14 days (iii) Death (iv) Oxygen requirement | (i) Mechanical ventilation (ii) Hospitalization >14 days (iii) Death (iv) Oxygen requirement |
| S. no | Trial registration number | Author, country | Title | Study duration in days | Study arm | Intervention group | Control group | Concomitant drugs | Outcome measures | Outcome measures applicable to this review |
|-------|--------------------------|----------------|-------|------------------------|-----------|--------------------|---------------|------------------|----------------|------------------------------------------|
| 8     | IRCT20150303021315 N17   | Malekzadeh et al., Iran | Subcutaneous tocilizumab in adults with severe and critical COVID-19: A prospective open-label uncontrolled multicenter trial | 100       | 1                   | Tocilizumab at a dose of 324 mg | (i) Antiviral agents   (ii) Hydroxychloroquine (iii) Interferon beta-1a (iv) Antibiotic agents | —              | (i) Hospital Stay (ii) Death (iii) Oxygen requirement (iv) Adverse events | (i) Hospital stay (ii) Death (iii) Oxygen requirement (iv) Adverse events |
| 9     | NCT04346355             | Salvarani et al., Italy | Effect of tocilizumab vs. standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial | 73        | 2                   | Tocilizumab at a dose of 8 mg/kg up to a maximum of 800 mg | (i) Tocilizumab IV + steroids (ii) Steroids (iii) Canakinumab | (i) Hydroxychloroquine (ii) Heparin (iii) LMWH (iv) Azithromycin | (i) Clinical worsening (ii) At 14 days: admissions to ICU (iii) At 14 days: deaths (iv) At 14 days: discharges | (i) Clinical worsening (ii) At 14 days: admissions to ICU (iii) At 14 days: deaths (iv) At 14 days: discharges |
| 10    | NCT04356937             | Stone et al., the United States | Efficacy of tocilizumab in patients hospitalized with COVID-19 | 57        | 2                   | Tocilizumab, 8mg per kilogram of bodyweight administered intravenously, not to exceed 800 mg | Placebo and standard of care | (i) Remdesivir (ii) Dexamethasone (iii) Hydroxychloroquine (iv) Glucocorticoids | (i) Death (ii) Intubation (iii) Oxygen requirement (iv) Time to clinical improvement within 28 days (v) Mortality at day 28 (vi) Safety outcomes included treatment-emergent adverse events, serious adverse events, and premature discontinuation of study drugs. | (i) Death (ii) Intubation (iii) Oxygen requirement (iv) Time to clinical improvement within 28 days (v) Mortality at day 28 (vi) Safety outcomes included treatment-emergent adverse events, serious adverse events, and premature discontinuation of study drugs. |
| 11    | NCT04257656             | Wang et al., China | Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial | 36        | 2                   | Remdesivir, 200mg on day 1 followed by 100 mg on days 2–10 in single daily infusions | Placebo and standard of care | (i) Lopinavir-ritonavir (ii) Interferons (iii) Corticosteroids | (i) Mortality (ii) Clinical deterioration (iii) Adverse events | (i) WHO ordinal scale (ii) Deaths (iii) Clinical deterioration (iv) Adverse events |
| 12    | NCT04405843             | Medina et al., Colombia | Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: A randomized clinical Trial | 17        | 2                   | Ivermectin and standard of care received 300μg/kg | Placebo and standard of care | (i) NSAIDS (ii) Macrolides (iii) Antiparitics (iv) Antibiotics (v) Glucocorticoids (vi) Immunomodulating (vii) Anticoagulants | (i) Deaths (ii) Clinical deterioration (iii) Adverse events | (i) Mortality (ii) Clinical deterioration (iii) Adverse events | (i) Mortality (ii) Length of hospital stay (iii) Negative RT-PCR result (iv) Length of hospital stay |
| 13    | NCT04276688             | 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 | 40        | 2 arms              | (i) Interferon beta-1b (ii) Lopinavir-ritonavir (iii) Ribavirin | Lopinavir-ritonavir | —                  | (i) Mortality (ii) Length of hospital stay (iii) Negative RT-PCR result | (i) Mortality (ii) Length of hospital stay (iii) Negative RT-PCR result |
| S. no | Trial registration number | Author, country | Title | Study duration in days | Study arm | Intervention group | Control group | Concomitant drugs | Outcome measures | Outcome measures applicable to this review |
|-------|---------------------------|-----------------|-------|------------------------|-----------|-------------------|---------------|-----------------|-----------------|------------------------------------------|
| 14    | ChiCTR2000029387          | Huang et al., China | 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 | 28       | 3                     | (i) Ribavirin (ii) Lopinavir/ritonavir (iii) Interferon-alpha | —             | (i) Azithromycin (ii) Hydroxychloroquine (iii) HIV protease inhibitor (iv) Biologicals (v) Ribavirin | (i) Death (ii) Length of hospitalization (iii) Negative SARS-CoV-2 results (iv) Adverse events | (i) Death (ii) Length of hospitalization (iii) Negative SARS-CoV-2 results (iv) Adverse events |
| 15    | NCT04292899              | Olender et al., multicenter | Remdesivir for severe coronavirus disease 2019 (COVID-19) versus a cohort receiving standard of care | 33       | 2                     | Remdesivir | No remdesivir | (i) WHO ordinal scale (ii) Time to clinical improvement (iii) Discharge rate at 28 days (iv) Mortality at 28 days (v) Negative PCR | (i) WHO ordinal scale (ii) Time to clinical improvement (iii) Discharge rate at 28 days (iv) Mortality at 28 days (v) Negative PCR |
| 16    | ChiCTR2000029757          | Li et al., China | Mortality reduction in 46 severe COVID-19 patients treated with hyperimmune plasma: A proof-of-concept single arm multicenter interventional trial | 48       | 2                     | Convalescent plasma | Standard of care | (i) Antiviral (ii) Anti-bacterial (iii) Steroids (iv) Human immunoglobulin | (i) Mortality (ii) Changes in PaO$_2$/FiO$_2$, LDH | (i) Mortality (ii) Oxygen requirement |
| 17    | NCT 04321421             | Perotti et al., Italy | Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial | 32       | 1                     | Plasma infusion | None | (i) Antiviral (ii) Antibiotics (iii) Hydroxychloroquine (iv) Anticoagulant (v) Steroids (vi) Human immunoglobulin | (i) WHO ordinal scale (ii) Time to clinical improvement (iii) Changes in PaO$_2$/FiO$_2$, LDH | (i) WHO ordinal scale (ii) Time to clinical improvement (iii) Changes in PaO$_2$/FiO$_2$, LDH |
| 18    | NCT04292730              | Spinner et al., multicenter | Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: A randomized clinical trial | 35       | 3                     | 10 days remdesivir | Standard of care | (i) Hydroxychloroquine/lopinavir/ritonavir (ii) Tocilizumab (iii) Azithromycin (iv) Remdesivir (v) Lopinavir/ritonavir (vi) Ivermectin | (i) Death (ii) Discharge (iii) Adverse events | (i) Death (ii) Discharge (iii) Adverse events |
| 19    | CTRI/2020/04/024775       | Agarwal et al., India | Convalescent plasma in the management of moderate COVID-19 in adults in India: open-label phase II multicenter randomized controlled trial (PLACID trial) | 84       | 2                     | Convalescent plasma (two doses of 200 ml) + best standard of care | Standard of care | (i) Mortality (ii) Clinical improvement on the World Health Organization ordinal scale | (i) Mortality (ii) Clinical improvement on the World Health Organization ordinal scale | (i) Mortality (ii) Clinical improvement on the World Health Organization ordinal scale |
Table 5: Description of study characteristics: quasi-experimental studies.

| S. no. | Trial registration number | Author, country | Title | Study duration in days | Study arm | Intervention group | Control group | Concomitant interventions | Outcome measures | Outcome measures applicable to this review |
|--------|---------------------------|-----------------|-------|------------------------|-----------|-------------------|---------------|---------------------------|-----------------|------------------------------------------|
| 1      | NCT04374071              | Fadel et al., United States | Early short-course corticosteroids in hospitalized | 8          | 2                     | Corticosteroid methylprednisolone 0.5–1 mg/kg/day divided in 2 intravenous doses for 3 days | (i) Standard care (ii) Lopinavir-ritonavir (iii) Ribavirin (iv) Hydroxychloroquine (v) Steroid | (i) Lopinavir-ribavirin (ii) Hydroxychloroquine (iii) Tocilizumab (iv) Methylprednisolone (v) Oral prednisone | (i) Death (ii) Respiratory failure requiring mechanical ventilation, (iii) Overall mechanical ventilation (iv) Length of stay (i) Mortality (ii) ICU transfer (iii) Ventilator needed | (i) Death (ii) Respiratory failure requiring mechanical ventilation, (iii) Overall mechanical ventilation (iv) Length of stay (i) Mortality (ii) ICU transfer (iii) Ventilator needed |
| 2      | NCT04374071              | Fatima et al., Pakistan | Comparison of efficacy of dexamethasone and methylprednisolone in moderate to severe COVID-19 disease. | 30         | 2                     | Intravenous methylprednisolone 1 mg/kg/day in 2 divided | Intravenous dexamethasone 8 mg/day given for 5 days | (i) Plasma therapy (ii) Antibiotics (iii) Tocilizumab | (i) Mortality (ii) ICU transfer (iii) Ventilator needed | (i) Mortality (ii) ICU transfer (iii) Ventilator needed |
| 3      | NCT4357106               | Olivares-Gazca et al., Mexico | Infusion of convalescent plasma is associated with clinical improvement in critically ill patients with COVID-19: A pilot study | 22         | 1                     | Convalescent plasma — | — | — | Mortality | Mortality |
| 4      | 2020-000890-25           | Philippe Gautret et al., France | Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial | —          | 2                     | Hydroxychloroquine 200 mg, 3 times per day for 10 days | No hydroxychloroquine | (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 | (i) Virological clearance at day 6 (ii) Virological clearance over the time (iii) Occurrence of side effects | (i) Virological clearance at day 6 (ii) Virological clearance over the time (iii) Occurrence of side effects |
Table 6: Comparison of recommendations.

| S. no. | Intervention | Drugs | National guidelines | Recommendations | WHO |
|--------|--------------|-------|----------------------|----------------|------|
| 1      | Corticosteroids | (i) To use in severe or critical patients | (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 | Recommended the use of systemic corticosteroid rather than no corticosteroids in severe and critical COVID-19 patients. | |
|        |               | (ii) Not to use in nonsevere or asymptomatic patients |                           |               | |
| 2      | Tocilizumab   | (i) To use in patients who have worsened despite the initial 24–48 hours of steroids (ii) To not use in patients who have not received a trial of steroids or with elevated markers only | For the use of tocilizumab in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence | Recommended the use of tocilizumab in patients with severe or critical COVID-19 infection. | |
| 3      | Ivermectin therapy | This is not recommended in the national guidelines | Against the use of ivermectin therapy in the use of COVID-19 hospitalized patients. Weak recommendation, low-quality evidence | Recommended against the use of ivermectin in patients with COVID-19 | |
| 4      | Hydroxychloroquine/chloroquine | (i) To use in proven or strong suspicion of secondary infection | Against the use of hydroxychloroquine alone or in combination with other antibiotics in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence | Recommended against the use of hydroxychloroquine or chloroquine for treatment of COVID-19 | |
|        |               | (i) To use in proven or strong suspicion of secondary infection after exposure | | | |
| 5      | Antibiotics   | (i) To use in all hospitalized patients (ii) To not use for "prevention" of secondary infections or in patients with no clear evidence of bacterial infection Prophylactic anticoagulation | No evidence available | No evidence available | |
| 6      | Anticoagulation therapy | (i) To use in severe patients with less than 10 days of symptoms (ii) To use in patients with isolated elevated D-dimers or no evidence of VTE | (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 | No evidence available | |
| 7      | Remdesivir    | (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 | For the use of remdesivir in hospitalized COVID-19 patients. Recommendation, high-quality evidence | Conditional recommendation against administering remdesivir in addition to usual care. | |
| 8      | Lopinavir/ritonavir | (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 | Against the use of ritonavir/lopinavir in hospitalized COVID-19 patients. No recommendation, moderate-quality evidence | Recommended against administering lopinavir/ritonavir for treatment of COVID-19. | |
| S. no. | Intervention               | National guidelines          | Recommendations                                                                 | WHO               |
|-------|---------------------------|-------------------------------|---------------------------------------------------------------------------------|-------------------|
| 9     | Convalescent plasma       | No evidence available         | Against the use of convalescent plasma in the management of hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence | No evidence available |
| 10    | Famotidine                | Not recommended in the national guidelines | For the use of famotidine in hospitalized COVID-19 patients. Weak recommendation, low-quality evidence | No evidence available |
| 11    | Immunoglobulin therapy    | No evidence available         | For the use of immunoglobulin therapy in hospitalized COVID-19 patients. Weak recommendation, moderate-quality evidence | No evidence available |
| 12    | Colchicine                | No evidence available         | Against the use of colchicine in hospitalized COVID-19 patients. No recommendation, low-quality evidence | No evidence available |
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.

(ii) For the use of prophylactic dose anticoagulants to treat COVID-19 hospitalized patients. Prophylactic: 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 use 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.

WHO v7.1 recommended against administering lopinavir/ritonavir for treatment of COVID-19.

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

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) For 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, based on which clinicians are expected to prescribe and treat patients [2]. While such guidelines are beneficial in which they are region-specific and keep in mind various economic factors and drug availability, they are not regularly updated due to the resources required for systematic reviews and evidence 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 antiocoagulation (especially therapeutic vs. prophylactic dosages) were also predominantly found to improve thromboembolic outcomes and mortality. However, variations in the type of antiocoagulant 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.

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
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 deters 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

[1] WHO, WHO Coronavirus (COVID-19) Dashboard, WHO, Geneva, Switzerland, 2020.
[2] Clinical Management Guidelines for COVID-19 Infections.https://covid.gov.pk/guideline 2020.
[3] D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, “Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement,” International Journal of Surgery, vol. 8, no. 5, pp. 336–341, 2010.
[4] G. H. Guyatt, A. D. Oxman, G. E. Vist et al., “GRADE: an emerging consensus on rating quality of evidence and strength of recommendations,” BMJ, vol. 336, no. 7650, pp. 924–926, 2008.
[5] National Heart Lung and Blood Institute, National Institute of Health Study Quality Assessment Tool, National Heart, Lung, and Blood Institute, Karachi, Pakistan, 2017.
[6] J. A. Sterne, J. Savović, M. J. Page et al., “RoB 2: a revised tool for assessing risk of bias in randomised trials,” British Molecular Journal, vol. 366, 2019.
[7] EPOC, CEPaOoC. Cochrane Effective Practice and Organisati on of Care, EPOC, Islamabad, Pakistan, 2017.
[8] S. Ramiro, R. L. M. Mostard, C. Magro-Checa et al., “Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study,” Annals of the Rheumatic Diseases, vol. 79, no. 9, pp. 1143–1151, 2020.
hospitalized with COVID-19: a single health system study,” Journal of the American College of Cardiology, vol. 76, 2020.

[40] Z. Pasquini, R. Montalti, C. Temperoni et al., “Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU,” Journal of Antimicrobial Chemotherapy, vol. 75, no. 11, pp. 3359–3365, 2020.

[41] S. A. Olender, K. K. Perez, A. S. Go et al., “Remdesivir for severe COVID-19 versus a cohort receiving standard of care,” Clinical Infectious Diseases, vol. 73, 2020.

[42] S. Antinori, M. V. Cossu, A. L. Ridolfo et al., “Compassionate use of remdesivir in patients with COVID-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: clinical outcome and differences in post-treatment hospitalisation status,” Pharmacological Research, vol. 158, Article ID 104899, 2020.

[43] S. Tong, Y. Su, Y. Yu et al., “Ribavirin therapy for severe COVID-19: a retrospective cohort study,” International Journal of Antimicrobial Agents, vol. 56, no. 3, Article ID 106114, 2020.

[44] Y.-Q. Huang, S.-Q. Tang, X.-L. Xu et al., “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-labeled prospective study,” Frontiers in Pharmacology, vol. 11, Article ID 1071, 2020.

[45] H. Abolghasemi, P. Eshghi, A. M. Cheraghali et al., “Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study,” Transfusion and Apheresis Science, vol. 59, no. 5, Article ID 102875, 2020.

[46] J. C. Olivares-Gazca, J. M. Priesca-Marín, M. Ojeda-Laguna et al., “Infusion of convalescent plasma is associated with clinical improvement in critically ill patients with COVID-19: a pilot study,” Revista de Investigación Clínica, vol. 72, no. 3, pp. 159–164, 2020.

[47] S. T. H. Liu, H.-M. Lin, I. Baine et al., “Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study,” Nature Medicine, vol. 26, no. 11, pp. 1708–1713, 2020.

[48] A. S. Bourinbaier and E. C. Fruthstorfer, “The effect of histamine type 2 receptor antagonists on human immunodeficiency virus (HIV) replication: identification of a new class of antiviral agents,” Life Sciences, vol. 59, no. 23, 1996.

[49] D. E. Freedberg, J. Coniglio, T. C. Wang et al., “Famotidine use is associated with improved clinical outcomes in hospitalised COVID-19 patients: a propensity score matched retrospective cohort study,” Gastroenterology, vol. 159, no. 3, pp. 1129–1131, 2020.

[50] J. F. Mather, R. L. Seip, and R. G. McKay, “Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19,” American Journal of Gastroenterology, vol. 115, no. 10, pp. 1617–1623, 2020.

[51] Z. Shao, Y. Feng, L. Zhong et al., “Clinical efficacy of intravenous immunoglobulin therapy in critical ill patients with COVID-19: a multicenter retrospective cohort study,” Clinical & translational immunology, vol. 9, no. 10, Article ID e1192, 2020.

[52] N. Gherebaghi, R. Nejadrahim, S. J. Mousavi, S. R. Sadat-Ebrahim, and R. Hajizadeh, “The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial,” BMC Infectious Diseases, vol. 20, no. 1, pp. 786–788, 2020.

[53] N. Schlesinger, B. L. Firestein, and L. Brunetti, “Colchicine in COVID-19: an old drug, new use,” Current Pharmacology Reports, vol. 6, no. 4, pp. 137–145, 2020.

[54] M. Scarsi, S. Piantoni, E. Colombo et al., “Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome,” Annals of the Rheumatic Diseases, vol. 79, no. 10, pp. 1286–1289, 2020.

[55] Health NIO, Therapeutic Management of Hospitalized Adults with COVID-19, Health NIO, Karachi, Sindh, Pakistan, 2021.

[56] R. A. Siemieniuk, J. J. Bartoszko, L. Ge et al., “Drug treatments for COVID-19: living systematic review and network meta-analysis,” Bmj (Clinical research ed.), vol. 370, Article ID m2980, 2020.

[57] S. Luul, E. E. Nielsen, J. Feinberg et al., “Interventions for treatment of COVID-19: a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project),” PLoS Medicine, vol. 17, no. 9, Article ID e1003293, 2020.

[58] J. W. Ju, J. Huang, G. Zhu et al., “Systemic corticosteroids and mortality in severe and critical COVID-19 patients in Wuhan, China,” Journal of Clinical Endocrinology & Metabolism, vol. 105, no. 12, pp. e4230–e4239, 2020.

[59] X. You, C.-H. Wu, Y.-N. Fu et al., “The use of methylprednisolone in COVID-19 patients: a propensity score matched retrospective cohort study,” PLoS One, vol. 15, no. 12, Article ID e0244128, 2020.

[60] A. Sarfraz, Z. Sarfraz, M. Sarfraz, H. Aftab, and Z. Pervaiz, “Tocilizumab and COVID-19: a meta-analysis of 2120 patients with severe disease and implications for clinical trial methodologies,” Turkish Journal of Medical Sciences, vol. 51, no. 3, pp. 890–897, 2021.

[61] M. Fernández-Ruiz, F. López-Medrano, M. A. Pérez-Jacobo Asín et al., “Tocilizumab for the treatment of adult patients with severe COVID-19 pneumonia: a single-center cohort study,” Journal of Medical Virology, vol. 93, no. 2, pp. 831–842, 2021.

[62] D. Yan, X. Y. Liu, Y. N. Zhu et al., “Factors associated with prolonged viral shedding and impact of lopinavir/ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection,” European Respiratory Journal, vol. 56, no. 1, 2020.

[63] A. Agarwal, A. Mukherjee, G. Kumar, P. Chatterjee, T. Bhatnagar, and P. Malhotra, “Convalescent plasma in the management of moderate COVID-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial),” Bmj, vol. 371, 2020.

[64] L. Li, W. Zhang, Y. Hu et al., “Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19,” Jama, vol. 324, no. 5, pp. 460–470, 2020.

[65] M. E. Balcells, L. Rojas, N. Le Corre et al., “Early anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: a randomized phase ii clinical trial,” 2020, https://www.medrxiv.org/content/10.1101/2020.09.17.20196212v1.

[66] V. A. Simonovich, L. D. Burgos Pratx, P. Scibona et al., “A randomized trial of convalescent plasma in COVID-19 severe pneumonia,” New England Journal of Medicine, vol. 384, no. 7, pp. 619–629, 2021.

[67] WHO, WHO COVID-19 Solidarity Therapeutics Trial, WHO, Geneva, Switzerland, 2021.

[68] J. C. Marshall, S. Murthy, J. Diaz et al., “A minimal common outcome measure set for COVID-19 clinical research,” The Lancet Infectious Diseases, vol. 20, no. 8, pp. e192–e197, 2020.