Mechanistic rationale of drugs, Primary endpoints, Geographical distribution of clinical trials against Severe acute respiratory syndrome-related coronavirus-2: A Systematic review

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Abstract

**Objective** To do a systematic review and critical appraisal of the ongoing clinical trials that are assessing various therapeutic interventions against SARS-CoV-2 with an aim to provide insight into the various interventions tested, clinical rationale, geographical distribution of the trials as well as the endpoints assessed in the studies.

**Design** Rapid systematic review and critical appraisal of the ongoing clinical trials against SARS-CoV-2.

**Data sources** ClinicalTrials.gov, World health organization (WHO) International Clinical Trials Registry Platform (ICTRP) and Cochrane COVID registry were assessed till May 11th 2020.

**Study selection** Studies on any intervention based randomized controlled trials (RCTs), prospective clinical studies on SARS-CoV-2 in patients ≥18 years of age. Studies on autopsy series, preclinical studies, diagnostic methods, mathematical modelling, epidemiology and health services research, pediatric populations were excluded.

**Data extraction** The data was extracted by two authors independently into pre-defined forms based on the SPIRIT 2013 checklist. The data was extracted on various domains such as trial number, study title, abstract of the study, interventions assessed, sample size, phase of the study, study sponsor, primary endpoint assessed and country of study.

**Results** The search resulted in 3242 ongoing studies of which 829 studies were included. There are 134 different drug-based interventions being assessed in 463 clinical trials as treatment options. Seventy-two studies assessed preventive options of which 53 are drug-based prophylaxis and 19 assessed vaccines. Herbal medicines are being assessed in 79 studies; convalescent plasma therapy in 56 studies; stem cell-based interventions in 42 studies; anesthesia-based interventions in 31 studies, machine-based interventions in 24 studies, mental health- based interventions in 18 studies, rehabilitation-based interventions in 12 studies and miscellaneous interventions in 32 studies. China accounts for 35% of all ongoing clinical studies followed by USA 23%, France 7%, Spain 3.3%, Canada 2%, multi-country studies account only for 1.5% (13) and other countries together account for 28%. Amongst the 463 studies assessing drug-based treatment options, studies that are funded by federal and academic institutions are 79.6%, pharmaceutical company funded studies are 15.11% and no funding information is available in 5.10%. The definitive outcomes like mortality are being assessed as primary outcome in 22.8% of the studies only and need for ventilator in 6.2% of the studies. Rest of the studies has primary outcomes such as clinical recovery (15.9%), viral clearance (17.4%), time to recovery (10.1%), oxygen improvement (5.6%), ICU admission (1.9%), lab and imaging (6.4%), adverse effects (5.3%) and symptom reduction (1.5%), no outcome reported (6.2%) which account for 71% of the studies. Amongst the pharmaceutical company funded drug-based studies, only 20% of the studies had mortality as the primary outcome. Only 5.5% of the ongoing clinical trials are specifically designed to assess the most vulnerable population like elderly, patients with comorbidities and cancer. The most common intervention being tested against COVID-19 are antimalarial medications with 105 clinical studies. Hydroxychloroquine is the most common drug being tested with 83 ongoing studies.

**Conclusion** Multiple intervention based clinical studies against SARS-CoV-2 are being performed throughout the world with a high concentration of clinical trials in the developed world. There is a high concern that most of the studies maybe repetitive; elderly and patients with comorbidities are being underrepresented; definite endpoints like mortality are being assessed in only one-fifth of the studies.
Introduction

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is the causative agent for coronavirus disease (COVID-19) that has led to nearly 5 million new cases and more than a quarter million deaths as of May 22, 2020 (1). The case fatality rate is significantly higher in elderly, patients with preexisting comorbidities like hypertension, diabetes, cardiovascular diseases, chronic respiratory disease and for cancer(2). The high rate of transmission, moderate case fatality, novel nature of the virus has made the virus a formidable pathogen and has left a huge burden on the health care infrastructure.

Enormous amount of research is ongoing for finding vaccines, therapeutic interventions to prevent, mitigate, treat and manage the complications of COVID-19 disease. Randomized clinical trials (RCT) form the backbone of evidence-based rationale approach for management of any disease. SARS-CoV-2 pandemic has led to a flurry of clinical trials being performed throughout the world. The interventions being tested are largely based on known antiviral activity against SARS and MERS (Middle Eastern Respiratory Syndrome), efficacy in the invitro and in vivo models of SARS-CoV-2, potential docking sites on the viral genome based on computational modelling studies and biological agents to counter the cytokine surge and widespread immune activation(3, 4). There has also been a surge in interest in repurposing previously approved FDA drugs like Ivermectin, Chlorpromazine, Isotretinoin, Nitazoxanide for possible anti-viral activity(5, 6). The simultaneous initiation of multiple clinical trials has led to redundancy of study design, lack of novelty and absence of pragmatic primary end points. We undertook this systematic review of ongoing interventional clinical trials to collate the available information on the study design, geographical distribution, endpoints assessed and various drugs that are being assessed in the fight against SARS-CoV-2 infections.
Methods
This systematic review has been performed and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (7). (Supplementary data)

Search strategy
ClinicalTrials.gov, World health organization (WHO) International Clinical Trials Registry Platform (ICTRP) and Cochrane COVID registries were assessed up to May 11th with the search terms coronavirus, SARS-CoV-2 by two independent investigators (BV, VT). The clinical trials from the initial search of the electronic databases were imported into reference manager software. An independent review of the clinical trials was done. The duplicates were removed and the titles of the clinical trials were evaluated. Trials relevant to the topic of interest were shortlisted. The clinical studies that fulfilled the inclusion criteria were shortlisted for final systematic review. Reasons for excluding clinical studies were documented.

Inclusion and exclusion criteria

Study selection
The following eligibility criteria were used:

Inclusion criteria: (i) Any intervention based randomized controlled trials (RCTs), prospective clinical study on SARS-CoV-2 ii) Patients ≥ 18 years of age.

Exclusion criteria: (i) Autopsy series, preclinical studies ii) studies reporting diagnostic methods, mathematical modelling, epidemiology and health services research iii) Studies in pediatric populations iv) Studies on SARS-CoV and MERS

Data extraction
The data was extracted by two authors independently using a standardized data extraction form based on the SPRINT checklist. The data was extracted on various domains such as trial number, study title, abstract of the study, interventions assessed, sample size, phase of the study, study sponsor, primary endpoint assessed and country where study is being done. Any discrepancies in extraction of data was
resolved by mutual discussion (BV, VT). Details on data extraction are provided in the Supplementary data.

Definitions
We stratified studies into intervention-based studies, observational studies, mathematical modelling studies, studies assessing various diagnostic methods for SARS-CoV-2, studies that assess health services research, epidemiological studies, studies on pediatric population.

Results

Study search and study characteristics
The search of the clinical trial databases resulted in 3242 ongoing studies of which 913 underwent full review and 829 studies were included in the systematic review (figure 1). Amongst the 829 articles, 463 assessed various drugs as treatment options against COVID-19; 72 studies assessed preventive options of which 53 are drug-based prophylaxis and 19 studies assessed vaccines; herbal medicines are being assessed in 79 studies; convalescent plasma therapy is being studied in 56 studies; stem cell-based interventions in 42 studies; anesthesia-based interventions in 31 studies, machine-based interventions in 24 studies, mental health-based interventions in 18 studies; rehabilitation-based interventions in 12 studies; miscellaneous interventions in 32 studies. China accounts for 35% (291) of all ongoing clinical studies followed by USA 23% (188), France 7% (63), Spain 3.3% (28), Canada 2% (20), multi-country studies account only for 1.5% (13) and other countries together account for 28% of the studies (Supplementary data). There are only 2.77% of clinical trials that specifically seek to enroll patients with comorbidities like Diabetes, hypertension, cardiac disease; 2% of the trials that are being done in the elderly and 0.70% in cancer patients accounting for a total of 5.5% ongoing clinical trials.
Drug based interventions as treatment against COVID-disease

There are 134 different drug-based interventions being assessed in 463 clinical trials throughout the world (Table 1). Amongst the 463 studies assessing drug-based treatment options, studies that are funded by federal and academic institutions are 79.6%; pharmaceutical company funded studies are 15.11% (70); no funding information has been provided in 5.10% (24) studies. The definitive outcomes like mortality was assessed as primary outcome in 22.8% of the studies only and need for mechanical ventilation in 6.2% of the studies. Rest of the studies had outcomes such as: clinical recovery (15.9%), viral clearance (17.4%), time to recovery (10.1%), oxygen improvement (5.6%), ICU admission (1.9%), labs and imaging(6.4%), adverse effects (5.3%) and symptom reduction(1.5%), no outcome reported(6.2%) which account for 71% of the studies. Amongst the pharmaceutical company funded drug-based studies, only 20% of the studies had mortality as the primary outcome and 7% had need for mechanical ventilation as an outcome.

The most common drug-based treatment intervention being tested against COVID-19 are antimalarial medications with 105 clinical studies. Hydroxychloroquine is the most common drug being tested with 83 ongoing studies of which hydroxychloroquine alone is being studied in 49 studies and hydroxychloroquine with azithromycin being studied in 22; Chloroquine is being tested in 31 studies. Antiviral medications are being tested in 76 clinical trials of which Lopinavir with Ritonavir in 28 studies, Favipiravir in 13 studies, Remdesivir in 8 studies, interferons in 14 studies; other antivirals in 13 studies. Immunosuppressants are being assessed in 82 studies- Interleukin-6 antagonists in 38 studies of which Tocilizumab based are 23 studies, Sarilumab in 7 studies; Corticosteroids in 15 studies; Immunosuppressants in 30 studies; Anti-inflammatory agents in 20 studies colchicine in 8 studies; Antioxidants and dietary supplements like vitamin C, D, Zinc in 16 studies; Antifibrotic agents in 9 studies; other miscellaneous interventions account for the rest of the studies. These studies are most commonly done in China (122) followed by USA (114) and France (47) (Supplementary data). The largest ongoing clinical trial is the WHO sponsored Solidarity trail which is a multi-center study with a sample size of 1,00,000 patients to assess Remdesivir, chloroquine or hydroxychloroquine, lopinavir plus ritonavir.
interferon-beta with control, with a primary endpoint of all-cause mortality(8, 9). NCT04292899 is a multi-center study with a sample size of 6,000 that is assessing Remdesivir with a primary endpoint of improvement on a 7-point Ordinal Scale on Day 14 (10). NCT04322682 is a Canadian study that is assessing Colchicine with a primary endpoint of all-cause mortality at day 30(11). Table 2 provides a summary of phase 3 clinical trials with sample size of more than thousand patients that assess various interventions in COVID-19 disease.

**Drug being tested as prophylaxis against COVID-disease**

Fifty-three drug-based studies are being assessed as prophylaxis in COVID-19. HCQ is the most commonly assessed prophylaxis drug being studied in 24 clinical studies; chloroquine in 2 studies; HCQ+ Azithromycin in 1 study; Chloroquine+ Azithromycin in 1 study; Nitazoxamide in 2 studies; other anti-viral medications include Camostat mesylate, interferons, Lopinavir + Ritonavir. Other immunomodulatory medications being assessed include anakinra, colchicine, corticosteroids, Levamisole, mycobacterium W in one study each. Table 3 provides a summary of the prophylactic interventions being assessed against COVID-19. The most common country where these studies are conducted are USA (17) followed by 4 each in France and China (Supplementary data). The largest of the prophylactic study is the Crown coronation study which is a multicenter study with a sample size of 55,000 that is assessing various doses of chloroquine in the effectiveness in preventing laboratory-confirmed symptomatic COVID-19 in healthcare workers with repeated exposures to SARS-CoV-2(12). The next largest study is the CRASH 19 study conducted in UK with an sample size of 10,000 that is assessing Aspirin, Losartan and Simvastatin with the all-cause mortality as the primary endpoint(13). WHIPCOVID study is a multicenter study assessing efficacy of weekly vs daily HCQ in preventing new cases of SARS-CoV-2 infection(14).

**Vaccines**

The most important option to prevent further waves of the COVID pandemic are vaccines. There are 19 vaccine-based studies of which are 8 are BCG and 1 measles vaccine-based studies; 11 are newer
vaccines candidates. The most commonly studied vaccine is the BCG vaccine in 8 studies followed by recombinant novel Coronavirus Vaccine (Adenovirus Type Vector) in two studies, aAPC Vaccine, Minigene Vaccine, recombinant chimeric COVID-19 epitope DC vaccine, bacTRL-Spike Vaccine, Measles vaccine, mRNA-1273 vaccine, nanoparticle Vaccine, ChAdOx1 nCoV-19 and INO-4800. China is leading the initiative with four ongoing human trials followed by USA with 3 trials. Supplementary data provides a summary of the ongoing vaccine-based studies around the world.

Mesenchymal stem cell therapy

There are currently 42 clinical studies that are assessing mesenchymal stem cell therapy-based interventions in COVID-19 disease. China is leading the initiative with 25 ongoing human trials followed by USA with 8 trials and Spain with 4 trials. The rationale for use of mesenchymal stem cells are the hypothesized immunomodulatory properties that can counter the cytokine storm. The various sources of stem cells that are being studied include cord blood, human menstrual blood-derived, mesenchymal stem cells exosomes atomization, human dental pulp, human stromal cells, umbilical cord blood mononuclear cells and umbilical cord Wharton’s Jelly derived mesenchymal stem cells (table 4).

Convalescent plasma therapy

Convalescent plasma therapy (CPT) involves infusion of plasma obtained from people who have recovered from COVID-19 and who have circulating neutralizing antibodies which provides short-term immunity against SARS-CoV-2 coronavirus. There are currently 56 ongoing studies that are assessing CPT with 20 studies being done in USA and 14 studies being done in China. The largest ongoing clinical trial is the CONCOR-1 study being done in Canada with a sample size of 1000 patients with the aim to assess if CPT reduces in-hospital mortality in patients hospitalized for COVID-19. (table 4)

Herbal medicines

There are currently 79 clinical studies assessing the efficacy of alternative medicines mainly the Chinese herbals that are being assessed in 77 studies followed by 1 study in Iran and one Ayurveda study in UK.
Supplementary data provides a summary of the various ongoing studies that are testing herbal medicines against COVID-19.

Anesthesia based interventions

There are currently 31 ongoing studies that assess various anesthesia-based interventions that include prone positioning (11), nitric oxide inhalation (7), ventilator settings (8) and modified intubation techniques (5). USA is performing 7 studies followed by Canada with 5 studies.

Machine based interventions

There are currently 24 ongoing studies that are assessing machine-based interventions like extra-corporeal membrane oxygenation (ECMO) (8), plasmapheresis (5), CytoSorb Adsorber (3), Bidirectional Oxygenation Valve (2), hyperbaric oxygen therapy (2), continuous renal replacement therapy (2), external diaphragmatic pacing (1), oXiris Membrane (1), and V/Q Vest (1).

Mental health

There is excess emotional distress to patients and healthcare providers during the COVID-19 pandemic. There are 18 studies that are assessing mental health-based interventions that include mindfulness (11) meditation (3), intelligent psychosomatic adjustment system (2), cognitive behavioral therapy (1), and psychological support. China is performing 8 studies followed by USA with 4 studies.

Rehabilitation

There are currently 12 studies that are assessing various rehabilitation initiatives like telerehabilitation-based exercises (6), general rehabilitation (2), pulmonary rehabilitation (2) anosmia rehabilitation (1), and rehab-meals (1). China and Turkey are leading with 3 studies each.

Others

There are 32 other intervention-based studies that were not categorized into the above distinctions. They include microbiota transplantation (3), Natural Killer Cell (CYNK-001) infusions (3), acupressure therapy at auricular point (3), hydrogen inhalation (3), radiation therapy (2), respiratory muscle training (2), digital stress through artificial intelligence (2), Ozone autohemotherapy (2), virtual monitoring (2),
expressive writing(1), face mask(1), internet based Solution(1), Medical Masks vs N95
Respirators(1),online distance learning(1), prayer(1), shadowboxing for pulmonary function(1), sleep psychology and music therapy (1), Zang-Fu Point-pressing’ massage(1) and endo-venous systemic Ozone therapy(1).

Discussion
In this systematic review, we critically appraise 829 ongoing clinical trials that are assessing various interventions like treatment, drug-based prophylaxis, herbal medicines, CPT, stem cell-based interventions, anesthesia-based interventions, machine-based interventions, mental health-based interventions, rehabilitation-based interventions and miscellaneous interventions. China and USA account for majority of the ongoing studies with concern that patients in middle- and low-income countries may have minimal access for enrollment into clinical trials. Multi-center multi-country collaborative studies account only for 1.5% of all ongoing clinical studies which show apparent lack of collaborative effort among researchers as well as difficult in universal applicability of the conclusions made from ongoing studies done in developed countries.

The major overwhelming nature of this pandemic has been case fatality rates of 1-10% seen in different healthcare settings and the high demand for ventilatory support. Despite this, 71% of the clinical trials have surrogate endpoints other than all-cause mortality or ventilatory support as the primary endpoint. In addition, the case fatality rate is significantly higher in elderly, patients with preexisting comorbidities like hypertension, diabetes, cardiovascular diseases, chronic respiratory disease and cancer. Despite this, only 5.5% of the ongoing clinical trials specifically seeks to enroll this subgroup of patients. This causes significant concern regarding applicability of the ongoing clinical trials to the general population and the degree of applicability of the clinical trial data to patients with co-morbidities(15, 16).
The most common interventions are drug based directed at treatment of COVID-19 disease in 463 clinical trials. Though the main pathophysiology behind mortality, intubation, ICU admissions are cytokine storm and macrophage activation, nearly 50% of studies are anti-viral activity based interventions with anti-malarial accounting for 105 studies and other anti-viral drugs accounting for 76 studies. The main clinical rationale for use of anti-malarial agent against SARS-CoV-2 was based on invitro efficacy. Despite lack of mortality benefit and possible increased risk of adverse events with HCQ in published clinical studies till date, it is still the most commonly studied drug against SARS-CoV-2. This calls for a need for an international repository of individual patient data and rapid assimilation of the available clinical evidence on deciding termination of potentially harmful interventions. Biological agents with immunosuppressive and immunomodulatory properties that have the potential to curb the cytokine storm and widespread macrophage activation are being studied with close to 100 studies ongoing.

The most important area for research in the current pandemic needs to be preventive studies. There are currently 72 studies with 19 vaccine based and 53 drug based preventive studies. There are currently 11 vaccines in human clinical trials. BCG vaccine is also being also studied for its proposed immunogenicity against SARS-CoV-2. Among the drug based preventive studies, 50% are using hydroxychloroquine with various aspects being tested including daily vs weekly dosing, pre vs post exposure prophylaxis. From our review, we feel there is a greater need for more preventive strategy-based studies since most of the countries are re-opening and the proposed timeline for the pandemic to subside is 1-2 years. CPT use in COVID-19 disease was promoted by the potential efficacy in SARS, MERS and Ebola. There are currently 56 studies that are ongoing and from some of the published data it has been shown to be safe and effective. There is a need for information from larger datasets.
There are 79 studies that are assessing herbal based medicines and 42 studies that are assessing mesenchymal stem cells therapy. Majority of these studies are being done in China (%). These interventions are questionable with a potential to harm patients. There is a trend to combine these interventions with western medicines and the potential drug interactions may lead to further adverse events. One of the important aspects that this systematic review shows is the lack of enough studies on rehabilitation and mental health-related interventions. There are only 30 studies that account only for 3% of all intervention-based studies that are ongoing. Home quarantine, emotional distress from loss of loved ones, loss of job, new oxygen requirements from COVID-disease, anosmia are some of the problems faced by patients recovering from COVID-19. There is a huge need for more studies that focus on alleviating these problems. Majority of the patients with severe or critical COVID disease are in ICU. There are only 31 ongoing studies that are ICU based interventions like prone positioning, nitric oxide inhalation. There is a greater need for study of potential interventions that can improve outcomes in patients admitted in the ICU.

**Strengths of the systematic review**

This is an extensive review of the ongoing clinical studies to give an insight into the various interventions being studied currently. We were also able to identify the outcomes being studied and provide inputs on the need for studies addressing definitive patient related outcomes like mortality, and need for mechanical ventilation and improvement of patients in the ICU. Our review also provides information regarding the utility of ongoing trials like HCQ based treatment, which have so far not shown benefit in larger studies, and re-assess the need for such studies and utilize resources for other interventions.

**Limitations**

Newer clinicals are being rapidly initiated and enrolled into the clinical trial registries which makes it difficult for the review to be up to date. Information regarding the status of clinical trials if they are active or have been terminated or completed is not clearly available from the databases. Though the review
accounted for the most of the clinical trial registries, despite our best attempt, it may not be exhaustive enough to account for retrospective registration of all studies.

Implications for practice

The majority of ongoing clinical trials seek to enroll patients that may not be representative of the actual population who are at risk of death and morbidity from COVID-19. There needs to be an emphasis on the rationality of the primary endpoints with need for all-cause mortality as the primary endpoint and other patient-related outcomes like need for mechanical ventilation and decreasing length of ICU stay as main secondary outcomes. There needs to be a higher rate of inclusion of patients with co-morbidities in clinical trials to reflect real world scenario for outcomes. Majority of ingoing studies are in the developed world and middle- and low-income countries are at a risk of grossly being underrepresented in the clinical trials.

Conclusion

This systematic review identifies the spectrum of clinical trials and the therapeutic interventions that are being assessed against SARS-CoV-2. Multiple intervention based clinical studies against SARS-CoV-2 are being done throughout the world with a high concentration of clinical trials being done in the developed world. There is a high concern for redundancy of studies and under-representation of elderly and patients with comorbidities. Definite endpoints like mortality are being assessed in only one-fifth of the studies. This review provides information for researchers for rationale design of future clinical studies.

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Footnotes:
Contributors: BPV conceived the study; VT, JM and BPV designed the study; BPV and VT screened titles and abstracts for inclusion. BPV and VT extracted and analyzed data. BPV, PG, P, HP and VT formulated the preliminary draft, all authors revised for critical content. All authors approved the final
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| Anti-viral mechanism of action                                      | Immunosuppressants (Cytokine surge prevention)                                                                 | Antioxidants and Dietary supplements                                                                 |
|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Inhibits TMPRSS2/ Prevents viral cell entry                        | Corticosteroids                                                                                                | Alpha lipoic acid; Vitamin-C                                                                      |
| Camostat mesylate                                                   | Interleukin-6 inhibitors                                                                                     | Vitamin-D; Zinc                                                                                    |
| Nafamostat                                                         | Tocilizumab; Sarilumab; Siltuximab                                                                        | Eicosapentaenoic acid free fatty acid                                                              |
| Inhibits S protein/ACE2 interaction                                 | Clazakizumab; CMAB806; Ulinastatin                                                                        | Triiodothyronine                                                                                   |
| (Inhibits membrane fusion of the viral envelope)                   | Naltrexone                                                                                                   |                                                                                                   |
| Umifenovir (Arbidol)                                                | Interleukin-1 antagonist                                                                                     | Anti-inflammatory                                                                                 |
| Angiotensin 1-7                                                    | Anakinra                                                                                                      | Aspirin; Naproxen; Colchicine                                                                      |
| Angiotensin Peptide                                                | Anti-IL-18 monoclonal antibody                                                                              | Ibufrofen; CM4620-Injectable                                                                       |
| Angiotensin receptor blockers-Losartan                             | Canakinumab                                                                                                   | Tradipitant (neurokinin-1 receptor (NK-1R) antagonist)                                             |
| Angiotensin converting enzyme inhibitors-Ramipril                  | Interleukin-8 antagonist                                                                                        | Escin; Tetrandrine (calcium channel blocker)                                                       |
| Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2)        | BMS-986253                                                                                                    | Bovactant(surfactant)                                                                             |
| Spironolactone                                                     | Interleukin-17 inhibitor                                                                                     | Ketamine; Fluvoxamine                                                                             |
| Inhibits Abl2 kinase activity (inhibits fusion with cell membrane) | TNF-alpha inhibitor                                                                                          | LY3127804(angiotoprotein-2 inhibitor)                                                              |
| Imitatinib                                                         | Adalimumab                                                                                                    | Metenkefalin + tridecactide                                                                        |
| Inhibits S protein and CD 147 interaction                          | XPro1595                                                                                                      | Anti-fibrotic agents                                                                               |
| Chloroquine                                                        | Janus kinase inhibitors                                                                                        | cSVF ; Defibrotide                                                                                |
| Hydroxychloroquine                                                 | Baricitinib; Ruxolitinib; Jakotinib                                                                        | Pirfenidone; Nintedanib                                                                           |
| Inhibits viral entry and endocytosis                               | TD-0903,                                                                                                      | Vazegepant (an intranasal, high-affinity calcitonin gene-related peptide (CGRP) receptor antagonist |
| Lopinavir; Darunavir; Ritonavir; Danprevir ASC09; Atovaquone       | Interferon gamma antagonist                                                                                   | Iron chelating agent                                                                               |
| Inhibitors of viral polymerase complex                             | Emapalumab                                                                                                    | Desferal                                                                                          |
| inhibits viral RNA dependent RNA polymerase                       | CS complement inhibitor                                                                                       |                                                                                                   |
| Remdesivir; Favipiravir; Ribavirin                                 | Eculizumab                                                                                                    | Miscellaneous                                                                                      |
| Triazavir                                                         | Ravulizumab                                                                                                   | FT516                                                                                             |
| Cap-dependent endonuclease activity inhibitor                      | IFX-1                                                                                                         | NK cell immunotherapy engineered to express a high affinity, non-cleavable version of CD16 (hnCD16) |
|                                                                   | Phosphoinositide 3-kinase inhibitor                                                                            | for enhanced antibody dependent cellular cytotoxicity (ADCC)                                       |
|                                                                   | Duvelisib                                                                                                     | Methotrexate-loaded Nanoparticles                                                                  |
|                                                                   | Immunomodulators                                                                                              |                                                                                                   |
|                                                                   | NK cell stimulant                                                                                             |                                                                                                   |
|                                                                   | AVM0703                                                                                                       |                                                                                                   |
|                                                                   | T cell stimulants                                                                                             |                                                                                                   |
| Drug                     | Mechanism                                                                 |
|-------------------------|---------------------------------------------------------------------------|
| Baloxavir marboxil      | Inhibits viral RNA dependent DNA polymerase                               |
| Emtricitabine/tenofovir |                                                                           |
| Azvudine                |                                                                           |
| Clevudine               |                                                                           |
| Sofosbuvir; Ledipasvir  |                                                                           |
| Inhibits viral RNA synthesis (NS5B protein) |                     |
| Daclatasvir             |                                                                           |
| Neuraminidase inhibitor |                                                                           |
| DAS181                  |                                                                           |
| Interferons; Interferon-beta; Interferon-alpha |                     |
| Interferon-lambda       |                                                                           |
| Super-Compound Interferon (rSIFN-co) |                     |
| Enhance Type 1 interferon production |                     |
| TAK-981                 |                                                                           |
| Inhibit nuclear transport of virus |                     |
| Ivermectin              |                                                                           |
| Viral helicase inhibition |                                                                     |
| Bismuth                 |                                                                           |
| Neuraminidase inhibitor |                                                                           |
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| Viral helicase inhibition |                                                                     |
Table 2: Summary of drug-based treatments in phase 3 clinical trials with sample size of more than thousand patients against SARS-CoV-2

| Study identification number | Country | Sample size | Intervention assessed | Primary endpoint |
|-----------------------------|---------|-------------|-----------------------|------------------|
| NCT04292899                | Multicenter study; sponsor-Gilead | 6000 | Remdesivir | The Odds of Ratio for Improvement on a 7-point Ordinal Scale on Day 14 |
| NCT04292730                | Multicenter study; sponsor-Gilead | 1600 | Remdesivir | The Odds of Ratio for Improvement on a 7-point Ordinal Scale on Day 11 |
| NCT04315948                | Multicenter study; sponsor-National institute of France | 3000 | Remdesivir; Lopinavir/ritonavir; Interferon Beta-1A; Hydroxychloroquine | Percentage of subjects reporting each severity rating on a 7-point ordinal scale on day 15 |
| NCT04324047                | France | 1000 | immune modulator drugs | Overall survival at day 14 WHO progression scale COVID 19 |
| ISRCTN83971151 Solidarity trial | Canada | 6000 | Colchicine | Number of participants who die or require hospitalization due to COVID-19 infection upto day 30 |
| NCT04322682                | Sponsor-Montreal heart institute | 100000 | Remdesivir, chloroquine or hydroxychloroquine, lopinavir plus ritonavir, and interferon-beta. | All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study |
| NCT04328012                | USA | 4000 | lopinavir/ritonavir; Hydroxychloroquine Sulfate; Losartan | National Institute of Allergy and Infectious Diseases COVID-19 Ordinal Severity Scale (NCOSS) at 60 days |
| NCT04345289                | Denmark | 1500 | Convalescent anti-SARS-CoV-2 plasma; Sarilumab; Baricitinib; Hydroxychloroquine | All-cause mortality or need of invasive mechanical ventilation at day 28 |
| NCT04358068                | USA | 2000 | Hydroxychloroquine +azithromycin | Proportion of participants who died from any cause or were hospitalized at day 21 |
| NCT04356495                | France | 1057 | Hydroxychloroquine; Imatinib; Favipiravir; Telmisartan | Proportion of participants with an occurrence of hospitalization or death at day 14 |
| NCT04358003                | USA sponsor- Marker Therapeutics AG | 2000 | Plasma Adsorption Cartridge | All-cause mortality at day 28 |
| Study identification number | Country | Sample size | Intervention assessed | Primary endpoint |
|----------------------------|---------|-------------|-----------------------|------------------|
| NCT04333407                 | United Kingdom | 3170        | Aspirin; Clopidogrel; Rivaroxaban; Atorvastatin; Omeprazole   | All-cause mortality at 30 days after admission |
| Phase 3 trial               | Sponsor-Imperial College London                      |             |                       |                  |
| NCT04333732                 | Multicenter study                                    | 55000       | Different doses of chloroquine                               | Effectiveness in preventing laboratory-confirmed symptomatic COVID-19 in healthcare workers with repeated exposures to SARS-CoV-2. |
| Phase 3 trial               | Sponsor- Bill and Melinda Gates Foundation            |             |                       |                  |
| Crown coronation study      | Multicenter study                                    |             |                       |                  |
| NCT04334967                 | USA                                               | 1250        | Hydroxychloroquine                                            | Percentages of enrolled patients needing hospitalization and mechanical ventilation at day 14 |
| Phase 3 trial               | Sponsor- Providence Health & Services                 |             |                       |                  |
|                             | USA                                               | 1250        | Hydroxychloroquine                                            | Outcome reported as the percent of participants in each arm who are COVID-19-free at the end of study treatment up to 12 weeks |
| NCT04328467                 | USA                                               | 3500        | Hydroxychloroquine                                            | Measure the difference in new cases of COVID-19 disease between randomized treatment arms at 8 weeks |
| Phase 3 trial               | Sponsor- University of Minnesota                     |             |                       |                  |
| NCT04341441                 | USA                                               | 3500        | Hydroxychloroquine daily vs weekly dosing                      | Positive serology or reverse transcriptase (RT-PCR) for COVID-19 up until day 28 |
| Phase 3 trial               | Sponsor- Henry Ford Health System                    |             |                       |                  |
| WHIP COVID study            | Singapore                                          | 1200        | Hydroxychloroquine                                            |                                               |
| NCT04342156                 | Sponsor- Tan Tock Seng Hospital                      |             |                       |                  |
| Phase 3 trial               | Singapore                                          | 1200        | Hydroxychloroquine                                            | Positive serology or reverse transcriptase (RT-PCR) for COVID-19 up until day 28 |
| NCT04343001                 | United Kingdom                                     | 10000       | Aspirin, Losartan and Simvastatin                              | Death up to 28 days from day of randomization |
| Phase 3 trial               | Sponsor-London School of Hygiene and Tropical Medicine |           |                       |                  |
| CRASH 19 study              | United Kingdom                                     | 10000       | Aspirin, Losartan and Simvastatin                              | Death up to 28 days from day of randomization |
Table 4: Summary of interventions used in the clinical trials as prevention against SARS-CoV-2 infection

| Prevention | Vaccines |
|------------|----------|
| **Pre and post exposure Prophylaxis** | **Recombinant Novel Coronavirus Vaccine** |
| Antiviral medications | (Adenovirus Type 5 Vector) |
| Hydroxychloroquine | aAPC Vaccine |
| Chloroquine | Minigene Vaccine |
| Lopinavir/Ritonavir | Recombinant chimeric COVID-19 epitope DC |
| Interferon alpha | BCG V |
| Camostat Mesylate | bacTRL-Spike |
| Peginterferon Lambda-1a | Measles |
| Nitazoxanide | RNA Vaccine Candidate |
| Anti-inflammatory | mRNA-1273 vaccine |
| Anakinra | Nanoparticle Vaccine |
| Colchicine | Recombinant novel coronavirus (adenovirus type 2 vector) |
| Corticosteroids | ChAdOx1 nCoV-19 |
| Immunomodulators | INO-4800 |
| Levamisole and Isoprinosine | *Non pharmacological interventions* |
| Lactobacillus Corynformis K8 | App based social distancing |
| Lenzilumab | Face masks vs N95 respirator |
| Miscellaneous | Internet based solutions |
| Vitamin C; Vitamin D; Zinc | Isolation strategy |
| Melatonin | |
| Mycobacterium w | |
| rhiFNa Nasal Drops | |
| Resistant Potato Starch | |
| Nitric oxide | |
| Bêta-cyclodextrin and citrox mouthwash | |
| Povidone-iodine 0.5% nasal | |
### Table 5: Summary of non-pharmacological interventions used in the clinical trials as treatment against SARS-CoV-2 infection

| Cell and plasma-based therapy                  |
|-----------------------------------------------|
| *Convalescent plasma therapy*                 |
| *Cell based therapy*                          |
| Cord blood mesenchymal stem cells             |
| Human menstrual blood-derived stem cells      |
| Mesenchymal stem cells exosomes atomization   |
| Human dental pulp mesenchymal stem cells      |
| Human stromal cells                           |
| Umbilical cord blood mononuclear cells        |
| Umbilical cord Wharton’s Jelly derived mesenchymal stem cells |

| Machine based interventions                   |
|-----------------------------------------------|
| Extra-corporeal membrane oxygenation          |
| CytoSorb Absorber                             |
| External diaphragmatic pacing                 |
| Hyperbaric oxygen therapy                     |
| Bi-directional oxygen valve                   |
| oXiris Membrane                               |
| Plasmapheresis                                |
| V/Q Vest                                      |
| Dialysis                                      |

| Anesthesia based interventions                |
|-----------------------------------------------|
| Nitric oxide                                  |
| Prone Positioning                             |
| Non-invasive oscillating device (NIOD)         |
| Sedation with Sevoflurane Versus Propofol      |
| Double-Trunk Mask on Oxygenation Titration    |
| Early CPAP                                    |
| Intubation Barrier Box                        |

| Miscellaneous                                 |
|-----------------------------------------------|
| *Chinese herbal medicines*                    |
| *Mental health and mindfulness interventions*  |
| Telerehabilitation                            |
| Acupressure Therapy                           |
| Respiratory muscle training                   |
| Auricular nerve stimulation                    |
| Expressive Writing                            |
| Hydrogen inhalation                           |
| Ozone Auto-hemotherapy                        |
| Prayer                                        |
| *shadowboxing for pulmonary function*         |
| Sleep psychology and music therapy            |
| Neck Inspiratory Muscle exercise              |
| Radiation therapy                             |
| Zang-Fu Point-pressing’ massage               |
| Virtual monitoring                            |


Clinical studies identified through database search of
WHO International Clinical Trials Registry Platform
ClinicalTrials.gov, European trial registry, PubMed =3242

Records after duplicates removed
(n = 3035)

Records screened
(n = 3035)

Records excluded
(Observational studies=1837; Modelling=207; Diagnostic studies=46; Non-SARS-CoV-2 studies=28 N=2122)

Trails assessed for eligibility
(n = 913)

Full-text articles excluded, with reasons
(Cancelled trials = 16;
Non COVID intervention=11
Health services=38
Epidemiology =6;
pediatrics=1; diet=1
anti-coagulation=11

Studies included in the analysis
(n = 829)

Therapeutic interventions=463
Prevention=72
Prophylaxis=53
Vaccines=19
Herbal n=79
Convalescent plasma=56
Stem cell therapy=42
Anesthesia based interventions n=31
Mental health = 18
Machine based interventions=24
Figure legends:

Figure 1: PRISMA flow diagram depicting the search strategy utilized in the systematic review