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RESEARCH ARTICLE

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The mechanistic rationale of drugs, primary endpoints, geographical distribution of clinical trials against severe acute respiratory syndrome-related coronavirus-2: A systematic review

Bhanu Prasad Venkatesulu MD[1] | Viveksandeep Thoguluva Chandrasekar MD[2] | Prashanth Giridhar MD[3] | Pragathee V. MBBS[4] | Harsh K. Patel MD[5] | Jacob Manteuffel MD[6]

[1]Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan

[2]Department of Gastroenterology and Hepatology, University of Kansas Medical Center, Kansas City, Kansas

[3]Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India

[4]Department of Internal Medicine, Karpagam Faculty of Medical Sciences and Research, Coimbatore, Tamil Nadu, India

[5]Department of Internal Medicine, Ochsner Medical Center, New Orleans, Louisiana

[6]Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan

Correspondence
Bhanu Prasad Venkatesulu, MD, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI 48202.
Email: bpmmc24@gmail.com

Abstract

There are numerous ongoing studies assessing treatment options for preventing, treating, and managing complications of coronavirus disease-2019 disease. The objective of this study was to do a systematic review and critical appraisal of the ongoing clinical trials 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. ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and PubMed were assessed till 11 May 2020. 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 China accounts for 35% of all ongoing clinical studies followed by USA 23% and other countries together account for 42%. 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. 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. Multiple intervention-based clinical studies against severe acute respiratory syndrome-related coronavirus-2 are being performed throughout the world with a high concentration of clinical trials in the developed world with concern that of elderly and patients with comorbidities are being underrepresented and definite endpoints like mortality are being assessed in only one-fifth of the studies.

KEYWORDS

clinical trials, COVID-19, hydroxychloroquine, systematic review, vaccines

1 | INTRODUCTION

Severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) is the causative agent for coronavirus disease-2019 (COVID-19) that has led to nearly 13 million new cases and more than a half-million deaths as of 11 July 2020.[1] The case fatality rate is significantly higher in elderly, patients with pre-existing comorbidities, such as hypertension, diabetes, cardiovascular diseases, chronic respiratory disease, and for cancer.[2-5] 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 healthcare 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 an evidence-based rationale approach for the 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 Middle Eastern respiratory syndrome (MERS), efficacy in the in vitro and in vivo models of SARS-CoV-2, potential docking sites on the viral genome based on computational modeling studies, and biological agents to counter the cytokine surge and withspread immune activation.[6,7] There has also been a surge in interest in repurposing previously approved Food and Drug Administration drugs such as ivermectin, chlorpromazine, isotretinoin, and nitazoxanide for possible antiviral activity.[8,9] The simultaneous initiation of multiple clinical trials has led to the redundancy of study design, lack of novelty, and absence of pragmatic primary endpoints. 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.

2 | METHODS

This systematic review has been performed and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supporting Information Data).[10]

2.1 | Search strategy

ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform and PubMed were assessed up to 11 May 2020 with the search terms coronavirus, SARS-CoV-2 by two independent investigators (BPV and VTC). 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 the final systematic review. Reasons for excluding clinical studies were documented.

2.2 | Inclusion and exclusion criteria

2.2.1 | Study selection

The following eligibility criteria were used. *Inclusion criteria*: (a) any intervention-based RCTs, prospective clinical study on SARS-CoV-2; and (b) patients ≥18 years of age. *Exclusion criteria:* (a) autopsy series, preclinical studies; (b) studies reporting diagnostic methods, mathematical modeling, epidemiology, and health services research; (c) studies in pediatric populations; and (d) studies on SARS-CoV and MERS.

2.3 | Data extraction

The data were extracted by two authors independently using a standardized data extraction form based on the SPRINT checklist. The data were 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 the study is being done. Any discrepancies in the extraction of data were resolved by mutual discussion (BPV and VTC).

2.4 | Definitions

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

3 | RESULTS

3.1 | 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 (CPT) 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;

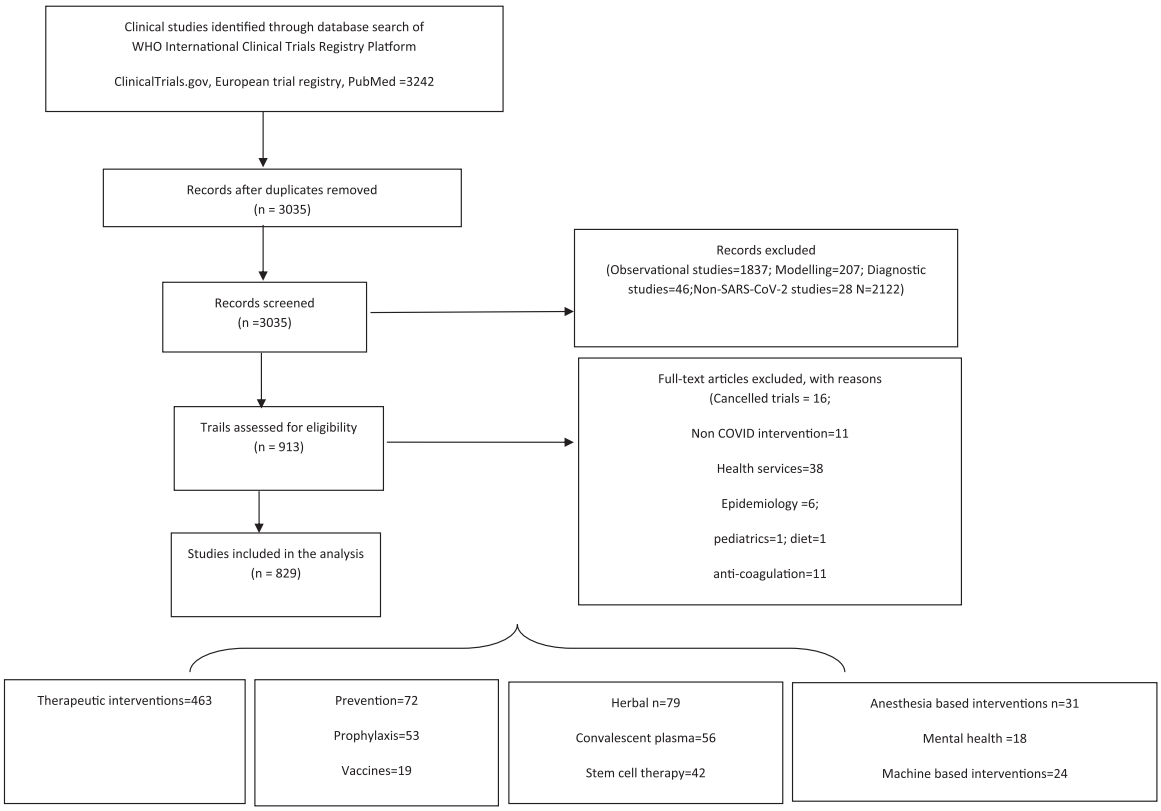

FIGURE 1 PRISMA flow diagram depicting the search strategy utilized in the systematic review

rehabilitation-based interventions in 12 studies; and 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), multicountry studies account only for 1.5% (13), and other countries together account for 28% of the studies (Supporting Information 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.

3.2 | 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 were 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 interventions being tested against COVID-19 are antimalarial medications with 105 clinical studies. Hydroxychloroquine (HCQ) is the most common drug being tested with 83 ongoing studies of which v alone is being studied in 49 studies and HCQ 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, and 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; immunomodulators in 30 studies; anti-inflammatory agents in 20 studies colchicine in 8 studies; antioxidants and dietary supplements such as 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) (Supporting Information Data). The largest ongoing clinical trial is the WHO-sponsored Solidarity trial which is a multicenter study with a sample size of 100 000 patients to assess remdesivir, chloroquine, or HCQ, lopinavir plus ritonavir,

TABLE 1 Summary of mechanisms of the drugs used in the clinical trials as treatment against severe acute respiratory syndrome coronavirus-2 infection

Antiviral mechanism of action inhibits TMPRSS2/ prevents viral cell entry	Immunosuppressants (cytokine surge prevention)	Antioxidants and dietary supplements
Camostat mesylate	Corticosteroids	Alpha-lipoic acid; vitamin C
Nafamostat	Interleukin-6 inhibitors	Vitamin D; zinc
Inhibits S protein/ACE2 interaction	Tocilizumab; sarilumab; Siltuximab	Eicosapentaenoic acid-free fatty acid
(Inhibits membrane fusion of the viral envelope)	Clazakizumab; CMAB806; Ulinastatin	Triiodothyronine
Umifenovir (Arbidol)	Naltrexone	Anti-inflammatory
Angiotensin 1-7	Interleukin-1 antagonist	Aspirin; naproxen; colchicine
Angiotensin peptide	Anakinra	Ibuprofen; CM4620-injectable
Angiotensin receptor blockers-Losartan	Anti-IL-1β monoclonal antibody	Tradipitant (neurokinin-1 receptor (NK-1R) antagonist)
Angiotensin-converting enzyme inhibitors-ramipril	Canakinumab	Escin; tetrandrine (calcium channel blocker)
Recombinant human angiotensin-converting enzyme 2 (rhACE2)	Interleukin-8 antagonist	Bovactant (surfactant)
Spironolactone	BMS-986253	Ketamine; fluvoxamine
Inhibits Abl2 kinase activity (inhibits fusion with cell membrane)	Interleukin-17 inhibitor	LY3127804(angiopotein-2 inhibitor)
Imatinib	Ixekizumab	Metenkefalin + tridecactide
Inhibits S protein and CD 147 interaction	TNF-alpha inhibitor	Antifibrotic agents
Meplazumab	Adalimumab	cSVF; defibrotide
Inhibits viral entry and endocytosis	XPro1595	Pirfenidone; Nintedanib
Chloroquine	Janus kinase inhibitors	Vazegepant (an intranasal, high-affinity calcitonin gene-related peptide (CGRP) receptor antagonist
Hydroxychloroquine	Baricitinib; ruxolitinib; Jakotinib	Iron chelating agent
Inhibits 3–chymotrypsin-like protease	TD-0903	Desferal
Lopinavir; darunavir; Ritonavir; danprevir	Interferon-γ antagonist	
ASC09; atovaquone, famotidine	Emapalumab	Miscellaneous
Inhibitors of viral polymerase complex	C5 complement inhibitor	FT516
Inhibits viral RNA-dependent RNA polymerase	Eculizumab	NK cell immunotherapy engineered to express a high affinity, non-cleavable version of CD16 (hnCD16) for enhanced antibody-dependent cellular cytotoxicity (ADCC)
Remdesivir; favipiravir; ribavirin	Ravulizumab	Methotrexate-loaded Nanoparticles
Triazavirin	IFX-1	Inhibitor of Bruton's tyrosine kinase (BTK)
Cap-dependent endonuclease activity inhibitor	Phosphoinositide 3-kinase inhibitor	Acalabrutinib
Baloxavir marboxil	Duvelisib	Agonist of peripheral chemoreceptors located on the carotid bodies
Inhibits viral RNA-dependent DNA polymerase	Immunomodulators	Almitrine
Emtricitabine/tenofovir	NK cell stimulant	Delta-opioid receptor antagonist
Azvudine	AVM0703	*Dalargin*
Clevudine	T cell stimulants	Human vasoactive intestinal polypeptide (VIP)
Inhibits viral RNA synthesis (NS5B protein)	Thymosin	Aviptadil
Sofosbuvir; ledipasvir	Anti-PD1 inhibitor	VEGF inhibitor
Inhibits viral transcription and translation (inhibits protein NS5A)	Nivolumab; camrelizumab	Bevacizumab
Daclatasvir	M1 suppression therapy	Androgen receptor blockade
Neuraminidase inhibitor	Progesterone	Bicalutamide
Oseltamivir	Myeloid-derived suppressor cells (MDSC) inhibition	Macrolide antibiotic

DAS181	Avdoralimab (C5a receptors (C5aR) inhibitor)	Carrimycin
Interferons; interferon-β; Interferon-α	Anti-GM-CSF monoclonal antibody	Unclear mechanism of action
Interferon-λ	TJ003234	Intravenous immunoglobulin therapy
Super-compound interferon (rSIFN-co)	GM-CSF	Suramin sodium
Enhance type 1 interferon production	Sargramostim	Etoposide (HLH treatment)
TAK-981	Gimsilumab	T89
Inhibit nuclear transport of virus	mTOR inhibitor	Oral LL-37 antiviral peptide (CAS001)
Ivermectin	Sirolimus	Thymus regeneration and immune restoration
Viral helicase inhibition	Ubiquitin ligase inhibition	Somatropin, metformin, and DHEA
Bismuth	Lenalidomide	
Calpain inhibitor	Thalidomide	
BLD-2660	Dihydroorotate dehydrogenase inhibitor	
Inhibit viral Claritin	Leflunomide	
Chlorpromazine	CCR5 receptor entry inhibitor	
Papain like protease (PLpro) inhibitors	Leronlimab	
Isotretinoin	TLR 2/6/9 agonist	
XPO1 inhibitor	PUL-042 inhalation	
Selinexor	Miscellaneous	
Other antiviral mechanisms	CD24Fc	
Nitazoxanide	Polyinosinic-polycytidylic acid	
	Recombinant cytokine gene-derived protein	
	Estrogen patch	
	Recombinant human plasma gelsolin (rhu-pGSN)	
	Mycobacterium w	

interferon-beta with control, with a primary endpoint of all-cause mortality.[11,12] NCT04292899 is a multicenter study with a sample size of 6000 that is assessing remdesivir with a primary endpoint of improvement on a seven-point Ordinal Scale on day 14.[13] NCT04322682 is a Canadian study that is assessing colchicine with a primary endpoint of all-cause mortality at day 30.[14] 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.

3.3 | 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 two studies; HCQ + azithromycin in one study; chloroquine+ azithromycin in one study; nitazoxanide in two studies; other antiviral 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 four each in France and China (Supporting Information Data). The largest of the prophylactic study is the Crown coronation study that 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.[15] The next largest study is the CRASH 19 study conducted in the UK with a sample size of 10 000 that is assessing aspirin, losartan, and simvastatin with the all-cause mortality as the primary endpoint.[16] WHIP COVID study is a multicenter study assessing the efficacy of weekly vs daily HCQ in preventing new cases of SARS-CoV-2 infection.[17]

3.4 | Vaccines

The most important option to prevent further waves of the COVID pandemic is vaccines. There are 19 vaccine-based studies of which are eight are BCG and one measles vaccine-based studies; 11 are newer vaccine candidates. The most commonly studied vaccine is the BCG vaccine in eight 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 the USA with three trials. Supporting Information Data provides a summary of the ongoing vaccine-based studies around the world.

TABLE 2 Summary of drug-based treatments in phase 3 clinical trials with sample size of more than thousand patients against severe acute respiratory syndrome coronavirus-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 seven-point Ordinal scale on day 14
NCT04292730	Multicenter study; sponsor-Gilead	1600	Remdesivir	The odds of ratio for improvement on a seven-point Ordinal Scale on Day 11
NCT04315948	Multicenter study; sponsor-National Institute of France	3000	Remdesivir; lopinavir/ritonavir; interferon β-1A; hydroxychloroquine	Percentage of subjects reporting each severity rating on a seven-point ordinal scale on day 15
NCT04324047	France Sponsor- Assistance Publique-Hôpitaux de Paris	1000	Immune modulator drugs	Overall survival at day 14 WHO progression scale COVID-19
NCT04322682	Canada Sponsor-Montreal heart institute	6000	Colchicine	Number of participants who die or require hospitalization due to COVID-19 infection upto day 30
ISRCTN83971151 Solidarity trial	Multicenter study Sponsor-WHO	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 Sponsor- Bassett Healthcare	4000	Lopinavir/ritonavir; hydroxychloroquine sulfate; losartan	National Institute of Allergy and Infectious Diseases COVID-19 Ordinal Severity Scale (NCOSS) at 60 d
NCT04345289	Denmark Sponsor-Thomas Benfield	1500	Convalescent anti-SARS-CoV-2 plasma; sarilumab; baricitinib; hydroxychloroquine	All-cause mortality or need of invasive mechanical ventilation at day 28
NCT04358068	USA Sponsor-NIH	2000	Hydroxychloroquine + azithromycin	Proportion of participants who died from any cause or were hospitalized at day 21
NCT04356495	France Sponsor- University Hospital, Bordeaux	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

TABLE 3 Summary of preventive phase 3 clinical trials with sample size of more than thousand patients against severe acute respiratory syndrome coronavirus-2 infection

Study identification number	Country	Sample size	Intervention assessed	Primary endpoint
NCT04333407 Phase 3 trial	United Kingdom Sponsor-Imperial College London	3170	Aspirin; clopidogrel; rivaroxaban; atorvastatin; omeprazole	All-cause mortality at 30 d after admission
NCT04333732 Phase 3 trial Crown coronation study	Multicenter study Sponsor-Bill and Melinda Gates Foundation	55 000	Different doses of chloroquine	Effectiveness in preventing laboratory-confirmed symptomatic COVID-19 in healthcare workers with repeated exposures to SARS-CoV-2
NCT04334967 Phase 3 trial	USA Sponsor- Providence Health & Services	1250	Hydroxychloroquine	Percentages of enrolled patients needing hospitalization and mechanical ventilation at day 14
NCT04328467 Phase 3 trial	USA Sponsor-University of Minnesota	3500	Hydroxychloroquine	Outcome reported as the percent of participants in each arm who are COVID-19-free at the end of study treatment upto 12 wk
NCT04341441 Phase 3 trial WHIP COVID study	USA Sponsor-Henry Ford Health System	3500	Hydroxychloroquine daily vs weekly dosing	Measure the difference in new cases of COVID-19 disease between randomized treatment arms at 8 wk
NCT04342156 Phase 3 trial	Singapore Sponsor-Tan Tock Seng Hospital	1200	Hydroxychloroquine	Positive serology or reverse transcriptase (RT-PCR) for COVID-19 up until day 28
NCT04343001 Phase 3 trial CRASH 19 study	United Kingdom Sponsor-London School of Hygiene and Tropical Medicine	10 000	Aspirin, losartan, and simvastatin	Death upto 28 d from day of randomization

3.5 | 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 the USA with eight trials and Spain with four trials. The rationale for the 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).

3.6 | Convalescent plasma therapy

CPT involves infusion of plasma obtained from people who have recovered from COVID-19 and who have circulating neutralizing antibodies that provide short-term immunity against SARS-CoV-2 coronavirus. There are currently 56 ongoing studies that are assessing CPT with 20 studies being done in the 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).

3.7 | 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 one study in Iran and one Ayurveda study in UK Table 5.

Supporting Information Data provides a summary of the various ongoing studies that are testing herbal medicines against COVID-19.

3.8 | 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 seven studies followed by Canada with five studies.

TABLE 4 Summary of interventions used in the clinical trials as prevention against severe acute respiratory syndrome coronavirus-2 infection

Prevention	Vaccines
Pre and postexposure 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 λ-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	Nonpharmacological interventions
Lactobacillus coryniformis 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	

3.9 | Machine-based interventions

There are currently 24 ongoing studies that are assessing machine-based interventions such as extracorporeal membrane oxygenation (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).

3.10 | 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 eight studies followed by the USA with four studies.

TABLE 5 Summary of nonpharmacological interventions used in the clinical trials as treatment against severe acute respiratory syndrome coronavirus-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
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
Extracorporeal membrane oxygenation
CytoSorb absorber
External diaphragmatic pacing
Hyperbaric oxygen therapy
Bidirectional oxygen valve
oXiris membrane
Plasmapheresis
V/Q vest
Dialysis
Anesthesia-based interventions
Nitric oxide
Prone positioning
Noninvasive oscillating device (NIOD)
Sedation with sevoflurane vs 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 autohemotherapy
Prayer
shadowboxing for pulmonary function
Sleep psychology and music therapy
Neck inspiratory muscle exercise
Radiation therapy
Zang-Fu Point-pressing' massage
Virtual monitoring

3.11 | Rehabilitation

There are currently 12 studies that are assessing various rehabilitation initiatives such as telerehabilitation-based exercises (6), general rehabilitation (2), pulmonary rehabilitation (2) anosmia

rehabilitation (1), and rehab-meals (1). China and Turkey are leading with three studies each.

3.12 | 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).

4 | DISCUSSION

In this systematic review, we critically appraise 829 ongoing clinical trials that are assessing various interventions such as 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 the majority of the ongoing studies with concern that patients in middle- and low-income countries may have minimal access for enrollment into clinical trials. Multicenter multicountry 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 pre-existing comorbidities such as hypertension, diabetes, cardiovascular diseases, chronic respiratory disease, and cancer. Despite this, only 5.5% of the ongoing clinical trials specifically seek 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 comorbidities.[18,19]

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 antiviral activity-based interventions with antimalarial accounting for 105 studies and other antiviral drugs accounting for 76 studies.[20] The main clinical rationale for use of antimalarial agent against SARS-CoV-2 was based on in vitro 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.[21,22] 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.[23] Biological agents with immunosuppressive and immunomodulatory properties that have the potential to curb the cytokine storm and withspread macrophage activation are being studied with close to 100 studies ongoing.[12]

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.[24] Among the drug-based preventive studies, 50% are using HCQ with various aspects being tested including daily vs weekly dosing, pre- vs postexposure prophylaxis. From our review, we feel there is a greater need for more preventive strategy-based studies since most of the countries are reopening and the proposed timeline for the pandemic to subside is 1 to 2 years.[25] CPT use in COVID-19 disease was promoted by the potential efficacy in SARS, MERS, and Ebola.[26] 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.

4.1 | 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 reassess the need for such studies and utilize resources for other interventions.

4.2 | 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 most of the clinical trial registries, despite our best attempt, it may not be exhaustive enough to account for retrospective registration of all studies.

4.3 | 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 comorbidities 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.

5 | 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 underrepresentation 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 the rationale design of future clinical studies.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

BPV conceived the study. VTC, JM, and BPV designed the study. BPV and VTC screened titles and abstracts for inclusion. BPV and VTC extracted and analyzed data. BPV, PG, VP, HKP, and VTC formulated the preliminary draft. BPV guarantees for the data. All authors revised for critical content and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA AVAILABILITY STATEMENT

Data used for this article will be provided upon due request to the corresponding author.

ORCID

Bhanu Prasad Venkatesulu http://orcid.org/0000-0003-2541-2055
Viveksandeep Thoguluva Chandrasekar http://orcid.org/0000-0001-5256-4113

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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