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REVIEW ARTICLE

Molecular mechanism, diagnosis, and potential treatment for novel coronavirus (COVID-19): a current literature review and perspective

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Abstract

Novel coronavirus disease 2019 (COVID-19) is a positive-sense single-stranded RNA virus which belongs to the Coronaviridae family. COVID-19 outbreak became evident after the severe acute respiratory syndrome coronavirus and the Middle East respiratory syndrome coronavirus in the twenty-first century as the start of the third deadly coronavirus. Currently, research is at an early stage, and the exact etiological dimensions of COVID-19 are unknown. Several candidate drugs and plasma therapy have been considered and evaluated for the treatment of severe COVID-19 patients. These include clinically available drugs such as chloroquine, hydroxychloroquine, and lopinavir/ritonavir. However, understanding the pathogenic mechanisms of this virus is critical for predicting interaction with humans. Based on recent evidence, we have summarized the current virus biology in terms of the possible understanding of the various pathophysiologies, molecular mechanisms, recent efficient diagnostics, and therapeutic approaches to control the disease. In addition, we briefly reviewed the biochemistry of leading candidates for novel therapies and their current status in clinical trials. As information from COVID-19 is evolving rapidly, this review will help the researcher to consider new insights and potential therapeutic approaches based on up-to-date knowledge. Finally, this review illustrates a list of alternative therapeutic solutions for a viral infection.

Keywords Coronavirus · COVID-19 · Diagnosis · Therapeutic · Molecular mechanism

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Abbreviations

CoVs	Coronaviruses
HCoVs	Human coronaviruses
SARS-CoV	Severe acute respiratory syndrome
MERS-CoV	Middle East Respiratory Syndrome
ORFs	Open reading frames
ACE2	Angiotensin-converting enzyme 2
APCs	Antigen-presenting cells
TH1	T-helper
ER	Endoplasmic reticulum
HLA	Human leukocyte antigen
MBL	Mannose-binding lectin
ARDS	Acute respiratory distress syndrome
PRRS	Porcine reproductive and respiratory syndrome
ESR	Erythrocyte sedimentation
CRP	C-reactive protein
PCR	Polymerase chain
RT-PCR	Real-time reverse transcription PCR
HRCT	High-resolution computed tomography scans
ELISA	Enzyme-linked immunosorbent assay
LAMP	Loop-mediated isothermal amplification

RdRp	RNA-dependent RNA polymerase
CCRAS	Central Council for Ayurvedic Sciences Research

Introduction

A pneumonia outbreak with uncertain etiology occurred in Wuhan, Province of Hubei, in the last week of December 2019 is severely impending for human health worldwide (Li et al. 2020b). Later on January 7, 2020, the Chinese administration announced the naming of a new form of coronavirus-2 (SARS-CoV-2) that belongs to the Coronaviridae family (Xiao et al. 2020). It is noteworthy that SARS-CoV-2 is 96% genetically similar to a bat coronavirus at the whole genome level (Zhou et al. 2020). Coronavirus disease (COVID-19) is an extreme acute respiratory syndrome with the most common symptoms of moderate infection include fever, dry cough, tiredness, sore throat or dyspnea. Patients infected with this virus suffer from other potential damage to vital organs, such as gastrointestinal, cardiac, renal, and nervous systems (Gavriatopoulou et al. 2020; Merad and Martin 2020; Rohollah et al. 2020; Bhaskar et al. 2020). Recent knowledge indicated that the SARS-CoV-2 transmission rate is higher than SRAS-CoV due to the protein structure's genetic makeup. Before COVID-19, many infectious diseases affected global populations, including plague, Spanish flu, cholera, Swine flu (H1N1), severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (Bramanti et al. 2019; Taubenberger and Morens 2006; Chowdhury et al. 2017; Ratre et al. 2020; Luk et al. 2019).

Till now, there are no effective vaccines available to prevent the spread of COVID-19 although many clinical trials of vaccines are underway (Verma et al. 2020b). SARS-CoV-2 has now spread to more than 205 other nations, including the United States, India, Russia, Brazil, Italy, Spain, Japan, Korea, Iran and Germany. In March, the WHO announced that COVID-19 was a pandemic and a significant health issue, causing severe infections in the respiratory tract (Cucinotta and Vanelli 2020; Mahase 2020). According to the latest statistics, more than 50 million people have been infected worldwide up to 10 December 2020, and more than 10, 35, 000 were died because of this disease. Every day, the number of infected people are growing worldwide. India has 95,53,100 cases registered to date. Fortunately, the death rate is very low in youngsters. As COVID-19 is a novel infectious disease, scientists and doctors are not much aware of it. In this critical circumstance, in-depth knowledge is highly essential for the future treatment and management of the disease. In this review, we summarized the pathophysiology, molecular mechanism, diagnosis, and possible therapeutic options for this disease. Because knowledge of COVID-19 is evolving rapidly, this review may help researchers accurately understand disease.

Pathophysiology of COVID-19

Coronaviruses (CoVs) are non-segmented nucleocapsid-protein enveloped + SS-RNA viruses that are known to cause infection in mammals, including humans and other host species (Pal et al. 2020). Genomic studies have revealed that the CoVs has the most abundant RNA genome of around 30–30 kb in length with a 5′-capping site and 3′poly-A tail region that promotes host genome transcription and translation. Based on the genomic structure and target host, this virus is generally categorized into four groups, including alpha, beta, gamma, and delta. Among these forms, only alpha and beta forms of viruses known to infect mammals and typically cause upper respiratory infections (Rabi et al. 2020). Seven human coronaviruses (HCoVs) have been identified to date, such as 229E, OC43, HKU1, NL63, SARS-CoV, MERS-CoV, and SARS-CoV-2 was identified as belonging to the beta coronavirus family.

In the host genome, the pathogenic in vivo appearance of SARS-CoVs falls in different stages. The binding of the virus to the host receptors, entry of the virus into the host cells by membrane fusion or endocytosis, the release of virus particles within the host cell followed by replication and biosynthesis of viral proteins, and budding/release of viral particles are sequential steps. According to the virologists, the pathophysiology and virulence mechanism of human SARS-CoV and SARS-CoV-2 are possibly similar (82% identical) to the work of non-structural proteins (nsps) and structural proteins (sps) (Chan et al. 2020a). To date, the coronavirus genome has recorded six open reading frames (ORFs), these ORFs can serve as a template for the biosynthesis of subgenomic mRNAs. Among these, ORF1a and ORF1b encode 16 nsps that are typically crucial for virus transcription and replication. Other ORFs encode four major sps: spike (S), membrane (M), envelope (E) and nucleocapsid (N), and other vital proteins (Snijder et al. 2003; Luk et al. 2019). Spike a glycoprotein surface consists of two structural components S1 and S2. Among them, S1 binds to the angiotensin-converting enzyme 2 (ACE2) receptor that highly expressed in the host genome's lung epithelial cells. S2 also contains a transmembrane domain, cytoplasmic domain, and fusion protein that facilitates virus fusion in the envelope and host cell membranes to enable viral fusion. Scientists are, therefore looking S2 as a promising target for antiviral drug therapy (Kirchdoerfer et al. 2016; Xu et al. 2020a). Zhou et al. (2020) recently reported that the novel SARS-CoV-2 could also identify ACE-2 receptors in human cells.

Unlike other coronaviruses, the SARS-CoV-2 has a unique furin cleavage site at the S1/S2 boundary ("RPPA" sequence) that makes this virus pathogenic. Other cell surface proteases such as transmembrane protease serine 2 (TMPRSS2) and cathepsin L also facilitate the cleavage of the complex S1/S2-ACE2 and help to activate viral spike proteins for entry into the host genome (Ou et al. 2020; Hoffmann et al. 2020). In pathogenesis, the envelope proteins play an essential role by facilitating the assembly and release of coronavirus. The N-terminal N-protein binds to the single positive RNA genome and plays a crucial role in the replication and transcription cycle. Currently, two groups of antiviral drugs, such as theophylline and pyrimidone, may inhibit the binding of viral RNA to N-terminal protein (Sarma et al. 2020).

When the virus reaches the body, the host's immune system it activates a sequence of inflammatory events triggered by antigen-presenting cells (APCs). APCs add foreign antigen to cells containing CD4+-T-helper (TH1) and release interleukin-12 to activate TH1. Besides, the activated TH1 cells trigger CD8+-T-killer cells which recognise and eliminate infected host cells. TH1 cells also activate B-cells to synthesize viral-specific antibody that is unique to viruses. The infection spreads in the mucosa of the nasal and larynx, then targets lung epithelial cells, which express ACE2 receptors in abundance (Chen et al. 2020a; Bennardo et al. 2020). Activated WBCs activate positive cytokines, including IL-6. However, the IL-6 level elevates in the extreme state of the disease, which raises the aggressiveness of coronavirus.

Molecular mechanism of COVID-19

Coronaviruses are ubiquitous pathogens that cause respiratory or gastrointestinal infections. A recent phylogenetic analysis found that 2015-SARS coronavirus sequence and human 2019-SARS-CoV-2 emerged in the congregation of a bat. In addition, the Bayesian Quick Unconstrained AppRoximation (FUBAR) analysis revealed genomic mutations in the viral S glycoprotein and nucleocapsid protein (Benvenuto et al. 2020). Compared to the ability of infection with coronaviruses, SARS-CoV-2 has a higher binding affinity to human ACE2 than SARS-CoV, which may explain the frequency of SARS-CoV-2 than SARS-CoV (He et al. 2020). Diverse work has shown that this link between SARS-coronavirus and ACE2 enables a smooth entry into human cells (Struck et al. 2012). Unlike non-ACE2 expressing cells in the ACE2-expressing cells, the novel SARS-CoV-2 uses ACE2 after binding to infected host cells as an entry receptor. Chemokine ligand 2 (CCL2) is the small chemical molecules that attract immune cells including lymphocytes, basophils, and monocytes. This also penetrated the various inflammatory reactions and in the S-ACE2 signaling (Hoffmann et al. 2020), and serves as a critical cytokine. Cheung et al. confirmed the increased expression of chemotactic protein CCL2/monocyte 1 in patients with SARS-CoV and hence CCL2 can be a promising therapeutic marker (Cheung et al. 2005).

Heurich et al. found that infected lung epithelial cells facilitate casein kinase II (CK II) which induces phosphorylation of the ACE2 receptor at the Ser-787 site, whereby SARS-CoV recognises and binds to the ACE2 receptor leading to a structural change of the ACE2 receptor. It also involved the establishment of ACE2 induced downstream signal transduction pathways, including ERK1/2 and AP-1(Heurich et al. 2014). Simmons and colleagues reported that the SARS-CoV accomplishes its entry into host cells via membrane fusion between the virus and lipid bilayer (Simmons et al. 2004). Another finding from Belouzard et al. revealed that the occurrence of a crucial proteolytic cleavage on the S protein of SARS-CoV at S2 position mediates the membrane fusion involving host and CoV pathogen (Belouzard et al. 2009). Besides CoV, the MERS-CoV required furin activation for membrane fusion (Millet and Whittaker 2014). In addition to membrane fusion, clathrin-dependent and independent endocytosis has been reported to be mediated by the SARS-CoV entry (Kuba et al. 2010). Once the virus enters the host, eventually, the viral RNA releases into the cytoplasm.

Further, it translates itself into two polyproteins and structural proteins followed by replication of the viral genome (Perlman and Netland 2009). Later, the newly formed envelope glycoproteins enter the cell organelles naming the endoplasmic reticulum (ER) or Golgi complex. The nucleocapsid contains the mixing of genomic RNA and capsid protein. Then the virus buds are sprout into the ER-Golgi intermediate compartment. Lastly, the vesicles containing the virus particles blend with the plasma membrane to discharge the virus (de Wit et al. 2016). Details related to this is graphically presented in Figs. 1 and 2.

Additionally, it has been reported that the SARS-CoV is involved in the antigen-dependent presentation of MHC I molecules, but MHC II also contributes to its presentation (Liu et al. 2010). Want et al., conducted a polymorphism-based study and found that the human leukocyte antigen (HLA) polymorphisms such as HLA-B*4601, HLA-B*0703, HLA-DR B1 * 1202, and HLA Cw*0801 are associated with the susceptibility of SARS-CoV (Keicho et al. 2009). In comparison, they found that the HLA-DR0301, HLA-Cw1502, and HLA-A*0201 play a vital role in SARS infection and functioning as protective alleles (Wang et al. 2011). It has also been observed that mannose-binding lectin (MBL) gene polymorphisms are associated with antigen presentation and thus linked to the risk of infection with SARS-CoV (Tu et al. 2015).

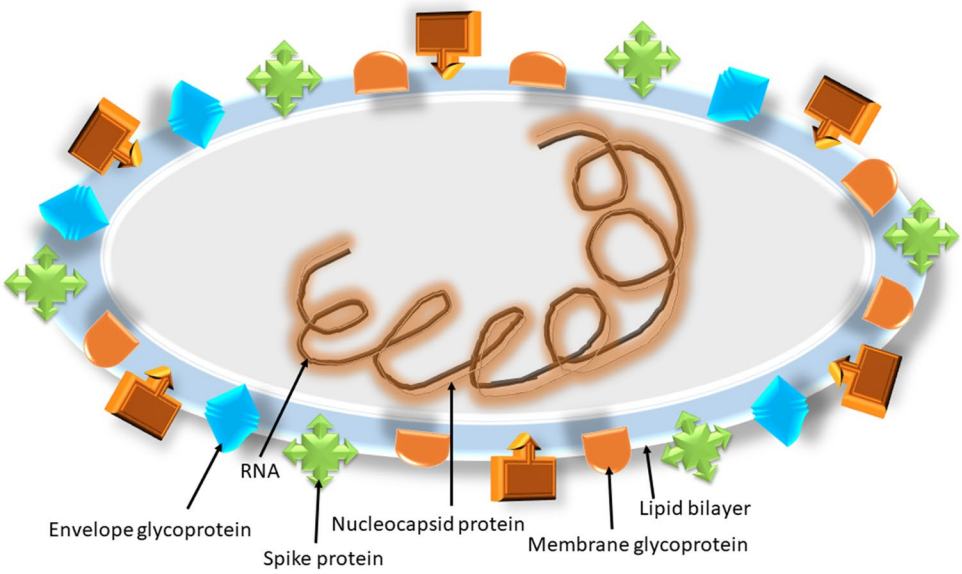

Fig. 1 Structure of SARS-CoV 2 (Modified from Shereen et al. 2020)

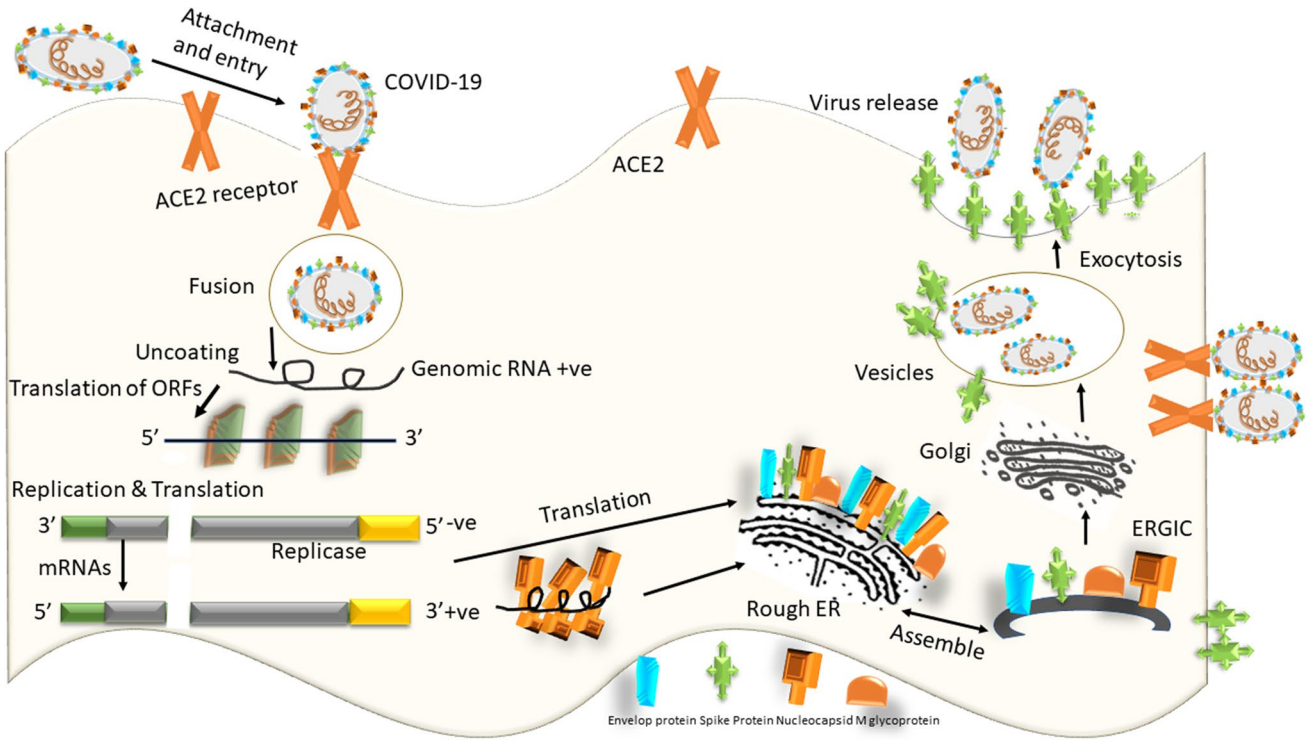

Fig. 2 Life cycle and mechanism of infection of SARS-CoV 2 in host cells. SARS-CoV 2 begins its life cycle when spike protein (S) binds to the cellular receptor ACE2. After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. Then SARS-CoV 2 releases RNA. Genome RNA gets translated into viral replicase polyproteins (pp1a and 1ab) and further cleaved into small products by viral proteinases. The polymerase generates a series of subgenomic mRNAs by discontinuous transcription and finally translated into appropriate viral proteins. Viral proteins and genome RNA are subsequently assembled into virions in the ER and Golgi body and then transported via vesicles and released out of the cell. *ACE2* Angiotensin-converting enzyme 2, *ER* Endoplasmic reticulum, *ERGIC* ER–Golgi intermediate compartment

Research has indicated that acute respiratory distress syndrome (ARDS) is the leading cause of death in COVID-19 and one of the main routes for the cytokine storm associated with ARDS. Nevertheless, lethal systemic inflammatory response leading to elevated levels of pro-inflammatory cytokines such as IFN-α, IFN-α, TNF-α, TGFβ, IL-1β, IL-6, IL-12, IL-18, IL-33 and chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 (Williams and Chambers 2014; Channappanavar and Perlman 2017). Xu et al. recently reported that the peripheral blood of SARS-CoV-2 patients displayed a substantial reduction in immune defence cells such as CD4+ and CD8+ T cells. In contrast, high concentrations of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) were also found in double-positive fractions within the same patients (Xu et al. 2020b). SARS-CoV viruses are adequate to employ many methods to prevent the survival of the immune system in host cells. Snijder et al. reported that SARS-CoV and MERS-CoV could provoke the assemblage of membrane vesicles that require for Porcine reproductive and respiratory syndrome (PRRS) and avoiding the host detection of their dsRNA (Snijder et al. 2006). These findings are valuable for the effective treatment of COVID-19.

Diagnostic approach

Many COVID-19 cases have moderate or non-specific symptoms for a correct diagnosis, while severe patients have respiratory problems, including fever, cough, tiredness, and shortness of breath, and decreased or diminished vocal fremitus on palpation (Xie et al. 2020a). Patient screening for precise diagnosis must be comfortable, low cost, quick, and the most reliable result. Studies into epidemiological history, clinical findings, and tests are essential for the clinical diagnosis of COVID-19. Imaging will be the first diagnosis. Suspected patients will undergo chest x-ray as soon as possible and an urgent CT scan based on severity (Shen et al. 2020a). The image can provide a better understanding of how the disease is progressing. Chest images may show interstitial changes in the preliminary process, and the presence of small plaques, especially in the lung periphery. This disease further deteriorates bilaterally and is primarily distributed with several infiltrative shadows in the middle and outer zones of the lung. In extreme cases, consolidation of the lung may occur (Pan et al. 2020b).

Laboratory assessment

In the early stage, the count of white blood cells generally appears normal or slightly low, with a smaller count of lymphocytes. But if the absolute count of lymphocytes is < 0.8/L or the counts of CD4+ and CD8+ T-cells are significantly decreased, this is a warning. But if the absolute lymphocyte count is $< 0.8 \times 10^9$/L or the CD4+ and CD8+ T-cell counts are decreases substantially, that's an alarm. In some patients, muscle enzymes, liver enzymes, and levels of myohemoglobin are elevated; in some critical cases, even an increased amount of troponin is observed. Infected patients mostly show high erythrocyte sedimentation (ESR) and C-reactive protein (CRP) levels, with normal procalcitonin levels and progressively decreased blood lymphocyte counts with elevated D-dimer concentrations. In severe patients, inflammatory factors are also increased. It is recommended that blood changes be rechecked every 3 days (Jin et al. 2020).

Detection methods based on nucleic acid are an essential tool for the diagnosis of viral agents. In particular, the polymerase chain reaction (PCR) is a "gold standard method" for virus detection due to rapid identification, high sensitivity and specificity. Molecular diagnosis methods like real-time PCR (RT-PCR) can be executed using blood, feces, and tissue samples of the upper part of the respiratory tract (nasopharyngeal and oropharyngeal), lower respiratory tract (expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage) from suspected patients with SARS-CoV-2 (Yu et al. 2020a). However, Nucleic acid detection has some drawbacks in its operation, such as the time-consuming and high risk of contamination. Nonetheless, current PCR methods appear to have functional specificity except for sensitivity, which means that negative test results did not guarantee that SARS-CoV-2 was absent. In addition, false-positive results may occur due to sample contamination, or false negative results may appear due to inadequate viral load. For people with high clinical suspicion but negative RT-PCR screening, chest CT can assist with clinical diagnosis.

A combination of CT scanning and swab examination appears to be more helpful (Xie et al. 2020b). Early detection and development of disease in patients with SARS-CoV-2 can be done with high-resolution computed tomography scans (HRCT) (Pan et al. 2020a). The CT images of patients with SARS-CoV and MERS-CoV indicate lung involvement close to SARS-CoV-2 infection; besides, HRCT scans have certain drawbacks, including other virus infections and irregular CT imaging. RT-PCR experiments can be used with the chest CT scan in combinations to boost false-positive outcomes (Chen et al. 2020b; Jiang et al. 2020). Although the detection of IgM and IgG antibody detection is highly responsive to enzyme-linked immunosorbent assay (ELISA) (Jia et al. 2020). A study found that 94.7% of SARS-CoV N-based IgG ELISA and 58.9% of S-based IgG ELISA and SARS-CoV-2 IgG/IgM are still being studied (Li et al. 2020a).

The Loop-mediated isothermal amplification (LAMP) is a novel method of amplification of DNAs and RNAs that enhances product with high sensitivity and specificity. The key benefits of this approach are low cost and less costly reagents and involving simple instruments (Shen et al. 2020b).

Recently Mohamed et al. demonstrated that the LAMP methods have 10 times more sensitivity than traditional RT-PCR in COVID-19 detection without false-negative events (Mohamed et al. 2020). The iLACO (isothermal LAMP based method for COVID-19)uses 6 primers for amplifying the ORF1ab gene sequences of 11 associated viruses. Yu et al. compared both methods and found that the iLACO sensitivity and accuracy are higher than the Taqman-based qPCR detection method (Yu et al. 2020b). Zhang et al. also stated that LAMP with a colorimetric detection method has a high sensitivity to COVID-19 and that these methods can be used in the diagnosis for the bulk (Zhang et al. 2020b). Comparison of three novel RT-PCR assays targeting RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and COVID-19 nucleocapside (N) genes showed that the RdRp/Hel assay did not cross-react with SARS-CoV and MERS coronaviruses and revealed high sensitivity and specificity for COVID-19 (Chan et al. 2020b).

In-silico approach

Kellner et al. demonstrated that the CRISPR-based SHERLOCK (Specific High-Sensitivity Enzymatic Reporter UnLOCKing) technique could be a diagnostic tool for COVID-19 to enable compact, multiplexed and ultrasensitive detection of RNA or DNA from clinically relevant samples (Kellner et al. 2019). SHERLOCK assays are set up with recombinase-mediated polymerase pre-amplification of DNA or RNA and subsequent Cas13-or Cas12-mediated detection via colorimetric read-outs and fluorescence. Cas13a can detect new coronavirus in the given sample. By using synthetic RNA fragments of the SARS-CoV-2 virus, target sequences of SARS-CoV-2 can be detected between 20 and 200 aM (10–100 copies per microliter of input). To improve the precision of the detection, scientists have implemented sequences unique to the current coronavirus to avoid interaction with the genomes of respiratory viruses. While the test has better readability without any difficulty, the testing of multiple patient samples also needs confirmation.

Till date, therapeutic approaches are still under trial. Cava et al. defined new functions and pathways of ACE2-correlated genes using gene expression profiles from the public datasets. Researchers found a network of 193 genes, 22 interactions and 36 possible drugs, including nimesulide, fluticasone propionate, thiabendazole and photofrin. Among all the potentially active drugs, didanosine is a real antiviral drug, while the others are mostly anti-inflammatory (Cava et al. 2020). Since sialic acids linked to glycoproteins and gangliosides and are used as invasive receptors by a wide range of viruses (Matrosovich et al. 2015). Several modeling approaches have been used to decipher protein molecular mechanisms sugar interactions that account for the interaction of viruses, membranes and amyloid proteins with cell surface glycolipids (Yahi and Fantini 2014; Flores et al. 2019).

The molecular mechanisms underlying the antiviral mechanisms of chloroquine against SARS-CoV-2 infection was unraveled using novel in-silico strategy (Fantini et al. 2020). EK1C4 is an inhalation formulation for SARS-CoV-2 patients to reduce viral loads in the lungs. Recently, Xia et al. stated that EK1C4 might help to prevent SARS-CoV-2 infection due to the high retention of its target. Peptide drugs are usually safer than chemical drugs, and EK1C4 is considered to be harmless for humans (Xia et al. 2020). While no successful drugs available against COVID-19, Joshi et al. conducted a nucleocapsid virtual screening of 318 phytochemicals against molecular targets such as main protease (Mpro) and ACE2. This study identified 11 plants for their antiviral, antibacterial and antifungal activity based on low binding energy compared to the reference molecule (Joshi et al. 2020). Sekiou et al. compared the efficacy of hydroxychloroquine, Quercetin, Hispidulin, Cirsimaritin, Sulfasalazine, Artemisin and Curcumin natural compounds against COVID-19 using AutoDock indicated that these compounds have better potential inhibition than hydroxychloroquine (Omar et al. 2020).

Current therapeutic option

Coronavirus belongs to a large family of viruses found in various types of animals, including caterpillars, bats, and camels. The newly discovered strain of this virus has been established as the cause of respiratory disease in humans. Occasionally, animal coronavirus has jumped to species and eventually infected humans so that it can appear more between humans, such as MARS-CoV, SARS-CoV, and now SARS-CoV2. Some countries are likely to have distributed COVID-19 in the early stages, before any inaccurate measurements. Nevertheless, Anderson and his colleagues suggest that while governments would not be able to reduce the death rate of COVID-19 infections, the remission of this pandemic may have an immense economic effect on a viral spread (Anderson et al. 2020)**.** To date, there are no definite treatments available to cure it. However, medical professionals are still looking for the best way to prevent these infections. People are now seeking alternative remedies to prevent their infections as a pandemic, which means that they could be globally prevalent.

Antivirus therapy

Drug therapy that is already approved for the treatment of other infectious diseases, including Ebola, Aids, HIV, malaria, is beneficial for the treatment of COVID-19. Apart from this antibodies-based protein processed using

recombinant technology and injected into the patient body can binds to SARS-CoV-2. This method can be a promising alternative that minimize the inflammation caused due the virus. Other therapeutic strategies, such as corticosteroids for viral therapy, are not recommended. Several drug therapies have been suggested based on current published evidence, such as lopinavir with a combination of ritonavir (400 + 100 mg), chloroquine (500 mg), and hydroxychloroquine (200 mg) per 12 h (Cascella et al. 2020). Recently, several preclinical studies have indicated that remdesivir has an inhibitory activity of RNA polymerase in vitro against RNA viruses, including Ebola, MERS-CoV and HCoV infections (Gordon et al. 2020; de Wit et al. 2020). Nowadays, in the USA, this drug has been re-used for the treatment of COVID-19. Recently, the new antiviral medication favipiravir (FabiFlu) has been approved in India to combat mild to moderate cases of COVID-19 (https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/coronavirus-vaccine-roundup-from-imperial-college-human-trials-to-treatment-here-are-all-the-fresh-updates-around-covid-19/photostory/76644042.cms). Traditional antiviral medications with a different formulations used in covid-19 therapy have been shown in Table 1.

Plasma therapy

Among the various treatment strategies, convalescent plasma therapy (CPT) is commonly prescribed for the treatment of COVID-19. Plasma, which is only a short-term solution for susceptible people after two weeks of healing, should be used to ensure high neutralisation of antibodies. Now, we need a good design of clinical trials and a well-managed plasma therapy program to prevent COVID-19 infection (Verma et al. 2020a)**.** Convalescent plasma transfusion from the recovered infected patient to newly infected patients can kick-start their immune system. Rajendran et al. found that, firstly, these treatments could reduce the mortality rate in critically ill patients. Second, it improved the neutralization of antibodies in newly infected patients. Thirdly, decreased flu-like symptoms, and other beneficial effects have been shown following administration of plasma therapy (Rajendran et al. 2020). Since this is just part of the treatment, there is no full solution for patients and their reaction can vary from individual to individual receiving plasma transfusion therapy (Table 2).

Antibodies

Based on the recently available study, the case fatality rate (CFR) of COVID-19 is unknown; more detailed studies are needed for identifying the actual number of infected individuals in any population. Nonetheless, we are oblivious to any completed large-scale serological survey of COVID-19 antibody detection. However, Immunotherapy may be a safer choice before the development of the vaccine that helps in developing and innate immunity to the virus. In addition, herd immunity is an alternative idea for combating COVID-19 by improving natural immunity in underdeveloped countries. In Sweden, the approach to herd immunity has been updated with significant criticism (Kwok et al. 2020). Furthermore, the monoclonal antibody will be a potential therapeutic intervention for treatment against COVID 19. The monoclonal antibodies developed against the virus are listed in Table 3.

Vitamin

Recently researchers have been found that vitamin plays a vital role in clinical therapies. For instance, vitamin D boosts cellular immunity by reducing the cytokine storm in COVID-19 by inducing pro and anti-inflammatory factors, and it also acts as a modulator of adaptive immunity (Cantorna 2010; Rondanelli et al. 2018; Grant et al. 2020). For infected patient's vitamin D might be a useful medication

Table 1 List of potential alternative drugs for treatment of COVID-19

S.N.	Therapeutic drug	Common name	Target	Effective concentration EC 50	References
1	Favipiravir (T-705)	Avigan	Influenza	61.88 µM	Sui et al. (2004)
2	Remdesivir (GS5734)		Ebola	0.77 µM	Sui et al. (2004)
3	Chloroquine /hydroxychloroquine	Aralen/plaquenil	Malaria	1.13 µM	Sui et al. (2004)
4	Lopinavir/ritonavir	Kaletra	HIV		
5	Pegylated interferon with ribavirin	Virazole	HBV,HCV	109 µM	Sui et al. (2004)
6	Teicoplanin	–	MERS-CoV and SARS-CoV	1.66 µM	Zhai et al. (2020)
7	Arbidol tablets	–	SARS-CoV 2	Under clinical trial	
8	Methylprednisolone	–	Severe novel coronavirus pneumonia:	Under clinical trial	
9	Nelfinavir (HIV-protease)	–	SARS-CoV		Yamamoto et al. (2004)

Table 2 Ongoing clinical trials of COVID-19 patients treated with convalescent plasma patients listed in World Health Organization International Clinical Trial Registry Platform (ICTRP) database 76

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR 2000029850	Efficacy and safety of convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19): a prospective cohort study	Zhejiang University School of Medicine	Recruiting	Convalescent plasma	18 years and older	N/A	15-02-2020	Interventional	20	China
ChiCTR 2000030179	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)	Hospital of Nanchang University	Recruiting	Convalescent plasma	18 years and older	N/A	24-02-2020	Interventional	100	China
ChiCTR 2000030046	A single-arm trial to evaluate the efficacy and safety of anti-2019-nCoV inactivated convalescent plasma in the treatment of novel coronavirus pneumonia patient (COVID-19)	Hospital of Jiangxia District, Wuhan (Union JiangnanHospital)	Recruiting	Convalescent plasma	18 years and older	N/A	07-02-2020	Interventional	10	China

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR 2000030010	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	Not recruiting	Convalescent plasma	18 years and older	N/A	19-02-2020	Interventional	100	China
ChiCTR 2000030039	Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19)	Affiliated Hospital of Xuzhou Medical University	Recruiting	Convalescent plasma	18 years and older	N/A	31-05-2020	Interventional	90	China
ChiCTR 2000030627	Study on the application of convalescent plasma therapy in severe COVID-19	The First Affiliated Hospital of Zhengzhou University	Recruiting	Convalescent plasma	18 years and older	N/A	01-02-2020	Interventional	30	China

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR 2000029757	Convalescent plasma for the treatment of severe and critical novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial	China–Japan friendship hospital	Recruiting	Convalescent plasma	18 years and older	N/A	14-02-2020	Interventional	200	China
NCT 04292340	The Efficacy and Safety of Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of Novel Coronavirus Pneumonia Patient (COVID-19): An Observational Study	Shanghai Public Health Clinical Center	Recruiting	Convalescent plasma	18 years and older	Phase 2 Phase 3	01-02-2020	Observational	15	China

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR 2000030312	A single-center, open-label and single-arm trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient	First people's hospital of Jiangxi district, Wuhan	Not recruiting	Convalescent plasma	18 years and older	N/A	29-02-2020	Interventional	24	China
ChiCTR 2000030702	Convalescent plasma for the treatment of common COVID-19: a prospective randomized controlled trial	China-Japan friendship hospital	Recruiting	Convalescent plasma	18 years and older	N/A	15-02-2020	Interventional	50	China

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR 2000030381	A randomized, open-label, controlled and single-center trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient	First people's hospital of Jiangxi district, Wuhan	Not recruiting	Convalescent plasma	18 years and older	N/A	29-02-2020	Interventional	40	China
ChiCTR 2000029818	Clinical Study for Umbilical Cord Blood Plasma in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19)	Guangzhou reborn health management consultation co., LTD	Not recruiting	Umbilical cord blood plasma	18 years and older	N/A	20-02-2020	Interventional	60	China
ChiCTR 2000030929	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia (COVID-19)	Renmin Hospital of Wuhan University	Not recruiting	Convalescent plasma	18 years and older	N/A	17-03-2020	Interventional	60	China

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
NCT 04323800	Convalescent Plasma to Stem Coronavirus: A Randomized, Blinded Phase 2 Study Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19	Johns Hopkins University	Not recruiting	Convalescent plasma	18 years and older	Phase 2	01-04-2020	Interventional	N/A	United States
NCT 04321421	Plasma From Donors Recovered From New Coronavirus 2019 As Therapy For Critical Patients With Covid-19	Foundation IRCCS San Matteo Hospital	Not recruiting	Convalescent plasma	18 years and older	N/A	17-03-2020	Interventional	N/A	Italy

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
NCT 04325672	Convalescent Plasma to Limit Coronavirus Associated Complications: An Open-Label, Phase 2A Study of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19	Mayo Clinic	Not recruiting	Convalescent plasma	18 years and older	Phase 2	01-04-2020	Interventional	NA	United States
NCT 04342182	Convalescent Plasma Therapy From Recovered Patients to Treat Severe SARS-CoV-2 Disease (CONCOVID Study)	Erasmus Medical Center|Maasstad Hospital	Recruiting	Convalescent plasma	18 years and older	Phase 2 Phase 3	01-04-2020	Randomized	426	Netherlands
NCT 04334876	Rapid SARS-CoV-2 IgG Antibody Testing in High Risk Healthcare Workers	Indiana University	Not yet recruiting	Diagnostic test: SARS-CoV-2 IgG Antibody Testing Kit	18 years and older	N/A	01-04-2020	Observational	340	United States
NCT 04338360	Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19	Mayo Clinic	Available	Convalescent plasma	18 years and older	N/A	N/A	N/A	N/A	United States

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
NCT 04333355	Safety in Convalescent Plasma Transfusion to COVID-19	Hospital San Jose Tec de Monterrey|Tecnologico de Monterrey	Not yet recruiting	Convalescent plasma	18 years and older	Phase 1	15-04-2020	Interventional	20	Mexico
NCT 04332835	Convalescent Plasma for Patients With COVID-19: A Randomized, Open Label, Parallel, Controlled Clinical Study (CP-COVID-19)	Universidad del Rosario	Not yet recruiting	Plasma, hydroxychloroquine, azithromycin	18 years and older	Phase 2 Phase 3	01-04-2020	Interventional	80	Universidad del Rosario
NCT 04325672	Convalescent Plasma to Limit Coronavirus Associated Complications: An Open label, Phase 2A Study of High-Titer Anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19	Johns Hopkins via a national IND	Not yet recruiting (stop)	Convalescent plasma	18 years and older	2A open label	27-03-2020	Interventional	5	United States

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
NCT 04323800	Convalescent Plasma to Stem Coronavirus: A Randomized Controlled Double Blinded Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. control (SARS-CoV-2 non-immune plasma) among Adults Exposed to COVID-19	Johns Hopkins University	NA	Convalescent plasma	18 years and older	Phase 2	01-04-2020	Interventional	150	United States
NCT 04332380	Convalescent Plasma for Patients With COVID-19: A Pilot Study (CP-COVID-19)	Universidad del Rosario	Not yet recruiting	Convalescent plasma	18 years and older	Phase 2	01-04-2020	Interventional	10	Spain
NCT 04327349	Investigating Effect of Convalescent Plasma on COVID-19 Patients Outcome: A Clinical Trial	Mazandaran University of Medical Sciences	Enrolling by invitation	Convalescent PLASMA	Age 30–70 years	N/A	28-03-2020	Interventional	30	Iran

Table 2 (continued)

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
NCT 04353206	Convalescent Plasma in ICU Patients With COVID-19-induced Respiratory Failure	Noah Merin	Recruiting	Convalescent plasma	18 years and older	Early phase 1	14-05-2020	Interventional	60	United States
NCT 04373460	Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004)	Johns Hopkins University	Not yet recruiting	Convalescent plasma	18 years and older	Phase 2	19-05-2020	Interventional	1344	United States

NA: not available

to prevent infections**.** Many reviews are suggesting that vitamin D loading doses of 200,000–300,000 IU capsules reduces the risk and severity of COVID-19 (Gasmi et al. 2020). Some recommended vitamin with their doses listed in Table 4.

Summary of meta-analysis

To date, several research groups are trying to resolve the present pandemic problem. In this perspective, many reaserchers have summarised reliable medical evidence by the meta-analysis of all published clinical trials against COVID-19, among them ten meta-analyses we have included with either therapeutic target as vaccines or placebo infections, chloroquine derives hydroxy-chloroquine, dexamethasone, lopinavir-ritonavir, remdesivir with placebo, hydroxy-chloroquine with azithromycin, tocilizumab, convalescent plasma. The results of all meta-analysis were inconsistent (Table 5).

Other treatments

In the current scenario, most of the studies using western medicine for the treatment of COVID-19 but Chinese traditional medicine also has a potential activity for COVID-19 (Zhang et al. 2020a). According to the latest clinical guidelines for the treatment of SARS or MERS patients are same, and both western medicine and traditional Chinese medicine are used for the treatment of COVID-19 in China (Li and De Clercq 2020; Li and Peng 2013). Due to the genomic homology, clinical evidence shows the safety and efficacy of traditional Chinese medicine in the treatment of COVID-19. Some of them include herbal folk therapies and herbal teas. It also suggested that some of them might not be safe to consume (Coghlan et al. 2015). According to the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy), Government of India, herbal medicines may helpful to combat the corona outbreak and at least reduce the infection. An autonomous body of AYUSH, CCRAS (Central Council for Ayurvedic Sciences Research), had developed AYUSH-64 for effective treatment without malaria. Scientific experts recommending that there is no adequate evidence for the use of Arsenicum Album in the fight against the symptoms of COVID-19. Besides, homoeopathy derived arsenic was recommended to take on an empty stomach. Due to the immunity boosting properties, anti-inflammatory ayurvedic drugs were also used against coronavirus. An evidence-based study shows that the intake of the antimalarial ayurvedic drugs (Ayush 64) developed by the Indian Ministry has a beneficial effect on COVID-19 (CCMI 2020).

Table 3 List of neutralizing monoclonal antibody and protease inhibitors

S.N.	Name	Experimental model	Mechanism	References
1	Anti-ACE2	Mouse	Target the spike protein of SARS-CoV-2 that inhibits virus binding cell receptors	Shanmugaraj et al. (2020)
2	CR3014	Ferret and in vitro	Binding to the 318–510 amino acid residues with high affinity on S1 fragment of SARS-CoV and-block the interaction of S1 subunit protein with cellular receptor ACE2 in vitro and in vivo	van den Brink et al. (2005), ter Meulen et al. (2006), Jan ter Meulen et al. (2004)
3	CR3022	In vitro	Binding to the 318–510 amino acid residues on S1 fragment of SARS-CoVand block the interaction of S1 subunit protein with cellular receptor ACE2	ter Meulen et al. (2006)
4	F26G18	In vitro	Binding to the linear epitope460-476amino acid residues on S1 fragment of SARS-CoVand block the interaction of S1 subunit protein with cellular receptor ACE2	Berry et al. (2010)
5	F26G19	In vitro	Binding to the conformational epitope (amino acid residues 359–362, 391–392, 424–427, and 486–492) on S1 fragment of SARS-CoVand block the interaction of S1 subunit protein with cellular receptor ACE2	Berry et al. (2010)
6	m396	In vitro	Binding to the conformational epitope amino acid residues 482–491 on S1 fragment of SARS-CoV and block the interaction of S subunit protein using CDR loops H1, H2, H3, and L3 with cellular receptor ACE2	Berry et al. (2010), Zhu et al. (2007)
7	1A9	In vitro	Binding to the Heptad repeat loops, including heptad repeat one and heptad repeat one domain on S2 fragmentof SARS-CoV and block the interaction of S2 subunit protein with cellular receptorACE2	Ng et al. (2014), Lip et al. (2006)
8	201	Mouse Syrian Hamster and in vitro	Binding to the 490–510 amino acid residues on S1 fragment of SARS-CoV and block the interaction of S1 subunit protein with cellular receptor ACE2 in vitro and in vivo	Greenough et al. (2005), Coughlin and Prabhakar (2012)
9	4D4	in vitro	Binding to the 12–261 amino acid residues of SARS-CoV and N-terminal of RBD and Inhibit the post-interaction in the viral permeation	Coughlin and Prabhakar (2012), Elshabrawy et al. (2012)
10	S230	in vitro	Binding to epitopes partially overlapping with receptor binding motifs on B domain of SARS-CoVand block the interaction of S1 subunit protein with cellular receptor ACE2 in vitro	Walls et al. (2019)

Table 4 List of important recommended vitamins and their dosages for treatment of COVID-19

S.N.	Vitamin name	Age group	Recommended dose	Disease	Target	References
1	25-hydroxyvitamin D	0–95 year	Daily or weekly 2000 IU/day (50 µg/day)	Acute respiratory tract infection	Reduce inflammation	Martineau et al. (2017), Autier et al. (2017), Martineau et al. (2019), Rejnmark et al. (2017), Bergman et al. (2013), Charan et al. (2012)
2	Vitamin-E (Tocopherol)	All age	One-year daily supplement	Respiratory tract infection	Enhance T-cell mediated immunity	Wu and Meydani (2014)
3	Vitamin-C (Ascorbic acid)	1–3 year to adult	Least 200 mg/day-2 g/day	Upper and lower respiratory tract infection		Monsen (2000)

Table 5 Summary of meta-analysis conducted by several groups for the treatment of COVID-19

S.N.	Therapeutic drug	Common name	Target	Comments/significance	References
1	Chloroquine derives hydroxy-chloroquine	Aralen/plaquenil	SARS-CoV 2	More useful to improve clinical and virological outcomes. But reduce mortality	Million et al. (2020), Pathak et al. (2020), Siemieniuk et al. (2020)
2	Dexamethasone	Decadron	SARS-CoV 2	Risk of mortality and benefits for severing clinical condition patients	Abeldano Zuniga et al. (2020), Siemieniuk et al. (2020)
3	Lopinavir-Ritonavir	Kaletra	HIV, SARS-CoV 2	Risk of mortality, adverse events	Abeldano Zuniga et al. (2020), Siemieniuk et al. (2020)
4	Remdesivir with placebo	Veklury	Ebola, COVID-19	Risk of mortality	Abeldano Zuniga et al. (2020), Siemieniuk et al. (2020)
5	Hydroxy-chloroquine with azithromycin	Aralen/plaquenil and zitromax	SARS-CoV 2	Not alter the rate of risk of virologic cure and risk of mortality, Not different from hydroxy-chloroquine alone	Ayele Mega et al. (2020), Chen et al. (2020c), (Tang et al. (2020), Fiolet et al. (2020), Abeldano Zuniga et al. (2020), Siemieniuk et al. (2020)
6	Tolicizumab	Actemra		Lower mortality was 12%	Malgie et al. (2020)
7	Convalescent Plasma	NA	SARS-CoV 2	Mortality and virological clearance	Abeldano Zuniga et al. (2020), Siemieniuk et al. (2020)
8	Vaccine vs placebo	NA	SARS-CoV 2	Significantly increase IgG level than placebo, total local events also changed ($P > 0.05$)	Yuan et al. (2020)

Conclusion

The advancement of COVID-19 infection depends upon the interface between the load of the virus and the human immune system. As the global demand for diagnosis and therapy continues to rise, it is essential to quickly develop various algorithms to identify and contain the virus successfully. The pathogenic effects of the virus tend to be mediated by binding to human receptor ACE2. If the virus has a high load in an individual, the level of infection could increase the number of deaths. Conversely, due to the undetectable virulence load, moderate and lower viral load displays false-negative effects. This load of virulence is determined by gender, age, nutritional status, dietary habits, co-morbidity, and physical condition. These parameters play a contributing role in the severity of the disease and the re-infection of individuals. From this perspective, it is essential to develop new, fast, reliable, feasible, compact and straight forward technologies for the detection of COVID-19. The worldwide collaboration of healthcare professionals to engage patients in clinical trials is essential. A multicentre mega-trial is vital for comparing the clinical outcome of patients treated with different combination drugs. There is no doubt that researchers are directed to gain insight into this disease and to develop an effective therapeutic option. As far as management is concerned, the first step that can be taken is to get the right advice and clear people's fears. Besides, much-fabricated knowledge about COVID-19 is being disseminated, which has triggered fear in society. Clear guidelines should be implemented at the group level, which will help patients heal as quickly as possible. Meantime, research will continue, and CP therapy or neutralizing antibodies are considered for treatment until the vaccine arrives.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Consent for publication All the authors have read the manuscript and have approved this submission.

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