Features of Pathobiology and Clinical Translation of Approved Treatments for Coronavirus Disease 2019

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Abstract

\textbf{Background:} Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is currently the most important etiological agent of acute respiratory distress syndrome (ARDS) with millions of infections and deaths in the last 2 years worldwide. Several reasons and parameters are responsible for the difficult management of coronavirus disease-2019 (COVID-19) patients; the first is virus behavioral factors such as high transmission rate, and the different molecular and cellular mechanisms of pathogenesis remain a matter of controversy, which is another factor. \textbf{Summary:} In the present review, we attempted to explain about features of SARS-CoV-2, particularly focusing on the various aspects of pathogenesis and treatment strategies. \textbf{Key Messages:} We note evidence for the understanding of the precise molecular and cellular mechanisms of SARS-CoV-2 pathogenesis, which can help design the appropriate drug or vaccine. Additionally, and importantly, we reported the updated issues associated with the history and development of treatment strategies such as, drugs, vaccines, and other medications that have been approved or under consideration in clinics and markets worldwide.

Introduction

The novel coronavirus-infected persons from Wuhan city, Hubei Province, China, were described in December 2019 [1]. To date, the acute respiratory distress syndrome (ARDS) related to novel coronavirus affected Ali Fallaha, Hadi Razavi Nikoo and Hamidreza Abbasi contributed equally.
SARS-CoV-2 Features (Morphology, Genome Organization, and Its Proteins)

SARS-CoV-2 includes pleomorphic spherical particles of 70–90 nm diameter with coronavirus-specific morphology that were derived from clinical samples and seen under a transmission electron microscope [9, 10]. Coronaviruses are enveloped viruses containing an unsegmented, single-stranded, positive-sense RNA genome of around 30 kb in length, which is enclosed by a 5′-cap and 3′-poly (A) tail [10, 11]. The genome organization of SARS-CoV-2 has similarities to that of other beta-coronaviruses. SARS-CoV-2 genome is demarcated by short RNA breakpoint sequences that lead to recombination at specific nonrandom locations within the viral genome, suggesting the evolutionary pattern of coronaviruses over vast distances in time [12].

The genome and subgenome produce 6 open reading frames (ORFs). The majority of the 5′ end is occupied by ORF1a/b, encoding sixteen nonstructural proteins (NSP1-NSP16) [11, 13]. One large polyprotein is initially produced from ORF1a/b and cleaved by the papain-like protease encoded within NSP3 and the 3C-like protease, to produce replication-transcription complex, which are necessary for viral transcription and replication. The remaining ORFs encode for 9 putative accessory proteins and 4 structural proteins (Spike-S, Envelope-E, Membrane-M, and Nucleocapsid-N) (Fig. 1) [14]. The specific role and function of each protein in the life cycle of the virus are shown in Table 1. Phylogenetic analysis of the SARS-CoV-2 S gene sequence illustrates that there are distinguished 27 amino acid substitutes in contrast to SARS-CoV-1/SARS-like coronaviruses. These substitutions are about higher infectivity and lower pathogenicity of SARS-CoV-2 than SARS-like coronaviruses [15]. SARS-CoV-2 evolved 2 major types L and S that differ in 2 SNPs. These are at positions of 8782 and 28114 that are located in ORF1ab (T8517C, synonymous) and ORF8 (C251T, S84L), respectively [16]. In addition, L type was the most prevalent, detected in 70% of the samples amplified, and S type was detected in 30% of the specimens. L and S types of SARS-CoV-2 have very small genetic differences and may not influence the immune response [4].

Four major structural proteins in SARS-CoV-2 are mentioned in brief below:

1. S is a large multifunctional transmembrane glycoprotein, and cleaved into S1 and S2 units. (2) Matrix glycoprotein (M) is the most abundant viral protein, which gave a definite shape to the viral envelope, and is essential for virus morphogenesis and assembly. (3) E is the smallest of the major structural proteins. It acts as a viroporin (ion channel) and is essential for various stages of the virus cycle, such as pathogenesis, assembly, and release of the virus. (4) N is the only structural protein that binds to the genomic RNA, and facilitates virion assembly, and enhances the transcription efficiency of the virus [17–20].

SARS-CoV-2 Pathobiology and Treatment Options

Binding to ACE2 and Entry

The first SARS-CoV-2 targets human cells, such as nasal and bronchial epithelial cells and pneumocystis,
through the binding of viral structural S glycoprotein to the angiotensin-converting enzyme 2 (ACE2), as a zinc-containing metalloenzyme, which is widely expressed in many cells [21]. The attachment of receptor-binding domain (RBD) located on the surface of S glycoprotein to ACE2 prompts endocytosis of the virus [22]. The S1 subunit binds to the ACE2 via its RBD, and the S2 subunit is responsible for membrane fusion (Fig. 2) [3]. Additionally, the priming of the virus S protein is mediated by different co-receptors and activators, including transmembrane serine protease 2 and endosomal/lysosomal cysteine proteases such as cathepsin B and L. Taken together, these events can cause downregulation of ACE2, through internalization and degradation of the protein, which in turn results in the loss of cilia and squamous metaplasia, which contribute to severe lung injury [23, 24]. In addition to the ACE2 receptor, SARS-CoV-2 could bind the putative alternative receptor CD147 to enter target cells. Research has shown that when CD147 protein expression is inhibited, cell infection with the new coronavirus is reduced by 50% [5, 25].

According to the WHO and COVID-19 treatment guidelines, many antiviral agents are known today as “effective compounds” against the SARS-CoV-2, but here we investigated the NIH- or WHO-recommended antiviral agents that are available at https://www.covid19treatmentguidelines.nih.gov [26] for a better understanding of their antiviral properties on SARS-CoV-2. These drugs can target viral replication machinery, RNA polymerase, and viral protease, or modulate inflammatory responses against SARS-CoV-2 [27, 28]. Characteristics of approved and under development therapeutics options such as medication class, product name, clinical phase, manufacturing, mechanisms of action, dosage, and limitation are shown in Table 2 and Figure 3.

Reduction of viral loads in COVID-19 patients treated with some antiviral agents that can inhibit the binding of SARS-CoV-2 to host cells was found in various phases of clinical trials, indicating the inhibitory effect of these molecules on viral envelope proteins and their host cell receptors/co-receptors [31, 32]. These are including antiviral drugs (ivermectin), neutralizing monoclonal anti-
bodies (bamlanivimab and etesevimab), recombinant human monoclonal antibodies (casirivimab, imdevimab, and sotrovimab), and convalescence plasma [33]. At the beginning of the pandemic, several studies reported data on the antiviral activity of ivermectin, hydroxychloroquine alone, or in combination with azithromycin against SARS-CoV-2 [34–36]. The updates obtained from different trials with thousands of COVID-19 patients indicated these drugs do not reduce mortality or the duration of mechanical ventilation, and even cause adverse drug reactions [37]. Convalescent plasma or serum from a patient who recovered from COVID-19 could be another option for prophylaxis of infection and treatment of COVID-19 patients, particularly after the onset of symptoms [38]. The antibody binds the S protein which prevents the entry of SARS-CoV-2 into the host cell and viral neutralization. In addition, the antibody modulates the inflammatory response, which is also more easily achieved during the initial immune response, a stage that may be asymptomatic [39]. There are reports that convalescent serum was used for the therapy of patients with COVID-19 in China during the current outbreak [40]. Recently, the connection of the SARS-CoV-specific human MAb CR3022 to SARS-CoV-2 RBD showed its potential as a remedial factor in the management of SARS-CoV-2. Indeed, it can be applied alone or in combination with other impressive treatments [41].

### Table 1. Function of nonstructural and structural proteins of SARS-CoV-2

| Protein name                                      | Function                                                                                                                                 |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| NSP1 (N-terminal product of the viral replicase) | Inhibition of host translation machinery and innate immune response (virulent factor)                                                |
| NSP2 (N-terminal product)                        | Binds to PHBs 1, 2 (prohibitin), supposed role in apoptosis induction                                                                  |
| NSP3 (papain-like proteinase)                    | Release NSPs 1, 2, and 3 from the N-terminal region of pp1a and 1ab                                                                     |
| NSP4 (double-membrane vesicle maker)             | Viral RTC and membrane rearrangement                                                                                                    |
| NSP5 (main proteinase or 3Clpro)                 | Cleaves at multiple distinct sites of NSP polyprotein                                                                                  |
| NSP6 (putative transmembrane domain)             | Induces the formation of autophagosomes                                                                                                 |
| NSP7 (RNA-dependent RNA polymerase)              | Part of the RTC, and forms complex with NSP8 and 12                                                                                     |
| NSP8 (multimeric RNA polymerase; replicas)       | Part of the RTC, and forms heterodimer with NSP8 and 12                                                                                    |
| NSP9 (RNA-binding protein)                       | May bind to helicase                                                                                                                     |
| NSP10 (growth-factor-like protein possessing 2 zinc binding motifs) | Modulates NSP16, as a methyltransferase stimulator                                                                                     |
| NSP11                                            | Unknown (consists of 13 amino acids and identical to the first segment of Nsp12)                                                         |
| NSP12 (RNA-dependent RNA polymerase)             | Part of the RTC, and copies viral RNA and methylation (guanine)                                                                          |
| NSP13 (RNA helicase)                             | Unwinds duplex RNA (helicase), part of the RNA polymerase complex, involved in virus replication                                         |
| NSP14 (proofreading exonuclease)                 | Proofreading of the viral genome, which prevents lethal mutagenesis and functions as a methyltransferase for mRNA capping               |
| NSP15 (RNA endonuclease)                         | Degraded RNA to hide from host defense                                                                                                  |
| NSP16 (2′O-ribose methyltransferase)             | 5′-cap RNA methylation                                                                                                                  |
| ORF3a                                            | Interactions with some structural proteins and involved in virus release, apoptosis, and pathogenesis                                   |
| ORF3b                                            | Apoptosis stimulator, and inhibits the antiviral innate immune response                                                                |
| ORF6                                             | Effective in viral pathogenesis, and inhibition of IFN induction                                                                         |
| ORF7a                                            | Apoptosis induction                                                                                                                     |
| ORF7b                                            | Unknown (an integral membrane protein, expressed in viral-infected cells)                                                              |
| ORF8                                             | May enhance replication and shows interaction with some structural proteins                                                             |
| ORF9b                                            | Shows interaction with some NSPs and interferon antagonist                                                                              |
| ORF10                                            | Its function is not clearly understood but may have an immune modulatory role                                                          |
| ORF14                                            | Unknown (consists of 73 amino acid residues)                                                                                             |
| S protein                                        | Mediates attachment and viral entry into the host cell                                                                               |
| E protein                                        | It acts as a viroporin and is essential for stages of the virus cycle, such as pathogenesis, assembly, and release of the virus         |
| M protein                                        | It is essential for virus morphogenesis and assembly                                                                                  |
| N protein                                        | It facilitates virion assembly and enhances the transcription efficiency of the virus                                                   |

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; N, Nucleocapsid; M, Membrane; S, Spike; E, Envelope; ORF, open reading frame; NSPs, nonstructural proteins; RTC, replication-transcription complex. *Concluded from previous studies [17–20].
Translation and Replication

After the attachment, the ACE2/S SARS-CoV-2 complex is internalized into the cytoplasm by receptor-mediated endocytosis and prompts uncoating of virion in the acidic endosomal vesicles to release of the single-stranded viral RNA [42]. The positive single-stranded viral RNA translated into replicase polyproteins pp1a/pp1b and other products such as nsp1-16 collectively constitute the functional replication-transcription complexes by the host cell machinery [43]. Ribosomal frame shifting during the translation process has been seen in the replication of SARS-CoV-2, which produces genomic and multiple copies of subgenomic RNA species [23, 44]. The assembly of viral particles takes place via the interaction of genomic RNA and viral envelope proteins (S, E, and M) at the endoplasmic reticulum and Golgi complex [45]. Finally, these virions are subsequently released out of the cells via exocytosis [46]. It has been shown that several antiviral drugs influence the viral replication machinery in different ways: (i) directly targeting the viral proteins, such as RdRp and viral protease, and (ii) interruption of viral replication machinery through modulating cellular factors [47, 48]. Remdesivir, favipiravir, ribavirin, sofosbuvir, and tenofovir revealed the interaction and inhibition of RdRp, resulting in the reduced viral RNA synthesis and mRNA capping [49]. Remdesivir is the best example of a novel nucleotide analog with strong therapeutic applications against a diverse range of human viruses such as Ebola virus disease, SARS-CoV-1 and MERS, and SARS-like coronaviruses that inhibit viral RNA synthesis [50]. In addition, other inhibitors including lopinavir, ritonavir (Kaletra), and darunavir have been tested in clinical trials in the treatment of COVID-19 patients. This class of drugs interferes with the processing of the viral polyprotein by blocking the function of viral protease. Among these drugs, remdesivir is the only FDA-approved antiviral agent for the treatment of COVID-19 [51].

Inflammatory Responses

Virus replication (Viral phase) in pneumocytes leads to the inflammatory response, including macrophages, natural killer cells, CD4+ T cells, cytotoxic T lymphocytes/CTLs, and antibody responses [52]. In later stages of infection, epithelial-endothelial barrier integrity is compromised, which potentially mediates lung injury, as well as extrapolummary systemic involvement caused by SARS-CoV-2 [53]. Viral replication and pathobiology of SARS-CoV-2 virus are shown in Figure 4A–D. Several therapeutics plans modulate inflammatory responses against SARS-CoV-2 by different mechanisms. Approved and under evaluation plans include (1) immunomodulatory (colchicine, corticosteroids, interleukin inhibitors [IL-1 and IL-6], and interferons) and (2) cell-based therapy (mesenchymal stem cell) [54–56].

Pathology

Pathophysiology of SARS-CoV-2-induced ARDS is a multifactorial process and is very similar to SARS-CoV-1
| Medication class | Product name | Examples for developer | Examples for clinical phases | Dosage | MOA | Limitation/side effects |
|-----------------|-------------|------------------------|-----------------------------|--------|-----|------------------------|
| **Antiviral**    | Remdesivir | Gilead sciences (NCT04280705) (different phases) | 100 mg/day for 10 days | It is an adenosine analog that binds to the viral RNA-dependent RNA polymerase and inhibits viral replication | Gastrointestinal symptoms, ALT and AST elevations, hypersensitivity, increases in prothrombin time. Liver function tests and prothrombin time should be obtained in all patients before remdesivir is administered and during treatment. |
| Ivermectin      | Various     | Phase 3 (NCT04834115) (different phases) | 0.2 mg/kg single dose, maximum dose 18 mg | Interfering with intracellular transport process and attachment of the spike protein to the cell membrane | Generally well tolerated. Dizziness, pruritis, nausea or diarrhea, and neurological adverse effects. |
| **Anti-SARS-CoV-2 monoclonal antibodies** | Bamlanivimab plus etesevimab | Lilly; Junshi Biosciences | Phase 3 (NCT04497987) (different phases) | BAM 700 mg and ETE 1,400 mg iv administered together as a single dose | Neutralizing monoclonal antibody that binds to the RBD of the S protein (blocking viral attachment and cell entry) | Nausea, dizziness, rash, pruritis, pyrexia, hypersensitivity, including anaphylaxis and infusion-related reactions. |
| Casirivimab plus imdevimab | Regeneron Pharmaceuticals | Phase 3 (NCT04452318) (different phases) | CAS 1,200 mg and IMD 1,200 mg IV administered together as a single dose | Recombinant human monoclonal antibodies that bind to the S protein RBD (blocking viral attachment and cell entry) | Hypersensitivity, including anaphylaxis and infusion-related reactions. |
| **Convalescent plasma** | Plasma from donors who have recovered from COVID-19 | Various | Phase 3 (NCT04361253) (different phases) | High-titer COVID-19 CP unit (about 200 mL) and based on the prescribing provider’s medical judgment and the patient’s clinical response | May contain antibodies that suppress the virus and modify the inflammatory response | TRALI, TACO, allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, hemolytic reactions, hypothermia, metabolic complications, transfusion-transmitted infections, thrombotic events, theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity. |
| **Cell-based therapy** | AdMSCs | Celltex Therapeutics Corporation | Phase 2 (NCT04428801) | Each subject receives 3 doses of 200 million autologous adipose-derived mesenchymal stem cells via intravenous infusion every 3 days | May reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-CoV-2 | Uncommon. Multiply or change into inappropriate cell types, tumor genesis, infection, and thrombus formation. |
| **Immunomodulators** | Colchicine | NHLBI; Bill and Melinda Gates Foundation; Government of Quebec | Phase 3 (NCT04322682) (different phases) | 0.5 mg twice daily for 3 days then once daily for 27 days | Anti-inflammatory with reducing of the chemotaxis of neutrophils, inhibit inflammasome signaling and decrease the production of cytokines | Diarrhea, nausea, vomiting, cramping, abdominal pain, bloating, loss of appetite, neuromyotoxicity (rare), and blood dyscrasias (rare) |
| **Corticosteroids** | Dexamethasone (prednisone, methylprednisolone, hydrocortisone) | Various | Phase 3 (NCT04327401) (different phases) | Dexamethasone: 6 mg IV or PO once daily, for up to 10 days | Anti-inflammatory effects of corticosteroids might prevent or mitigate systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. | Hyperglycemia, secondary infections, reactivation of latent infections, psychiatric disturbances, avascular necrosis, adrenal insufficiency, increased blood pressure, peripheral edema, and myopathy. |
| Fluvoxamine | Various | Phase 3 (NCT04668950) | Various dosing regimens used | Probably reduction in the production of inflammatory cytokines and expression of inflammatory genes | Nausea, diarrhea, dyspepsia, asthenia, insomnia, somnolence, and sweating. |
| Medication class | Product name | Examples for developer | Examples for clinical phases | Dosage | MOA | Limitation/side effects |
|------------------|--------------|------------------------|-----------------------------|--------|-----|------------------------|
| Interferons      | Interferons Alfa | Cadila Healthcare Limited | Phase 2 (NCT04480138) (different phases) | Nebulized IFN alfa-2b 5 million international units twice daily | Stimulate the expression of several genes that contribute to shifting the host cells toward an antiviral activity | Flu-like symptoms (e.g., fever, fatigue, myalgia), injection site reactions, liver function abnormalities, decreased blood counts, worsening depression, insomnia, irritability, nausea, vomiting, and induction of autoimmunity |
| Interferons beta | Shahid Beheshti University of Medical Sciences | | Phase 4 (NCT04350671) (different phases) | IFN beta-1b 8 million international units subcutaneous every other day, up to 7 days total | Stimulate the expression of several genes that contribute to shifting the host cells toward an antiviral activity | Flu-like symptoms (e.g., fever, fatigue, myalgia), leukopenia, neutropenia, thrombocytopenia, lymphopenia, liver function abnormalities, injection site reactions, headache, hypertonia, pain, rash, worsening depression, and induction of autoimmunity |
| Interleukin-1 inhibitors | Anakinra | Hellenic Institute for the Study of Sepsis | Phase 3 (NCT04680949) (different phases) | Dose and duration vary by study | Human IL-1 receptor antagonist | Neutropenia, anaphylaxis, headache, nausea, diarrhea, sinustitis, arthralgia, flu-like symptoms, abdominal pain, injection site reactions, and liver enzyme elevations |
| Interleukin-6 inhibitors | Sarilumab | Sanofi; Regeneron | Phase 2/3 (NCT04315298) (different phases) | 400 mg IV (single dose) | Anti-interleukin-6 receptor monoclonal antibodies | Neutropenia, thrombocytopenia, GI perforation, HSR, increased liver enzymes, HBV reactivation, and infusion-related reaction |
| | Tocilizumab | Hoffmann-La Roche | Phase 3 (NCT04409262) (different phases) | A single dose of tocilizumab 8 mg/kg actual body weight IV The dose should not exceed tocilizumab 800 mg | Anti-interleukin-6 receptor monoclonal antibodies | Infusion-related reaction, HSR, GI perforation, hepatotoxicity, treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes, and HBV reactivation |
| | Siltuximab | Judit Pich-Martinez | Phase 2 (NCT04329650) (different phases) | Dose and duration unknown | Anti-interleukin-6 monoclonal antibody | Infusion-related reaction, HSR, GI perforation, neutropenia, HTN, dizziness, rash, pruitus, and hyperuricemia |
| Kinase inhibitors | Acalabrutinib | AstraZeneca | Phase 2 (NCT04380688) (different phases) | Dose and duration unknown | Bruton’s tyrosine kinase inhibitor that leads to immune and inflammation suppressing | Hemorrhage, cytopenia, atrial fibrillation, and flutter, infection, headache, diarrhea, fatigue, and myalgia |
| | Baricitinib | Eli Lilly and Company | Phase 3 (NCT04421027) (different phases) | 4 mg PO once daily for 14 days or until hospital discharge (for adults) | Janus kinase inhibitor that leads to immune and inflammation suppressing | Lymphoma and other malignancies, thrombosis, GI perforation, liver enzymes, HSV reactivation, and changes in lymphocytes, neutrophils, Hgb, and liver enzymes |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAM, bamlanivimab; ETE, etesevimab; CAS, casirivimab; IMD, imdevimab; CP, convalescent Plasma; TRAIL, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; IV, intravenous; PO, by mouth; FLU, influenza; GI, gastrointestinal; HSR, hypersensitivity reaction; HBV, hepatitis B virus; HTN, hypertension; HSV, herpes simplex virus; Hgb, hemoglobin; MOA, mechanisms of action; COVID-19, coronavirus disease-2019; NIH, National Institutes of Health. *Concluded from different studies in the NIH [https://www.covid19treatmentguidelines.nih.gov] [29].
Fig. 3. Featured and critical data for approved and under development of therapeutics plans. These plans can treat COVID-19 patients in various stages such as attachment, entry, replication and hyper inflammation phase [80]. COVID-19, coronavirus disease 19; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; S, spike; ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane serine protease 2; 3CLpro, 3C-like protease; PLpro, papain-like protease; M, Membrane; N, Nucleocapsid; E, Envelope.

Fig. 4. Molecular and cellular mechanisms of SARS-CoV-2 pathogenesis, from air to the blood: SARS-CoV-2 adjusted to alveoli epithelial cell (A); the infection cycle of the SARS-CoV-2 starts with the binding of the virion to the receptor ACE2 via receptor-mediated endocytosis and its proliferation (B); immune responses to SARS-CoV-2 including (C) (1) macrophages that efficiently capture and kill viruses, and produce NO and cytokines; (2) NK cells that secrete cytokines and kill infected host cells that fail to express sufficient peptide-MHC class I and infected DCs; (3) CD4+ T cells, which reciprocally license DCs for T-cell activation; (4) CTLs that kill virus-infected host cells by death ligands (FAS/FASL) and by cytokines or perforin/granzyme; (5) neutralizing antibody production that bounds to the virus and engaged FcRs on an NK cell, macrophage, or neutrophil that triggers the ADCC. On the other hand, these antibodies can bind to the complement component C1l, resulting in the activation of MAC and destruction of the infected cell. Another complement component such as free C3b binds to the virus surface and mediated phagocytosis by neutrophil CR1 receptors. D The viral spread to the cardiovascular system. NK cells, natural killer cells; DCs, dendritic cells; CTLs, cytotoxic T lymphocytes; ADCC, antibody-dependent cellular cytotoxicity; MAC, membrane attack complex; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ACE2, angiotensin-converting enzyme 2.

(For figure see next page.)
SARS-CoV-2 (COVID-19) Virus

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and MERS infectious patients, with less severe pathogen-
esis [57, 58]. The clinical symptoms of SARS-CoV-2 can
be asymptomatic, symptomatic, mild, and also lead to se-
vere disease with multi-organ failure. In the symptom-
atic phase or Viral phase, in which the clinical manifesta-
tions of the disease usually start 5 days after exposure,
patients may experience symptoms such as fever, dys-
pnea, sore throat, chest pain, expectoration, cough, and
myalgia, but fever, cough, and fatigue are common symp-
toms of COVID-19 [59]. At the present, there are differ-
ent confirming diagnostic methods for the detection of
SARS-CoV-2 in patients, around the time of symptom
onset, in laboratories, as follows: (1) nucleic acid tests like
real-time RT-PCR or next-generation sequencing; (2) an-
tibody or antigen detection tests, including enzyme-
linked immunosorbent assay; (3) chest computed tomog-
raphy and spectroscopic techniques [60–63]. Real-time
RT-PCR on nasopharyngeal and oropharyngeal swabs is
considered the “gold standard” for confirming the diag-
nosis in clinical cases of COVID-19 [64, 65]. Besides clin-
ical symptoms, the blood biochemistry indexes such as
the total white blood cell, lymphocyte, platelet, and
thromboplastin time decline, while C-reactive protein,
lactate dehydrogenase, aspartate transaminase, alanine
aminotransferase, cytokine level, and bilirubin increase
in most patients [66]. ARDS is a prevalent phenomenon
in patients, followed by anemia, acute heart injury, and
secondary infections [67]. Reports illustrate that middle-
aged and older people with chronic and underlying dis-
eases, especially high blood pressure and diabetes, are
susceptible to respiratory failure and have poorer prog-
noses, but it does not mean that children are lesser than
old people susceptible to SARS-CoV-2 [68–70]. In the
later stages of infection or the thrombo-inflammatory
phase, ARDS is a common complication, and resulted
from the occurrence of cytokine storms and immune reg-
ulatory network imbalance, which is finally followed by
anemia, acute heart damage, multiple organ failure, and
secondary bacterial infections [71]. Bilateral severe inter-
istitial inflammation of the lungs is found in the chest
computed tomography pictures or chest X-ray, which is
named ground-glass opacity and involves a local lobe but
later expands to multiple lung lobes [67].

Vaccines

With the threat of millions of people being infected
and health-care systems becoming overwhelmed, the race
is on to develop a vaccine that will protect individuals and
slow the spread of the disease [72]. S protein plays a sig-
nificant role in the induction of protective immunity
against SARS-CoV-2 by mediating T-cell responses and
neutralizing antibody production [73]. In the past few de-
cades, scientists would develop vaccines that induce the
body to produce antibodies that recognize and block hu-
man coronaviruses with the use of S protein as the target
[74]. Nonetheless, the expanded vaccines have minimal
usage, even between strains close together of the virus,
owing to an absence of cross-conservation [75]. Recently,
researchers identified the at least target domain of the vi-
rus’s S protein that is critical for docking with ACE2 re-
ceptor and this region or RBD located in the S1 subunit
of the S protein [76–78]. Furthermore, several studies
strongly reported that viral structural proteins such as N,
M, and E proteins have the potential for inclusion within
future vaccine candidates to stimulate T-cell responses,
and may significantly contribute to the recovery from
COVID-19 [1].

In addition, inactivated and live attenuated vaccine
platforms can induce broad and strong immune respons-
es, in comparison to the other platforms, because they
have the whole virion including structural and nonstruc-
tural proteins [1, 79, 80]. According to the vaccine track-
er reported by the World Health Organization, October
2021, nearly 300 vaccine candidates are currently under
various phases of development. In total candidate vac-
cines, 194 and 123 are in clinical and preclinical phases,
respectively, that are available at https://www.who.int/
publications/m/item/draft-landscape-of-covid-19-candi-
date-vaccines. There are 10 platforms for COVID-19
vaccines including, PS, nonreplicating viral vector
(VVnr), replicating viral vector (VVr), VVnr in combina-
ion with an antigen-presenting cell (VVnr + APC), VVr
in combination with an antigen-presenting cell (VVr +
APC), virus-like particle, inactivated virus, live attenuat-
ed virus, mRNA vaccine (RNA), and DNA [30, 81, 82].
Around 11 vaccine candidates have been approved up to
now in clinics and markets worldwide. Additionally, their
platforms, clinical phase, manufacturing, and dosage are shown in Table 3 and Figure 5.

Conclusion

The pandemic of the newly identified coronavirus that
is also known as COVID-19 is the third highly pathogen-
ic human coronavirus. SARS-CoV-2 has less mortality
than SARS-CoV-1 and MERS, but it has spread fast all
over the world and has been declared a public health
Table 3. COVID-19: Authorized/approved and in developing vaccines

| Platform          | Developer                                              | Phase     | Candidate vaccine                                                                 | Doses | ID            | Refs |
|-------------------|--------------------------------------------------------|-----------|-----------------------------------------------------------------------------------|-------|---------------|------|
| Virus based       | Codagenix/Serum Institute of India                     | Phase 1   | COVI-VAC                                                                          | 1–2   | NCT04619628   | [82] |
|                   | Bharat Biotech international Limited                   | Phase 3   | Whole-virion inactivated SARS-CoV-2 vaccine (BBV152)                              | 2     | NCT04641481*  | [83] |
|                   | Sinopharm + China National Biotec Group Co + Beijing   | Phase 4   | Inactivated SARS-CoV-2 vaccine (vero cell), vaccine name BBIBP-CoV                 | 2     | NCT0486358*   | [84] |
|                   | Institute of Biological products                       |           |                                                                                   |       |               |      |
|                   | Organization of Defensive Innovation and Research       | Phase 3   | CoronaVac; inactivated SARS-CoV-2 vaccine (vero cell)                              | 2     | NCT04758630*  | [85] |
|                   | Sinovac Research and development Co., Ltd              | Phase 4   | QazCovid-in® – COVID-19 inactivated vaccine                                      | 2     | NCT04691908   | [86] |
|                   | Research Institute for Biological Safety Problems, Rep of Kazakhstan | Phase 3   |                                                                                   |       |               |      |
|                   | Shifa Pharmed Industrial Co                             | Phase 2/3 | COVID-19 inactivated vaccine                                                      | 2     | NCT02021202049567N3 | [87] |
| Nucleic-acid based| AnGes + Takara Bio + Osaka University                   | Phase 2/3 | AG0301-COVID19                                                                    | 2     | NCT04655625   | [88] |
| DNA               | Pfizer/BioNTech + FosunPharma                          | Phase 4   | BNT162b2 (3 LNP-mRNAs), also known as "comirnaty"                               | 2     | NCT04760132*  | [89] |
| RNA               | CureVac AG                                              | Phase 3   | CVnCoV vaccine                                                                     | 2     | NCT04674189   | [90] |
| Protein and       | University of Hong Kong, Xiamen University and, Beijing | Phase 2   | DelNS1-2019-nCoV-RBD-OPT1 (intranasal flu-based-RBD)                              | 2     | ChCTR2000039715 | [91] |
| peptide-based     | Wantai Biological Pharmacy                             |           |                                                                                   |       |               |      |
| VWr               | Gamaleya Research Institute; Health Ministry of the Russian Federation | Phase 3   | Gam-COVID-VacAdeno-based (rAd26-S+Ad5-S)                                         | 2     | NCT04530396*  | [92] |
|                   | AstraZeneca + University of Oxford                     | Phase 4   | ChAdOx1-S – (AZD1222)                                                            | 1–2   | NCT04760132*  | [93] |
|                   | CanSino Biological Inc/Beijing Institute of Biotechnology | Phase 4   | Recombinant novel coronavirus vaccine (adenovirus type 5 vector)                  | 1     | NCT04892459*  | [94] |
|                   | Janssen Pharmaceutical                                 | Phase 4   | Ad26.COV2.S                                                                        | 1–2   | EUCTR2021-002327-38-NL* | [95] |
|                   | Federal Budgetary Research Institution State Research | Phase 3   | EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19) | 2     | NCT04780035*  | [96] |
|                   | Center of virology and Biotechnology “vector”          |           |                                                                                   |       |               |      |
|                   | Anhui ZhifeiLongcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences Novavax | Phase 3   | SARS-CoV-2 rS/Matryx M1-Adjuvant (full-length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with matrix M) | 2     | NCT04611802   | [97] |
|                   | Razi Vaccine and Serum Research Institute               | Phase 3   | RaziCov pars, recombinant spike protein                                           | 3     | IRTC201202060259N3 | [98] |
| VLP               | Medicago Inc                                           | Phase 3   | Coronavirus-like particle COVID-19 (CoVLP)                                         | 2     | NT05040789    | [99] |

COVID-19, coronavirus disease-2019; VLPs, virus-like particles; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; Wnr, nonreplicating viral vector; LAV, live attenuated virus; Vv, replicating viral vector; IV, inactivated virus. *Authorized/approved.
Fig. 5. Vaccines platforms against COVID-19. A Different vaccine platforms such as PS, VVnr, VVr, VLP, IV, LAV, mRNA (RNA), and DNA (DNA) vaccines can be considered to protect individuals, resulting in the reduction of the disease spread. B Distribution of approved and ongoing platforms in different clinical phases. COVID-19, coronavirus disease-2019; VLP, virus like particle; PS, protein subunit; IV, inactivated virus; VVnr, nonreplicating viral vector; LAV, live attenuated virus; VVr, replicating viral vector.
emergency of international concern by the WHO. Despite extensive research and a flood of articles published daily on SARS-CoV-2, and advances in effective management of COVID-19, we will require in-depth studies about SARS-CoV-2 pathogenesis. For the discovery of an effective drugs and vaccines against SARS-CoV-2, identification and evaluation of the available data on different molecular and cellular mechanisms involved in SARS-CoV-2 pathogenesis is very promising.

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Conflict of Interest Statement

The authors declare that no conflict of interest exists.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33.
2. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report, 73; 2020.
3. Perlman S. Another decade, another coronavirus. N Engl J Med. 2020;382:760–2.
4. Tang X, Wu C, Li X, Song Y, Yao X, Wu X, et al. On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev. 2020;7(6):1012–23.
5. Bhan H, Zheng ZH, Wei D, Zhang Z, Kang WZ, Hao CQ, et al. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. MedRxiv, 2020.
6. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2):taaa021.
7. Ozma MA, Maroufi L, Khodadadi E, Kose Ş, Esposito I, Gannarob K, et al. Clinical manifestation, diagnosis, prevention and control of SARS-CoV-2 (COVID-19) during the outbreak period. Infez Med. 2020;28(2):153–65.
8. Habashi NM, Camporota L, Gatto LA, Niehaus G. Functional pathophysiology of SARS-CoV-2-induced acute lung injury and clinical implications. J Appl Physiol. 2021;130(3):877–91.
9. Prasad S, Potdar V, Cherian S, Abraham P, Basu A. Transmission electron microscopy imaging of SARS-CoV-2. Indian J Med Res. 2020;151(2–3):241.
10. El Jamali SM, Salih C, Stock A, Uriarte-Haparnas NI, Glicksberg BS, Teruya-Feldstein J, et al. Atypical lymphocyte morphology in SARS-CoV-2 infection. Pathol Res Pract. 2020;216(9):153063.
11. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe. 2020;27(3):325–8.
12. Rabaan AA, Al-Ahmed SH, Haque S, Sah R, Tiwari R, Malik YS, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV: a comparative overview. Infez Med. 2020;28(2):174–84.
13. Koyama T, Platt D, Parida L. Variant analysis of SARS-CoV-2 genomes. Bull World Health Organ. 2020;98(7):495.
14. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23.
15. Elaswad A, Fawzy M, Basiouni S, Shehata AA. Mutational spectra of SARS-CoV-2 isolated from animals. PeerJ. 2020;8:e10609.
16. Awadasseid A, Wu Y, Tanaka Y, Zhang W. SARS-CoV-2 variants evolved during the early stage of the pandemic and effects of mutations on adaptation in Wuhan populations. Int J Biol Sci. 2021;17(1):97.
17. Gorkhalf R, Koirala P, Rijal S, Mainali A, Bhattarai HK. Structure and function of major SARS-CoV-2 and SARS-CoV proteins. Bioinform Biol Insights. 2021;15:11779322121025876.
18. Yoshimoto FK. The proteins of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 or n-CoV19), the cause of COVID-19. Protein J. 2020;39(3):198–216.
19. Yadav R, Chaudhary JK, Jain N, Chaudhary PK, Khanra S, Dhamija P, et al. Role of structural and non-structural proteins and therapeutic targets of SARS-CoV-2 for COVID-19. Cells. 2021;10(4):821.
20. Mariano G, Farthing RJ, Lale-Farjat SL, Bergeron JRC. Structural characterization of SARS-CoV-2: where we are, and where we need to be. Front Mol Biosci. 2020;7:344.
21. Evans N, Martinez E, Petrosillo N,Nichols J, Islam E, Pruitt K, et al. SARS-CoV-2 and human immunodeficiency virus: Pathogen picker attack. HIV/AIDS. 2021;13:361.
22. Ramírez Hernández E, Hernández-Zimbón LF, Martínez Zúñiga N, Leal-García JJ, Ignacio Hernández V, Ucharima-Corona LE, et al. The role of the SARS-CoV-2 S-protein glycosylation in the interaction of SARS-CoV-2/ACE2 and immunological responses. Viral Immunol. 2021;34(3):165–73.
23. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271–e8.
24. Ji W, Wang W, Zhao X, Zai J. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission from snake to human. J Med Virol. 2020;92.
25. Ibrahim IM, Abdelmalek DH, Elshahat ME, Elifyky AA. COVID-19 spike-host cell receptor GRP78 binding site prediction. J Infect. 2020;80(5):554–62.
26. https://www.covid19treatmentguidelines.nih.gov.

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Author Contributions

Ayyoob Khosravi designed and supervised the study with the help of Abasalt Hosseinzadeh Colagar. Ali Fallah wrote the first draft of the manuscript with support from Azadeh Mohammad-Hasani. Parts of the manuscript were also written by Hadi Razavi Nikoo and Hamidreza Abbasi. Hamidreza Abbasi designed the figures and tables with the help of Ali Fallah. Ayyoob Khosravi, Hadi Razavi Nikoo, and Abasalt Hosseinzadeh Colagar participated in the final editing the manuscript. Hamidreza Abbasi played the main role in the submission of the manuscript. All authors give final approval of the manuscript to be submitted.
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DOI: 10.1159/000520234

68 Hyde Z. Difference in SARS-CoV-2 attack rate between children and adults may reflect bias. Clin Infect Dis. 2021: ciab183.

69 Kuppusamy M, Loganathan S, Wankhar W, Gurugubelli KR, Mahadevappa VH, Lepcha L, et al. Angiotensin-converting enzyme 2 (ACE2): COVID-19 gate way to multiple organ failure syndromes. Respir Physiol Neurobiol. 2021; 283:103548.

70 Preskorn SH. The 5% of the population at high risk for severe COVID-19 infection is identifiable and needs to be taken into account when reopening the economy. J Psychiatric Prac. 2020;26:219–27.

71 Bilich T, Nelde A, Heitmann JS, Maringer Y, Roerden M, Bauer J, et al. T cell and antibody kinetics delineate SARS-CoV-2 peptides mediating long-term immune responses in COVID-19 convalescent individuals. Sci Transl Med. 2021;13(590):eaab7517.

72 Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260–3.

73 Liu R, Moise L, Tassone R, Gutierrez AH, Terry FE, Sangare K, et al. H7N9 T-cell epitopes that mimic human sequences are less immunogenic and may induce Treg-mediated tolerance. Hum Vaccin Immunother. 2015;11(9):2241–52.

74 Wu Y, Li C, Xia S, Tian X, Kong Y, Wang Z, et al. Identification of human single-domain antibodies against SARS-CoV-2. Cell Host Microbe. 2020;27(6):891–e5.

75 Gangadavi S, Badavath VN, Thakur A, Yin N, De Jonghe S, Acevedo O, et al. Kobophenol a inhibits binding of host ace2 receptor with spike rbd domain of sars-cov-2, a lead compound for blocking covid-19. J Phys Chem Lett. 2021;12(7):1793–802.

76 Kalathiyu U, Padariya M, Mayordomo M, Lisowska M, Nicholson J, Singh A, et al. Highly conserved homotrimer cavity formed by the SARS-CoV-2 spike glycoprotein: a novel binding site. J Clin Med. 2020;9(5):1473.

77 Callaway E. The race for coronavirus vaccines: a graphical guide. Nature. 2020;580:576–7.

78 Jiang S, He Y, Liu S. SARS vaccine development. Emerg Infect Dis. 2005;11(7):1016.

79 Ndwandwe D, Wiysonge CS. COVID-19 vaccines. Curr Opin Immunol. 2021;71:111–6.

80 van Riel D, de Wit E. Next-generation vaccine platforms for COVID-19. Nat Mater. 2020;19(8):810–2.

81 World Health Organization. Draft landscape of COVID-19 candidate vaccines: WHO. 2021. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

82 https://clinicaltrials.gov/ct2/show/NCT04619628

83 https://clinicaltrials.gov/ct2/show/NCT04641481

84 https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-000930-32/BE.

85 https://clinicaltrials.gov/ct2/show/NCT04655625.

86 https://clinicaltrials.gov/ct2/show/NCT04760132.

87 https://clinicaltrials.gov/ct2/show/NCT04674189.

88 https://clinicaltrialsregister.eu/ctr-search/trial/2021-000930-32/BE.

89 http://www.chictr.org.cn/historyversionpuben.aspx?regno=ChiCTR2000039715.

90 https://clinicaltrials.gov/ct2/show/NCT04530396.

91 https://clinicaltrials.gov/ct2/show/NCT04892459.

92 https://clinicaltrialsregister.eu/ctr-search/trial/2021-002327-38/NL.

93 https://clinicaltrials.gov/ct2/show/NCT04780035.

94 https://clinicaltrials.gov/ct2/show/NCT0466085.

95 https://clinicaltrials.gov/ct2/show/NCT04611802.

96 https://clinicaltrials.gov/ct2/show/NCT05040789.