REVIEW

Origin, Pathogenesis, Diagnosis and Treatment Options for SARS-CoV-2: A Review

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Abstract

Emerging viral infections are among the greatest challenges in the public health sector in the twenty-first century. Among these, most of the viruses jump from other species of animals to humans called zoonotic viruses. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), by crossing species-barrier, has infected the human population for the third time in the current century and has caused the coronavirus disease-2019 (COVID-19) . Mutation and adaptation for years have greatly influenced the co-evolution and existence of coronaviruses and their possible hosts including humans. The appearance of SARS-CoV-2 in China thrust coronaviruses into the limelight and shocked the world. Presently, no coronavirus vaccines are clinically available to combat the virus's devastating effects. To counter the emergence of the COVID-19 pandemic, it is therefore important to understand the complex nature of coronaviruses and their clinical attributes. SARS and MERS outbreaks had ultimately led to socio-economic deprivation in the previous decades. In addressing the recent disastrous situation, the COVID-19 pandemic still needs some lessons from prior experience. In this review, we have highlighted the chronological order of coronavirus strains, their genomic features, the mechanism of action of SARS-CoV-2, and its disastrous repercussions on the world. We have also suggested some therapeutic options that could be effective against the COVID-19.

Keywords HCoV · SARS-CoV · MERS-CoV · SARS-CoV-2 · COVID-19 · pandemic

Introduction

In late 1960, a team of scientists was analyzing various strains of animal and human viruses including mouse hepatitis virus, transmissible swine gastroenteritis virus, and infectious bronchitis virus. During the investigation, a new virus with a crown-like structure termed "corona" was identified known as coronavirus (McIntosh et al. 1967a; Tyrrell et al. 1975; Witte et al. 1968). Over the past three decades, a few viral epidemics have occurred in China such as the 1997 outbreak of avian influenza, SARS in 2003 (Rodriguez-Morales et al. 2020), and severe fever thrombocytopenia syndrome in 2010 (Rodríguez-Morales et al. 2018). In December 2019, another infectious coronavirus outbreak was reported in Wuhan city of China, causing the SARS-like disease in humans. The World Health Organization (WHO) officially declared this as 2019-nCoV (2019- novel coronavirus) and is presently named as severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2). The designation of name 2019-nCoV was based on the analysis of the evolutionary history of new coronaviruses and related viruses i.e., SARS-CoV. Later, the Shanghai public health clinical center sequenced the complete genome of 2019-CoV and claimed for a bat origin (Chan et al. 2020a). The presence of intermediate hosts between humans and most probably bats is still being investigated for the spread of SARS-CoV-2. It was reported from the outset that the novel CoV infected cases were linked epidemiologically to the seafood market in Hunan, China (Huang et al. 2020). Consequently, findings for the transmission of 2019-nCoV from human to human was again verified by the infectious

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disease affecting fifteen medical practitioners following close intact with the infectious person at the Wuhan hospital (Wang et al. 2020b). As of 21 April 2021, a total of 143,587,922 cases of COVID-19 from around the world were reported by World Health Organization (WHO).

Coronaviruses belonging to the *Coronaviridae* family are positive sense, enveloped, single-stranded RNA viruses, and have a genome that ranges from 26 to 32 kb in length (Su et al. 2016). Coronaviruses have been reported both in avian hosts and numerous mammals, which include bat, masked palm civets, dogs, and camels, and were initially considered to be pathogens causing moderate to severe diseases in immuno-competent individuals until coronavirus emerged in 2002 inducing a SARS-CoV outbreak (Drosten et al. 2003; Fouchier et al. 2003; Ksiazek et al. 2003; Zhong et al. 2003). At least, there are seven species of coronaviruses currently known to infect humans and can cause common or/and serious diseases. For more than 30 years, HCoV-229E, OC43, NL63, and HKU1 have been the only existent human coronaviruses, causing only mild symptoms of common cold, respiratory tract illness, and pneumonia (Annamalay and Le Souëf 2017; Wong and YUEN 2008). The remaining three coronaviruses, named SARS-CoV (emerged in 2002-2003, led to the spread of SARS and cause serious illness) (Drosten et al. 2003; Zhong et al. 2003) and the MERS-CoV appeared in Saudi Arabia in 2012, caused infection in humans and camels (Zaki et al. 2012); SARS-CoV-2 which emerged in 2019 in Wuhan, China, spread throughout the world and serious efforts are being made to control its outspread (Xu et al. 2020b; Zhu et al. 2020).

The pathological process of SARS-CoV-2 has not been studied well but is likely to be similar to SARS-CoV-1. Even after so many years of intensive research, human coronaviruses lack a preventive vaccine. As far as the treatment of SARS-CoV-2 is concerned, until now there is no clinically available vaccine against SARS-CoV-2 which can be presumed as being effective. So preventive measures aimed at reducing the risks of transmission and flattening the pandemic curve in the target population are considered the best tool. Certain drugs approved by Food and Drug Administration (FDA) that have shown efficacy against pathogens similar to SARS CoV-2 are now under clinical trials for current pandemic treatment. Supportive procedures like ventilation during treatment and Convalescent plasma therapy, application of corticosteroids, immune suppressants are also under practice (Guo et al. 2020).

The current article aims to explain the different strains of the human coronavirus through the co-evolution and cross-species transmission events resulting in the novel human coronaviruses that have caused a global pandemic. This will enable a more apt and valuable phylogenetic relationship and history of these coronaviruses to be plotted, enabling researchers to better understand the continuously evolving novel coronavirus.

Evolutionary History

With the devastating effects of the novel coronavirus, there has been an urgency to understand its origin (Lu et al. 2020). A series of evolutionary events of coronavirus isolates is being believed to have led the species to the existing state, which is SARS-CoV-2 (Zhou et al. 2020a). This means that for reaching this novel state, the coronavirus species has gone through many different evolutionary events, with each organism evolving into a more diversified form, ultimately leading to zoonotic transmission of the virus to humans, and subsequently to the SARS-CoV-2. These evolutionary events dictate the process of evolution and transmission of different strains of the coronavirus from avian to civets (SARS-CoV-1), to camels (MERS), to bats (Bats-Associated coronaviruses), ultimately leading to humans' infections (Zu et al. 2020). For researchers to better control the virus's further evolutionary activities, they have to understand the evolutionary patterns of this virus right from the start. This will help them in better analyzing its future directions (Lai et al. 2020) and help researchers in their search for a treatment or vaccine for this deadly disease (Yang et al. 2020a).

The members of the *Coronaviridae* family has been investigated in different species, from fish and birds to mammals (Shereen et al. 2020). First characterized in the 1960s, since then HCoV is found to be one of the major causes of respiratory infections (Ye et al. 2020), both in children and adults (Cui et al. 2019). There are generally considered four different genera for the coronaviruses, Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Alpha Coronaviruses include human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63). Beta Coronaviruses include human coronavirus OC43 (HCoV-OC43), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), human coronavirus HKU1 (HCoV-HKU1), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and SARS-CoV-2. Gamma coronaviruses include avian infectious bronchitis virus (IBV). Delta Coronaviruses include porcine delta coronavirus (PdCoV). The Spike protein of coronaviruses consists of S1 and S2 subunits. S1 subunit acts as a receptor-binding domain and further comprises of two more domains, the N-terminal domain (S1-NTD) and the C-terminal domain (S1-CTD) while the S2 subunit is required for the fusion of virus and host cell membrane as shown in the Fig. 1 (Li 2015). Strains of human coronavirus share non segmented similar genomic organization of coding region in the order 5′ end- ORF1a/b replicase, spike, envelope, membrane, nucleocapsid-3′ end. At least six ORFs made up the genomic and subgenomic sequence of coronavirus. 16 nsps (non-structural proteins) (1–16 nsp) are encoded by the first ORF that represents almost 67% of the entire viral genome (ORFa/b), except gamma-CoVs that lack nsp1. Two protease domains papain-like

(a) Schematic of spike-receptor binding mechanism
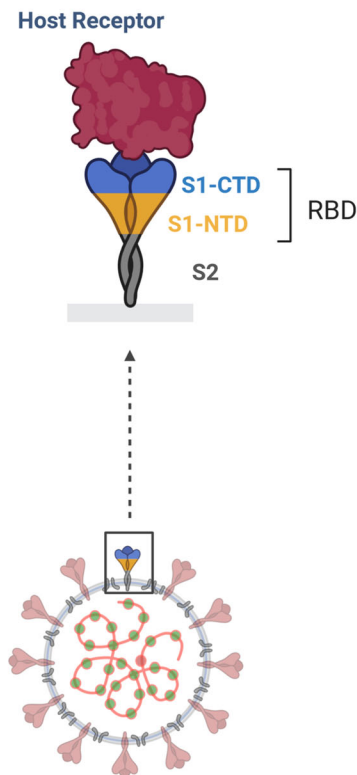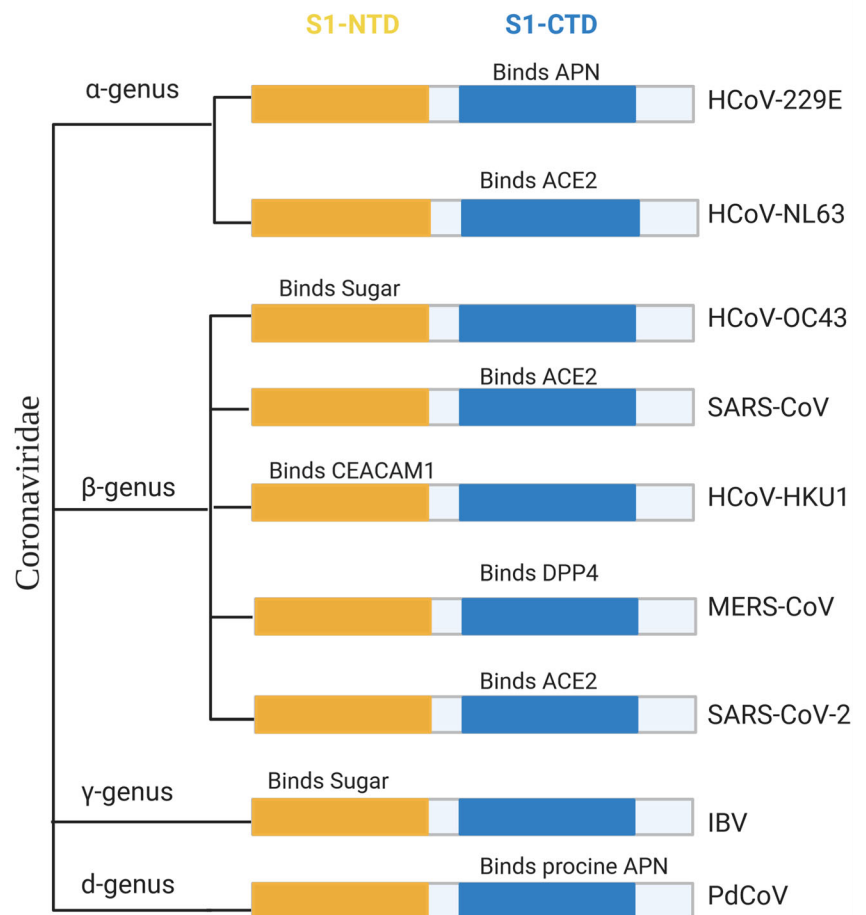
(b) Receptor Binding Domain (RBD)

Fig. 1 a Schematic representation of the spike protein receptor binding mechanism. **b** Receptor binding domain of *Coronaviridae* family. Yellow boxes indicate a known receptor binding domain in the N terminal region of S1 and blue boxes indicate a known receptor binding domain in the C terminal region of S1. Known receptor indicated in the boxes: APN, aminopeptidase N; ACE2, angiotensin-converting enzyme 2; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; DPP4, dipeptidyl peptidase 4. Made with biorender.com.

protease (PL2pro) in nsp3 and a 3C-like protease in nsp5 which are encoded by ORF1a sequence in the genome is conserved in all types of CoVs (Chan et al. 2020a). There are also accessory proteins encoded by four genera of coronavirus which vary in sequence and number even among the strains belonging to the same genera, thus raising important questions about their evolution and origin as shown in Fig. 2 (Forni et al. 2017). Alpha-CoVs such as HCoV 229E and HCoV NL63 utilizes aminopeptidase N (APN) and angiotensin-converting enzyme-2 (ACE-2) respectively as their major receptor for entering the host cell. In Beta coronavirus angiotensin-converting enzyme 2 (ACE2) act as the main receptor in SARS-CoV, MERS-CoV use dipeptidyl peptidase 4 (DPP4) as its primary receptor. Sugar and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) residues are utilized as receptors in HCoV-OC43 and HCoV-HKU1, respectively. In gamma coronavirus such as infectious bronchitis virus (IBV) sugar is used as receptors or co receptors and delta coronavirus use host aminopeptidase N (APN) as its

receptor (Li 2015). While alpha coronaviruses and beta coronaviruses are responsible for infections in mammals (De Sabato et al. 2019), gamma coronaviruses and delta coronavirus mostly infect birds (Singh et al. 2020).

The 2003 outbreak of the SARS started intensive research aimed at finding novel coronaviruses in humans (Yang et al. 2020b).In most viral diseases, the origin of the viral entity greatly helps in the phylogenetic analysis of the disease, providing a stronger framework to be used for the treatment of these diseases (Xu et al. 2020a). This is because studying the origin and evolutionary history of viruses helps scientists in better understanding how the virus functions, its structure, its genetics, and how much it relates to other members of its species, which helps them in devising out a way to treat its infection more effectively. Lee and colleagues found that a major proportion of coronavirus diversity was found in bats and avian species (Chan et al. 2015), these animals to be the natural reservoirs of the virus (Wang et al. 2020c). Existing literature shows that co-evolution and co-divergence of
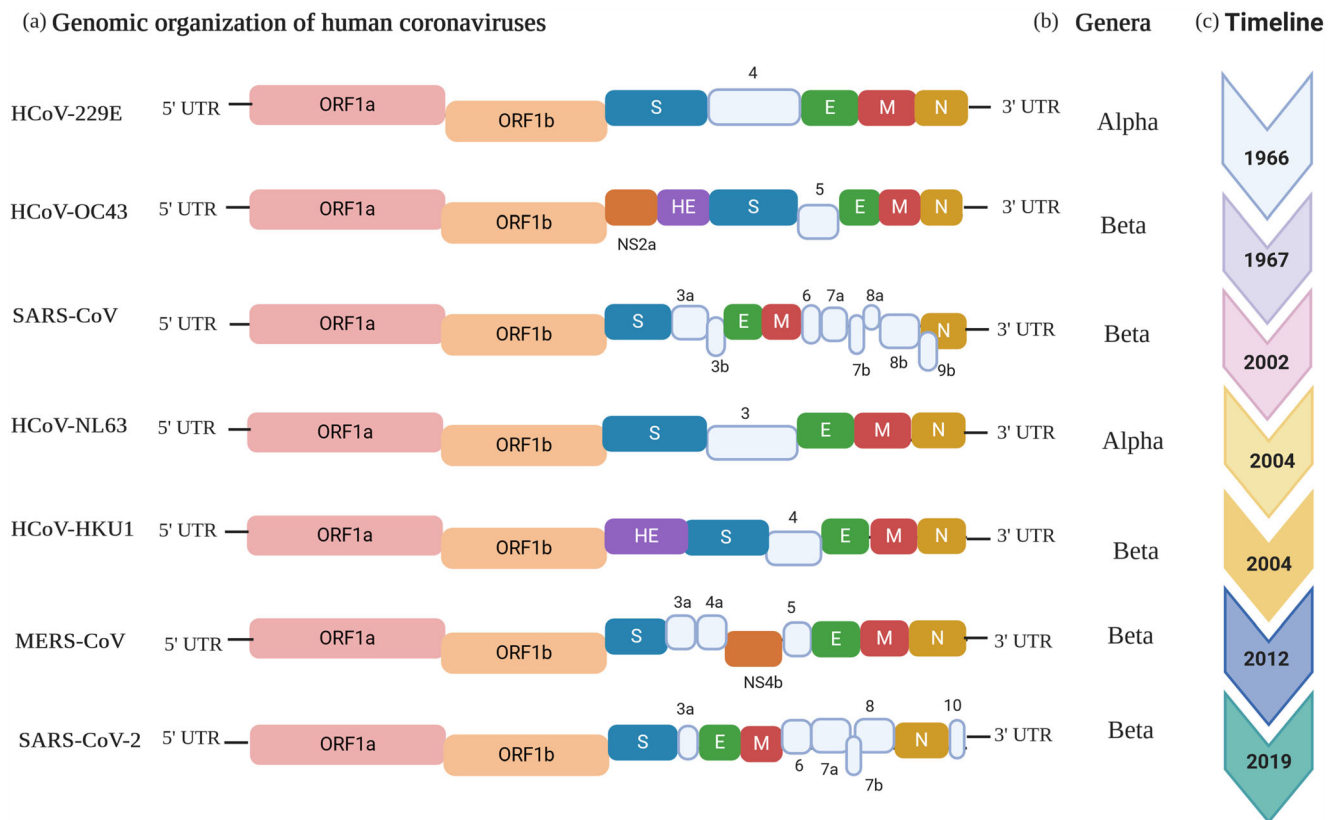
Fig. 2 a Genomic organization of different human coronaviruses. The ORF1a (pink) and ORF1b genes (orange) encode highly conserved 16 non-structural proteins in all coronaviruses. The structural genes encode the structural protein spike (blue), envelope (green), membrane (red), nucleocapsid (yellow) that are common to the coronaviruses. The other genes (non-colored) are unique to different coronaviruses with regards to genomic organization, number, sequence, and function. **b** The genera of human coronaviruses. **c** Timeline of their origin. Made with biorender. com.

coronaviruses with their hosts led to cross-species transmission events of these viruses, ultimately leading to human infections (Wu et al. 2020a). This evolutionary history can help in understanding the pattern of evolution or mutation that this virus may undergo in the future (Chen et al. 2020d). However, there is still a dire need for identifying markers to 1) associate with potential spill-over of animal viruses to human populations and 2) to predict their possible severity in human patients.

HCoV-229E

The first reported case of the coronavirus infection in humans can be dated back to 1965 when a boy was infected with symptoms much like the common cold but was negative for any other common infections like the influenza virus, herpes simplex virus, adenoviruses, and so on (Tetro 2020). Initially, the viral strain causing the infection was named as B814 (Pfefferle et al. 2009). Another infection of an unknown respiratory virus in students of the University of Chicago led to the formation of cell culture of the strain that caused the infection. This strain ultimately became a prototype for the HCoV-229E species (Corman et al. 2015). Both the B814 strain and the HCoV-229E strain were found to be very similar to the avian coronavirus, infectious bronchitis virus (IBV) under electron microscopy (Van Der Hoek et al. 2004). The HCoV-229E species became the first species of the coronaviruses that infected humans (Aldridge et al. 2020). When first studied in students at the University of Chicago, the HCoV-229E species was found to be ether-liable, causing cytopathic effects after six days (Parang et al. 2020), while it consists of particles around the size of 89nm, and had RNA as their genetic material (Gaunt et al. 2010). The virus is a single-stranded, enveloped, and positive-sense RNA virus (Paules et al. 2020). The virus has a 27,271 bp linear RNA molecule as the genetic material (Bonavia et al. 2003). The major modes of transmission for the HCoV-229E were droplet-respiration and fomites (Xia et al. 2018). Isolated from the plasma of a Haitian child in 2016, the presence of HCoV-229E can be confirmed by common molecular and serological approaches (Brian and Baric 2005).

HCoV-0C43

After the discovery of the HCoV-229E species, virus samples from patients with the common cold were taken and the

human embryonic trachea organ cultures (OC) were used for their inoculation (Vijgen et al. 2006). None of the patients showed any antibody response to the HCoV-229E, declaring that there weren't any of the OC strains, including the B814 strain, resembling the HCoV-229E (Nathalie et al. 2016). While the B814 and most of the OC strains were lost over time, the OC-43 strain was further propagated and ultimately became the prototyping culture for the HCoV-OC43 species (St-Jean et al. 2006). Much like the HCoV-229E species, the HCoV-OC43 species is an enveloped, single-stranded RNA virus (Liang et al. 2013). Isolated from a child hospitalized for pneumonia, the HCoV-OC43 has a 31.5kb RNA as its genetic material (Chen et al. 2013). Together with the HCoV-229E, the HCoV-OC43 is responsible for one-third of the common colds (Nilsson et al. 2020).

SARS-CoV

Long after the discovery of the role of HCoV-229E and HCoV-OC-43 in the common cold in humans, it was thought that these were the only two species of the human coronaviruses (Giannis et al. 2020). However, a SARS patient (in 2002) was reported in Guangdong province in China (Holmes and Enjuanes 2003). This was the first case of the 2002-04 SARS epidemic. In June 2003, there were 8,422 cases reported with a case fatality rate (CFR) of 11%, with the most affected country being China (Jernigan et al. 2004). The epidemic was attributed to a novel species of the human coronavirus, called SARS-CoV (Jiang et al. 2005). The studies conducted in May of the same year found the presence of the SARS-CoV in masked palm civets which could be used to isolate the coronavirus (Li et al. 2005). It was reported that the SARS-CoV epidemic was likely due to the crossing of the barrier from palm civets to humans (Zhong and Zeng 2006). In 2017 a long-held research aimed at finding the origin of the SARS-CoV in China reported their findings. The team reported that the same coronavirus that caused the SARS-CoV epidemic of 2003 was found in horseshoe bats found in a remote cave in the Yunnan province in China, stating that these bats are the likely reservoirs for the virus(Holmes and Enjuanes 2003). Much like the first two human coronavirus species, the SARS-CoV was found to be an enveloped, single-stranded RNA virus (Wan et al. 2020b). The virus has about 14 open reading frames with approximately 30kb RNA (Chen et al. 2020d). The SARS-CoV epidemic was contained on 5 July 2003, when WHO declared the epidemic to be over (Ashour et al. 2020).

HCoV-NL63

In 2004 HCoV-NL63 was identified in Holland in immuno-suppressed infants suffering from respiratory symptoms (Cui et al. 2019). Research has shown that HCoV-NL63 is not a

recent virus in the human population; it is derived from an ancestor of HCoV-229E. HCoV-NL63 has a single-stranded RNA genome that has 27,553 nucleotides that are capped and poly adenylated (Bastien et al. 2005). If HCoV-NL63 entry occurs through a fusion with the plasma membrane and subsequent fusion with the endosomal membrane or hydrolysis is not quite clear. The entry of HCoV-NL63 is not very susceptible to lysosomotropic substances. HCoV-NL63 can use endosomes but is not strictly dependent on pH-dependent cleavage, or fusion may occur through the plasma membrane (Chiu et al. 2005). The virus tends to have a seasonal occurrence, appearing more commonly in temperate climates during the winter months. For more tropical and extreme climates, the virus does not follow a particular season (Cui et al. 2019).

HCoV-HKU1

In January 2005, HCoV-HKU1 was first identified in a 71-year-old man of Hong Kong (Kanwar et al. 2017). HKU1 is closely linked to the HCoV-OC43 group II prototype (Esper et al. 2006). The virus is an enveloped, single-stranded positive-sense RNA virus and has 29,926 nucleotides. The GC content is the minimum of all documented coronaviruses, at 32 % (De Wit et al. 2016). Quick detection of HKU1 infections is performed by RT-PCR with the help of HKU1-specific monoclonal antibodies (mAb) (Esper et al. 2006). Studies indicate that HCoV-HKU1 can worsen the condition of people with underlying illness (Cui et al. 2019). HCoV-HKU1-positive specimens were frequently found in temperate countries like the USA and Italy during the winter-spring season (Lim et al. 2016). During the 2005–2006 winter-spring season, HCoV-HKU1 strains spread in northern Italy (Esper et al. 2006). Coronavirus-HKU1 accounted for an estimated 1.6% of adult respiratory infections (Assiri et al. 2013).

MERS-CoV

MERS -CoV was isolated from 60 years old man's sputum of Saudi Arabia in 2012 who was hospitalized for severe acute pneumonia and kidney failure (Pyrc et al. 2007). Initially, bats were focused for the MERS-CoV reservoir but later on, a serological survey of Oman and Canary Islands dromedary camels showed the presence of a huge number of MERS-CoV-neutralizing antibodies in the camels (de Groot et al. 2013). Between humans and camels,>99% similarity of MERS-CoVs was found by full-length genomic sequencing (Graham et al. 2013). Later serological evidence confirms dromedary camels as the reservoir of MERS-CoV by showing MERS-CoV presence in camels of the Middle East, Northern Africa, and Eastern Africa dating back to 1983. Due to traveling by infected individuals, MERS-CoV expands outside the Arabian Peninsula (Graham et al. 2013; Wu et al. 2020b)

Spread of MERS-CoV between humans by nosocomial transmission is predominantly higher (43.5–100% of MERS reported cases) as compared by transmission between family members and relatives (13–21% of MERS reported cases). MERS-CoV has positive-sense RNA genomes of 30.1 kb. MERS-CoV avoids host detection of their dsRNA by replicating in virus-induced double-membrane vesicles that lack host pattern recognition receptors (PRRs) (de Groot et al. 2013). Since September 2012, 2,494 laboratory-confirmed cases of MERS with 858 deaths in 27 countries have been reported (Oboho et al. 2015).

SARS-CoV-2

Several people in December 2019 in Wuhan showed severe symptoms of pneumonia with an unknown cause of pathogenesis (Pyrc et al. 2007; She et al. 2020). Wuhan is the most populous city of Hubei province and is the transportation hub of China. Initial cases were linked to the wholesale seafood market of Hunan that trade lives animals then sudden exponential increase in the numbers of cases that did not have previous exposure to live market make it clear that it is capable of human to human transmission (Ye et al. 2020). The virus was previously named as Wuhan coronavirus but the International Committee on Taxonomy of Viruses (ICTV) named it as SARS-CoV-2 and the disease as COVID-19 (Shirato et al. 2014). The information of different human coronaviruses is described in Table 1.

Compare to other RNA viruses that have a significantly high mutation rate that could be associated with the recombination and mutations in the virus, SARS-CoV-2 show less mutation due to its proofreading activity and thus mutate less rapidly. About 13 variation sites have been observed in SARS-CoV-2 ORF1ab, S, ORF3a, ORF8, and N areas, including 28,144 in ORF8 and 8,782 in ORF1a with a mutation rate of 30.53% and 29.47% respectively [83]. Population genetic analyses of 103 SARS-CoV-2 genomes suggested that SARS-CoV-2 evolved into two main forms L and S, well-defined by two separate Single Nucleotide Polymorphism (SNPs) showing almost complete association across the sequenced viral strains to date. Although the L type (~70 %) is more common than the S type (~30 %), the ancestral form was found to be the S type (Abdul-Rasool and Fielding 2010). At the junction of two subunits, S1 and S2 of the spike protein polybasic Furin cleavage site are located that that determine the viral infectivity and host range (Li 2015). The mortality rate varies depending on the geographic area as that mortality rate is three times higher (15.2%) out of China, compared to that (5.6%) in China. Although the difference in mortality rate inside and outside China depends on multiple factors, it is also linked with viral mutations and evolution capability (Bastien et al. 2005). However, further information is needed to fully understand this virus and its associated pathogenesis.

Pathophysiological process of COVID-19

Transmission route

Currently, the major routes of transmission are the infected respiratory droplets with a diameter of over 0.0002 inches and touch transmission. Recent studies revealed the diagnosis of SARS-CoV-2 in the urine sample of the confirmed patients which suggests a possibility of fecal transmission (Peng et al. 2020). Nevertheless, there is a growing amount of evidence to indicate that human to the human transmission may occur during the incubation time of Covid-19, which is expected to be between 2 to 10 days (Wu et al. 2020c).

SARS-CoV-2 entry and replication

Coronavirus spike S protein was reported to be a major determinant of virus entry into the host cell. Entry relies on the binding of S protein to the cellular receptor. SARS-CoV-2 attach to the ACE2 as a target for entry (Hoffmann et al. 2020). According to the Cryo-EM structure-based studies of spike protein, it is found that the SARS-CoV-2 Spike protein has a 10 to 20-fold greater affinity to the ACE2 receptor than the SARS-CoV receptor which potentially leads to the rapid virus spreading (Wrapp et al. 2020). Some human organs have a high degree of ACE2 mRNA expression including the heart, blood vessels, intestinal tract, lungs, alveolar cells, gallbladder, kidney, testis, and renal tubule. (Zou et al. 2020). In the cytoplasm, the viral RNA genome is released after entering the cell and translated by two-third amount, into two polyproteins (pp), while the remaining viral RNA transcribed into a clustered form of subgenomic mRNAs. These two polyproteins; pp1ab and pp1a code for sixteen nonstructural proteins (nsp1 to nsp16) that make up the viral replicase transcriptase complex (De Wit et al. 2016). Different nonstructural proteins have different functions e.g. two proteases nsp3 and nsp5, papain-like proteases, and 3C like proteases respectively cleave the polyproteins and rearrange the membranes that are produced from the rough endoplasmic reticulum (RER) into double-membrane vesicles (DMV). In these vesicles, viral transcription and replication will occur (Knoops et al. 2008). Nsp12 codes for RNA dependent RNA polymerase which helps in both viral RNA transcription and replication. Nsp14 performs the exoribonuclease function of proofreading the viral RNA genome to avoid the accumulation of harmful mutations (Sevajol et al. 2014). Different viral structure proteins are first translated and then embedded into the endoplasmic reticulum. These proteins are capable of driving along the secretive pathway into the endoplasmic reticulum Golgi intermediate compartment (ERGIC) (Perlman and Netland 2009). Viral RNA genomes are encapsulated by nucleocapsid protein buds which are then incorporated into the ERGIC membranes thus forms mature virions. Finally, these

Table 1 Strains of coronavirus circulating in the human population

Strains of coronavirus	Incubation period	Transmission	Natural host	Intermediate host	Human To Human transmission	Symptoms	Detection method	References
HCoV-229E	2-5 days	Respiratory droplets Fomites	Bats	Camelids	No transmission takes place	Malaise, Headache, Nasal Discharge, Sneezing, Fever and, cough	Tissue cultures, inoculation of healthy adult volunteers	(Hamre and Procknow 1966; McIntosh et al. 1967b; Pachetti et al. 2020; Pyrc et al. 2007; Tyrrell et al. 1993)
HCoV-OC43	2-5 days	Respiratory droplets Fomites	Rats	Cattles	No transmission takes place	Headache, Nasal discharge, Sore throat, Fever and cough	Organ cultures, inoculation of healthy adult volunteers, electron microscopy	(Cheng et al. 2007; Hamre and Procknow 1966; McIntosh et al. 1967b; Tyrrell and Bynoe 1965; Tyrrell et al. 1993)
SARS-CoV	2-11 days	Respiratory droplets Fomites Fecal-oral	Bats	Civet cat	Transmission takes place	Myalgia, Headache, Dry cough, Dyspnea, Respiratory, distress, Diarrhea	Cell culture, electron microscopy, consensus primers, random RT-PCR	(Drosten et al. 2003; Hamre and Procknow 1966; Ksiazek et al. 2003; Peiris et al. 2003; To et al. 2013; Tyrrell et al. 1993; Van Der Hoek et al. 2004)
HCoV-NL63	2-4 days	Respiratory droplets Fomites	Bats	Un identified	No transmission takes place	Cough, Rhinorrhea, Tachypnea, Fever, Hypoxia, Croup	Cell culture, VIDISCA, electron microscopy, RAP-PCR	(Abdul-Rasool and Fielding 2010; Hamre and Procknow 1966; Tyrrell et al. 1993; Van Der Hoek et al. 2004)
HCoV-HKU1	2-4 days	Respiratory droplets Fomites	Mouse	Un identified	No transmission takes place	Fever, Running nose, Cough, Dyspnea	Consensus primers	(Hamre and Procknow 1966; Lau et al. 2006; Tyrrell et al. 1993; Van Der Hoek et al. 2004; Woo et al. 2005)
MERS-COV	2-13 days	Respiratory droplets Fomites	Bats	Camel	Transmission takes place	Cough, Chill, Sore throat, Pneumonia, Diarrhea, vomiting, Acute renal impairment	Reverse transcription loop-mediated isothermal amplification (RT-LAMP)	(de Groot et al. 2013; Gao et al. 2016; Hamre and Procknow 1966; Hilgenfeld and Peiris 2013; Tyrrell et al. 1993)
SARS-CoV-2	3-6 days	Respiratory droplets, Fecal- oral	Bats	Pangolin(could be origin as well)	Transmission takes place	Fever, fatigue, cough, gastro intestinal problems, diarrhea, diabetes mellitus, hypertension, Ground glass opacities	Reverse transcription-polymerase chain reaction (rRT-PCR), Serological testing, CT-SCAN	(Chen et al. 2020a; Chiu et al. 2005; Hamre and Procknow 1966)

virions are released by the plasma membrane to infect the other cells shown in Fig. 3 (Jahangir et al. 2020). However, the viral life cycle needs more elaborations to open opportunities for the discovery of novel drugs that can specifically target virus replication, translation, assembly, and/or release.

Antigen presentation leads to immune dysfunction

Once the virus enters the cell, its antigen is processed and presented by the antigen-presenting cells (APC), which is the core part of the body's natural anti-viral immune system. Major histocompatibility complex (MHC) or human leukocyte antigen (HLA) in humans presents antigenic peptides and are then easily recognized by cytotoxic T lymphocytes, T-helper cells, and B-lymphocytes. Subsequently, antigen presentation activates the humoral and cellular immunity of the body that is regulated by virus-specific B and T cells (Li et al. 2020c). IgG and IgM antibodies are produced when coronavirus-associated SARS infection occurs. According to studies, at the end of 4th month, the IgM antibody vanishes while the IgG antibody can persist for a longer period indicating that IgG can play a protective role in the first place (Li et al. 2003, 2020c). The most recent study shows a significant reduction in the amount of CD4$^+$ and CD8$^+$ T cells in the blood of patients infected with SARS-CoV-2, while their status is hyper activated. High amounts of pro-inflammatory and cytotoxic granules have also been identified indicating over activation of T cells and antiviral immune response (Li et al. 2020c; Xu et al. 2020d). Also, a few studies have confirmed that lymphocytopenia is a common condition in patients infected with COVID-19 which leads to severe disease state and increases the risk of death (Chan et al. 2020b; Chen et al. 2020c; Xu et al. 2020d).

Damage-Response Framework and Clinical Biomarkers

The damage response framework (DRF) is a complex, integrated theory of infectious disease and microbial pathogenesis. Its emphasis the host damage as a major outcome of host microbe interactions. Correlators of immune protection, such as virus-specific antibodies, which control disease, and correlates of immune dysregulation, such as proinflammatory cytokine overexpression, which can stimulate disease, are both part of the microbe–host relationship. Taking various correlates into account may help us better understand COVID-19 pathogenesis and clinical manifestations. Fever and respiratory symptoms describe the initial SARS-CoV-2 syndrome. This is a sign that the immune system is attempting to control the viral infection. Low viral loads or immune responses that do not cause clinical signs, symptoms, or damage to the host may suggest asymptomatic transmission. Asymptomatic carriers will also spread the virus, infecting more vulnerable individuals who will ultimately experience clinical symptoms of

disease. Severe COVID-19 patients have alarming clinical and laboratory biomarkers, such as high serum ferritin, lymphopenia, D-dimers, thrombotic propensity, inflammatory bursts and, disseminated intravascular coagulation (DIC) that lead to multiple organ failure (MOF) and death. The baseline level of serum ferritin (500 ng/mL) is a prognostic marker for severe and fatal COVID-19, as well as an independent risk factor for disease severity and bilateral lung infiltration. By contributing to the cytokine storm through pro-inflammatory effects, ferritin is a major mediator of immune dysregulation, especially in cases of excessive hyperferritinemia. When plasmin cleaves fibrin to break down clots, it produces the D-dimer, which is a relatively small protein fragment. The concentration of circulating D-dimer can be used as a prognostic biomarker to diagnose thrombotic conditions like arterial thrombosis, pulmonary embolism and, DIC. Serious infections can cause lymphopenia, which can be a sign of sepsis. The period of COVID-19 is also influenced by lymphocyte counts. Lower lymphocyte counts have been linked to a longer period of COVID-19 symptoms (Zafer et al. 2021).

ARDS is caused due to cytokine storm

Acute Respiratory Distress Syndrome (ARDS) is a potentially fatal condition that inhibits adequate oxygen from entering into the lungs and causing death for most respiratory diseases (Thompson et al. 2017). The inflammation induced by SARS-CoV-2 is responsible for viral transcription and replication, virus-induced down-regulation, and shedding of ACE2, antibody-dependent enhancement (ADE), and cellular injury (Fu et al. 2020). Initial viral replication can induce massive endothelial and epithelial cell death leading to vascular permeability and triggering the formation of pro-inflammatory chemokines such as CCL2, CL5, CXCL8, CXCL10, etc. and cytokines such as ILF-1B, ILF-12, 6, 18 and 33, IFN-a, and TNF-a (Cameron et al. 2008; Channappanavar and Perlman 2017; Jin et al. 2020; Li et al. 2020c; Yang 2020). Furthermore, ACE2 down-regulation and shedding can also lead to the renin-angiotensin system (RAS) dysfunction which regulates the blood pressure (Imai et al. 2008; Li et al. 2020c). ADE is a popular phenomenon of virology and has been reported in many viral infections that it can enhance infection and clinical progress (Fierz and Walz 2020).It can promote the adsorption of the virus antibody complex by interacting with Fc receptors leading to increased target cell infection. Fc receptor interaction with anti-S protein neutralizing antibody complexes can promote inflammatory reactions as well as continuous viral replication in the patient's lungs (Takada and Kawaoka 2003). All the events discussed above can initiate a severe attack causing multiple organ damage, ARDS, and ultimately results in death in serious cases of SARS-CoV-2 infection (Wang and Ma 2008) as shown in Fig. 4. However, viral pathogenesis needs to be further explored.
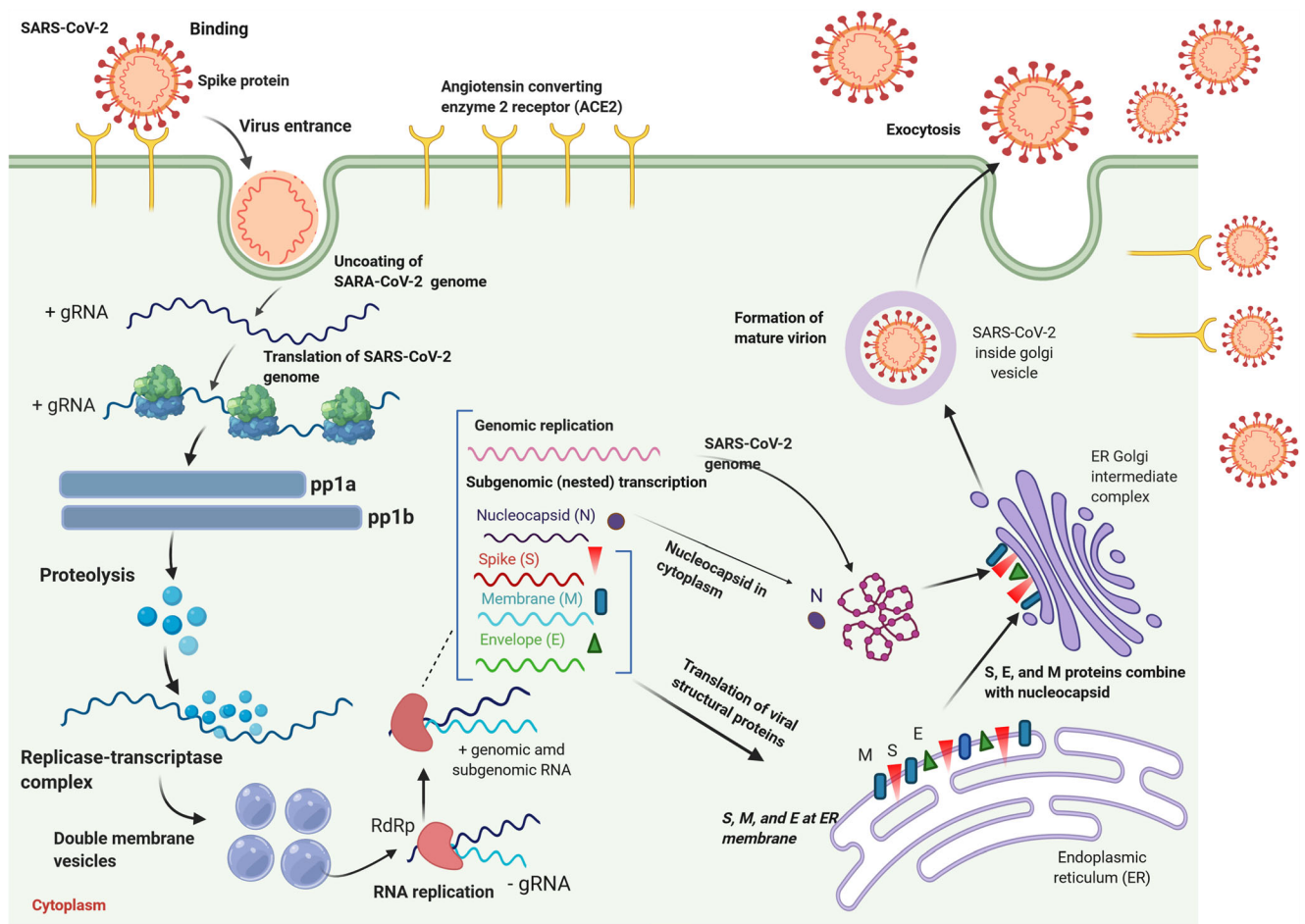
Fig. 3 SARS-CoV-2 life cycle in the host cell. The spike proteins of the virus bind to cellular receptors i.e., Angiotensin-converting enzyme 2 (ACE2). Upon entry via endosomal pathways, the viral RNA is released in the cytoplasm. Polyproteins are produced by the translation of ORF1a and ORF1b genes. The polyproteins (pp1a and pp1b) are cleaved by the protease of the Replicase-transcriptase complex (RTC). The RTC drives the production of RNA copies of the genome. A nested set of sub-genomic RNAs is produced in a fragmented transcription manner during the transcription. The closest ORF (of the segmented RNA) to the 5'end is translated to produce the structural proteins of SARS-CoV-2. In the cytoplasm, the nucleocapsid are assembled followed by budding into the lumen of the endoplasmic reticulum (ER)–Golgi intermediate compartment. Through exocytosis, the virions are released from the infected cell. Made with biorender.com.

Symptoms and general pathological findings

The mean incubation time for SARS-CoV-2 infection is around 5.2 days (Jiang et al. 2020). COVID-19 has different ways of affecting various people. Most infected people develop symptoms that are mild to moderate. About 1:1 ratio of males (50.7%) and female (49.3%) COVID-19 patients with an overall median age of 57.0 years were identified. Almost all cases are community-acquired. The most common clinical symptoms are fever (91.7%), fatigue (75%), cough (75%), and gastrointestinal problems (39.6%), while diabetes mellitus (12.1%) and hypertension (30%) were the most prominent comorbidities. Ground glass opacities (89.6%) were the most typical indicator of chest imaging technology findings. Several patients self-reported drug hypersensitivity (11.4%), and urticaria (1.4%). Allergic disorders have not been identified by patients at all. Eosinopenia (52.9%) and lymphopenia (75.4%) were found in most cases. Some of these patients

have been characterized by hypoxemia and dyspnea which can quickly lead to septic shock, coagulation disorder, and ARDS, and multiple organ dysfunction syndromes (MODS) within a week (Guan et al. 2020; Han et al. 2020; Wang et al. 2020a). The symptoms of SARS-CoV-2 and other beta-coronaviruses are generally similar. (Rothan and Byrareddy 2020). Mainly respiratory system infected by COVID-19 included the pathogenesis of RNAaemia, severe pneumonia, ground-glass opacities along cardiac injury (Guan et al. 2020; Rothan and Byrareddy 2020).

Microbiome: Barrier to SARS-COV-2 Studies showed that different case fatality ratio of COVID-19 in different individuals depend on viral load and immune response. However viral load is not distinct factor as asymptomatic and COVID-19 patients can have same viral load. Although in some acute phase numerous cycling T cells efficiently stop the SARS-COV-2 infection yet in many cases immune response is not able to stop infection. Microbiota composition appears to be a
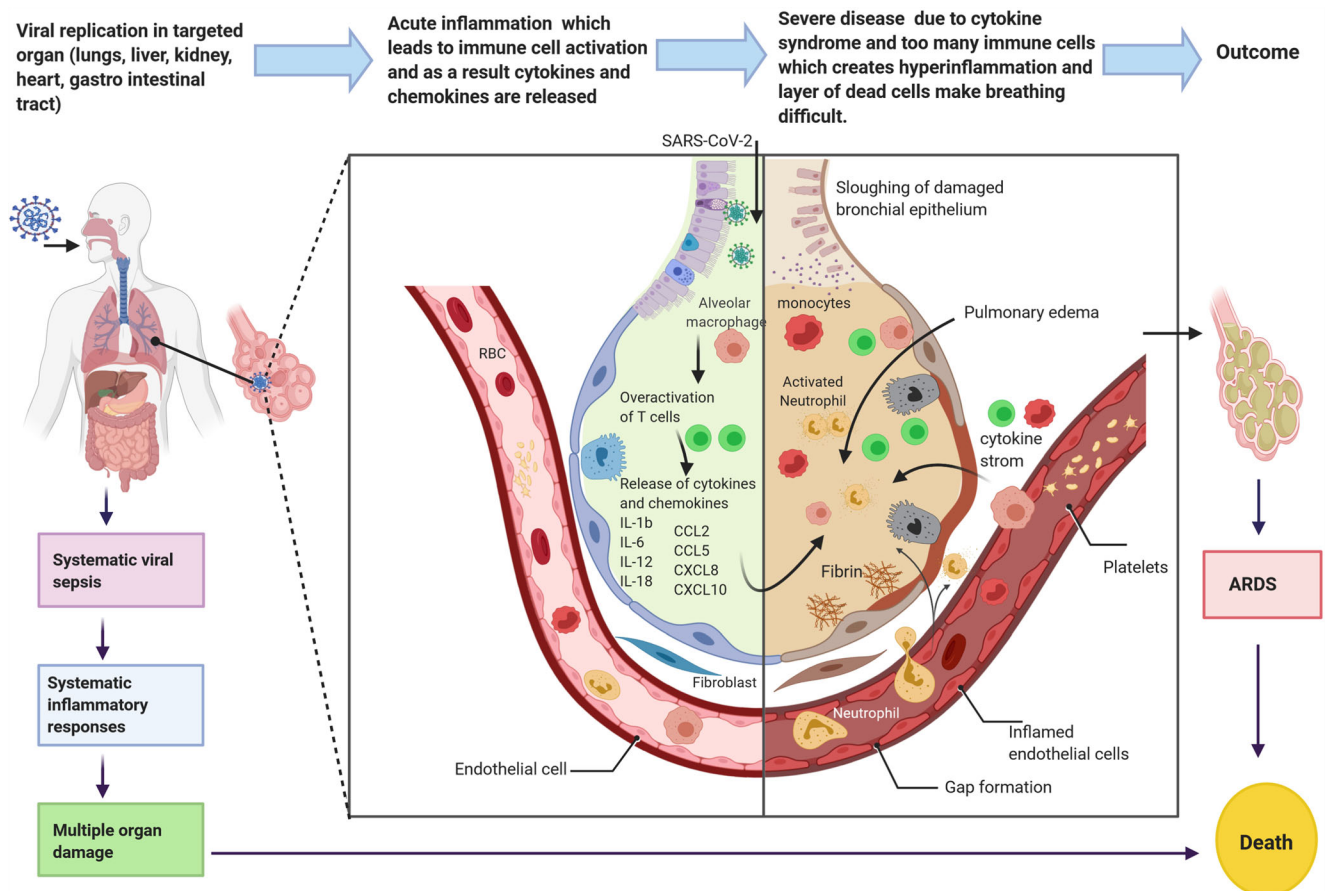
Fig. 4 Pathophysiological process of COVID-19. A normal alveolus (left) and a damaged injured alveolus of the acute respiratory syndrome (right). Made with biorender.com.

significant factor for different immune response of population to SARS-COV-2. Microbiota play a prominent role in reduction of pathogenic viruses such as infectivity of CoV viruses surpassed by using B.subtilis peptidoglycans. Microbiota also possess ability to modulate immune response. Daily consumption of probiotic strains greatly reduces the pro-inflammatory interleukin IL-6 which is much higher in SARS-COV-2 non survival patients so their chances of survival increase. Thus, it can be proposed that fatality ratio in COVID-19 case depend on health of microbiome. Modification of microbiome by probiotic intervention can protect from viral infection. Excessive use of antibiotics, stabilizers and food additives has led to increase level of microbial dysbiosis that is linked with chronic obstructive pulmonary disease (COPD), diabetes, heart disease, obesity and inflammatory disease. Obesity is linked with high case fatality ratio in COVID-19 thus improving the microbiome health by daily supplementation of postbiotic in form of wheat, sourdough bread, sour dairy products, yoghurts and other fermented products can significantly reduce the case fatality ratio (Janda et al. 2021).

Diagnosis of COVID-19 For the treatment and control of coronavirus disease (COVID-19), early diagnosis is essential. There are many technologies available for its diagnosis, but

mainly diagnostic tests fall into two major categories:Molecular testHigh throughput sequencing and real-time quantitative polymerase chain reaction (RT-qPCR) are two widely used nucleic acid detection technologies for COVID-19 (Zhou et al. 2020b). In clinical diagnostics, there is minimal use of high throughput sequencing technology because it is costly and highly dependent on the use of sensitive equipment. Therefore, RT-qPCR is the most efficient, general, and straight forward approach for the identification of SARS-CoV-2 in blood, respiratory droplets, or fecal contamination (Corman et al. 2020). The identification of RT-qPCR also shows high specificity and sensitivity for other coronavirus infections. It is accurate, fast, and cost-effective; however, using this method, we cannot specifically interpret the nucleic acid (NA) sequence of amplified gene variants, and therefore all target variants that have been effectively amplified are assumed to be valid. In addition to these drawbacks, the preparation of samples, laboratory standards, and technical inaccuracies can lead to inaccurate-negative findings (Adams et al. 2021). The sequencing system and batch of fluorescent quantitative kits were approved by the China Food and Drug Administration (CFDA) (Loeffelholz and Tang 2020). Some advanced fast viral nucleic acid diagnostics tests have been

devised to solve the issue of poor detection capacity (Yam et al. 2003).Serological testSerological tests are used for the detection of immunoglobulins against SARS-CoV-2. They have generated significant interest as an alternative to RT-PCR in the detection of acute infection. A significant advantage of these serological testing over RT-PCR is that they can identify patients who have been previously ill with SARS-CoV-2, even though they were not tested while they were acutely ill (Winter and Hegde 2020). As such serological tests may also be used as surveillance tools to better understand the epidemiology of SARS-CoV-2 and possibly inform individual risk of future illness. Serological testing can be effective for fast case identification and the successive sequence of events to effectively classify close contacts, and identify the cluster of cases (Bastos et al. 2020).Other techniquesSHERLOCK (Specific High Sensitivity Enzyme Receptor unlocking) tool based on the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas13 system was commonly used for the detection of dengue and Zika virus. Cas13a (formerly known as C2c2) can be reconfigured efficiently with CRISPR RNAs and provide a framework for precise sensing of RNA. The activated form of Cas13a participates in the "collateral" cleavage of neighboring non-selected RNAs upon the identification of its RNA target. The target RNA sequences then initiate Cas13a, and then the active Cas13a cleaves the reporter RNA authorizing the target RNA to be detected in real-time (Palaz et al. 2021). Recently, it is reported that this technology can be used for the detection of SARS-CoV-2 infection (Myhrvold et al. 2018). Another method is nanopore platform can both sequence and analyze the tests at the same time, thus letting us verify whether the tested sample contains SARS-CoV-2 in a few minutes after the sequencing of the sample (at the high speed). The results of this experiment showed the detailed and specific NA sequences and can thus represent whether the virulence genes get mutated during virus spread, hence provide substantial knowledge for more epidemiology analysis (Peto et al. 2021). Another interesting approach to RNA virus detection is the use of programmable RNA sensors. Green et al. created toehold switch sensors that attach to and can detect any RNA sequence essentially. Therefore, as SARS-CoV-2 is also an RNA virus, potentially the same method may be used to establish a rapid and precise identification (Kabir et al. 2021). Some clinical research laboratories should use certain immunological testing kits for targeting viral antigens. It is therefore important and urgent to develop other specific and sensitive auxiliary techniques for COVID-19 diagnosis (Shi et al. 2020).

Computerized Tomography (CT) imaging technology

CT scans or chest radiograph is a noninvasive, traditional, high precision, and high-speed imaging technology (Pan et al. 2020). Consolidative lungs opacification and bilateral lungs ground glass opacities often with circular morphology are found in the periphery of the central portion of the lungs. These kinds of CT images are also seen in patients infected with other coronaviruses. Studies showed that SARS-CoV-2 evolved as there is an accumulation of ground-glass opacities (Jeffrey 2020; Pan et al. 2020). According to the study, a CT scan needs to be considered for the diagnosis and comprehensive evaluation of COVID-19 disease in affected areas with a high probability of disease pre-testing. In short, CT imaging technology has high specificity for COVID-19 diagnosis. This technique is used already in medical practice (Xu et al. 2020c).

Treatment

Time is one of the dominant limiting aspects to pinpoint a potent cure. Research for a new potent molecule and its development is quite laborious and time taking process that is not suitable for adoption during the pandemic. Before marketing and making it public, a drug has to pass 3 different clinical trial phases (Cascella et al. 2020). FDA approves a drug and its treatment mechanism after ensuring the specific route it adopts is safe for the host's body. Consequently, the researchers go for drug repurposing in which identification and selection of potent molecules are done from pre-existing molecules in the library. Considering the structure and infection strategies the virus adopts, various phenomena can be used as targets for treatment including receptor binding and membrane fusion inhibition, RNA synthesis inhibition, enzyme inhibition, exocytosis inhibition of new viruses from the host cell, and so on (Wan et al. 2020a). With the help of therapeutic anti-inflammatory drugs, post-viral respiratory symptoms are tried to be diminished. To make a host win this battle, helping strategies such as plasma containing neutralizing monoclonal and polyclonal antibodies can be infused into the circulatory system of the patient (Chen et al. 2020b).

Antiviral drugs

Chloroquine (CQ), a drug well-known for its effectiveness in treating malaria and autoimmune disease and hydroxychloroquine, has shown encouraging inhibitory results against viruses. Such drugs obstruct the lysosomal activity and autophagy, changing signaling pathways membrane stability, and transcription mechanism, that inhibits cytokine formation and influencing the production of various costimulatory molecules (Schrezenmeier and Dörner 2020). Remdesivir (GS-5734) a nucleotide analog that inhibits RNA polymerases (RdRp) can also be used (Gordon et al. 2020). Both SARS-CoV-1 and SARS-CoV-2 viruses have 82% similar RNA and their RdRp enzyme shares 96% sequence similarity. So, the drugs effective against RdRp of

SARS-CoV can also be effective against SARS-CoV-2 RdRp. For Ebola virus treatment Remdesivir was tested for its effectiveness, hence, data about its safety, side effects had already been noted and could help in reducing time for clinical trials against COVID-19 (Amanat and Krammer 2020). Against RdRp in the genus Betacoronavirus, several other effective compounds and drugs such as favipiravir, ribavirin, penciclovir, galidesivir can also be used (Ko et al. 2020). For Th1 and Th2 induced Lung injuries, which is a postviral respiratory symptom in COVID-19 patients, several corticosteroids were used (Huang et al. 2020). As they inhibit cytokine-induced transcription factors (NFkB, AP1) thus obstructs viral replication (Kovalovsky et al. 2000). Baricitinib inhibits the AAK1(Adaptor-related protein complex 2) gene that initiates clathrin assembly during endocytosis by interacting receptors present on the cellular membrane and collects accessory factors for endocytosis thus it inhibits receptor-mediated viral endocytosis (Stebbing et al. 2020).

IDX-184, Ribavirin, and Sofosbuvir can tightly bind to RdRp leading to viral replication inhibition. More promising results were shown by IDX-184 as compared to Sofosbuvir as inhibitors for RdRp (Elfiky 2020).

Combination therapy involves trials for giving combined formulas that could give more effective results. Remdesivir in combination with lopinavir/ritonavir is under clinical trial to check its efficacy (Grahadi et al. 2020). Lopinavir works against retroviruses by inhibiting protease, used for treating HIV infection, and for COVID-19, it is under consideration. Ritonavir which is also a protease inhibitor (inhibits cytochrome P450 3A) enhances lopinavir's half-life and their combined use showed improved effectiveness. Ribavirin in combination with interferon-α was recommended by the National Health Commission of China (Grahadi et al. 2020; Lim et al. 2020). Oseltamivir, a neuraminidase inhibitor used against the influenza virus, can also be combined with ritonavir/lopinavir. Antiviral nelfinavir an HIV-1 and HIV-2 protease inhibitor combined with cepharanthine that prevents viruses from attaching and entering the host cell. Because of their different action mechanism, their combination shows a synergistic effect in the in-vitro experimental setup and blocks the replication of viruses as shown in Table 2. Predicted effectiveness can be enhanced by the combined formula that decreases viral replication and transmission risks (Dong et al. 2020; Muralidharan et al. 2020).

Vaccination

During the last decade, much research in the field of vaccine development has been done that has resulted in the formation of various candidates including DNA vaccines, recombinant proteins, and cell-culture-based vaccines. Studies done during MERS and SARS-CoV vaccine development make us understand designing a pathway for a vaccine formation. We already have a much clear picture of target antigens that could play an important role at the platform for SARS-CoV-2 vaccine development. However, due to polygenetic differences between these viruses, neutralizing antibodies for the former viruses could not be used in SARS-CoV-2 (Luke et al. 2016). Chinese researchers identified the first genomic sequence of SARS-CoV-2 and have made it public (Amanat and Krammer 2020).

Recently, 200 expectant vaccines list has been released by WHO that are under pre-clinical trials and can be divided into 5 categories based on the nature of the antigen introduced: weakened live vaccines, DNA vaccines, vital replicative, and non-replicating vector vaccines, vaccines including fragments of pathogens (Docherty et al. 2020). 60 number of vaccines have already entered phases of clinical trials. ChAdOx1 nCoV-19 is made from a weakened version of a common cold virus adenovirus (ChAdOx1) virulent in chimpanzees. It has been modified in a way that it could not replicate in the human body. Tested on more than 300 people, it showed safe results with temporary side effects till 23rd April 2020 (Pang et al. 2020). The attenuated virus is only able to produce spike protein present on the surface of SARS-CoV-2, stimulating antibodies production in the host preparing it to cope up with COVID-19 infection in the future (Pandey et al. 2020). COVID-19 vaccines based on the whole inactivated SARS-CoV-2 include CoronaVac (Sinovac Biotech, China) and BBIBP-CorV (Sinopharm, China). These vaccines based on inactivated SARS-CoV-2 (Isakova-Sivak and Rudenko 2021). The immune response produced against Spike proteins but also other SARS-CoV-2 antigens. Vaccines based on Spike protein mRNA are BNT162b2 (Pfizer, US) and mRNA-1273 (Moderna, US). Results of the phase III trial enrolling 45,539 participants demonstrated BNT162b2 vaccine to be 95% effective. And results of the phase III trial US enrolling 30,000 showed mRNA-1273 vaccine to be 94% effective (Forni and Mantovani 2021). However further work needs to be done in this direction.

Convalescent plasma transfusions

Specific antibodies of human origin can be obtained from plasma of a recovered patient who was affected by a specific disease had developed humoral immunity. Convalescent blood products (CBP) that can be obtained artificially include convalescent whole blood, just plasma, or serum, intravenous or intramuscular immunoglobulin, Ig, and polyclonal or monoclonal antibodies (Marano et al. 2016). A situation where there is a continuously rising curve of the pandemic, the absence of an accurate and patented treatment, and no specific drug or vaccine has been found that could prevent the infection or completely cure it. This situation made researchers move toward a historic plasma transfusions method that can

Table 2 Some of the common candidate drugs against SARS-CoV-2

Candidate Drug	Mechanism	References
Hydroxychloroquine	Lowers endosomal pH and accumulate free cytotoxic heme	(Magro 2020)
Remdesivir	Adenosine analogue causes premature termination of viral progeny	(Tu et al. 2020)
Favipiravir	Viral RNA-dependent RNA polymerase inhibitor	(Khambholja and Asudani 2020; Tu et al. 2020)
Azithromycin	Immunomodulatory effects	(Damle et al. 2020; Tu et al. 2020)
Ribavirin	Nucleoside analogue brings about mutation in viral genome	(Hung et al. 2020)
Galidesivir	Adenosine analogue causes mutation in viral genome	(Li and De Clercq 2020; Tu et al. 2020)
Baricitinib	Janus kinase 1 and 2 inhibitor	(Zhang et al. 2020)
Oseltamivir	Competitive neuraminidase inhibitor	(Lythgoe and Middleton 2020)
Lopinavir	Antiretroviral, binds to viral protease	(Meini et al. 2020)
Ritonavir	Viral protease inhibitor	(Sa Ribero et al. 2020)
Interferon alpha	Cytokines that provide innate immunity	(Li et al. 2020a)
Corticosteroid therapy	Steroidal hormones that can modulate overactive immune responses	(Li et al. 2020b)
Conveselant plasma	Contains Antibodies, enzymes and other proteins protective against virus	(Li et al. 2020b; Lythgoe and Middleton 2020)
Tissue plasmogen activator	Assists in dissolving clots formed due to vascular leakage, alleviates breathing difficulties associated with COVID-19	(Li et al. 2020b; Lythgoe and Middleton 2020)

play a significant role in passive immunization and post-infection replacement therapy in severely ill patients with COVID-19 infection. Infectious diseases have been treated successfully using convalescent plasma therapy. Mortality rate and viral load reduction during SARS-CoV and MERS-CoV outbreaks are the results of plasma replacement therapy (Zhang and Liu 2020). Until the development of a completely effective and approved treatment, serum infusion from recovered patients is going to be very helpful in the current situation of the COVID-19 pandemic (Schroeder Jr and Cavacini 2010). However, with the advancements in the exploration of specific antiviral drugs against SARS-CoV-2; there will be a decrease in the plasma-based therapies.

Passive immunization

Administration of pathogen-specific antibodies can help a host to develop a rapid immune response that remains for a shorter period against specific pathogens (Ying et al. 2014). To prevent the actual infection, vaccination or immunization can be used. The plasma containing a combination of various monoclonal antibodies that have specificity for different epitopes can be used to neutralize a wide range of native and mutant viruses (Abbas et al. 2019; Shanmugaraj et al. 2020). The drawbacks related to intravenous Ig and whole plasma therapy, such as impurity, high risk of blood-borne pathogen contamination, have been overcome by screening monoclonal antibodies which can provide effective therapeutic methods with reduced side effects (Lu 2020). Even though the monoclonal Ig technique has given encouraging results in neutralizing antigens in SARS-CoV and MERS-CoV, producing them at a large-scale is laborious, time, and money consuming. Polyclonal antibodies are also under clinical trials. From

animal models testing for IgG during MERS-CoV infection, we have already been introduced with the technique of producing IgG antibodies by transgenic cows, and a similar approach can be used for COVID-19 (Duan et al. 2020).

Conclusion

Coronaviruses are back in the spotlight because of the recent SARS-CoV-2 outbreak. The analysis of the coronaviruses in mammals and bats has significantly altered our conception of the importance of zoonotic origin and animal reservoirs. Effective preventive strategies must be put in place to control it against the global spread. In the meantime, further consideration should be given to the intermediate host and the mechanism of cross-species spread. Further work is needed to investigate the pathogenesis and replication of coronavirus. It must be noted that diagnostic performance is going to be affected by the type of specimen collection and the time of symptoms development so, steps for either treatment or prevention must be taken accordingly. Evaluation of drug dosage should be done carefully in case of patients suffering from cardiovascular diseases or multiple organ failure. Transverse study of seroprevalence must be done to find factors like age-specificity and spatial distribution, if present, in case of prior exposure. Additionally, considerable efforts are required to develop antiviral drugs and vaccines. Continuous examination of immunological parameters should be done in recovered patients to observe long-term impacts on the immune system. The associated factors that help in protection against COVID-19 should be identified as they may become a key for developing immunotherapeutic or vaccines. The outbreak of COVID-19 represents a setback to our preparation to tackle this pandemic. Continued research in this field will shed light

on the evolutionary pathway of SARS-CoV-2, with significant implications for the prevention and control of COVID-19 in humans.

Abbreviations ACE2, Angiotensin-Converting Enzyme 2; ADE, Antibody-Dependent Enhancement; APC, Antigen-Presenting Cells; APN, Aminopeptidase N; ARDS, Acute Respiratory Distress Syndrome; CBP, Convalescent Blood Products; CEACAM1, Carcino Embryonic Antigen-related Cell Adhesion Molecule 1; CFDA, China Food and Drug Administration; CFR, Case fatality ratio; COVID-19, The Coronavirus disease-2019; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CT, Computerized Tomography; DIC, Disseminated Intravascular Coagulation; DMV, Double-Membrane Vesicles; DPP4, Dipeptidyl Peptidase 4; DRF, Damage Response Framework; ERGIC, Endoplasmic Reticulum Golgi Intermediate Compartment; FDA, Food and Drug Administration; HLA, Human Leukocyte Antigen; IBV, Infectious Bronchitis Virus; ICTV, International Committee on Taxonomy of Viruses; mAb, monoclonal antibodies; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; MHC, Major Histocompatibility Complex; MODS, Multiple Organ Dysfunction Syndromes; MOF, Multiple Organ Failure; ORF, Open Reading Frame; PdCoV, Porcine Delta Coronavirus; PRRs, Pattern Recognition Receptors; RAS, Renin-Angiotensin System; RER, Rough Endoplasmic Reticulum; RTC, Replicase-transcriptase complex; RT-qPCR, Real-Time Quantitative Polymerase Chain Reaction; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; WHO, World Health Organization

Author's contribution HS, MM, SI, MS, AS conceived the idea, designed the conceptual framework, and wrote the manuscript. MD, MA did proofreading. HS made the diagrams and arranged tables. HS, AS, MD compiled the final draft. All authors have contributed, seen, and approved the manuscript.

Declaration

Conflict of interest The authors declare no conflict of interest

Ethical approval Not applicable

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