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Review article

COVID-19: A brief overview of diagnosis and treatment

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Keywords: SARS-CoV-2, COVID-19, pandemic, diagnosis, respiratory disease, therapy, Drug evaluation history.

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Abstract

In late December 2019, several pneumonia cases caused due to 2019-nCoV were reported in Wuhan, China. The disease caused by this novel virus was termed as Coronavirus Disease-19 (COVID-19) by WHO on the 11 February, 2020. The outbreak of COVID-19 has spread to more than 150 countries with over 12,552,765 confirmed cases and over 561,617confirmed deaths worldwide as of July 12, 2020. The Department of Health and Human Services (HHS) and WHO have declared COVID- 19 as a global emergency affecting multiple countries and has made provisions to meet the requirements across the globe addressing the disease. The current review systematically summarizes the overview of the current status of COVID-19 across the globe along with the virulence characteristics of the pathogen, diagnostic approaches, the recent trends in diagnosis, therapeutics under study, and approved therapies for the treatment of the disease. A short summary of all the ongoing work in India, with respect to technologies to combat COVID-19 have been discussed in brief herein. This concise study shall be helpful for the future researchers with the updated knowledge on COVID- 19.

Introduction

Towards the end of December 2019, a bunch of pneumonia cases caused by an unknown pathogen were reported in Wuhan City, Hubei province in China. The causative agent was later found to be a novel coronavirus, provisionally named as 2019 novel coronavirus (2019-nCoV) by World Health Organization (WHO) on January 7 [1]. On 30 January 2020, WHO declared this novel disease outbreak as the sixth public health emergency of international concern [2, 3]. On February 11, 2020, the International Virus Classification Commission (ICTV) categorized 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [4], based on the study performed by the coronavirus study group [5]. The name was selected since the virus is genetically similar to the coronavirus which caused the SARS outbreak of 2003. Also, on February 11, WHO named the highly infectious disease condition as Coronavirus Disease 19 (COVID-19) which is caused by SARS-CoV-2 [6]. An unprecedented outbreak of this disease has now spread to more than 150 countries with over 12,552,765 confirmed cases and over 561,617 confirmed deaths worldwide (Figure 1) as of July 12, 2020. On 11th of March 2020, COVID-19 was declared as a pandemic disease by WHO and calls for the immediate action [7].

It is known that coronaviruses circulate in a range of animals. Sometimes these viruses make a jump from animals to humans and the process is called a 'spillover'. MERS-CoV and SARS-CoV are known to be transmitted from the intermediate hosts, camels and civet cats, respectively [8]. Though intermediate source and transfer of SARS-CoV-2 is not known, the fast human to human transfer has been confirmed. It is spread from human-to-human by droplets or direct contact. The mean incubation period of infection is predicted to be 6.4 days and a basic reproduction number of 3.28, with a median of 2.79 [9]. The spread of this disease is faster than any other coronavirus disease that have crossed the animal-human barrier. SARS-CoV-2 has high transmissibility and

infectivity, in spite of low mortality rate as compared to SARS and MERS. Currently, there is no well-established vaccine or antiviral treatment for COVID-19. Disease management in most of the nations involves treating of symptoms, supportive care, and isolation. In this review, we summarize the current understanding of the COVID-19, nature of the SARS-CoV-2, its characteristics, diagnostics and therapeutics.

Coronaviruses

Coronaviruses types and genomic organization of SARS-CoV-2

Coronaviruses consist of a large diverse family of viruses. They contain a core of a genetic material surrounded by an envelope with protein spikes which gives an appearance of crown (Figure 2). Crown in Latin is called corona and that's how these viruses get their name. Coronaviruses (CoVs) belonging to the family Coronaviridae are enveloped, single positive stranded RNA genome, ranging from 26 to 32 kilobases in length which is probably the largest known genome for RNA virus [10]. They can be categorized into four genera: Alpha-, Beta, Gamma-, and Delta coronavirus as described in Table 1. Alphacoronaviruses are human coronavirus NL63 (HCoV-NL63), while the beta coronaviruses include the most commonly known SARS-CoV and MERS-CoV [10].

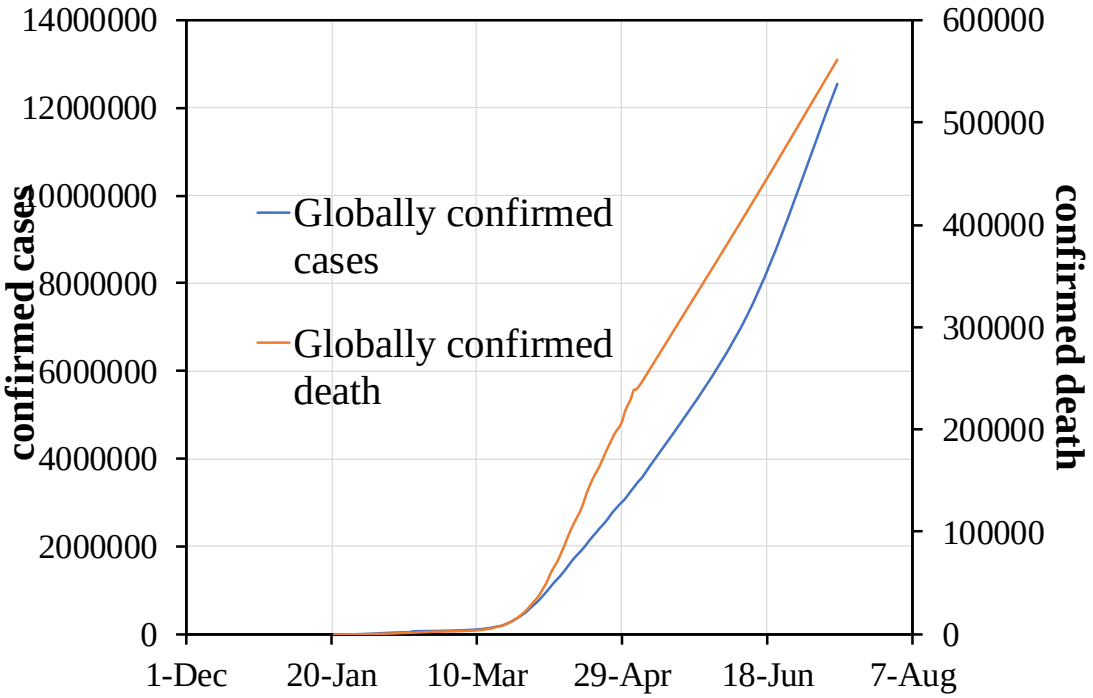

Figure 1. Global trend of confirmed COVID-19 cases and associated deaths from January 21 through July 12, 2020. (Data were obtained from WHO Coronavirus Disease (COVID-2019) Situation Reports (Coronavirus Disease (COVID-2019) Situation Reports 1−174; World Health Organization, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

Table 1. Types of Coronaviruses.

Genus	Virus Name
Alphacoronaviruses	Human coronavirus 229E (HCoV-229E) Human coronavirus NL 63 (HCoV-NL63)
Betacoronaviruses	Human coronavirus HKU1 Human coronavirus OC43 (HCoV-OC43) Middle East respiratory syndrome-related coronavirus (MERS-CoV or HCoV-EMC; causes MERS) Severe acute respiratory syndrome coronavirus (SARS-CoV-1; causes SARS) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2or 2019-nCoV; causes COVID-19)
Deltacoronaviruses	IBV, TCoV
Gammacoronaviruses	Night Heron CoV, Wigeon CoV

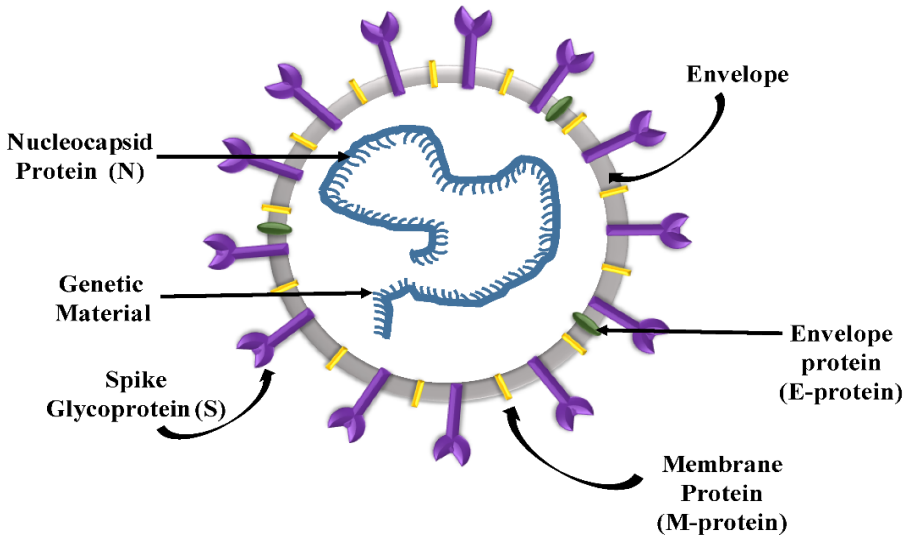

Figure 2. Structure of human coronavirus.

These coronaviruses can causes respiratory and sometimes gastrointestinal symptoms. Respiratory diseases range from common cold to pneumonia and in most people the symptoms tend to be generally mild. However, there are some types of coronaviruses which can cause severe diseases. These include the SARS-CoV, first identified in the Guangdong, China in November 2002 [11] and MERS-CoV that was first identified in Saudi Arabia in 2012 [12]. The SARS-CoV-2 was first identified in China in 2019. The genomic characterization revealed that SARS-CoV-2 is closely related (with 88% identity) to two bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, found in 2018 in Zhoushan, China, but genetically distinct from SARS-CoV (about 79% similarity) and MERS-CoV (about 50% similarity) [13]. Therefore, it has been postulated that bats could be the possible primary reservoir. Phylogenetic analysis showed that SARS-CoV-2 belong to the subgenus Sarbecovirus of the genus Betacoronavirus [13].

The SARS-CoV-2 genome, like other betacoronaviruses, is a single-stranded, non-segmented RNA genome, containing two flanked untranslated regions (5′-and 3′-UTRs) along with a single long open reading frame encoding a polyprotein [14, 15]. The single-stranded RNA genome of the SARS-CoV-2 was 29891 nucleotides in size, encoding 9860 amino acids [15]. The arrangement of the genome of SARS-CoV-2 is in the order of 5′, replicase genes (ORF1a/b)encoding large replicase polyprotein 1a (pp1a) and pp1ab, genes encoding structural proteins (spike glycoprotein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N) and several other accessory genes, such as ORF3b and OFR8 [15]. The polyproteins (pp1a and pp1ab) are later cleaved by papain-like cysteine protease (PLpro) and 3C-like serine protease (3CLpro) to yield non-structural proteins, such as RNA-dependent RNA polymerase (RdRp) and helicase (Hel), which are necessary enzymes involved in the transcription and replication [14-16]. The structural proteins (S, E, M and N), are a must for virus–cell-receptor binding and interactions during viral entry and virion assembly [14,16]. These proteins therefore, can serve as potential targets to develop antiviral agents against SARS-CoV-2.

Entry mechanism of SARS-CoV-2

All the coronaviruses enter into the host cells by spike glycoprotein that gives it a crown-like appearance due to the presence of spikes on their surface. The spike protein is composed of two domains; S1 and S2 that are considered to be the most essential for host tropism and transmission of the disease. Figure 3 depicts the entry mechanism of SARS-CoV-2 in the host cell.

It is mediated through receptor binding and membrane fusion mechanism [13]. The receptor-binding domain (RBD) of betacoronaviruses is generally situated in the C-terminal domain of S1 [13, 17]. Lu *et al.* performed the homology modelling of RBD and found that SARS-CoV-2 is similar structure to that of SARS-CoV in terms of RBD, though there are some amino acid variations at key residue [13]. Structural analysis strongly suggests that SARS-CoV-2 may use host receptor angiotensin-converting enzyme 2 (ACE2) to enter the cells [18].

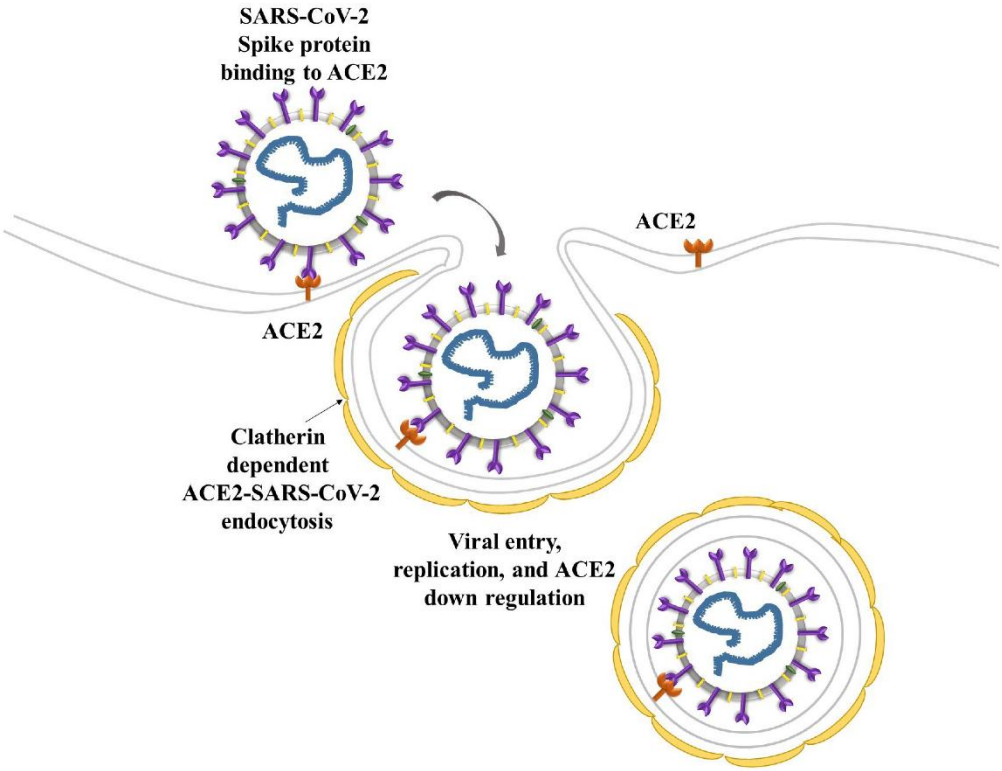

Figure 3. Entry mechanism of SARS-CoV-2 into the host cell.

The study on molecular modeling suggested that SARS-CoV-2 RBD has a stronger interaction with ACE2 as compared to SARS-CoV [19]. The entry in the host cells are mediated using both the endosomal pathway and/or the non-endosomal pathway [16, 20]. The endosomal pathway begins with the conformational change in the S protein after binding to the receptor which facilitates the fusion of envelope with the cell membrane and entry in the cell [4]. Upon entry into the host cells, the virus releases its genome as a single-stranded positive RNA [4]. Further, using the host cell protein translation machinery, it is translated into viral polyproteins, which are then cleaved into effector proteins by viral proteinases [21]. The interaction between the S protein of the virus and ACE2 on the host cell surface is significant because it initiates the infection process.

Pathogenesis

The pathogenesis of the life-threatening coronavirus initiates with the binding of the spike protein of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) of the human body and gain access to the host environment. The virus intelligently maneuvers the pathogenesis by operating its two functional subunits (S1 and S2). The potential role of S1 is to bind the virus to the receptor, and S2 helps in the fusion of viral and cellular membranes. The presence of the furin cleavage site, cleaved entirely during biosynthesis in SARS-CoV-2, stands distinct from other SARS-CoV viruses that make the former virus more violent in pathogenesis. On the contrary, the other SARS-CoV viruses gain access without cleavage to the host cell. The ingression of the SARS-CoV-2 into the host human body triggers the stimulation of the immune response in two phases, namely, innate and adaptive immune response. The human body confronts with an instantaneous innate immune response, the first line of defense action leading to the rapid expression of interferon type-1 cells (IFN-1) [22]. The dysregulation of the defensive phase of protection due to surge in the replication of virus propagates to the development of 'cytokine storm,' a condition where multiple chemokines and cytokines, namely, interleukins (ILs) and tumor necrosis factor (TNF), monocyte chemoattractant protein (MCP) are infiltrated in the plasma in response (e.g., IL1β, IL-2, IL7, TNF-α, GSCF, monocyte chemoattractant protein-1 MCP1) [23]. Several case reports of autopsy suggest the presence of the coronavirus trace particles in the cytoplasm of tracheal and bronchial mucosa epithelial and alveolar type II pneumocytes under electron microscopy. Also, multiple reports show the lesions in multiple organs and tissues with significant damages seen in the

pulmonary region by this virus. These reports form the basis to consider the virus responsible for causing respiratory dysfunction and multiple organ failure, which may be due to aggression of the cytokine storm, causing self-attack and creating an extreme worst condition of the patient. Some case reports also show patients progressing with Acute Respiratory Distress Syndrome (ARDS) and septic shock with multiple organ failure leading to death in about 10% of patients. The extreme cases observed in ARDS and lung damage in this pandemic suggests the ACE2 receptors to be the entry site for the SARS-CoV-2 virus as they are present in excess in the ciliated cells of the airway epithelium and alveolar cells of humans [23, 24].

Clinical manifestations

The symptoms observed in patients infected with SARS-CoV-2 are the most common, as observed in the influenza virus. The SARS-CoV-2 viral infection is clinically manifested as fever, dry cough, dyspnoea, chest pain, fatigue, and myalgia in general, along with lesser-known symptoms like headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting. The majority of the cases have shown bilateral pneumonia. In contrast with SARS-CoV and MERS-CoV, the SARS-CoV-2 infected patients show fewer upper respiratory tract symptoms, namely, rhinorrhoea, sneezing, or sore throat, which again infers the virus targeting the lower respiratory tract where enormous ACE2 receptor cells are known to be present. In the case of pregnant and non-pregnant women, no differences were observed in signs and symptoms. Critically-ill COVID 19 patients in ICU have reported complications such as hypoxemia, acute ARDS, arrhythmia, shock, acute cardiac injury, and acute kidney injury leading to multiple organ failure [25, 26]. The most general signs and symptoms of COVID 19 patients are shown in Figure 4.

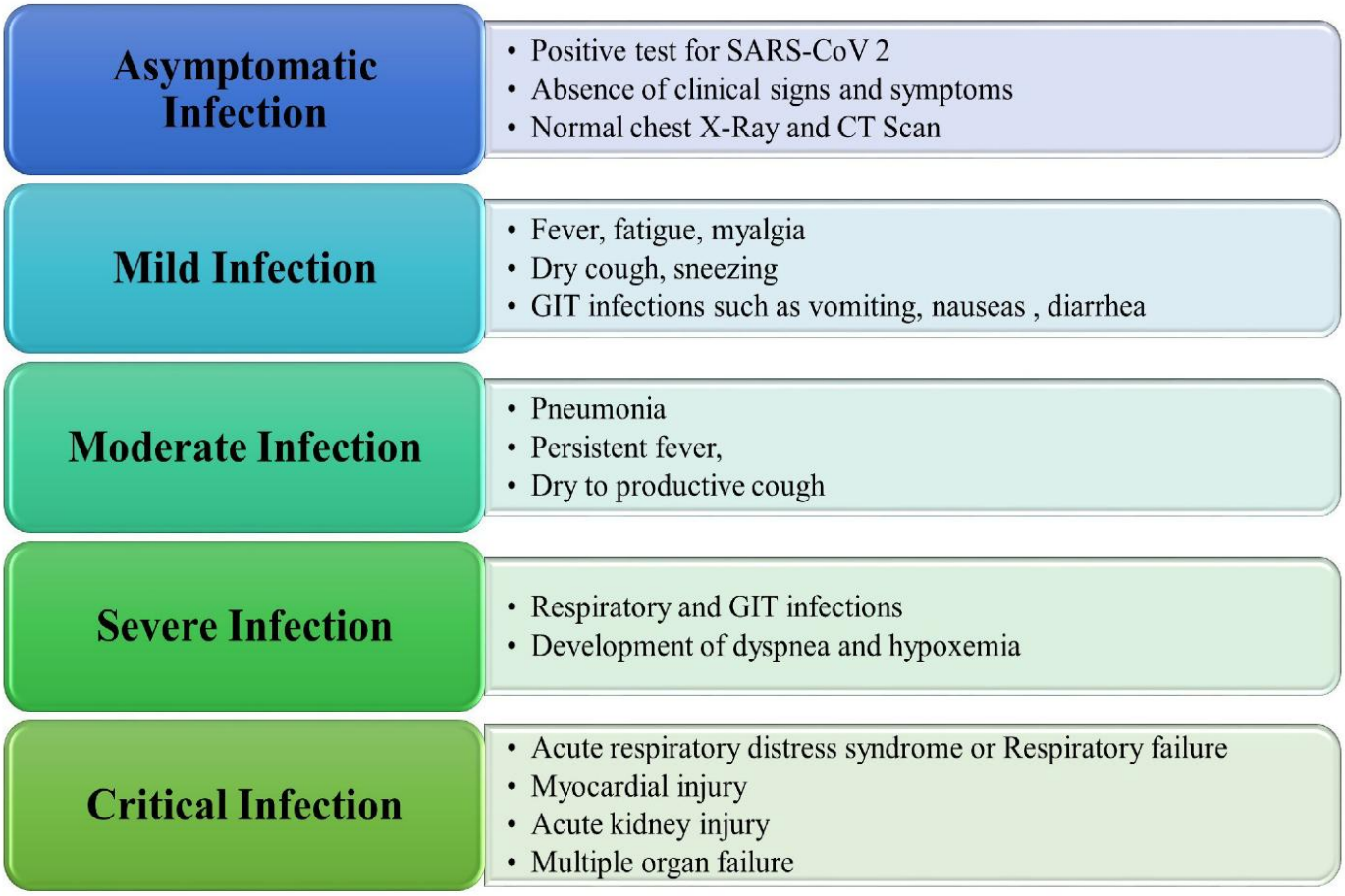

Figure 4. Clinical manifestations of COVID-19.

Diagnosis of COVID-19

During the outbreak of pandemic COVID-19, rapid collection, and accurate testing of the sample specimens collected from the suspected patients is of utmost priority to manage the clinical situation and control the community spread of the disease. Centers for Disease Control and Prevention (CDC) [27] and WHO [28] have published a guideline that recommends consideration of clinical manifestations and epidemiological factors as the frontline diagnosis of the suspected patients. The screened patients will then be taken for clinical testing using the diagnostic kit in order to rationalize the use of kits in a situation where there is a limited supply of the kits. On February 10 2020, Geneva, Switzerland, WHO, and Foundation for Innovative New Diagnostics (FIND) have formalized a strategic collaboration to strengthen the diagnosis of COVID-19. Both organizations work closely to update on the technical guidance of laboratory testing and provide access to i*n-vitro* diagnostic kits by several manufacturers across the world to low and middle-income countries [29]. The following website https://www.finddx.org/covid-19/pipeline/ provides information on the diagnostic kits which are in the pipeline commercially and under development for diagnosis of COVID-19. On the basis of the determination made by the Secretary of the Department of Health and Human Services (HHS) on February 4, 2020 that there is an emergency situation concerning public health, the health regulatory bodies can proceed to call for the authorization of emergency use of *in vitro* diagnostics which are not approved earlier to meet the diagnostic requirements for the rapid diagnosis and containment of the disease [30]. In response to this guideline, USFDA has made available the molecular-based laboratory-developed tests authorized under Emergency Use Authorization (EUA) on March 31, 2020, for use in the United States of America (USA). These tests are to be performed in the laboratories that have developed the test and certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA) [31].

Since the clinical manifestations of the patients infected with COVID-19 are very generalized, including respiratory symptoms, cough, fever, dyspnea, and viral pneumonia, laboratory examination is very crucial for such patients to be diagnosed [6]. Various laboratory examinations include the Nucleic Acid Amplification Test (NAAT) using the Reverse Transcriptase-Polymerase Chain Reaction or real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) method; Computerized Tomography (CT scan); Point of Care testing (POCT); Serological assays for the detection of IgG and IgM antibodies, and the basic haematological parameter assessment. The various strategies adopted for the screening of the symptomatic and asymptomatic patients of COVID 19 are shown in Figure 5.

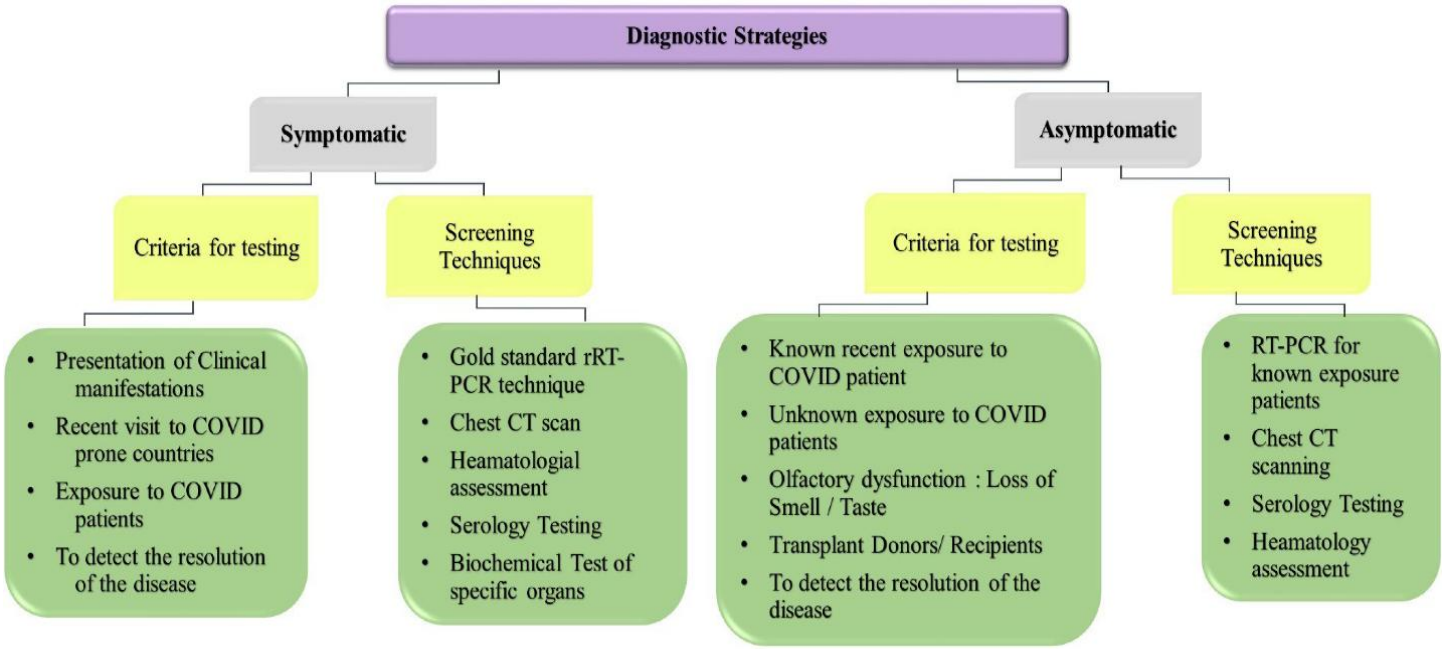

Figure 5. Diagnostic Strategies.

Nucleic acid amplification test (NAAT)

The CDC and WHO health regulatory agencies have passed the technical guidance to the clinical practitioners of the countries to examine the sample specimens (oropharyngeal secretions, nasopharyngeal secretions, sputum, serum) collected from the suspected patients of SARS-CoV-2 using the rRT-PCR method due to its selectivity and specificity [28, 32]. This method is characterized as the "gold standard" for SARS-CoV-2 detection [33].

NAAT is a molecular diagnostic assay technique used to amplify the copies of the minute genetic material present in the sample specimens to a detectable amount and are analyzed using specific instruments. NAAT comprises RT-PCR based and non-PCR based like isothermal nucleic acid amplification (i.e. loop-mediated isothermal amplification (LAMP) and nucleic acid sequence-based amplification) [33]. The basic principle of the RT-PCR test involves the extraction of the genetic material present in the regions of nucleocapsid by use of the reagents consisting of the primers, probes, reverse transcriptase and DNA polymerase enzymes, and the buffer solution. Once the extraction is completed, viral RNA sequence is converted to complementary DNA (cDNA) using the reverse transcriptase enzyme. During the PCR reaction, a single copy of cDNA is amplified to several copies during the heating and cooling cycle at specific temperatures. The PCR product containing the amplified concentration of the DNA strands results in the fluorescent signal. At every amplification cycle, the fluorescence intensity is measured using the specified instruments for the detection. When the threshold of fluorescence intensity outbars the limits, the patient is declared as positive to SARS-CoV-2 [34]. The real-time RT-PCR method developed by different researchers targets the Orf1a, Orf 1b, Orfa, nucleocapsid (N) gene, RNA dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and E (envelope) genes of SARS-CoV-2 [35]. Most of the diagnostic kits approved for use under EUA in various countries target one of the genes or multiple genes of the SARS-CoV-2 genome.

Another approach of NAAT is LAMP, which is a novel method used for exponential amplification of DNA and RNA sequences. The method is highly efficient under isothermal conditions, highly specific for target sequence, and can produce a detectable number of copies within less time as compared to the PCR method [36]. The method is very simple and easy to perform with the defined primers. Laura Lamb *et al.*developed a rapid detection kit for the diagnosis of the novel coronavirus using the RT-LAMP method. The method involved the use of 6 primers and can produce copies in less than 30 minutes. The developed method showed high specificity for SARS-CoV-2 when the selected primers were compared with sequences of other known coronaviruses [37]. The RT-LAMP method is easy to use, simple, specific, accurate, rapidly detecting and requiring less laboratory infrastructure over the WHO recommended rRT-PCR technique for the diagnosis of SARS-CoV-2 [38]. In the outbreak situation like COVID 19, such rapid diagnosis kits become the need of the hour.

Although the rRT-PCR testing is considered to be the gold standard diagnostic test, the lack of sensitivity and specificity shows false negative and false positive cases that pose the challenges in identifying the suspected COVID patients. The rapid mutation observed in several studies of the SARS-CoV-2 genome can be one of the causes producing false-negative assays that tend to mismatch the primer and probes with the target genome sequences. Additionally, the target channel for the perfusion of the present coronavirus being ACE-2 receptor present abundantly in lower respiratory alveolar cells, it is suspected that the high viral loads to be present in such region and minimal in the nasal, oral, nasopharyngeal, oropharyngeal regions [39]. On the contrary, some studies also show the accurate site of sampling to be the nasopharyngeal region that contains a high viral load. Hence, the sample specimens collected from the upper respiratory tract regions mainly from nasal or oral may show false-negative results [40]. Other reasons showing the false-negative cases could be the day of sample collection post-infection of the virus, i.e., during the presymptomatic and asymptomatic conditions, anatomical location carrying the sufficient viral loads, sampling technique of the healthcare provider, handling, storage, and transportation conditions of the sample specimens. Some reports also have shown false-positive cases, which may be attributed to the sample contamination problems. Hence, such scenarios should not be overruled, and the patients suspected with the symptoms should be under vigilance to limit the spread of the disease [41].

All the diagnostic kits which are approved by USFDA under EUA, Research use only (RUO), and which are under development are provided at the following weblink https://www.finddx.org/covid-19/sarscov2-eval-molecular/ along with the target genes of the diagnostic kit.

Computerized Tomography (CT Scan)

The current scenario with the extreme spike in the cases of COVID-19, low sensitivity, and low availability of RT-PCR based diagnostic kits leads to misdiagnosis and delayed diagnosis. Due to this inefficiency, a large population remains undiagnosed without immediate treatment and poses a threat to the community transfer [42]. Chest CT is a routine imaging technique for the diagnosis of pneumonia, which can now be extended to diagnose COVID-19. It is comparatively simple, sensitive, and faster to RT-PCR based diagnosis [6]. It can be beneficial in diagnosing patients suspected to have contracted SARS-CoV-2 infection but have reported

negative RT-PCR results [43, 44]. Several studies have reported the use of CT imaging as the auxiliary examination in the diagnosis of COVID pneumonia. Wang *et al.* reported temporal changes in the CT findings showing an increase in the lung abnormalities quickly after the onset of symptoms with peak levels reaching 6-11 days followed by persistently high levels in a longer duration [45].

Point of Care Testing (POCT)

The conventional point of care testing remains the lateral flow immunoassay that detects the antibodies in sample specimens developed due to infections. Increased availability of the rapid detection kits based on POCT helps in the early isolation of the diseased patients [46]. Hence, USFDA and WHO health regulatory agencies are actively taking steps for increased availability of the diagnostic kits at the state level. Many researchers are working on novel methods to develop rapid, sensitive, accurate POCT kits to enable faster diagnosis of the disease. A novel method named "Blue paper" test, which is under development by Mikael Franzén is a rapid, inexpensive test based on Sandwich Eliza principle with color change detection. The researcher is working on 2 alternatives for the detection of the COVID-19. The first approach being the paper-based antigen-antibody complexation approach, and the second being the use of the same reagents in the test-tube form [47]. In a recent news release, Iceni Diagnostics have expressed their proposal to work on a novel glycan based diagnostic approach for the detection of COVID-19. The company has developed glyconanoparticle based diagnostics for the diagnosis of the Influenza virus. Generally, viruses are covered by the sugar chains named glycans, and they use them for the infection process. These glycans surrounding the virus are resistant to mutation during the evolution process of the virus. So, the diagnosis will remain valid even if there is any mutation in the genetic code. The same principle will be used in the development of the Glycan Based Diagnostic for COVID-19. The kit will be highly efficient due to the robustness of the results [48].

Serological assay

Serology test is basically dependent on blood serum to detect the presence of antibodies generated due to prior exposure to the pathogen. The exposure of the specific components of the pathogen called antigens initiates the immune response in the individual as the human body considers the pathogens as foreign materials. Serological test are often used for diagnosing viral infections to determine the immune response to the pathogen of interest. This can be achieved by various methods like neutralization test, immunofluorescent (IFA) assay, Enzyme-linked immunosorbent assay (ELISA), and Western Blot techniques [49].

Xiao *et al.* reported for the first time the presence of IgM and IgG antibodies (Abs) in the serum from the 34 hospitalised patients infected with SARS-CoV-2. The study reports the presence of IgM Abs during the initial state of infection followed by declination whereas, IgG remains in serum for longer durations [50]. Xiang *et al.* studied the sensitivity of two different diagnostic methods namely, ELISA and Gold-Immunochromatographic Assay (GICA) for the presence of IgM and IgG Abs in the serum of SARS-CoV-2 infected patients and reported that both the methods show 80-87% sensitivity for both the Abs [51]. Another study by Lin *et al* reports the chemiluminescence-immunoassay method based on the recombinant nucleocapsid antigen and the magnetic beads specific for the detection of IgG Abs of SARS-CoV-2 genome. A recently published research letter by Hui zeng *et al* reports the presence of antibodies IgM and IgG in a newly born infants from COVID 19 infected mothers with negative RT-PCR test on newly born infants [52]. Hence, these research report the use of serological testing could result in a very rapid diagnostic process and help in controlling the transfer of the infection affected globally.

The serological testing does not provide the confirmatory results for the presence of COVID-19, since the results only show exposure to the pathogen in the past. Hence, combining serological testing with RT-PCR methods can provide confirmation of the patient being infected by SARS-CoV-2. On April 1st, 2020, USFDA has approved the first antibody testing kit of Cellex Inc. which gives the result in 15 mins under EUA for distribution in the countries like USA and China. The kit is based on the lateral flow assay method, which detects IgM and IgG to the nucleocapsid protein of SARS-CoV-2 [53, 54]. The following weblink of John Hopkins-Centre for Health Security details the list of diagnostic kits based on serologic assay approved by USFDA, kits which are distributed in other countries and kits which are under development
http://www.centerforhealthsecurity.org/resources/COVID-19/Serology-based-tests-for-COVID-19.html.

Assessment of Haematological parameters

The severity of the patients contracted with SARS-CoV-2 infection is also assessed observing the haematological parameters. Pneumonia like infection is known to have a large impact on the immune system of the persons affected with the disease. In a study reported by Chen *et al.* [55], patients admitted for the treatment of COVID 19 have shown abnormal levels of platelets, white blood cells (WBC), lymphocytes, liver enzymes, lactate dehydrogenase, serum creatinine etc. Some of the critically ill patients have also reported the presence of C-reactive protein whose lesions in the lung have increased to a greater extent because of the progression of the disease to the lung. C-reactive protein is positively correlated with the lung lesion and disease severity in a

study carried out by L. wang on 27 patients [56]. Fan *et al.* also reported the data of the patients admitted to the ICU showing severe lymphopenia and raised levels of lactate dehydrogenase [57]. Recently published, Chinese Clinical Guidance on 4th March 2020 for COVID 19 Pneumonia Diagnosis and Treatment (7th edition) recommends lymphocyte and white blood cell count as one of the clinical manifestations for the diagnosis of the COVID disease [58].

Sample collection and handling

Diagnosis of the suspected patients should be conducted according to the interim guidelines shared by the CDC in the presence of the healthcare supervisor. Due to the dynamic outbreak of COVID 19, it is essential to follow the updated procedures for the diagnosis as recommended by the CDC. The guidance is revised based on the current need of the situation and is updated on their official website regularly. The guidance now enlists multiple options for the collection of specimens from different anatomical regions due to the lack of sensitivity of the RT-PCR testing, a confirmatory test, as explained earlier. The emergency outbreak has led the approval of diagnostic kits at a faster pace to meet the needs of society, which fails to validate the sensitivity of the approved kits.

The COVID suspected patients are now, initially diagnosed by taking sample specimen from the various anatomical regions namely, nasopharyngeal, oropharyngeal, nasal mid-turbinate swab, anterior nares (nasal swab), Nasopharyngeal wash/aspirate or nasal wash/aspirate (NW) to avoid the false-negative results and obtain the confirmatory reports. Of the various sampling locations, nasopharyngeal sampling remains the most preferred sampling site for both the patient as well as the sampling supervisor. The sensitivity of the sampling site has also been published in various technical documents showing minimal false-negative results. In addition to that, the CDC also recommends sampling from the nasopharyngeal region using the flocked or spun polyester swab only as other materials tend to inactivate the virus. A sterile swab of the above-mentioned material with flexible shaft usually of wire or plastic inserted into one side of the nostril parallel to the palate slowly, until it reaches the middle region equidistant from the nostrils to the outer opening of the ear. The swab is gently swirled, left for few seconds to absorb the moisture present, and is removed out slowly by continuous rotation. In case the sample specimen obtained is not sufficient from one side of the nostril, the other side, too, is subjected to sample collection. Sample collected are stored at 2-8^{0}C for 3days after collection, and in case if the samples are not tested immediately, then storage should be under -70^{0}C or below.

Therapies for COVID-19

In the present outbreak of COVID-19, when there are no treatments available, a lot of research is encouraged towards development and identification of effective antiviral agents to combat the disease. Figure 6 represents the timeline of the major events of the drug evaluation history of COVID-19. The effective treatment options which can be considered against SARS-CoV-2 can be either the use of anti-viral drugs or use of any specific therapeutic molecule which interrupts with the different stages of viral lifecycle or the receptor proteins located on the host cell surface to inhibit the virus binding and thus, blocking the virus attachment, entry or replication into the host cell.

Therapeutic drugs against COVID-19

Drug development and screening, using the live virus, requires highly sophisticated instruments and setups with the proper safety measures which poses as a big obstacle in the present situation. A useful approach to drug discovery against this condition is to test whether the existing drugs are effective in treating the viral infection. The repurposing of the known drugs for a new application of treating the novel COVID-19 may prove to be a quick process of getting a therapy in the emergency situation of disease spread. There are several studies which concluded the use of the already existing drugs for the treatment of the disease.

The following drugs are being recommended in several countries to be administered to the patients and there are several success stories too.

Chloroquine

Chloroquine (CQ) has been the drug of choice since past 80 years for the treatment of malaria until the phase when different regions started reporting parasitic resistance against CQ [59]. CQ and its derivative, the 4-aminoquinoline drug hydroxychloroquine exhibit similar properties with respect to structure, pharmacokinetics and efficacy as also their antiviral properties [60]. In vitro, CQ has been studied for several viral infections including RNA viruses such as HIV [61, 62], Hepatitis [63], Chikangunya [64, 65], Dengue [66], Ebola [67] and DNA viruses such as Herpes Simplex virus [68] but the results are not always reproducible in clinical trials. It is because of all these reports, studies were encouraged for finding out the efficacy of CQ against the new SARS-CoV-2. Based on this, several clinical trials were carried out, all over the world by administering CQ to SARS-CoV-2 infected patients. Andrea et.al., in their work, enlisted about 23 the clinical trials carried out by China and conclude that the pre-clinical rationale and clinical trial evidences suffice the data to show effectiveness of CQ for COVID-19 and suggest the use CQ along with expert opinions for the treatment of COVID-19 [69].

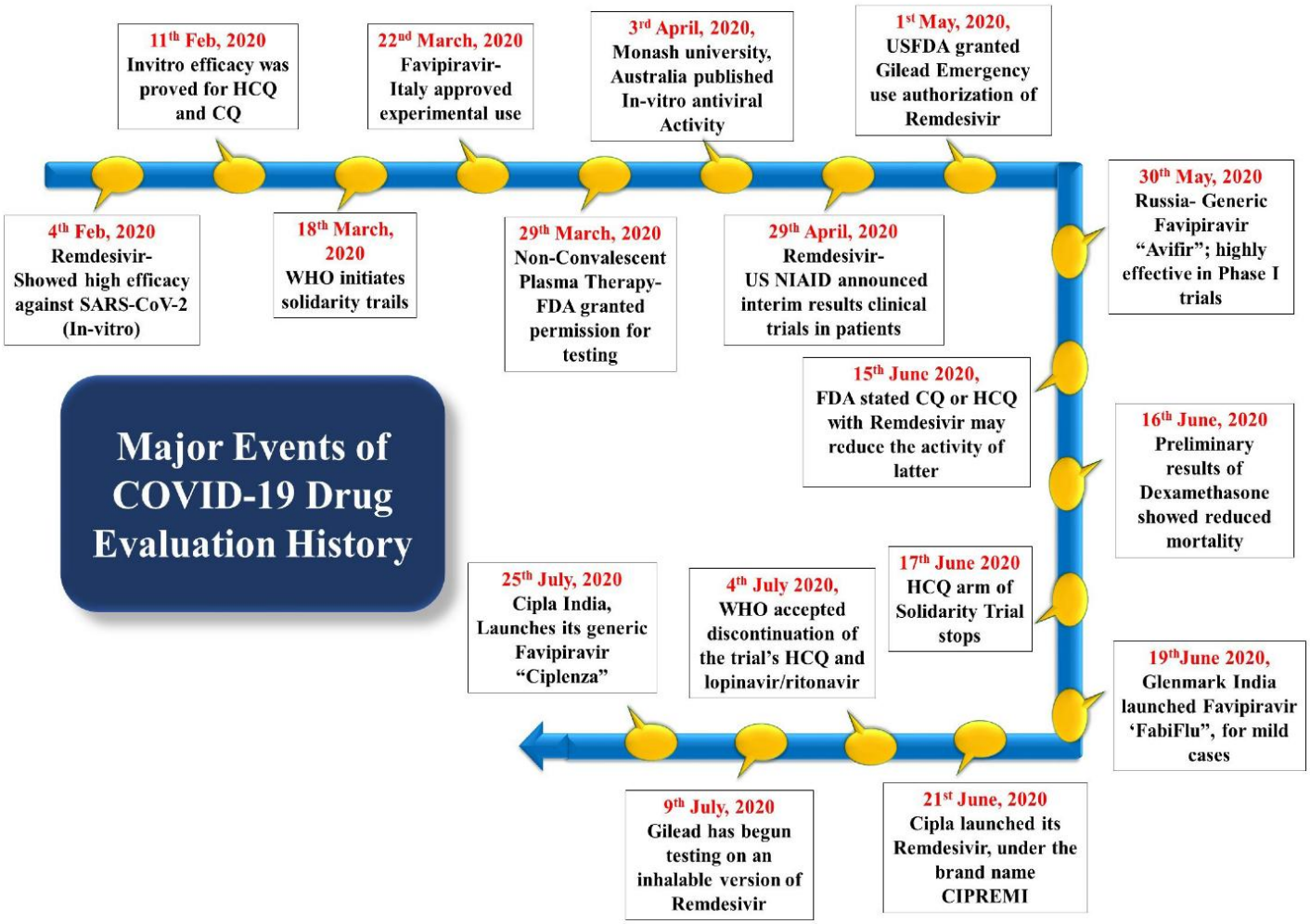

Figure 6. Timeline of the major events of the drug evaluation history of COVID-19.

The anti-viral and anti-inflammatory actions of CQ may be responsible for its effectiveness against SARS-CoV-2. The most common mechanism of CQ is by increasing the endosomal pH and thus preventing its pH dependent entry into the target cells [60, 70, 71]. It can also hinder the post-translational modifications of viral proteins required for viral replication and growth [60]. In addition, CQ has the ability to inhibit the quinone reductase-2, required for sialic acid biosynthesis, which the virus uses as a receptor [71]. Though, CQ may be the drug of choice in the present condition of medical emergency, caution should be observed while using it as a therapy, considering the detrimental effects of the drug. Ethical guidelines should be a must before declaring CQ as the therapy for COVID-19 [72].

Hydroxychloroquine (HCQ) has a similar mechanism of action to that of CQ, owing to its similarity in the structure. HCQ is comparatively proven to be safer than CQ due to its polar nature contributed by the additional hydroxyl group in the structure. Moreover, CQ has a narrow therapeutic and safety index, thus making HCQ a safer alternative. Long-term usage of HCQ is clinically proven to be safe which allows higher dose with less drug-drug interactions [71]. In one of the recent pre-proofs, the researchers, through their study on patients have concluded that a combination of HQ and Azithromycin show synergistic effect in treating COVID-19. The latter helps in preventing the severe respiratory infections caused due to viral infection [73].

Teicoplanin

A glycopeptide antibiotic, Teicoplanin, has been recently found to be active against SARS-CoV. In coronaviruses, teicoplanin prevents the release of viral genome at an early stage of the viral life cycle. It has shown to be effective against other viruses such as Ebola virus, influenza virus, hepatitis virus, Human Immunodeficiency Virus (HIV) and forms of coronaviruses [74]. It inhibits cleavage of viral spike protein at low-pH by cathepsin L in the late endosomes, thereby terminating the continuation of the virus replication cycle [75]. Junsong Zhang *et al.*, hypothesized

that teicoplanin and its homologs could prevent the entry of novel SARS-CoV-2 into the target cells through their study on pseudoviruses. The required inhibitory concentration (IC 50) for Teicoplanin in vitro was found to be 1.66 μM, which is quite lower than the concentration achieved in human blood (8.78 μM for a daily dose of 400 mg) [76].

Melatonin

Cytokine storm and repressed immune function are the most prevalent features of COVID-19, which in turn lead to high inflammation [21]. Melatonin indirect anti-viral activity due to its anti-oxidative, anti-inflammatory and immune boosting activities, making it a suitable adjuvant therapy for treating COVID-19. Melatonin causes an upregulation and downregulation of several inflammatory pathways. It causes a reduction in pro-inflammatory cytokines [77]. It acts as an antioxidant and scavenges the free radicals, preventing the corresponding damage. Melatonin as a potent antioxidant and immune regulator not only suppresses the oxidative stress but also controls innate immune response and promotes the adaptive immune response. This supports the use of melatonin in Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS) caused by COVID-19 when inflammation is most severe. Melatonin has an established good safety profile. Although the evidence of melatonin application in direct treatment of COVID-19 is so far not clear, its use by COVID-19 patients would be really beneficial, as predicted [78].

Remdesivir

Remdesivir is a prodrug having a parent adenosine analog, GS-441524. Both of these yield nucleoside triphosphate (NTP) after metabolism by the host cell [79]. A number of in vitro and in vivo studies have proven the usefulness of the drug against novel coronavirus [80]. As a nucleoside analog, it interferes with the viral genome replication process. The active form of the prodrug competes with adenosine triphosphate (ATP) to get incorporated in the RNA strand. The incorporation the altered nucleoside analog in the new strand causes premature termination of RNA synthesis, interrupting the growth of the RNA strand. Although CoVs have a proof-reading process, Remdesivir skips this viral proofreading activity and maintains antiviral activity [81]. A study in Vero E6 cells showed that the EC50 value of remdesivir is 1.76 μM. Since, its mechanism is quite promising, it should be tested in patients for COVID-19 [79].

Favipiravir

Favipiravir is a guanine analogue which has been approved for influenza treatment so far. It is known to be inhibitory to the RNA-dependent RNA polymerase of RNA viruses such as influenza, Ebola, chikungunya, and a recent study reported its activity against SARS-CoV-2 (EC50=61.88μM in Vero E6 cells) [14]. Favipiravir is able to block the replication of flavi-, alpha-, filo, bunya-, arena-, noro, and other RNA viruses [82]. Favipiravir, once taken, gets converted into its active form giving a phosphoribosylated form (favipiravir-Ribosyl triphosphate) in cells. This active form is identified as a suitable substrate for viral RNA polymerase, hence, causing an inhibition of RNA polymerase activity [83]. Therefore, it is predicted that favipiravir can have antiviral action on SARS-CoV-2, due to its similarity with other viruses. The preliminary results of the trials suggest that it is more potent that lopinavir/ritonavir and had no significant side effects [84].

Chlorpromazine

Coronavirus uses the clathrin dependent endocytosis mechanism for entry into the cells. Chlorpromazine is an inhibitor of clathrin- dependent endocytosis. Moreover, the two steroids ouabain and bufalin, are inhibitors of the Na+/K+-ATPase found in the plasma membrane. These can inhibit the MERS-CoV infection at very low concentrations by interfering the clathrin-mediated endocytosis pathway. All these drugs are FDA approved and hence should be tested for COVID-19 [85].

Ivermectin

The FDA-approved anti-parasitic drug, Ivermectin, has shown broad spectrum anti-viral activity in-vitro. It is proven to be an inhibitor of SARS-CoV-2 as shown by Leon Caly *et. al.* [86]. It has an established safety profile for human use. Ivermectin warrants further investigation for possible therapy for COVID-19.

Miscellaneous

A series of antiviral drugs, apart from those mentioned above, have been studied by several researchers to prove their efficacy against novel SARS-CoV-2. Lopinavir/ritonavir combination works synergistically to inhibit the protease of the virus for a long period of time [84]. The combination has so far not been tested on patients but it may help to combat the infections [87]. Similarly, Darunavir, another protease inhibitor may also serve the purpose along with Ritonavir by the same mechanism of action [88]. Another drug, Beclabuvir, can inhibit the RNA-dependent RNA polymerase of newly emerged novel coronavirus (SARS-CoV-2). Beclabuvir is a non-nucleoside polymerase inhibitor that potentially inhibits nonstructural proteins of the virus [89]. Nitazoxanide, a commercial antiprotozoal agent, approved for diarrhoea treatment, has an antiviral action against a wide range of viruses. When tested on Vero E6 cells, it was found to inhibit the SARS-CoV-2 at a low-micromolar concentration, which shows its possible efficacy against SARS-CoV-2 [90].

Therapeutic strategies for COVID-19

Apart from repurposing the already existing drugs, there are certain strategies which are been worked upon to combat the disease and are being proposed to be helpful. But, in our opinion, all these strategies require a good amount of work to be done, before being implemented on the patients. Moreover, this is a slow and difficult process with several challenges and may not yield significant outcomes for a few months. This would require a great amount of time and efforts to be invested which is difficult in the present condition. Still, it is important that newer strategies should be worked upon continuously, which would have more benefits over the drugs, and help in the long run.

Mesenchymal stem cells

Jiajia Chen *et. al.*, from their studies on menstrual blood derived mesenchymal stem cells, concluded that mesenchymal stem cells are able to reduce the inflammatory response and combat the cytokine storm. Their ability to improve the lung function may be due to reduction in the secretion of the inflammatory factors [91].

Monoclonal antibodies

Antibodies with passive immunization which can recognize the viral epitopes can decrease the multiplication of the virus. The S-protein of the novel virus could be an important target for developing monoclonal antibodies to block the fusion of the virus to the host cells. Therefore, different epitopes of the SARS-CoV-2 would be meaningful targets [92]. A combination of several potent antibodies could decrease the probability of the virus escape. Computational simulation of antibody-antigen complexes is being used and are proving to be of great help to design therapeutic antibodies [93].

ACE2 inhibition

It is found that the SARS-CoV-2, like SARS coronavirus, uses the ACE2 as a receptor for entering the host cell. The virus binds to the said receptor through its S protein on its membrane which causes the fusion between viral membrane and cell membrane. This is how the virus inserts its genome inside the host cells, replicates inside and creates replicas of its virions to infect other cells. If the patients are administered with agents that bind to the ACE2 protein, there would not be any site available for the virus to attach and hence, would not spread [94]. There are two approaches to inhibit this binding to ACE2. The first approach is to use small RBD from the SARS S protein which are the key domains for binding to the ACE2 receptor during entry. A second approach can be to administer an antibody that binds to ACE2 protein, thus preventing SARS-CoV-2 infection [95]. Another important strategy is to use a soluble form of ACE2 receptor which can bind to the S-protein of the virus, thus neutralize the virus itself and not shield the host cells. Such a soluble ACE2 protein may also help in the treatment of pathophysiology of pneumonia [95].

Interferon therapy

Targeted delivery by PEGylated interferon α-2a and -2b, could be used to stimulate innate immunity in patients infected with SARS-CoV-2, and trials involving interferons have been initiated. A targeted drug delivery with PEGylated interferon and a nucleoside could act synergistically against SARS-CoV-2, but this is still to be tested. Subcutaneous interferon therapies may result into several side effects because of which it has to be monitored [14].

Convalescent plasma

The said approach involves the administration of the antibodies from the patients suffering from the infection, in order to stop the spread of the disease [96]. In one of the studies, 5 patients were given plasma transfusion from 5 recovered patients along with other anti-viral agents. Following the treatment, improvements in clinical condition were observed [97]. There are evidences to show that convalescent plasma from the recovered patients can be used as a treatment without severe side effects. Therefore, it might be worthwhile to check the safety and efficacy of convalescent plasma transfusion for treating SARS-CoV-2-infected patients [98].

Renin-angiotensin-aldosterone system (RAAS) inhibitors and COVID-19

In the early days of the pandemic, it was hypothesized that patients taking Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin II (Ang II) Receptor Blockers (ARBs) could experience an increased severity of COVID-19. The hypothesis was based on two facts; one of these was the understanding that RAAS inhibitors upregulate the expression of ACE2 and SARS-CoV-2 enters the host cell by binding to the ACE2 receptors. Secondly, the fact that the disease was more prevalent in individuals with diabetes and hypertension [99]. On the one hand, ACE2 over expression may increase the binding of the virus to cells whilst on the other, it inactivates Angiotensin II, which is responsible for the lung damage caused in the patients. This discrepancy led to an urgent need for studies to decide about the administration of RAAS inhibitors and guide the clinicians. Studies were carried out at several places specifically on COVID-19 patients suffering from diabetes and hypertension and were being administered these drugs. It was found that neither ACE inhibitors nor ARBs were associated with the likelihood of increased severity of the disease. There was no association observed between these drugs and severe COVID-19. In fact, the patients who received an ACE inhibitor or ARB while in

hospital had improved outcomes over those who received neither medication. Furthermore, the withdrawal of RAAS blockers in these COVID-19 patients would increase the morbidity and mortality risk, considering the myocardial damage caused in the infection [100]. The cause can be explained from the RAAS mechanism in normal and infectious condition as shown in Figure 7. Under normal conditions, the stimulation of the RAAS system causes the generation of Angiotensin (1-7) from the metabolism of Angiotensin II by ACE2. Angiotensin (1-7) are responsible for the protective signal and prevent the lung injury otherwise caused due to Angiotensin II. In an infected patient, the virus binds to the ACE2 receptor, reducing the concentration of the receptors available for Angiotensin II binding. The resultant increased concentration of Angiotensin II is responsible for increase inflammatory response and lung injury. For a patient administered with RAAS inhibitors, the concentration of Angiotensin II is decreased, which prevents the damage caused to the lungs by its inflammatory response. Professional scientific community, therefore, advised that patients should not discontinue ACE inhibitors and ARB therapy during the SARS-CoV-2 infection. There are suggestions nowadays that RAAS inhibition might be effective in decreasing the severity of COVID-19 infection [101].

Indian scenario of advances in COVID-19 technologies

India is one amongst many countries which are in the forefront to take all possible steps and contribute to alleviate the pandemic situation. With the growing cases of COVID 19 in India, the Government of India has taken initiatives in various ways to contain and control the spread of the disease and monitoring them with great dedication.

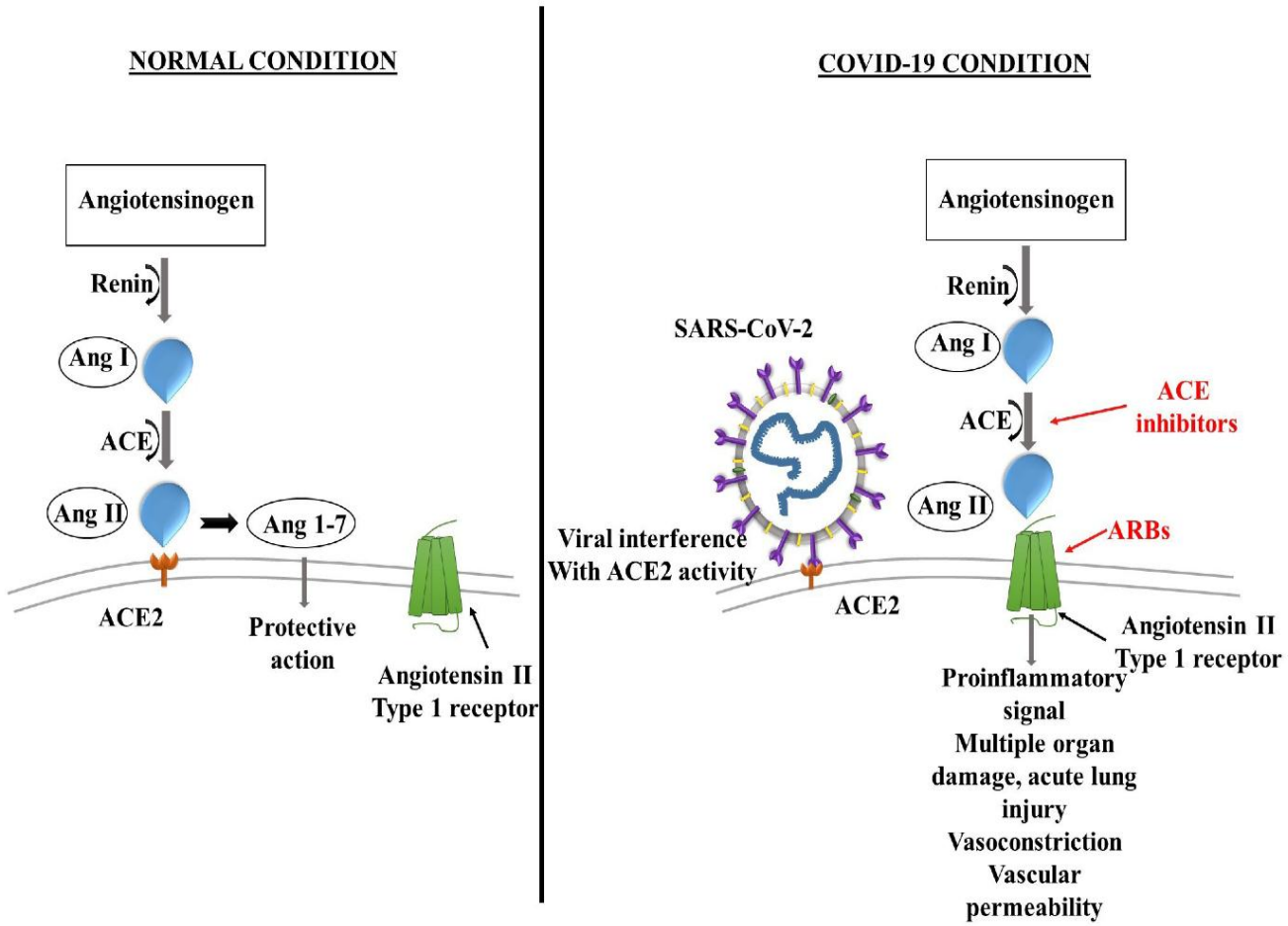

Figure 7. Schematic representation of the Renin-Angiotensin system in the normal and COVID-19 condition.

Diagnosis

India to combat this challenge of COVID 19, with a limited and expensive supply of diagnostic kits, welcomes "MAKE IN INDIA" suppliers of diagnostic kits. India had been importing the diagnostic kits from Germany earlier to make the diagnosis PAN India, but due to lockdown on airlines, it is challenging to have access, and the high cost of the foreign kits discourages the poorer from doing the testing. The Indian Council of Medical Research (ICMR)-National Institute of Virology (NIV), Pune, the apex laboratory for viral diagnosis and research in India, is responsible for the validation of the performance of the diagnostic kits. Indian authorities granted approval to 3 firms for the local manufacture of the diagnostic kits and make them available in large numbers for the diagnosis in India. Besides these firms, India has also granted permission to 2 other firms manufacturing real-time RT-PCR diagnostic kits. Recently, DCGI has granted permission to 12 companies from other countries to import serological test kits detecting the IgG/IgM antibody in less than 15 mins. These kits shall also give information on the people who were infected and recovered without visiting the hospitals or were asymptomatic to the SARS-CoV-2 infection.

Vaccines

Antiviral vaccines can be broadly classified as Gene-based vaccines that deliver gene sequences encoding protein of antigens that are produced by host cells. These include live-virus vaccines, recombinant vaccine vectors, or nucleic acid vaccines. Protein-based vaccines are prepared by whole-inactivated virus, individual viral proteins usually manufactured in vitro. Recombinant vaccine vectors and nucleic acid vaccines are best suited for faster manufacturing since there are platform manufacturing technologies available in which upstream supply chains and downstream processes are the same for each product. In the present situation of the pandemic, a vaccine might prove as a boon to the entire world. While a lot of vaccine development is ongoing in several countries, Indian companies and academia is working on as many as seven vaccine candidates, out of which, two have achieved success and proceeded for clinical trials.

1. Covaxin

Bharat Biotech, a Hyderabad based company produced COVAXIN and this emerged as one of the first homegrown vaccines to depict great potential and was approved by DCGI, India for regulatory approvals to start Phase I and II clinical trials. The authorities have also issued an August 15 deadline for the end of the clinical trials and further start large-scale production and use of the vaccine. This vaccine uses an inactive version of the spike protein. The vaccine has been found to strengthen the body's immunity and speed up production of antibodies, which could defend the body against such viral agents. ICMR had also written to 12 institutes where human trials are to be held for the vaccine and it is noteworthy that over 1000 potential participants who will undergo testing have been identified. The company has also announced plans of a collaborative study with the University of Wisconsin and another with researchers based out of Thomas Jefferson University.

2. ZyCOV-D

Ahmedabad-based Zydus Cadila has also secured clearance from the regulatory board to start clinical trials of their indigenously developed vaccine. A research program for developing a steady vaccine has been done in collaboration with multiple teams across India and Europe and the prototype, earmarked ZyCOV-D works by boosting the production of antibodies in the host body and actively fight the virus mutation. The pharmaceutical giant is also working on several other medicines and treatments to fight the COVID-19 pandemic.

Immune Boosters

The balanced nutrition is paramount as an adjuvant therapy to allopathic drugs to combat the coronavirus by boosting the innate immune response and stabilize the second phase of hyper-inflammatory and oxidative stress conditions [102]. Immune Boosters that exert anti-inflammatory and anti-oxidant properties can aid in strengthening the immune response. Essential dietary immune boosters include the list of various micronutrients, including Vitamin A, Vitamin C [103], Vitamin D [103, 104], complex Vitamin B [105], several minerals that are enlisted as Copper, Selenium, Zinc [106], Iron; omega -3 fatty acids; and essential amino acids. A randomized, double-blind clinically controlled phase IIa study investigates the use of hydroxychloroquine with dietary supplements of Vitamin C, D, and zinc for the treatment of COVID-19. Additionally, the bioactive of the Indian herb that possesses synergistic effects showing anti-viral and immune-boosting activity can be promising amid this COVID crisis as a prophylaxis treatment. A study reports, the withanolides of *Withinana Somnifera*, an Indian herb has shown better binding effects to the potential targets of the SARS-CoV-2 virus through *in silico* docking study, paving the way for herbal ayurvedic drugs for the treatment of patients entangling with the deadly virus [106]. Ayurvedic Science is a boon to India which encompasses a vast knowledge of immune-boosting herbs. The Ministry of Ayush has unveiled the principles of Ayurveda and laid down several guidelines that enlist several ayurvedic medications and procedures for strengthening immunity [107]. One such medication released known as traditional "*kadha"* or the decoction made of Ocimum *tenuiflorum* (Tulsi), Cinnamomum *verum* (Dalchini), Piper *nigrum* (Kalimirch), Zingiber *officinale* (Shunthi), and Vitis *vinifera* (Munakka) for

self-care immune boosters. However, there is no scientific documented evidence showing the effect of these phytoconstituents as immune boosters. Pukar *et al.* have made efforts in investigating the role of phytoconstituents of the AYUSH recommended herbal tea in immune-strengthening effect through *Gene set* enrichment analysis [108].

Treatment drugs

With a vaccine still a long distance away and no sign of the coronavirus infections slowing down in the country, homegrown pharmaceutical companies have been granted with a green signal to launch generic versions of Remdesivir and Favipiravir, anti-viral drugs that have shown promising results for treating Covid-19 patients.

The Drugs Controller General of India has given nod to a few companies India to roll-out their COVID-19 treatments in the market. These companies include Glenmark, Hetero and Cipla. The names of medicines by these companies are FabiFlu, Covifor and Cipremi which contain Favipiravir, Remdesivir and again Remdesivir, respectively. All the three formulations have shown convincing results and are therefore being slowly recommended for use under strict medical observation. While medical experts have cautioned against seeing these potential drugs as a 'magic bullet' against the deadly virus, they can be helpful in reducing the viral load as India continues to post new record highs in infections on a daily basis. Remdesivir and Favipiravir are two of the 130 under experimentation drugs worldwide to treat Covid-19.

1. FabiFlu

Glenmark Pharmaceuticals announced the launch of anti-viral drug Favipiravir, so far used for treating influenza with a brand name FabiFlu for treatment mild to moderate COVID-19 patients. After nearly 18 global clinical trials in over 3,000 patient subjects, it was found that Favipiravir has efficacy for treating COVID-19 patients. Glenmark's trial was on 150 patients, the data was corroborated with other trials in USA, Canada, Italy, China, France and UK. In India a clinical trial was conducted by Glenmark in 90 mild and 60 moderate Covid-19 patients at 11 sites. Within four days of treatment, Favipiravir was found to give a reduction in viral load and offered faster symptomatic and radiological improvement. FabiFlu is a prescription medication with a recommended dose of 1,800 mg twice daily on day one, followed by 800 mg twice daily up till day 14. As stated by Glenmark, Favipiravir was chosen as it had proven in-vitro efficacy and it has an established therapeutic safety margin. The most important advantage of Favipiravir is that it is an oral drug, while Remdesivir is an intravenous drug. Glenmark is now embarking on a second trial for combination of two anti-viral drugs Favipiravir (Approved drug for novel flu pandemics) with Umifenovir (Approved drug for Influenza). The safety of this combination is well established. However, there are a few risks and contradictions associated with the drug, restricting its use in patients with history of abnormalities in metabolism of uric acid or having gout.

2. Covifor

Following Favipiravir, DCGI approved launch of Hetero's COVID-19 drug, Remdesivir, with brand name Covifor. The drug will be packed in a 100 mg vial which is to be administered intravenously in a hospital set up under the supervision of a healthcare practitioner. Covifor would be the first generic brand of Remdesivir, prescribed for the treatment of COVID-19 in adults and children, hospitalised with severe symptoms of the disease.

3. Cipremi

The U.S. FDA issued an Emergency Use Authorization (EUA) to Gilead Sciences Inc. for emergency use of Remdesivir for treating COVID-19 patients. Gilead Lifescinces Inc, in May, extended a non-exclusive license to Cipla to produce its generic version of the drug. Cipla's Remdesivir is a lyophilized powder for Injection. A randomized clinical trial was conducted at numerous centres around the world and Remdesivir was proven to be efficacious in clinical recovery when compared to placebo. Training on the usage of the drug, patient consent documents, post marketing surveillance and Phase IV clinical trials in Indian patients are recommended as a part of risk management. The drug is most affective on the patients who need continuous oxygen support or are on ventilator. This is a significant milestone for the company in such an impeded situation [109].

4. Others

Tocilizumab, an immunosuppressant which is commonly used to treat rheumatoid arthritis. It has been used to treat more than 100 severely ill Covid-19 patients in Mumbai. A randomised control trial is also being conducted across several centres in India. Another drug, Itlolizumab — a medicine used for those suffering with skin disorder psoriasis, rheumatoid arthritis and autoimmune disorders, is also being used in India. DCGI gave a nod to Biocon for its Itolizumab injection 25 mg/5ml solution for emergency use in treating cytokine release syndrome (CRS) in moderate to severe ARDS (acute respiratory distress syndrome) patients. Itolizumab is the first novel biologic therapy approved in the world for treating patients with moderate to severe COVID-19 patients. Biocon has repurposed Itolizumab for the treatment of CRS in moderate to severe ARDS patients due to COVID-19 [110]. DCGI has approved Mylan's Remdesivir, with brand name Desrem, for the treatment

of suspected or laboratory confirmed severe incidences of Covid-19 in adults and children.

Conclusions

The outbreak of COVID 19 pandemic is a serious concern globally. With the fast-growing research on novel coronavirus, the scientists are able to help the community in understanding and providing sufficient knowledge of the virus, helping the future researchers to come up with novel diagnostic procedures to control the spread of the disease by isolating the diagnosed patients from the community and approaching various therapeutic strategies for the treatment of the infected patients. Government agencies of the countries and health regulatory bodies of the world are taking proactive actions to contain and control the spread of the disease and have increased their level of preparedness to combat the disease. It is now, the responsibility of every individual to observe the government guidelines and practice them diligently to flatten the curve of the increasing COVID patients.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that there are no competing conflicts of interest.

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