



Challenges and Opportunities to Develop Diagnostics and Therapeutic Interventions for Severe Acute Respiratory Syndrome- Corona Virus 2 (SARS-COV-2)

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ABSTRACT

Severe Acute Respiratory Syndrome-Corona Virus 2 (SARS-CoV-2) or Corona Virus Disease 19 (COVID-19) is playing havoc all over the world since December 2019. Despite being a family member of coronaviridae, which has previously affected mankind twice in last one decade, the novel corona virus, as it is named left medical practitioners and scientists defenseless. The major challenge is twofold identification and therapeutic intervention. Several approaches, including real-time PCR have already been taken for quick identification of Covid19. Due to very fast evolving rate, accurate identification is still a challenge for most of the detection methods developed in last three months. Several proposals for therapeutic intervention have also put forth by scientists, ranging from vaccine to RNA therapy. In this article, a comprehensive review is made from the scattered scientific literatures and is fine-tuned further with possible diagnostic and therapeutic interventions.

INTRODUCTION

The novel corona virus or SARS-CoV-2 is alleged to be originated from the city of Wuhan, China, has been currently turned into a pandemic and affected almost every country (213 countries) throughout the world (<https://www.worldometers.info/coronavirus/countries-where-coronavirus-has-spread/>). Corona virus is a unique class of virus, that exists under the large viral of coronaviridae, which is a single stranded positive RNA sense virus. The size of virus particle ranges from 70-90 nm [1]. Due to presence of spikes on the outer surface, which resembles a crown under an electron microscope, these viruses are called as corona virus, as per Latin word 'corona' which means 'crown' [2]. Further, the corona viruses are sub-classified into alpha, beta, gamma and delta subtypes. These viruses are endemic in non-human vertebrates, such as bats, civet cat, camel as well as Pangolin and few of them are able to infect human [3]. According to Center for Disease Control and Prevention (CDC), USA, till date, seven different types of corona virus have been found to infect humans. Alpha and beta corona virus have been found till date to infect humans. There are two alpha subtypes namely 229E, NL63, and five beta subtypes namely OC43, HKU1, SARS-CoV (severe acute respiratory syndrome), MERS-CoV (Middle East respiratory syndrome) and COVID-19 (corona virus disease 2019)

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(<https://www.cdc.gov/coronavirus/types.html>). SARS-CoV was first identified in the year 2002, which has infected the low respiratory tract of several individuals in Foshan, China, and has resulted in Acute Respiratory Distress Syndrome (ARDS), multi-organ failure and septic shock with high Case Fatality Ratio (CFR). Later, it has been transported to Hong Kong from where it has been spread globally, infected about 8098 people, led to the mortality of 774 individuals, and was controlled in the year 2003. However, a higher virulent strain of SARS causing CoV named MERS has been first identified in Jordan in the year 2012 and has spread rapidly, infected around 2494 individuals with 34.4% of fatality rate in Middle East countries. In 2019, the same virus has been evolved into novel coronavirus with capability to spread rapidly and cause respiratory as well as immunity related complication in individuals, especially among older age group people [4]. According to Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses, virus is officially named as Severe Acute Respiratory Syndrome-Corona Virus 2 (SARS-CoV-2) which was intermittently called 2019 novel corona virus (2019-nCoV) [5]. In the current paper, we shall mention the disease as COVID-19 and viruses as SARS-CoV-2.

SARS-CoV-2 is airborne, swiftly evolving and highly contagious in nature, which is evident by the infection numbers, which is escalating at an exponential rate in past 5 months. Till now, the mortality rate is calculated between 2%-3%, however, there are numerous factors, including age, comorbidity of the patient and health facility, that influence the mortality rate [6]. As a result, the reported mortality rate is found to have less than 1% in some countries whereas higher than 10% in some other countries [7]. There are various studies that have been conducted on the virus incubation period in human which in turn helps the policy makers to quarantine and observe suspected individual [7]. The results suggested the incubation time may vary greatly, but 14 days of isolation and observation may be sufficient to determine the infection [8]. There are different theories of mechanism of SARS-CoV-2 infection that have come forward and different treatment approaches have been proposed. Out of multiple approaches to contain the infection and treat the infected patients, one model has been adapted globally, which is early detection of the infected individual and treat them in a quarantine facility. Hence, it is evident that we need a sensitive and a rapid diagnostic system to identify the infected, but asymptomatic patients. The second part is, of course, finding suitable and target specific therapeutic interventions. Vaccine is considered to be a hopeful therapeutic agent against Covid-19 to combat them and control its transmission. As of now total 115 various types of vaccine candidates have been identified out of which 78 are confirmed based on publicly available data and 5 of which has been approved for clinical trial [9]. For developing any successful and precise therapeutic and diagnostic measures, it is important to know the genetics of SARS-CoV-2 and its exclusive structure.

MOLECULAR BIOLOGY OF SARS-COV-2

Corona virus has the largest genome among all the single stranded RNA viruses known till date with 26-32 kb of size. It possesses a 5' cap and a 3' poly-A tail. There are 14 Open Reading Frame (ORF) in SARS-CoV-2, which encodes for 27 unique proteins [10]. In the 5' end, there are two ORFs, namely ORF1a and 1b that encodes for two polypeptides, such as pp1a and pp1ab. The frame shift of one nucleotide towards 5' end (-1 frame-shift) between ORF1a and ORF1b produce two polypeptides. Polypeptide1a (molecular weight 440-510 kDa) gets cleaved into 11 Nonstructural proteins (Nnsps) and polypeptide1ab (molecular weight 740-810 kDa) gets sliced into 15 Nsps [11]. In the 3' end, other ORFs generate four Exemptional Structural Proteins, namely Spike (S), Envelope (E), Nucleoprotein (N), Membrane (M) and eight distinct accessory type of proteins, namely 3a, 3b, p6, 7a, 7b, 8b, 9b and ORF14 [10]. Moreover, it is worthy to note that the proteolytic polypeptide cleavage is facilitated via Nsp3 and Nsp5 [11].

Among structural type of proteins, Spike protein (S) (~150 kDa) is a glycoprotein, which has a significant role in the attachment of the virus to cells. It is glycosylated and it has three domains-N terminal domain consists of S1 and S2 subdomain and protrude outwards, a domain of transmembrane and a cytoplasmic structure at the C terminal end. It intermingles with the Angiotensin Converting Enzyme 2 in human (hACE2), after being cleaved by Transmembrane Serine Protease 2 (TMPRSS2) at the S1 and S2 junction [12]. Membrane (M) protein is comparatively smaller (~25-30 kDa) but more abundant. It has three transmembrane domains and plays a significant role in membrane dynamics like shaping the virion and membrane curvature and nucleocapsid binding [13]. The Envelope (E) protein is also a small, yet extremely Diverse Protein (~8-12 kDa). Although E protein is not fully characterized, yet it is speculated that E protein may be a transmembrane protein ion channel activity. Also, E protein enables the viral assembly and release and certain studies indicated that the E protein is essential in pathogenicity, especially viral lethality [14]. Nucleocapsid (N) protein is a heavily phosphorylated protein, which plays a variety of functions. It has an affinity towards both host and viral RNA, but phosphorylation of the N protein changes the affinity towards viral RNA over host RNA [15]. Also, N protein found to play role in viral genome packaging, acts as a structural subunit of replicase complex and mediates the tethering of the viral genome to replication transcription complex [16]. Also, it was found to influence host cell response by modulating chaperone activity and cell cycle regulation [17].

Non-Structural Proteins (Nsp) of Betacoronaviridae family members have a diverse function ranging from blocking the host immune response to RNA polymerization. Non-structural proteins are categorized as Nsp1 to Nsp 16. Inhibition of the immune system is caused by different Nsp is

different ways. Nsp1 inhibits interferon signaling [18], Nsp3 blocks host innate immune response and are essential in cytokine storm by promoting cytokine expression [19], Nsp5 acts like Protease (3CLpro) and cleaves pp1a [20] and inhibits interferon signaling [21]. Nsp6 restricts autophagosome expansion [22], Nsp12 acts like RNA dependent RNA polymerase by its C terminal domain [23], Nsp14 and 15 has an exo- and endo-ribonuclease activities [24] and Nsp15 helps the viral machinery to evade double stranded RNA sensors [25]. Nsp16 along with Nsp10 mediates ribose 2'-O methylation [26]. So, it is evident that beta coronaviridae family has an extremely sophisticated genome organization and understanding its function at the molecular level will help to design effective therapeutic measures.

The virus particle attaches the human cell via spike protein and hACE2 binding. Upon binding, spike protein is cleaved by TMPRSS2 and helps the processed S protein to fuse with host membrane [15]. In SARS-CoV-2, the cell entry is preactivated by proprotein convertase furin, hence, the dependence on host protease is reduced. Cell mediated endocytosis helps the virus to internalize into the human (host) cell [27]. After entering into the host cell, lysosomal proteases like cathepsin cleaves the viral structure and helps to release the genomic RNA inside the cell. Later, the virus develops a 'slippery' sequence (5'-UUUAAAC-3') and a pseudoknot RNA structure to translate two polypeptides by frame-shifting mechanism. The polypeptides are cleaved into Nsps and some of the Nsps take part in Replication-Transcription Complex (RTC) formation to provide an amiable environment for viral replication [15].

PATHOPHYSIOLOGY OF SARS-COV-2

The pathophysiology of any pathogen-mediated infections are required to be understood elaborately for the effective designing of treatment modalities and drugs to combat them [28]. SARS-CoV-2, which is a new virus pathogen that has ability to cause Severe Acute Respiratory Syndrome (SARS) and has infected 13 million people from December 2019 to May 2020 [29]. The pathophysiology of SARS-CoV-2 is in high demand to be revealed in recent times as it is a new virus (novel Coronavirus or 2019-nCoV) [4,30], no proper treatment methods until now, governments have implemented lockdown measures to reduce the crowd for mitigating the spread of this virus, which eventually declines the economy of a country [31] and understanding their pathophysiological pathways can help to combat this viral infection effectively in the upcoming days [32]. The SARS-CoV-2 virus was first recognized in certain respiratory illness patients from December 2019, in the city of Wuhan, China [33], and received this name as its 80% of the genome sequence is similar to SARS-CoV (coronavirus family, that caused SARS), which has spread rapidly in the year 2002 [34]. These types of viruses possess Ribonucleic Acid (RNA) as their genetic materials, which provides them enhanced potential to mutate rapidly and can

generate sub-species [35]. The viral genome is protected by a protein capsid [36] and a Spike (S) protein, which binds with the host cell [37]. The protein capsid in SARS-CoV-2 is made up of three unique protein groups, such as E (capsid protein), M (membrane protein) and N (nucleoprotein) [38]. Even though, other proteins in the capsid are useful in the maintenance of genome structural integrity, the spike proteins are the one, that can bind with receptors in humans to initiate its replication [39]. The SARS-CoV-2 infection and its transmission from the person to another starts via microdroplets, that are airway generated by the infected person and expelled, while sneezing, coughing or other similar activities [40] as displayed in figure 1. The microdroplets with the virus particles will reach another person and can enter them via epithelial conjunctiva and the upper respiratory tract cells [41]. However, the aerosol transmission of viral particles is still under investigation and it has been estimated that these particles can reside in an unventilated space for several hours [42]. Recently, several researchers suggested that the aerosol can stay longer in the air with the viral load, which may transmit the virus effectively in a closed or air conditioned environment [43,44].

The virus with the double domain surface glycoproteins (spike protein), that are inhaled will bind with the epithelial cell in the nasal cavity via Angiotensin Converting Enzyme Type 2 (ACE2) receptor and initiates its replication by the stages, such as entry, uncoating, replication, transcription, translation, virion assembly and release [45,46]. It has been proven in the *in vitro* data that the coronaviruses family possesses enhanced ability to bind with the ciliated cells in the respiratory tract as the primary target in the conducting airways [47]. The virus will replicate in the epithelial cells and spreads to other parts of the respiratory tract in the initial 1-2 days of infection, which is called as an asymptomatic state [48]. In this stage, a person infected with the virus can be identified by analyzing their nose and throat swab samples, which will contain high viral load [49]. However, recent studies also proved that the existence of virus (low viral load) can be detected in saliva, sputum, tracheal and pharyngeal swabs, pleural effusion fluid, broncho-alveolar lavage and in certain cases, urine and semen [50]. The samples from the patients will be subjected to Real-Time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) analysis to detect the single RNA sequence of SARS-CoV-2 to label them as positive or negative cases [51].

In the next phase, the virus spread more in the respiratory tract cells and the viral load will increase along the conducting airways, which eventually activates an innate immune response to show certain mild to severe symptoms, such as uncomfortable to breathe and fever [52]. The immune response will vary with the age, gender and various other factors in covid-19 positive patients and the cytokine-based innate immune response will be triggered to protect the unaffected cells as well as inhibit the replicating virus

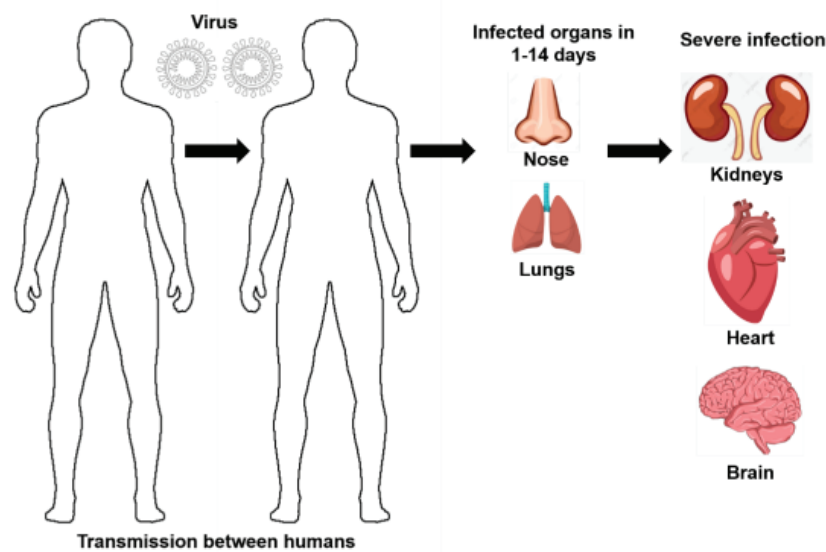


Figure 1 Transmission of SARS-CoV-2 and its effect on different organs in the host.

[53]. Above 80% of the SARS-CoV-2 infected patients are either asymptomatic or with mild symptoms such as fever, if their immune response is better without any comorbid conditions [54]. However, these patients can spread the virus to others through air transmission as mentioned earlier [55]. It is worthy to note that the level of CXCL 10, which is an interferon responsive gene, which is expressed in viral infected epithelial cells along with other beta and lambda interferons. This CXCL 10 gene possesses superior ratio of signal to noise in the response towards type 2 alveolar cells and are recommended to be beneficial as a potential disease marker for SARS diagnosis [56-58].

The rest of 20% population affected by SARS-CoV-2 will progress to the next stage, which will show moderate symptoms, such as pneumonia with fever and cough without hypoxemia, severe symptoms, including pneumonia with hypoxemia, which leads to critical conditions in patients such as Acute Respiratory Distress Syndrome (ARDS), along with other conditions namely encephalopathy, shock, heart failure, acute kidney injury, myocardial injury and coagulation dysfunction [59]. Out of this 20% severely infected patients, 2% of fatality rate can be observed, mostly for patients with comorbid conditions and age [60]. In this stage, the viral load will increase in the lungs' gas exchange units and critically contaminates the sub pleural and peripheral type 2 alveolar cells [61,62]. Later, the lung cells will undergo apoptosis, due to high viral load and starts to gradually spread towards other organs [57]. The result from the pathological studies revealed that the SARS-CoV-2 possess ability to diffuse damage in the alveolar region with a few giant multinucleate cells and hyaline membranes rich in fibrin [63]. Thus, vigorous response of innate and acquired immunity as well as epithelial cell regeneration are required

to treat severe symptom exhibiting patients and recover them from the infection [64]. The 2% mortality rate in infected patients is mostly due to reduced immune response in old-age and comorbid populations with reduced ability to repair the damaged epithelial cells. In addition, these groups of infected patients will have reduced mucociliary clearance, which eventually facilitates the escalated virus spread in the gas exchange units of the lungs and leads to death [65].

Effect of SARS-CoV-2 in various organs

Apart from general pathophysiology, which is focused in the lungs, SARS-CoV-2 have a specific mechanism of action to infiltrate damages in other organs. It has been reported that the kidney, heart and brain are the most affected organs, due to corona-type virus infection, especially SARS-CoV-2, other than the lungs.

Lungs: Lungs are the most affected organ due to any nasal pathogenic viral infections and SARS-CoV-2 also severely affect these organs. It can be noted that the lung serves as a replication spot for these novel coronaviruses, cause pulmonary damage and spread to other organs after severely affecting the lungs and nasal pathway [11]. Ziehr, et al. [66,67]. stated the respiratory pathophysiology of mechanically ventilated, severely infected SARS-CoV-2 patients. The study was performed in Massachusetts General Hospital and Beth Israel Deaconess Medical Center among 66 patients with the severe infection of SARS-CoV-2 and are managed with invasive mechanical ventilation to support patients with respiratory failure. Out of 66 patients, 12% of patients already had pre-existing pulmonary disease and 34% of patients are former or current smokers with a median age of 58 years. In this study, 85% of patients are identified to have trifling to moderate Acute Respiratory Distress

Syndrome (ARDS) and are confirmed by Berlin criteria to admit them in the Intensive Care Unit (ICU). The mechanical ventilation for 16 was proven to successfully improve the respiratory failure condition in severely infected, 62.1% of SARS-CoV-2 patients, a tracheostomy was performed in 21.2% of patients, 75.8% of patients were discharged from ICU and 16.7% of patients were dead. This study revealed that the respiratory failure in SARS-CoV-2 patients was exhibited in a similar gas exchange and mechanics of the respiratory system, and the effect of mechanical ventilators is based on the pre-existing co-morbid conditions and age factor of patients. Further, the pathophysiology revealed that the pre-existing therapies for ARDS along with the mechanical ventilation facility will be beneficial in recovering the patient from the respiratory viral infection [68].

Kidney: Recently, several reports demonstrated that the SARS-CoV-2 viruses target and damage kidney cells, next to the lungs. Martinez-Rojas, et al. [69] reported that SARS-CoV-2 viral infection can lead to multi-organ failure. The study emphasized that the attachment of viral particles with ACE2 promotes them to infect distinct host cells by disrupting the homeostasis of renin-angiotensin-aldosterone system. These disruptions largely lead to abnormalities in renal parts, such as hematuria, proteinuria and Acute Injuries in Kidney (AKI). Further, these coronavirus types possess ability to infect tubular epithelial cells and podocytes, that can eventually lead to renal abnormalities. Likewise, Diao, et al. [70] showed via retrospective glomerular filtration rate analysis, among 85 infected SARS-CoV-2 patients, that the viral infection affects kidneys, next to the lungs. The results revealed that the 27.06% of SARS-CoV-2 infected patients developed acute renal failure condition, while 65.22% of elderly patients with comorbid conditions, such as hypertension and heart failure are easier to develop renal failure and lead to mortality. The postmortem report of kidney tissues stained with hematoxylin and Eosin stains revealed severe acute tubular necrosis and lymphocyte infiltration. Further, the study established the viral nucleoprotein antigen accumulation in the kidney tubules via immunohistochemistry analysis and the existence of virus-like particles in kidneys, via electron micrographs. The study concluded that the infection of SARS-CoV-2 induces, CD68+ macrophages to infiltrate tubulointerstitium and enhances the deposition of complement C5b-9 on tubules. Likewise, Zhang, et al. [71] demonstrated the genetic roadmap of kidney participation in the SARS-CoV-2 infected patients. In this study, the protein and gene expression of ACE2 level is determined in kidney with its spatial characterization via The Human Protein Atlas [72]. The ACE2 receptor is expressed in several organs, including kidney, and the corona virus binds and replicates in humans via ACE2 receptor to cause acute respiratory illness [73]. However, the viral RNA has also been noticed in the urine samples, which has concluded the involvement of kidney in Covid-19 infection. The study concluded that the existence of ACE2 receptor in the kidney tubules will cause injury, which eventually leads to

the consequences of covid-19 infection in the kidney [74]. Further, Zhang and Liang also mentioned the latent risk of the kidney as a defenseless organ to the infection caused by novel coronavirus 2019 [75]. In the study, they have reported the prevalence of non-respiratory symptoms, such as myalgia, diarrhea and fatigue in moderate cases and acute kidney injury in severe cases, affected with SARS-CoV-2. Further, pathophysiological studies exhibited that the acute kidney injury can be a multifactorial mechanism, that are triggered via 2019-nCoV direct infection, which elevates responses of inflammation and immunity and leads to toxic reactions, due to respiratory failure [75]. Contrarily, Wang, et al. [76] reported by analyzing 116 patients infected by covid-19 and admitted in a hospital in Wuhan, China, that the infection caused by SARS-CoV-2 does not lead to an acute and direct injury in the renal structures. This study showed that the severe injury in the lungs due to viral load has led to multiple organ damage, including kidney.

Cardiovascular system: Apart from the lungs and kidneys, certain patients have also exhibited damages in the cardiovascular system. Zheng, et al. [77] reported that the infection of SARS-CoV-2 virus in humans can lead to acute myocardial injury and chronic damages to the cardiovascular system. In addition, covid-19 patients with preexisting cardiovascular diseases are under the high risk category, and the viral infection can lead to death. Likewise, Groß, et al. [78] revealed the implications of ACE2 receptor-dependent SARS-CoV-2 interaction on the cardiovascular system of the host. In this study, the authors provided a molecular insight on the reason behind the increased mortality rate among elderly, covid-19 infected people with immunocompromised condition and cardiovascular disease, due to cardiopulmonary failure. The study showed that the binding of corona type virus with ACE2 can degrade angiotensin II, which is a master Renin-Angiotensin-Aldosterone System (RAAS) regulator and converts them into vasodilatory molecules with cardio-protective effects. This mechanism potentially leads to cardiovascular system failure in elder patients and cause death. Additionally, Chen, et al. [79] revealed that the novel coronavirus 2019 possess ability to cause fulminant myocarditis, which causes inflammation in cardiac cells and patients with this syndrome have high mortality of about 40-70%. This study showed that the several infected patients of covid-19 will have increased levels of cardiac troponin I and new-onset arrhythmias causing cardiopulmonary failure.

Brain: It has been reported recently that the brain and central nervous system is also affected by the viral infection caused by 2019-nCoV. Natoli, et al. [80] demonstrated the neurological impact of SARS-CoV-2 via neurological sequelae from animal models of MERS and SARS. In this study, the affinity of the covid-19 viral spike protein with ACE2 receptor has been identified in neurons, which revealed their neuro-invasive potential, similar to SARS and MERS. Thus, the translational lessons from the animal models infected

with SARS and MERS provided ample evidence that SARS-CoV-2 can enter and damage the brain. Further, Moriguchi, et al. [81] reported that the SARS-coronavirus-2 can lead to meningitis or encephalitis in severely affected patients. In a particular case reported by the authors, the patient had fever and fatigue in day 1 and prescribed with Laninamivir and antipyretic agents for 2-5 days. Later, the patient developed severe symptoms and became unconscious after 9th day. The nasopharyngeal swab analysis of the patient did not detect the presence of any viral load, however, the viral load was detected in cerebrospinal fluid. Furthermore, Zanin, et al. [82] mentioned that novel coronavirus can induce spine and brain demyelinating lesions in severely infected patients. The study suggested that the virus can cause Systemic Inflammatory Response Syndrome (SIRS)-like immune disorder and can trigger hypoxic neurotoxicity and injuries in central nervous system. Moreover, Paniz-Mondolfi, et al. [83] reported the existence of 2019-nCoV in the capillary and neural endothelial cells in the frontal lobe tissue of the severely infected patient via postmortem examination. The study emphasized that the virus present in the neural tissue can worsen neurological symptoms and damage central nervous system.

Other organs: In children, mostly the virus does not show any symptoms as they possess a less quantity of ACE2 in their upper respiratory tract. However, there can be milder symptoms such as fever and cough [84]. In addition, Verdoni, et al. [85] reported that the children affected with SARS-CoV-2 in the Italian epicenters are developing a severe Kawasaki-like disease, which is an acute self-limiting vasculitis of the medium caliber vessels. In certain cases, the binding nature of corona virus with ACE2 has led to a potential damage in the gastrointestinal tract. Interestingly, Grassia, et al. [86] reported that the patients with preexisting inflammatory bowel diseases are not developing severe symptoms against SARS-CoV-2 and several investigations are under research to identify, which drug or factor reduces the symptom. Kumar, et al. [87] revealed the enhanced ACE2 expression in 2019-nCoV infected patients, especially in the tissues of gastrointestinal with the digestive pathogenesis symptoms and also emphasized mortality related to diabetes and recurrence of diseases in the patients of covid-19. Moreover, Carvalho, et al. [88] showed that the gastrointestinal infection of SARS-CoV-2 can lead to hemorrhagic colitis, which can lead to detection of virus in fecal samples and symptoms, such as vomiting, diarrhea, nausea and pain in the abdomen. However, extensive research in the future will reveal several unanswered questions in the pathophysiology of this viral infection, which affects multiple organs.

DIAGNOSTIC APPROACHES TO IDENTIFY SARS-COV-2

Rapid diagnosis of infectious agents is a key step to fight against an outbreak. When a new virus infects human,

diagnosis becomes a challenging task. The diagnosis is divided into 3 major parts- specimen collection, virus isolation and identification. It is worthy to note that the PCR method is highly beneficial in the detection of the virus, while it exists in a person. Another technique applied with limited success is immunodiagnostic method. Here, the detail procedure shall be discussed to shed light on diagnostic procedure.

Specimen collection

Being an airborne pathogen, in the early stage of infection, corona virus targets upper respiratory tract. When a patient with mild pneumonia and history of coming in contact with suspected individual reaches the lab or hospital for testing, the Nasopharyngeal (NP) or Pharyngeal (OP) swab is collected. NP swab collection generally elicits tears and OP swab collection create a 'gag' response. Some reports suggest NP swab has a much higher identification rate compared to OP swab. As SARS-CoV 2 is airborne and highly contagious, hence, utmost care should be taken by the medical personnel who is collecting the samples. Personal Protective Equipment (PPE) should be used while collecting the Covid19 samples [89]. In crisis situation like scarcity of PPEs, non-availability of health care personnel due to high patient number, saliva or nasal wash samples that are collected by the clinicians can be utilized as specimens for the patients who are showing pneumonia like symptoms. Sputum from lower respiratory tract can be used as a specimen. Serum samples should be collected in two separate occasions, acute which is in the first week of illness and convalescent which is over 2-3 weeks.

Specimen transport

Collected specimen should be kept in viral transport medium and transported in refrigerated condition. As per WHO and CDC guidelines (<https://www.cdc.gov/coronavirus/2019-ncov/downloads/Viral-Transport-Medium.pdf>), Viral Transport Medium (VTM) is constituted as follows: Hanks Balanced Salt Solution (HBSS) mixed with calcium and magnesium ions, but a pH indicator like phenol red should not be present. This medium should be supplemented with sterile and heat inactivated Fetal Bovine Serum (FBS) and antibiotics e.g. gentamicin and amphotericin B. According to Indian Council of Medical Research (ICMR) guidelines (https://www.mohfw.gov.in/pdf/5Sample%20collection_packaging%20%202019-nCoV.pdf), specimen samples must be kept in VTM and transported to the lab in refrigerated condition ($\leq 4^{\circ}\text{C}$). The testing of the sample should be done when kept at $\leq 4^{\circ}\text{C}$ within 5 days. Longer storage is possible at -70°C . Bronchoalveolar lavage storage time is much less ($\leq 48\text{h}$) compared to NP and OP swab. Biopsy or autopsy tissue samples should be transported in sterile normal saline and should be tested ≤ 24 h. serum samples should be collected in a serum separator tube and transported in 4°C . It can be stored around 5 days before testing at 4°C .

Covid-19 diagnosis

Diagnosis is an important part of fighting a pandemic. In a large population, identifying the potential candidates is a challenging task. In addition to this, diagnosis of a relatively unknown virus is always challenging. Multiple approaches have been proposed (Table 1). Some of the key approaches are documented in the current review.

Real time PCR

It is also named as reverse transcription quantitative PCR. It is regarded as the gold standard to detect SARS-CoV-2 all across the globe. Currently, several COVID-19 testing are conducted with the genetic material of virus that is collected from throat and nose swabs, using a workhorse molecular biology tool known as reverse transcription polymerase chain reaction RT-PCR. The principle of this test is to amplify a specific sequence of viral genes, where short sequences of complementary genes named primers can help to initiate the copying process. As it is a highly specific and sensitive technique, scientist and medical practitioners depend on this technique. Dozens of labs and research consortia around the world worked round the clock to develop testing kits to fulfill the demand. Labs, throughout the world, have modified their PCR for SARS-CoV-2 tests, via distinct primers that can target specific sequence of the viral genes. Examples are the US FDA's emergency use authorized kits by Roche Diagnostics Cobas and Logix Smart COVID-19 test kit. Other kits like Nova cyst by French Clinical Diagnostics, Bioeasy kit by Shenzhen Bioeasy Biotechnology Co Ltd, China are being used by European countries. Already, certain reports from Spain have mentioned that the Bioeasy kit is recognizing only 30 of the positive cases [90-92].

LOOP MEDIATED ISOTHERMAL AMPLIFICATION

It is a Nucleic Acid Amplification Test (NAAT), where rapid analysis can be obtained. It is widely applied to various types of pathogen detection like virus, bacteria

and protozoa (especially malaria). The simplicity of the technique enables it to be converted into mobile unit and can be used at the point of care like railway station, airport, and rural areas. Reverse transcription loop mediated isothermal amplification process or RT-LAMP is a cheaper and faster process compared to qRT PCR. It depends on one step amplification technique. Unlike PCR, which needs thermal cycling, RT LAMP is carried out at a temperature between 60-65°C and use DNA polymerase. This technique employs a set of four primers [93] to recognize six unique sequences in target DNA sequence. There are forward as well as backward inner primers with dual sequences of primer. The first set is for initial stage priming and the second is for later stage self-priming process. Among four primers, both primers are utilized at the early stage, but later the strand displacement is done by inner primers. In the first report, the reaction is carried out at 65°C for 1 hour [93]. Later it was observed that the inclusion of two additional primers can shorten the reaction time by half [94]. The current LAMP method uses total six primers which are specific against eight unique sites. Besides inner and outer primers, which are able to identify six distinct sites, the loop of two primers elevates the speed and the efficiency of amplification [95]. Previously, the efficacy of LAMP was shown to detect SARS [96] and RT-LAMP assay for MERS detection [97] corona virus with high sensitivity. In LAMP, reverse transcription reaction is done in the same tube prior to amplification; hence it makes the identification process faster. In one Covid 19 detection kit, researchers have designed an RT-LAMP system, where viral detection limit is 80 copies of viral RNA molecule/mL of sample [98] and the reaction can be completed in 20 min at 65°C. The designed primers are specific to ORF1ab, S, N1 and N15 genes. In another work, researchers have identified Covid 19 in a one or two stage process. In the two-stage isothermal amplification termed as Penn-RAMP by the authors, the first stage conducted at 38°C termed as recombinase polymerase amplification and second stage LAMP at 63°C. The amplicon was detected by leuco crystal violet stain and colorimetric identification was possible [99]. In another study, researchers have targeted N gene. They have shown the limit of detection 118 copies and

Table 1: Different diagnostic techniques with their advantages and disadvantages.

Diagnostic technique	Advantages	Disadvantages
Real time PCR or qRT PCR	<ul style="list-style-type: none"> High sensitivity Confirmatory test 	<ul style="list-style-type: none"> False positive may arise if the primers are incorrect (Toms, et al. 2020) Minor contamination during sample collection affects the result
Loop mediated isothermal amplification	<ul style="list-style-type: none"> Cheap compared to qRT PCR Less complex instrument Can be used at the point of care 	Primer designing is complex and may produce confusing result
Imaging technique	Direct observation of the condition of the internal organs	<ul style="list-style-type: none"> Expensive instrumentation, often available in specialized hospitals Highly trained manpower Not a confirmatory test
Serological test	<ul style="list-style-type: none"> Easy to conduct with basic diagnostic lab facilities Less expensive compared to qRT PCR 	<ul style="list-style-type: none"> Early detection not possible Indirect test High level of variability Patients with other infection may give false positive results Virus specific identification requires high viral titre

with the help of fluorescent dye, it can be identified with 30 min and if the initial template number is 200 copies, then it can be identified in visual detection at 40 min [100]. In another study, researchers have targeted ORF1ab region and the reaction was conducted at 65°C. The visible color change was observed within 20 min when the template RNA copy number was 1000. The detection capability was further extended by using SYBR green dye [101].

Imaging techniques

Imaging techniques are highly beneficial in any disease diagnosis. As Covid 19 is an acute respiratory syndrome, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography-Computed Tomography (PET-CT), lung imaging by ultrasound and application of artificial intelligence is analysis and decision outcome plays crucial role in treatment assessment and modalities [102]. Although RT-PCR based screening is considered as gold standard, yet it has detection limit and a patient with respiratory illness cannot be opted out of Covid-19, even if the RT-PCR result is negative. Chest CT acts as a complementary examination for RT-PCR. The characteristic images of infected lungs, such as ground glass opacity and pulmonary fibrosis are used to consolidate the diagnosis [103]. 18F-Fluorodeoxyglucose (FDG)-PET CT is also employed to measure the effect of SARS-CoV-2 on the lungs. The axial image shows ground glass opacity and increased 18F-FDG uptake. The increased uptake takes place because of highly activated neutrophils swarm in the infected area. Supported by sample collection site (e.g: nasopharyngeal swab eliminates influenza) and RT-PCR data, 18F-FDG-PET CT may give crucial information about the patient [104].

Serological Test

Many reports have emerged that young adults and children, who have not been exposed to any of the coronaviral family members may show very minimal or no symptoms and simply behave as carriers to transmit the infection to others. Here is the necessity for a test that could show the extent of viral spread in a community and provide useful public-health information. A serological test-based detection would perfectly fulfill this requirement. A Singapore based group from Duke-NUS Medical School used serological tests to aid in contact tracing, but at the time the test had not been broadly validated for clinical use. Another group from New York City hospital used serological tests to better understand how quickly COVID-19 patients start to develop antibodies to the virus. It could also help to identify recovered patients who could then donate their SARS-CoV-2 antibody-rich serum to help treat critically ill patients. Another key application would be to identify people who have developed likely immunity to the virus. They might be able to treat patients safely or take on other front-line jobs during the pandemic [91,105].

THERAPEUTIC APPROACHES AGAINST COVID-19

Vaccine development

The most alarming situation is that there is no proper medical prescription for patients to mitigate the effects of this viral disease. In addition, there is no vaccine available to control the spread which will lead an escalation in the positive cases, in the upcoming days. The SARS-CoV-2 has S protein on the surface of the virus, guiding its entry into the host cell. More interestingly the Receptor Binding Domain (RBD) of S protein has the potential role in this matter. Therefore, the target of this study is the RBD domain to stop the viral infection. COVID-19 recovered patient has antibody against SARS-CoV-2 [106]. The RBD domain is the most exposed part of SARS-CoV-2, however, there is no recommended treatment for COVID-19 as there exists no proper suggestion from randomized controlled trials [107]. Interestingly, US based Vir Biotechnology, Inc. have developed VIR-7831 and VIR-7832, with high affinity towards the S protein of SARS-CoV-2. Therefore, S protein, particularly the RBD domain of S1 and S2 subunit would be a critical vaccine contender for long run COVID-19 treatment [108]. Likewise, a ChAdOx1 nCoV-19 vaccine prepared by Oxford university, mRNA-1273 prepared by Moderna, Inc. and BNT162 by Pfizer pharmaceutical company shows promising results to develop immunity in hosts against SARS-CoV-2 viruses by targeting their spike proteins [109-111]. Similarly, INO-4800 prepared by Inovio pharmaceuticals (USA) is a DNA-based synthetic vaccine, that targets antigen in the surface of S protein and protein-based vaccine was synthesized by targeting ectodomain soluble spike protein immunogen in emulsion to combat against the replication of SARS-CoV-2 virus in the host [55,112]. Further, PicoVacc vaccine targeting neutralizing antibody of coronavirus and CoroFlu fabricated by Bharat Biotech International Ltd. as a nasal flu vaccine to produce neutralizing antibody against viruses were also recently recommended as a probable vaccine to produce immunity against SARS-CoV-2 in human hosts [113,114]. Furthermore, Shenzhen Geno-Immune Medical Institute of China prepared LV-SMENP-DC vaccine by using lentiviral vector with the synthetic minigene to produce antigen-specific cytotoxic T-lymphocytes and pathogen-specific artificial antigen-presenting cell to inhibit viral protein as an effective vaccine candidate against 2019-nCoV [53]. However, all these vaccines are in Phase I clinical trials and it will take a long time to reach the commercial pharmaceutical market.

Antiviral drugs

Several preexisting antiviral drugs that are used in the treatment of previously common infections caused by viruses, such as SARS, MERS, Ebola and Nipah are currently utilized for SARS-CoV-2 treatment. Remdesivir is a capable

antiviral drug that are used for Ebola treatment and are prescribed for 2019-nCoV treatment as it is a nucleotide-based antiviral drug [115]. Similarly, Ribavirin is also a nucleotide-based antiviral drug, that are used for the treatment of certain viral hemorrhagic fevers, respiratory syncytial virus and hepatitis C, and are prescribed for SARS-CoV-2 treatment [116]. Likewise, Galidesivir and BCX4430 are the other antiviral nucleotide analogues with the ability to effectively treat Ebola, Hepatitis C and Marburg virus, and are recommended for the treatment of severely infected patients with covid-19 [114-117]. Moreover, Baricitinib, that targets Janus kinase and are already in usage as a curative agent for rheumatoid arthritis without any inflammatory response and Lopinavir, which targets viral 3CLpro proteases and are permitted for HIV treatment in combination with ritonavir are also recommended for covid-19 treatment in some countries [115,118]. Furthermore, Arbidol is a potential drug antiviral efficacy that is beneficial in preventing the entry of influenza type coronaviruses by inhibiting ACE2 binding spike protein of the virus and Darunavir, that are used to reduce the infection of HIV, are also widely suggested against SARS-CoV-2 for effective treatment [119,120]. Besides, Nitazoxanide, that can target and inhibit the protein expression of the virus, which are already in use for the treatment of diarrhea caused by viral, protozoan and helminthic infection, were also under extensive research to be beneficial for SARS-CoV-2 infection treatment [13]. However, extensive trials in preclinical as well as clinical arenas are vital to confirm the effectiveness of these drugs against Covid-19 and can only be used in combinations, instead of a single drug.

Repurposed drugs

The SARS-CoV-2 virus has been transmitted to almost 200 countries within 3 months and there is no specific drug to counteract the infection or its associated complications. A new drug, that are specific to counteract the covid-19 infection, will take a long time (several months or even years) to reach the commercial market as it should cross the barrier of preclinical and clinical trials. Thus, already existing drugs that are utilized for other infection treatments are repurposed to help SARS-CoV-2-affected patients. The main purpose of designating these already existing drugs is that they are approved and certified to be safe of human for the treatment of other infections. BCG vaccine, which is commonly used against tuberculosis, is repurposed and are under extensive research to be used as a vaccine candidate for the current covid-19 infection to improve immunity in patients [121]. However, *in vitro*, *in vivo* and clinical analysis are compulsory to confirm their efficacy in improving immunity of the host against SARS-CoV-2. Later, Chloroquine phosphate used as an effective antimalarial drug are repurposed for severely infected covid-19 patient treatment and early studies showed that they are effective in reducing upper respiratory issues in SARS-CoV-2 infected patients. However, elderly patients may develop

cardiovascular problems, when high doses of these drugs are prescribed, which a major limitation of this drug is [122]. Similarly, Hydroxychloroquine in combination with antibacterial agent named azithromycin were prescribed to covid-19 patients for combating pneumonia-like complications. Even though, these drugs are already in use for the treatment of malaria and bacterial infections, it may lead to cardiovascular issues in elderly patients and cannot be prescribed for patients of all age groups [123-126]. Further, convalescent plasma from the processed blood of covid-19 disease recovered patients were used to treat severely infected patients as it will contain antibodies to improve immunity against SARS-CoV-2. Furthermore, initial studies in Italian and Chinese epicenters showed promising results among high risk patients. However, the extraction of plasma is a costly and time-consuming process, which cannot be affordable in developing and underdeveloped countries [16,17,127]. All these reports presented the extensive researches which will help in upcoming days to understand the exact pathophysiology of this viral infection is required to design novel or repurpose preexisting drugs to combat and eradicate this infection in the near future.

Rehabilitation programs

In addition to diagnostic, vaccine development, antiviral drugs and drug repurposing approaches, rehabilitation programs were also considered to be a significant method for the recovery of SARS-CoV-2 infected patients. Zhu, et al. [128] reported the early possible pulmonary rehabilitation for SARS-CoV-2 pneumonia with the experience from an Intensive Care Unit (ICU) in Shenyang, China. In this study, a 41-year-old man with SARS-CoV-2 infection was successfully treated with 11 days of mechanical ventilation and 9 days of oxygenation via extracorporeal membrane along with conventional supportive care. Further, an individualized and meticulous ICU rehabilitation program was provided to the patient after weaning process. The ICU rehabilitation program includes four components, such as postural change and prone position, respiratory training to restore respiratory muscle strength and lung volume, early mobilization and physical exercises, and psychological intervention as well as sleep promotion. Later, Aytur, et al. [129] released a guideline for the acute and subacute rehabilitation based on the pulmonary rehabilitation principles in SARS-CoV-2 infection. In this study, they have provided several guidelines of pulmonary rehabilitation required for mild disease, mild and severe pneumonia as well as acute ARDS stage. Further, they also drafted the regulations for rehabilitation approaches after discharging the patient infected by COVID-19 from hospitals. In both these studies, it is noteworthy that physiotherapy plays a key role in the rehabilitation process to regain muscle strength of lungs and to improve mobilization of the patient with certain psychological impact. Jangra and Saxena (2020) also mentioned that physiotherapy can play a crucial role in the respiratory rehabilitation and management of patients with

SARS-CoV-2 infection. Dyspnea is a condition in SARS-CoV-2 infected patients, where the lung muscle is tightened and inspiratory muscle training as well as breathing exercises can be beneficial to improve dyspnea. Moreover, physiotherapy was reported to be useful for assisting the positioning of COVID-19 patients to relax them from respiratory distress and to prevent secondary complications. Furthermore, early rehabilitation via physiotherapy can be recommended to recovered patients for limiting or preventing ICU-acquired weakness [130]. Likewise, Dehesh (2020) stated that stress may lead to negative effects on COVID-19 patients with back pain or musculoskeletal disorders, which can be reduced with firm physiotherapy guidelines [131]. Similarly, Diwate (2020) agreed to the fact that physiotherapy is useful in the physical rehabilitation and treatment of COVID-19 patients and recommended 'expert consensus and recommendation for physiotherapy management for COVID-19 in Indian set up' guidelines, which is approved by Maharashtra State Council for Occupational Therapy and Physiotherapy, Mumbai (India) for physiotherapists to decide and plan treatment for SARS-CoV-2 infected patients [132]. All these studies emphasized that physiotherapy can be a beneficial approach for the proper rehabilitation, during and after ICU-based treatments for COVID-19 patients.

CONCLUSION

SARS-CoV-2 viruses are spreading rapidly in the last few months and the recent studies showed that their strain virulence is reducing rapidly. However, the elderly people and patients with comorbidity are under high risk and are prone to mortality, due to this viral infection. Thus, social distancing, lockdown measures, rapid diagnosis in large scale and preexisting drugs are the only available strategies to combat the pandemic of this viral infection, until the discovery of a potential vaccine. Scientist are working hard to identify a potential drug and vaccine candidate, where are few are successful and are under in phase I clinical trials, which gives promising status that a vaccine will be available within next year. Even before the vaccine, rapid diagnostic tools and drugs to reduce or treat the health complications instigated by the infection of virus, will be available in markets as mentioned in this review. In the near future, more critical knowledge on the pathophysiology of SARS-CoV-2 viruses will be available, which will eventually lead to the discovery of highly efficient and target specific drug or vaccine to eradicate this viral infection and save lives of several millions of people.

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