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A Systematic Review on Coronavirus Disease 2019 (COVID-19)

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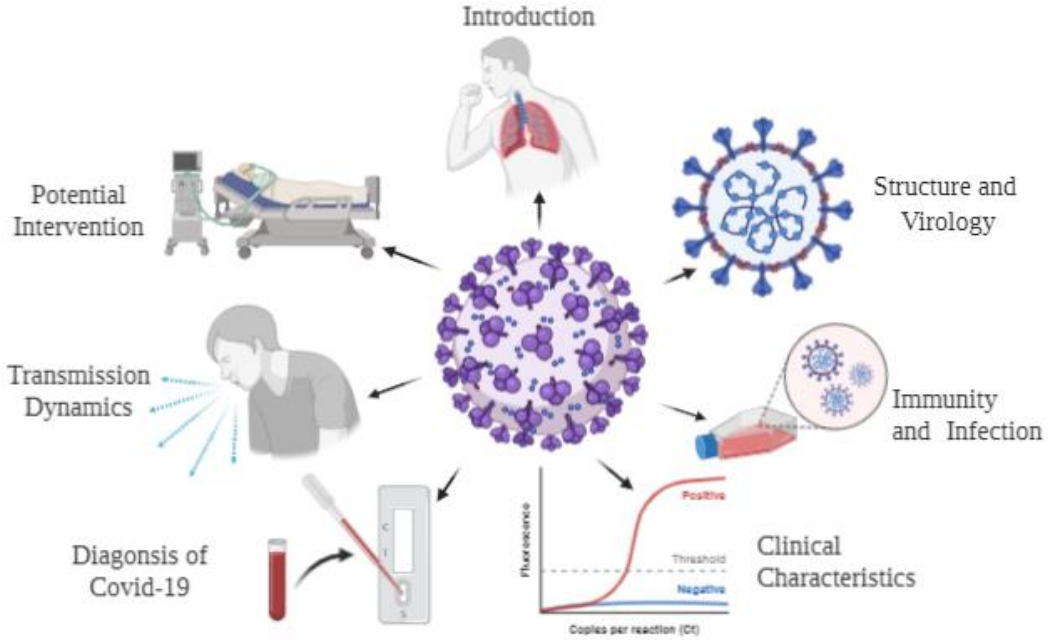

Abstract: Emerging and reemerging pathogens is a global challenge for public health. Recently, a novel coronavirus disease emerged in Wuhan, Hubei province of China, in December 2019. It is named COVID-19 by World Health Organization (WHO). It is known to be caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that affects the lower respiratory tract and manifests as pneumonia in humans. Coronaviruses (CoVs) are structurally more complicated as compared to other RNA viruses. This viral epidemic has led to the deaths of many, including the elderly or those with chronic disease or compromised immunity. Viruses cause infection and diseases in humans of varying degrees, upper respiratory tract infections (URTIs) cause common cold while lower respiratory tract infections induce pneumonia, bronchitis, and even severe acute respiratory syndrome (SARS). The costs of COVID-19 are not limited. It equally affects all the

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medical, sociological, psychological, and economic aspects globally. This is regarded as the third deadly outbreak in the last two decades after Severe Acute Respiratory Syndrome SARS (2002–2003) and Middle East Respiratory Syndrome MERS (2012). Based on the sequence homology of SARS-CoV-2, different animal sources including bats, snakes, and pangolins have been reported as potential carriers of this viral strain. Real-time RT-PCR represents the primary method for the diagnosis of new emerging viral strain SARS-CoV-2. The transmission dynamics suggest that SARS-CoV-2 is transmitted from person-to-person through direct contact or coughing, sneezing, and by respiratory droplets. Several anti-viral treatments including lopinavir/ritonavir, remdesivir, chloroquine phosphate, and abidor are also suggested with different recommendations and prescriptions. Protective and preventive strategies as suggested by various health organization *i.e.* WHO and US Center for Disease Control and Prevention (CDC) must be adopted by everyone. This review covers the important aspects of novel COVID-19 including characteristics, virology, symptoms, diagnostics, clinical aspects, transmission dynamics, and protective measures of COVID-19.

Keywords: Coronavirus, sequence homology, transmission, virology, diagnosis, virus control, vaccination.

1. Introduction

Emerging and reemerging pathogens is a global challenge for public health [1]. Very recently, a novel coronavirus which was temporarily named “2019 novel coronavirus (2019-nCoV)” emerged in Wuhan, China, home to 11 million people [2]. Coronaviruses (CoVs) primarily cause multiple respiratory and intestinal infections in humans and animals [3]. Although the history of CoVs began in the 1940s [4, 5], the identification of the first human CoVs was reported in the 1960s, as causative agents for mild respiratory infections.

Coronaviruses are non-segmented positive-sense RNA viruses and have been placed to the family Coronaviridae and the order Nidovirales [6]. Based on genetic and antigenic criteria, CoVs have been organized into four groups: α-CoVs, β-CoVs, γ-CoVs, and δ-coronavirus (Table 1) [3, 7]. Outbreaks of the two ß-coronaviruses, one being the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) [8-10] while the other Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [11, 12] have induced more than 10,000 cases in the past twenty years, with mortality rates of 37% for MERS-CoV and 10% for SARS-CoV [13, 14]. SARS-CoV also caused a major viral outbreak in Guangdong (China) in 2002 and 2003 [15]. MERS-CoV was the pathogen responsible for severe respiratory disease outbreaks in 2012 in the Middle East [12].

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Coronaviruses not only infect humans but also infect mammals and birds which harmed the farming industry [16-20].

Table 1: Organization of CoV's species

Group	Species
α-CoVs	Transmissible Gastroenteritis Coronavirus (TGEV) Canine Coronavirus (CCoV) Porcine Respiratory Coronavirus (PRCoV) Feline Coronavirus (FeCoV) Porcine Epidemic Diarrhoea Coronavirus (PEDV) Human Coronavirus 229E (HCoV-229E) Human Coronavirus NL63 (HCoV-NL63)
β-CoVs	Bat Coronavirus (BCoV) Porcine Hemagglutinating Encephalomyelitis Virus (HEV) Murine Hepatitis Virus (MHV) Human Coronavirus 4408 (HCoV-4408) Human Coronavirus OC43 (HCoV-OC43) Human Coronavirus HKU1 (HCoV-HKU1) Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV)
γ-CoVs	Avian Infectious Bronchitis Virus (IBV) Turkey Coronavirus (TCoV)
δ -CoVs	Bird Coronavirus

Some coronaviruses were originally implied as enzootic infections, limited only to their natural animal hosts. But they have transversed the animal-human species barrier and progressed to be established as the source of zoonotic diseases in humans [21-23]. Consequently, these cross-species barrier jumps conceded the CoVs like the SARS-CoV and MERS- CoV to manifest as

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virulent human viruses. Their existential history is unknown so far but often they are linked with mild infections and in the worst case scenario, a new high virulent strain appears after few years. This review aims to provide a brief knowledge of the pathogenicity and history of SARS, as well as the lessons learned. The other purpose is to review the characteristics, virology, immunity and infection, clinical characteristics, diagnosis, and management of patients infected with SARS-CoV-2 and transmission dynamics for a better understanding of this deadly coronavirus and suggests its prevention, treatment, and management strategies.

2. Characteristics of Coronaviruses

2.1. Structure

These viruses are called coronaviruses (CoVs) because of their crown-like unique appearance (Figure 1). Coronaviruses (CoVs) are structurally more complicated as compared to other RNA viruses. Among all RNA viruses, CoVs have the largest virus genomes of size about 26 - 32 kb (kilobases). These viruses have a spherical shape and a diameter of ≈ 100 nm [24, 25].

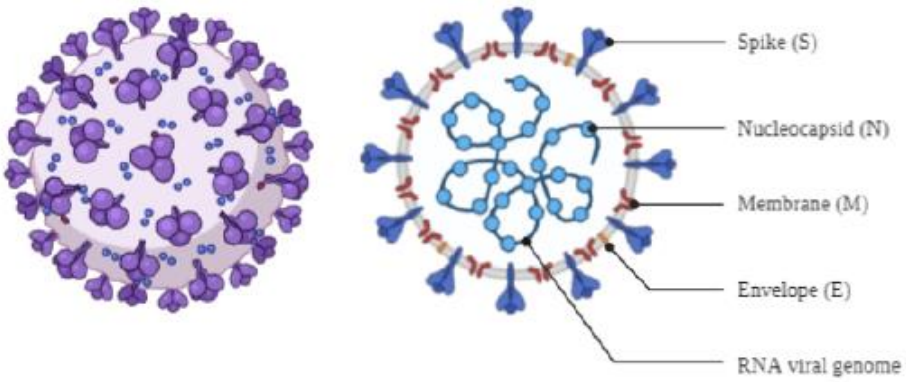

Figure 1: Structure of Coronavirus

The major part of CoVs structure consists of four or five structural proteins. Minor components are also present which include non-structural and host cell-derived proteins [26]. The protein coat (capsid) around CoVs protects the genetic material of these viruses. All viruses are made up of Nucleocapsid (N), Spike (S), Envelope (E), and Membrane (M) structural proteins and some also encodes a hemagglutinin–esterase (HE) protein [27]. Although these proteins are structurally complicated and carry a range of functions, they occupy only a third of the coding capacity in the CoVs genome [28, 29]. A major portion of the genome, some two-thirds located at the 5’ end encodes two long open reading frames 1a and 1b that together encode the polyprotein precursors

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pp1a and pp1ab of the virus. Several viral proteases are also present in polyprotein which together develop pp1a and pp1ab into 16 non-structural proteins (nsp1–16) that are necessary at different phases of the virus replication [27]. Cellular membranes are encountered by the virus surface proteins, S, M, and E to initiate the infection again during the replication phase that is transformed and fused into the endoplasmic reticulum and Golgi intermediate compartment (ERGIC) [30]. Finally, budding of the developed virions takes place into the secretory pathway [28, 29]. Among all the proteins in CoVs, the spike proteins (S) play an important role in the activation and initial attachment of the virion with DPP4 (dipeptidyl peptidase 4) host cell receptor. The RBDS (receptor- binding domains) of the S proteins exclusively recognize the human angiotensin-converting enzyme 2(ACE2) [31].

Hence, this protein has a major role in the spread of coronavirus specifically from humans to humans and cross-species as well. Furthermore, numerous non-structural proteins also act together with membranes as is in common with other positive-strand RNA (Ribonucleic acid) viruses. Virus replication takes place in specialized cellular compartments induced by viral proteins that transform host membranes to originates sites for replication that are veiled from the cellular inducers of innate immunity [32]. The blend of various membrane intermingling factors and numerous sites of membrane interfaces make coronaviruses (CoVs) to more genetic variables and infectious virus [33].

2.2. Virology of Coronavirus

The International Committee for Taxonomy of Viruses proclaims: Coronaviruses (CoVs) belong to two subfamilies: Torovirinae and Coronavirinae which are members of the family: '*Coronaviridae'*, and order: *Nidovirales*. Coronavirinae (subfamily) is further categorized into four major classes: Alpha-coronaviruses (α-CoVs), Beta-coronaviruses (β-CoVs), Gamma-coronaviruses (γ-CoVs), and Delta-coronaviruses (δ-CoVs) (Figure 2) [3]. HCoV-NL6 and HCoV-229E are Alpha-coronaviruses while SARS coronavirus, HCoV-HKU1, HCoV-OC43, and MERS coronavirus are the Beta-coronaviruses. Both kinds of coronaviruses (α-coronavirus and β-coronavirus) infect just mammals, while the γ-coronavirus and δ-coronavirus habitually infect birds [34]. According to currently reported databases, it has been observed that all human coronaviruses (CoVs) originate from animals: MERS-CoVs, HCoV-229E, SARS-CoVs, and HCoV-NL63 originate from bats while HKU1and HCoV-OC43 are possibly derived from rodents [25, 35].

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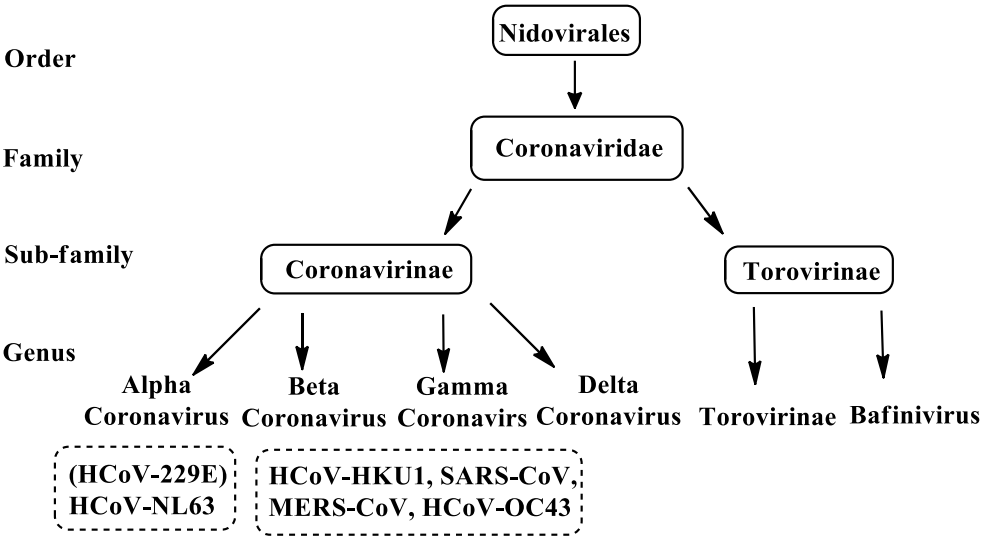

Figure 2. Classification of Coronavirus

The novel coronavirus (2019-nCoV) is the seventh (7th) member of the CoVs' family that infects human beings, after Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). The novel coronavirus (2019-nCoV) is a Beta-coronavirus (β-CoV) [36] of group 2B, which has about 70% resemblance in genetic sequence with SARS coronavirus [37]. The genetic sequence of this coronavirus (2019-nCoV) became accessible to the world health organization (WHO) by employing genome sequencing. The origin of the novel coronavirus (2019-nCoV) infection has been established as bats. Zhou and his coworkers, through full-length genome sequences, established that novel coronavirus are ≈ 96% alike at the whole genome level to a bat coronavirus (CoV) [38]. Wu and collaborators executed the phylogenetic study on the whole viral genome. They concluded that 2019-nCoV was strongly linked with SARS-nCoV alike coronavirus, formerly reported from bats in China [39]. Ji and team-mates accomplished extensive sequence studies and evaluation in combination with RSCU (relative synonymous codon usage) partiality amongst various animal genera established on the novel coronavirus (2019-nCoV) RNA (Ribonucleic acid) genome sequence. They concluded that the novel coronavirus is possibly a recombinant virus among the bat coronavirus (CoV) and additional permutation coronavirus (CoV) with an indefinite source. Because of the virus's relative synonymous codon usage (RSCU) closest to the snake, they established that the indefinite source is probably the snake [40]. Zhu and coworkers employed algorithmic techniques to study the gene sequences of 2019-nCoV and other CoVs and to identify possible viral hosts. They concluded that minks and bats could-be the two possible hosts of the 2019-nCoV [41]. The novel coronavirus (2019-nCoV) exhibited an analogous form of infection to other CoVs (SARS-nCoVs, MERS-nCoVs, and Bat SARS-like CoVs) in humans. Xu and coworkers while modeling the spike protein

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of the receptor for novel coronavirus (2019-nCoV) stated that the enzyme ACE2 (angiotensin-converting enzyme 2) may be the possible receptor for this novel virus [42]. Likewise, ACE2 is also a preferred receptor for SARS coronavirus and NL63 virus [43-45]. They also reported that the binding affinity between the novel coronavirus and angiotensin-converting enzyme-2 is greater than the threshold needed for virus attack, although being smaller than that between SARS coronavirus and angiotensin-converting enzyme 2 (ACE2). Zhou and team-mates performed virus infectivity analyses and established that ACE2 is necessary for novel coronavirus to penetrate HeLa cells [46]. They also concluded that the angiotensin-converting enzyme-2 (ACE2) may be the receptor for novel coronavirus. Zhao and coworkers examined lung tissue cells in eight healthy persons. They concluded that the Asian donors have almost five times more angiotensin-converting enzyme-2 expressing cell ratio as compared to American, African, and white donors [47, 48]. These results indicated susceptibility of Asian population, though more data and confirmation are required to derive such results.

3. Immunity and infection (Host response)

Host immune response consists of multiple tissues, cells, and molecules that are responsible for the protection of the host from an invasion of pathogenic microorganisms like viruses. The immune response is a key factor to control viral infection and works to stop viral gene transfer and blocks or reduce pathogenic transgene expression [49]. The innate immune system recognizes the invading virus using different types of cell or body receptors. Several types of receptors like pattern recognition receptors (PRRs) detecting viral DNA or RNA, induce type I interferons (IFNs) and other pro-inflammatory cytokines inside infected cells [50]. The adaptive immune response is an antigen-specific, long term response to the viral infection that takes several days to weeks for its development. Native T cells proliferate and produce long term memory cells that completely remove the viral infection and are useful to cure a viral infection in the future [51]. A balance between host viral interaction and an immune response is very important as a deficiency in immune response will increase viral infection. While overactive immune response will lead to immunopathological disorders [52]. Here we will briefly discuss the human immune response to coronavirus and its infection.

3.1. Innate Immune response

The innate immune system acts as the first line of defense and produces rapid and broad response against viral invasion and replication. Recognition of pathogen-associated molecular patterns (PAMPs) helps detect viral infections by making use of pattern recognition receptors (PRRs).

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NOD-like receptors, Toll-like receptors, RIG-like receptors, and C-type lectin-like receptors are the main types of PRRs. Some of the free molecular receptors like IF16, STING, DAI, and cGAS are also present freely in the cytoplasm [53].

3.1.1. Toll-like receptors

Toll-like receptors are a group of toll-like proteins, found in both invertebrates and vertebrates. These receptors recognize pathogens by PAMPs of nucleic acid (DNA, RNA) proteins, lipids, and lipoproteins [54]. Depending on localization and associated PAMP ligands, these receptors are categorized into two types. One type which consists of TLR 1,2,4,5,6 and 11 primarily recognizes viral membrane components such as proteins, lipids, and lipoproteins and is present on the cell surface. The second type comprises TLR 3,7,8 and 9; and is found in intracellular components which include lysosome, endosome, and endoplasmic reticulum (ER); and detect viral DNA or RNA for initiation of immunity response in the cell [55]. Different types of TLRs induce different biological responses by activating TIR domain-containing adapter molecules. For example, surface TLR1-2-6 and TLR-5 mainly induce inflammatory cytokines. Further type I interferon and cytokine inflammatory response is generated by TLR3 and TLR4. This difference was understood by the finding of the TIR-domain which includes molecules that are activated by different TLRs using different signaling paths. MYD88 has first discovered molecules that are universally activated by all TLRs except TLR-3 and activate inflammatory response by the activation of mitogen-activated protein kinase and transcription factor NF-κB. While TLR-3 and TLR-4 use activate transcription factor IRF-3 and NF-κB that induces activation of inflammatory factor and type I interferon [56]. Alison et al after a series of experiments revealed that in mice, TLR signaling is very important to protect it from SARS-CoV infection. Balanced immune response based on both MYD88 and TRIF signaling pathways induces the most efficient host response to viral infection [57]. Feline infectious peritonitis (FTIP) is a fatal intestinal disease induced by feline coronavirus (FCoV). TLR (2,4 and 8) receptors detect FCoV viruses by their structural proteins and nucleic acid patterns that generate inflammatory pathways of action against viral infection [58].

3.1.2. RIG-I-like receptors

RIG-I-like receptors (RLRs) are a group of H receptors that include (MDA5, RIG-I, and LGP-2). These are nucleic acid-based receptors that detect pathogens (viruses) and viral infections based on RNA sequences to generate antiviral response [59]. These RLR receptors use molecular machinery for recognition of RNA and activate signaling through mitochondrial adaptive signaling (MAV) that further activates antiviral response by the manifestation of cytokines involving type I and type III interferons. N-terminal caspase recruitment structure present on MDA5 and RIG-I

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interacts with downstream adapter MAVs. C-terminal termination Domain (CTD) and viral RNA helicase structure identify RNA that needs ATP to induce conformational changes to generate Caspase Recruitment Domain CARD structure that interacts with MAVS to induce immune response [60].

The most common viral characteristics recognized by RLRs are double-stranded RNA (dsRNA) or 5' RNA (ppp-RNA) generated during viral replication and transcription of the viral genome [61]. RIG-I detects diversity of RNA viruses which includes Hepatitis C virus, Newcastle disease virus, Influenza virus, measles virus by ppp-RNA, and 5'-end of double-stranded RNA. While MDA5 receptors recognize RNAs of poliovirus, picornavirus, and encephalomyocarditis virus by characteristic RNA strand greater than 1 kbp [62, 63]. A coronavirus is a group of positive-sense RNA viruses and both RIG-I and MDA5 respond to their invasion [64]. But these large RNA viruses have genetic space that encodes for several proteins to stop immunity response. For example, SARS coronavirus encodes Papin like protease (PLpro) to inhibit interferon III activations by RIG-I receptors [65]. Middle East Coronavirus (MERS) encodes ORF86B protein that inhibits the interaction between MDA5/RIG-I receptors and MAVS that stops the activation of interferon III as an immune response [66]. The nucleocapsid protein of SARS-coronavirus has been found effective in the suppression of RNA in mammals that affects the response of MDA5 receptors [66]. SARS and MERS-coronaviruses also avoid host detection of dsRNA by replicating in virus-induced double-membrane vesicles that lack PRRs for viral dsRNA identification. Moreover, capping of viral mRNA with complexes such as nsp-10 and nsp-16 generated by both MERS and SARS coronavirus are helpful in inhibiting immune response of MDA5 and interferons [67-69].

3.1.3. C-Type lectin-like Receptors

C-type lectin receptors are a huge group of soluble receptors comprising of higher than 100 members present on myeloid cells. They bind to carbohydrates in a calcium-dependent manner and their lectin activity is facilitated by carbohydrate-recognition domains (CRDs). Due to their multiple signaling pathways and large motif structure, CLRs perform a variety of functions such as induction of endocytosis, platelet activation, cell adhesion, and natural immune response. Based on molecular structure and cellular activation CLRs are mainly divided into two types as macrophage-induced C-type lectins (Mincles), and dectin-2 receptors. Mincles are directly activated by type II transmembrane receptors. While the dectin—2 receptors are activated by the activation of HAM-like motifs within the intracellular tail of receptors (Dectin-1 and DNGR-1 receptors) [70-72]. This leads to the activation of molecules like MAPKs and NF-κB that triggers

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the diversity of cellular immune response such as maturation, chemotaxis, and cell phagocytosis [73].

CLRs are very important in viral detection and activation of immune response and research revealed that deadly viruses such as HIV and dengue viruses disrupt the function of these receptors to stop immune response against viral infection [74]. Avian coronavirus is a poultry virus and infects respiratory epithelium and other respiratory organs. DC-SIGN/L-SIGN (C-type lectin receptors) are found to be effective in detection and inhibition of viral infection [75]. CD209L; a CLR receptor of human lungs expressed in endothelial cells and type II alveolar cells are found to be the potential target of SARS-CoV and other enveloped viruses (such as Sindbis and Ebolavirus).A large protein S glycoprotein (spike protein) encoded by SARs-CoV binds with ACE2 and CD209L during viral invasion and infection [76].

3.1.4. Type I Interferons

Type I interferons are key effector cytokines of host immune response against viral infections. They limit the viral spread with an immunomodulatory response that enhances the phagocytosis of antigens and activation of natural killer cells to restrict viral infection to the target cell. Thus the production of IFNs precisely influences the existence of the virus in the host [77, 78]. Type I interferons are further classified into IFN-I, IFN-II, and IFN_III according to their cognate receptors and IFN transcribing genes. Upon viral invasion, PRRs like toll-like receptors (TLRs), nucleotide receptors (NLRs), scavenger receptors (SR), RIG-like receptors, and nucleotide-binding oligomerization domain-like receptors (NLRs) activate NF-kB and IRF7 signaling pathways to induce the pro-inflammatory response of interferons [79].

Murine coronavirus; known as the mouse hepatitis virus (MHV), is recognized by MDA5 as a PRR receptor. These receptors induce Type I IFN and secretion of IFN- β in animal brain cells. This approves the importance of IFNs in the immune response against viral infection [80]. IFN-α activated by plasmacytoid dendritic cells (pDCs) is also found effective in potential control against mouse (MHV) coronavirus and human Severe Acute Respiratory Syndrome (SARS) coronavirus [81]. Viral infections are lethal if they suppress or stop production or activation of type I interferons. SARS coronavirus encodes the production of M protein that antagonizes activation of IFN-stimulated response and stops the transcription process of type I interferons. Porcine Epidemic Diarrhea Coronavirus (PEDV) that causes acute diarrhea in swine; encodes endoribonuclease that suppresses the activity of type I interferons [82, 83]. SARS coronavirus-2; known as a novel coronavirus (COVID-19), is found to be more sensitive than SARS coronavirus against Type I interferons pretreatment. COVID-19 has a more sensitive response with increased

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STAT 1 phosphorylation and stimulated gene induction (SGI) protein synthesis. Single-cell RNA technology was used recently to understand the human immune response against COVID-19. Detection of the viral invasion, gene expression level, and type I interferon response was found to be a key factor to control viral infection and life-threatening stage in humans [84]. Thus, a complete understanding of type I interferon immune response will be useful in the treatment of acute coronavirus infections.

Dendritic cells (DCs) are the antigen cells that initiate and modulate the immune response by effectively stimulating B and T lymphocytes which combine the innate and adaptive immune response. B-cells are precursors of antibody-secreting cells that directly recognize native antigen through B-cell receptors. T lymphocytes cannot directly recognize antibody and need major histocompatibility complex (MHC) presented on the surface of APC for recognition of antigen fragments. Immature dendrite cells can easily move while mature DCs efficiently activate T cells for initiation and regulation of immune response against viral infection [85, 86].

Upon viral invasion dendrite, cells receive signals that initiate and regulate the cell-dependent immune response. Dendrite cells have a very efficient mechanism that detects pathogens and signals for the activation and differentiation of antigens specific T cells to induce an immune response against viral infection [86]. Dendritic cells are principal antigen-presenting cells (APC) that activate cytotoxic T lymphocytes CTL response with the help of CD4+ T cells which induces long term immune response through CD8+ CTL antiviral activity. Sometimes, viruses directly or indirectly hinder immune response by modulating dendritic cells. Viruses might exploit or disable immune response by interfering with dendrite cells or CD4+ cell activities [87]. For example, human respiratory epithelial cells have been found highly vulnerable to MERS-CoV. MERS-Coronavirus readily infect and replicate in human macrophages and dendritic cells that trigger the abnormal production of pro-inflammatory cytokines or chemokines leading to immense apoptosis in these cells [88]. SARS coronavirus also modulates the response of both immature and mature DCs proving its ability to suppress the innate and adaptive immune response of humans against these viral infections [89].

3.2. Adaptive immune response

3.2.1. The immune response of T cells

T cells are lymphoid cells that originate from hematopoietic stem cells produced in the bone marrow. They are further divided into four main types as CD4+ helper cells, CD8+ cytotoxic cells, memory t cells, and natural killer T cells. Activated by PRRs, T cells secrete cytokines that attack

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infected cells and stimulates the growth of other T cells [90]. Regulatory T cells play a very important role in balancing between activation and response of CD4+ T cells, and CD8+ T cells and reduce the risk of autoimmunity or overwhelming inflammation [91]. Cytotoxic T cells attack viruses or virally infected cells while memory t cells are prepared against future infections. Both CD4+ T cells and CD8+ T are involved in response to the invasion of the SARS-coronavirus M antigen [92]. Experiments on a mice model revealed that CD4+ T cells regulate primary immune response and eliminate virally infected cells from the lungs while CD8+ memory cells do not affect viral replication or clearance at the time of infection [93]. By screening the patients recovered from SARS-CoV T-cells response to SARS coronavirus was studied. Data showed that CD4+ T cells mostly produce TNFα, IFNγ, and IL-2 while a very small percentage of cells also respond by producing inflammatory cytokines. On the other hand, CD8+ memory cells mostly produce TNFα, macrophage inflammatory protein (MIP) 1α, IFNγ, or MIP 1β alone or in combination [94]. It has been found that the number of T cells in the blood is significantly reduced during the acute phase of SARS infection. Therefore, an appropriate response of CD4+ T cells is necessary to cure coronavirus infections. Existing data show that CD8+ memory T cells persist up to 6 years of post-infection in recovered SARS patients [95]. Vaccination to enhance T cell process will provide robust and long term treatment against severe coronavirus infections.

3.3. Antibody response to coronavirus

Natural antibodies are glycoproteins termed as immunoglobin (Igs) that are produced in response to immune reactions. Based on binding structures, antigens are further divided into five types such as IgG, IgA, IgM, IgE, IgD, and camelid antibodies. They are key components of adaptive immune response and provide broad-spectrum, fast response against viral invasion. Their functionalities include the recognition and removal of nascent cells and other self-antigens to restrict viral infection [96, 97]. The immune response of antibody is a complex dynamic mixture of monoclonal antibodies that target different antigen domains expressed on the enveloped glycoprotein of the virus. Coronavirus uses its spike protein to facilitate its invasion through a special receptor DPP4 (dipeptidyl peptidase-4). This receptor then transmits signals for activation of the innate and adaptive immune response [98]. Human monoclonal antibody m336; detached from the human genome library, effectively neutralize MERS-CoV by interacting with the receptor-binding region of spike protein in vitro analysis [99]. Monoclonal antibody m336 was also found effective to cure MERS-CoV infection in monkeys and rabbit lung tissues [100, 101]. Mun et al. cured MERS coronavirus in mice model by inoculation of AddaVax-adjuvanted S377-588-Fc vaccine that produced neutralizing antibodies against MERS infection [102]. Newly identified novel coronavirus (2019-nCoV) has created a disastrous situation all around the globe by infecting more

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than a million people in 213 countries with 51000+ deaths [103]. However, there is no proper antiviral medication or vaccines possible to cure COVID-19 infection. Xiaolong et al. recently reported that CR3022 a human monoclonal antibody can potentially bind with spike protein of 2019-novel coronavirus. More experiments can be helpful to develop antibodies that can completely bind with spike protein and stop the COVID-19 invasion [93]. This could be helpful in the rapid treatment of novel coronavirus infection by neutralizing monoclonal antibodies as compared to waiting for a time-consuming vaccination process. Figure 3 illustrates the Immune Response (Innate and adaptive) against Coronavirus infection.

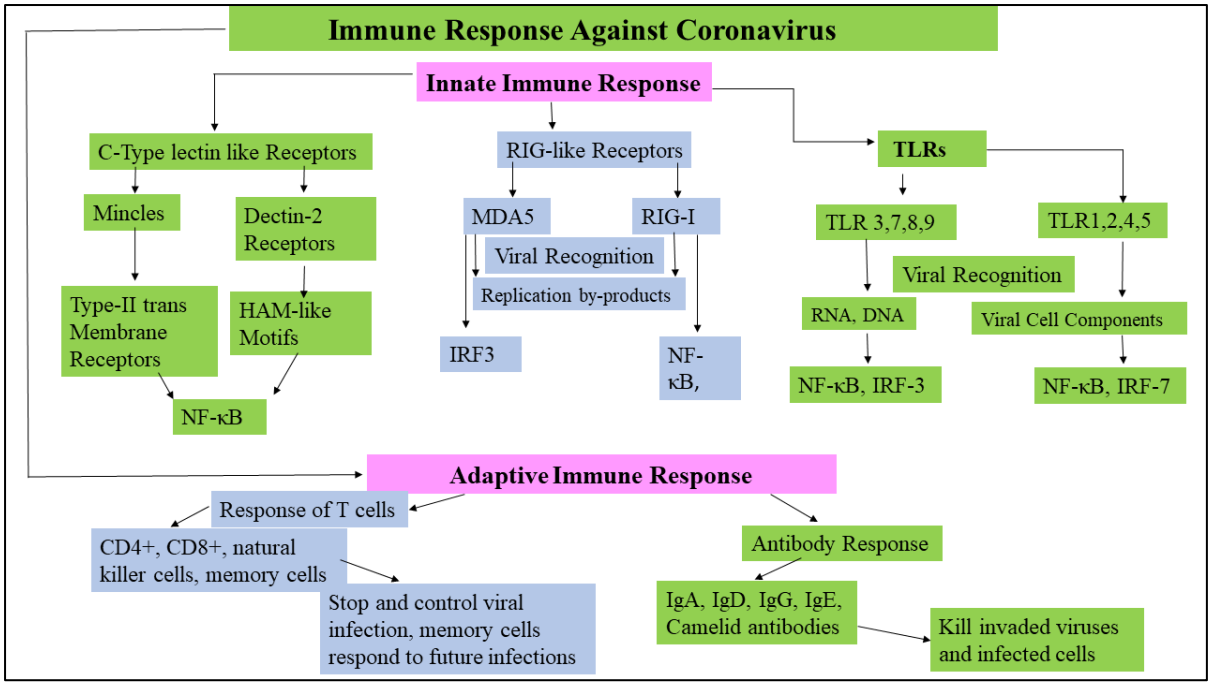

Figure 3: Immune Response (Innate and adaptive) against Coronavirus infection

4. Clinical Characteristics

The clinical purview of COVID-19 extends from asymptomatic to extremely severe health conditions like collapsing of the respiratory system, severe pneumonia and ultimately leading to the deterioration of multi-organ systems. The COVID 19 largely proliferates via droplets, respiratory tract, and its secretions and also through direct contact [104].

ACE2 protein (a functional receptor for coronavirus) residing on the lung epithelial cells assists in perceiving the track of this infection and the way this disease extends itself [105] Epidemiological investigations suggest the incubation period to be from 1 to 14 days, and mostly 3 to 7 days [106]. The COVID 19, being infectious, is highly impartible in humans, essentially targeting the older

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population. People with older age and other cerebrovascular diseases are more susceptible to this infection. The median age of the patients is found to be 47 to 59 with no significant gender parity as the ratio of male to female patients is 56% to 45% [107]. Younger ones are mildly affected but may still act as carriers of this infection.

4.1. Laboratory testing and diagnostic criteria

Cases of COVID-19 are confirmed by the nucleic acid amplification test (NAAT) by real-time polymerase chain reaction **(**PCR). As reported by WHO, respiratory material is collected from upper respiratory tracts such as oropharyngeal/nasopharyngeal swabs, nasal secretions, or lower respiratory tract namely sputum or bronchoalveolar lavage. Specimens are stored at 2 to 8 degrees Celsius. In addition to this, other samples can also be collected, as COVID-19 has been detected in blood and stool as well [108]. Serological methods for the detection of lgM, lgG antibodies are also performed. However, this method alone is not reliable for detection and it should be backed with RT-PCR. Samples obtained from severely infected patients have had a lesser count of CD4 and CD8 lymphocytes, higher levels of CRP (C-reactive protein), CK (creatine kinase) and LDH (lactate dehydrogenase). Several inflammatory factors are also found in severe and critical illness states.

4.2.Clinical symptoms

Typical signs and symptoms of COVID-19 include fever (87.9%), dry cough (67.7%), shortness of breath (18.6%), etc. Atypical symptoms are nausea (5%), sore throat (13.9%), diarrhea (3.7%), headache (13.6 %), fatigue (38.1), congestion (4.8%), chills (11.4%), myalgia (14.8%). [109]. According to the Chinese CDC report, considering the stern clinical indications of this malady, it has been sectioned into mild, moderate, severe, and critical categories [110].

4.2.1. Mild Infection

Patients with mild COVID-19 infection have indications of upper respiratory tract deterioration along with mild fever, dry cough, sore throat, nasal congestion, headache, muscle pain, or malaise. 81% of the reported cases have had a mild infection.

4.2.2. Moderate infection

Patients have mild pneumonia and other few respiratory infection manifestations like cough and shortness of breath. No severe conditions are reported yet.

4.2.3. Severe infection

Besides having mild or moderate clinical symptoms, patients are shown to have rapid breathing, lack of consciousness, dehydration, raised the level of liver enzymes, and other injuries related to the dysfunctioning of vital organs. Overall, 13.8% of the reported cases are severely infected.

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4.2.4. Critical infection

In addition to severe clinical indications, respiratory failure where mechanical ventilation becomes mandatory for survival e.g., Acute Respiratory Distress Syndrome (ARDS), sepsis, and collapsing of organs where patients' condition is monitored in ICU, are observed. 4.7% of the total are critical cases and the mortality rate for critical patients is 49%. Patients with other underlying diseases like cardiovascular, diabetes, chronic respiratory diseases, hypertension, cancer have higher mortality rates i.e., 10.5%, 7.3%, 6.5%, 6%, and 5.6% respectively as compared to others with no such previously mentioned diseases [111].

4.2.5. Acute Respiratory Distress Syndrome (ARDS)

ARDS is a preliminary step leading to respiratory failure. The degree of hypoxia, considering PaO2/FiO2 as standard, determines various forms of ARDS. The value of PaO2/FiO2 ranging in between 200mmHg and 300mmHg indicates mild ARDS while those between 100mmHg and 200mmHg are the indicator of moderate ARDS. PaO2/FiO2 of less than 100mmHg refers to severe ARDS [112]. 30% of the patients have had ARDS.

Chest imaging like chest radiograph, computed tomography scan, and lung ultrasound can also be utilized for confirmation of infection. CT scan of the reported cases is found to have ground-glass opacity(56%), consolidation(29%), lobes (71%), and bilateral involvement (76%) [113].

4.2.6. Sepsis

Sepsis is the body's ultimate riposte to infection, leading to the dysfunctioning of organs and becoming life-threatening. Patients suffering from COVID-19 and having sepsis as well, exhibit a broad range of manifestations involving multi organs deterioration. Severe dyspnea, hypoxemia, reduced urine output, changed mental response and renal impairment are the typical symptoms [114].

4.2.7. Clinical Outcomes

Patients with older age are more prone to COVID-19. And among these, the most favorite victims of this malady are the ones with weaker immune systems and other cerebrovascular diseases. Patients with severe illness involve Acute Respiratory Distress Syndrome, liver dysfunctioning, arrhythmia, acute cardiac damage, and kidney impairment [115].

5. Diagnosis of COVID-19

For diagnosis, nasal secretions, sputum, blood, and bronchoalveolar lavage (BAL) are collected from patients and suspected people. The samples and specimens are then subjected to some specific serological and molecular tests that are COVID-19 specific. Computed tomography technique (CT) and X-Ray could prove helpful in the detection of severely infected patients [116].

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Chest CT can also be considered a standard method for COVID-19 but it has limitations in the identification of the specific virus and discrimination between viruses [35, 38, 117-121]. Detection of viral nucleic acid can help in the diagnosis of asymptomatic carriers. And for that purpose pharyngeal swab can be utilized. Real-time polymerase chain reaction (rRT-qPCR) for effective diagnosis of SARS-CoV-2, is performed over respiratory secretions. In a short period, viral RNA can be detected while Serological tests employ Enzyme-Linked Immunosorbent Assay (ELISA) [121]. Still, Real-time polymerase chain reaction (RT-PCR) remains the primary means for the diagnosis of new emerging virus strain of COVID-19 [119, 122-128].

5.1. Differential Diagnosis

There is a need to distinguish COVID-19 from SARS CoV, MERS CoV, influenza virus, parainfluenza virus, and adenovirus. The current studies of 2020 are summarized to diagnose 2019-nCoV through RT-PCR and gene assays. Apart from the molecular test that is RT-PCR, serological test methods (i.e. ELISA) are also described to compare these diagnostic techniques (Table 2). The recent studies of MERS-CoV are also included in Table 2 to enhance the understanding regarding different types of infectious classes of viruses. Therefore, a comparative study of diagnosis is made to differentiate COVID-19, SARS-CoV-2, and MER-CoV as shown in Table 2. It reveals that the molecular test is more sensitive and selective than other methods. Studies also described that nested PCR has an additional step of pre-amplification or incorporating the N gene to enhance sensitivity.

Table 2: Systematic search outcomes of COVID-19, SARS-CoV-2 and MERS-CoV diagnosis

COVID-19					
sr. no	Author Year	Test	Samples/Population	Findings	Ref
1	Shirato et al. (Japan) 2020	Nested RT–PCR Real-time RT–PCR	Different specimens from the same patient were taken and primers detected the COVID-19 sequence for the spike (S) protein (S set).	Specificity was evaluated by comparing the tests with six other human coronavirus sequences. The results were satisfactory. Sufficient sensitivity (~5– 50 copies for the control RNA) was achieved by both sets. No cross-reactivity with other respiratory viruses was found.	[129]

2	Corman et al. (Germany) 2020	Real-time RT–PCRNxTAG respiratory pathogen panel gene assay	29 original samples with human respiratory viruses were collected from the Charité, RijksinstituutvoorVolksgezondheiden Milieu (RIVM), Bilthoven, Erasmus University Medical Center, Rotterdam, Public Health England (PHE), London, and the University of Hong Kong.	The RdRP gene, E gene, and N gene assays exhibited high sensitivity while the E gene and RdRP gene revealed the best results (5.2 and 3.8 copies per reaction) with 95% detection ability. COVID-19 was successfully discriminated from SARS-CoV making use of artificial nucleic acid technology. Synthetic nucleic acid technology was used to differentiate COVID-19 from SARS-CoV.	[130]
3	Chu et al. (China) 2020	1-step Quantitative Real-time RT-PCR	The specimens were collected from the two suspected COVID-19 patients (Beijing). Sputum samples were collected from the patient 1 after 5 days of corona symptoms while the throat swab sample was collected from the patient 2 for RNA extraction.	Serially diluted RNA samples revealed the 10 times high sensitivity for N gene assay than the ORF-1b gene assay. These assays could not test qualitatively to these samples at the testing site and also exact viral copy statistics cannot be measured.	[131]
4	Chan et al. (China) 2020	RT-PCR Sanger sequencing Phylogenetic analysis	In this study, phylogenetic analysis of gene sequencing of five patients (family cluster) was performed who returned from Wuhan to Shenzhen (China) and also a family member who didn't have a travel history.	The throat swabs of all the patients were negative by point-of-care multiplex RT-PCR. While RT-PCR of the five patients was positive for gene encoding for the internal RDRP (RNA-dependent RNA polymerase) and Spike protein of COVID-19. Phylogenetic analysis also confirmed the 2019-nCoV which is adjacent to SARS.	[132]

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5	Corman et al. (Germany) (2020)	RT-PCR gene assays	Respiratory samples were collected from the Charite medical center and a total of 75 clinical samples were tested.	All the essays were sensitive to COVID-19. The lowest detection limit (LOD) was recorded 5.2 RNA copies/ reaction, at a 95% hit rate; 95% CI: 3.7-9.6 RNA for E gene assay. RdRP gene assay exhibited the LOD of 3.8 RNA copies/reaction, at 95% hit rate; 95% CI: 2.7-7.6 RNA copies/reaction. The obtained signals of 2019-nCoV were compared with the signal probe of SARS-CoV. The use of PCR-generated targets leads to the generation of fluorescent signals in these assays.	[130]
			SARS-COV-2		
6	Li et al. (China) 2020	Rapid IgM-IgG Combined Antibody Test	525 blood samples were collected from 8 various clinical sites. PCR confirmed that 397 patients were COVID-19 positive and 128 patients were negative.	It was found that IgM-IgG combined antibody sensitivity was 88.66% and specificity was 90.63%. Additionally, fingerstick blood, serum, and plasma of venous blood were also used for the diagnosis of SARS-CoV-2.	[133]
7	Li et al. (USA) 2020	Multiplex PCR and a Multiplex-PCR-based Metagenomic Method	The universal human reference RNA from Agilent Technologies, Inc. (Cat#74000); The plasmids containing SARS-CoV-2 from SangonBiotech, Shanghai (China); PCR primer was designed by Paragon Genomics, Inc.	The target peaks were achieved with good characteristics after exposing the positives with the assay. Additionally, SARS-CoV-2 and novel pathogens at low sequencing depth were also diagnosed by the multiplex-PCR-based metagenomic method.	[134]

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8	Bordi et al. (Italy) 2020	QIAstat-Dx Respiratory Panel (QIAGEN, Milan, Italy)	A total of 126 suspected cases were found and nasopharyngeal swab samples of 54 patients were taken from the INMI (Italy) and 9 cases were shifted to Lazio Region while other cases were referred to the INMI Laboratory of Virology.	The only 3 patients had positive SARS-CoV-2 which was confirmed by the INMI laboratory. The rest of the patients were suffering from the respiratory pathogens other than SARS-CoV-2.	[135]
9	Wang et al. (China) 2020	Real-Time RT-PCR	1070 specimens were collected from 205 patients with COVID-19. All the specimens were taken from three hospitals in Beijing, Shandong, and Hubei.	SARS-COV-2 was identified in the specimens of the patients. The live virus was also detected in the feces of the patients. The COVID-19 was positive with lower respiratory tract samples.	[136]
10	Amanat et al. (USA) 2020	Enzyme-Linked Immunosorbent Assays (ELISA)	59 banked human serums were collected with confirmed prior viral infections.	Serological assays have high sensitivity and selectivity for the detection of COVID-19 seroconverters in human serum. Scaling can be adjusted in these assays to detect various antibodies.	[137]
			MERS-CoV		
11	Shirato et al. (Japan) 2019	Two real-time RT-PCR assays	i. TRIzol reagent was purchased from Thermo Fisher Scientific, Waltham, MA, USA; ii. QIAamp Viral RNA Mini Kit was obtained from Qiagen, Hilden, Germany; iii. SimplePrep reagent DNA was obtained from TaKaRa Bio Inc., Shiga, Japan.	MERS-CoV was successfully detected by a multiplex Corman assay connected to a mobile PCR device, the PicoGene PCR1100. These assay identified MERS-CoV with high sensitivity and selectivity compatible with clinical specimens.	[138]
12	Hecht et al. (Germany)	RT-PCR kit	The sample was collected from 33 patients of Riyadh (Saudi	MERS-CoV was diagnosed in the two steps according to	[139]

	2019		Arabia) and pre-characterized via RT-PCR.	WHO recommendation. Among 33 samples, 54.55% of patient's tests were positive, 33% of patient's tests were negative, and 6% of patient's tests were unclear. It was concluded that the combination of RealStar MERS-CoV RT-PCR kit 1.0 with the RealStar® MERS-CoV (N gene) RT-PCR kit 1.0 can be the suitable and a confirmatory assay for MERS-CoV diagnosis.	
13	Okba et al. (Netherland) 2019	S1 ELISA Protein Microarray	Serum samples were collected from South Korea after the collected 6, 9, and 12 months of the disease.	It was confirmed that iELISA was 100% specific and 92.3% sensitive. The performance of iELISA was according to that of the MERS-CoV S1 protein microarray. The same pattern of specificity showed in the S1 microarray.	[140]
14	Kim et al. (Korea) 2016	6 Commercial MERS-CoV RNA diagnosis kits:(i)UltraFast kits detect upE and ORF1a simultaneously (Nanobiosys, Korea); (ii) LightMix (Roche Molecular Diagnostics, Switzerland); (iii) AccuPower (Bioneer, Korea); (iv) Anyplex	56 Nasopharyngeal Swabs were taken out of which 28 were positive for other respiratory viruses. The specificity and clinical sensitivity were further measured from the other 18 lower respiratory specimens.	All the kits identified all the positive specimens (100%). The comparative analysis of the kits revealed that AccuPower and PowerChek exhibit the least sensitivity in the presence of PCR inhibition.	[141]

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	Screening: envelope gene (upE) Confirmation: ORF1a (Seegene, Korea); (v) DiaPlexQ (SolGent, Korea); (vi) PowerChek (Kogene Biotech, Korea)

Several FDA approved diagnostic kits are also available for commercial use. Recently, FDA has given clearance to diagnostic kits of Abbot Laboratories and Navacyt which detect COVID-19 in minutes [142, 143]. Some of the new FDA approved COVID-19 diagnostic kits are shown in Table 3 [144].

Table 3: New FDA approved commercial rapid diagnostic kits for COVID-19.

Sr/no	Product Name	Manufacturer (Country)
1	Real-time fluorescent RT-PCR kit	BGI Biotechnology (Wuhan) Co., Ltd (China).
2	TaqPath COVID-19 COMBO KIT	Thermo Fisher Scientific, Inc (USA).
3	abTES™ COVID-19 Real-time qPCR I Kit	AITbiotech Pte Ltd (Singapore).
4	AllplexTM 2019-nCoV Assay	Seegene Inc (South Korea)
5	TIB MOLBIOL Lightmix® Modular Wuhan CoVRdRP-Gene	TIB MOLBIOL Syntheselabor GmbH-Eresburgstraße (Germany)
6	GENESIG® Real-time PCR (COVID-19) CE IVD Kit	Primerdesign Ltd (United Kingdom)

5.2. Diagnostic Challenges of COVID-19

Diagnosis of COVID-19 is still a challenge because laboratory diagnosis and radiology images do not always fulfill the clinical features and patient's contact histories. The manifestations of the COVID-19 are assorted and very quickly. Evaluation for early-stage detection using radiology images is a tough task. Therefore, the suspected patients with persistent fever and positive result

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Chest CT test, have to make a fast diagnosis with molecular tests and serological methods [145-148].

With the emergence of COVID-19 in China, the genomic test was the first test in the identification of disease-associated pathogens but it was complex and expensive so large scale detection was not an easy task. Then RT-PCR was introduced which is the primary diagnostic method of COVID-19 but it has also some limitations such as technique complexity, low detection limit, false sampling, and sample preparation problems. False-positive and false-negative results of the RT-PCR method also caused serious problems. A COVID-19 patient discharged from the hospital after having negative RT-PCR twice was found with RT-PCR positive later. There are many factors behind these "false negative" cases including sample contamination, genome mutation, and deletion [149-153].

6. Transmission Dynamics

It is important to study the transmission dynamics of epidemic disease in its early stages. We can get insight into its epidemiological scenario by studying the transmission pattern of respective diseases with time. Furthermore, it can also be estimated whether the outbreak controlling measure is showing measurable effects or not [154]. The novel coronavirus is found to be transmitted by person-to-person with direct contact or through coughing, sneezing by respiratory droplets [155]. According to a Centre of Disease Control and Prevention report, COVID-19 can spread through the contaminated things that may be touched by an infected person likes clothes, the handle of doors, transport vehicles, etc. Mostly, when a person has symptoms of respiratory virus, it becomes highly contagious. However, it is evident from recent research that COVID-19 is transferred from human-to-human interaction during the incubation period of 2 to 10 days, in which this virus remains asymptomatic [156]. Reproductive rate R° proved that the COVID-19 spread as compared to other pandemics is more severe. Following the report published by The New England Journal of Medicine, the reproductive Rate R° of COVID-19 in Wuhan was approximately 2.2. It is indicative of the fact that on average each infected person is spreading this disease to 2.2 other people. During the influenza pandemic in 1918, R° was estimated at 1.80. While R° for EBOLA virus disease (EVD) was estimated in the range of 1.47-1.90 during its outbreak in West Africa, in 2014. In general, when R° is greater than 1 the disease epidemic cannot be controlled. It can be reduced to 1 by isolation of patients and careful infection control [157]. According to WHO August 16, 2020, a total of 21,294,845 confirmed cases of COVID-19 and 761,779 death cases are confirmed, all over the world [158,159].

7. Protective measurements

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Various health organizations including WHO and the US center for disease control and prevention (CDC) have issued some protective measures to control the novel outbreak of COVID-19. A distance of a minimum 3ft must be maintained between two persons if either of them is having a cough or sneeze. Everyone must wash his/her hands as frequently as possible. Respiratory hygiene must be followed by everyone *i.e.* cover your nose with a tissue or bent elbow while sneezing or coughing. Use a face cover while others are around. Practice social distancing. Clean and disinfect the frequently touched surfaces which include tables, doorknobs, countertops, toilets, sinks, phones and light switches with EPA approved disinfectants [160, 161].

7.1. Potential interventions

Up till now isolation of the infected person is considered to be the most effective way of treatment as well as a prerequisite for blocking the source of infections. They are evaluated based on risk as moderate/high and are encouraged to report their conditions daily. Currently, COVID-19 is treated primarily via symptomatic treatments and antiviral therapies [162].

Patients with mild symptoms need supportive treatments at the early stage of infection. For patients with critical conditions, high-flow oxygen therapy, glucocorticoid therapy, extracorporeal membrane oxygenation, and administration of convalescent plasma are usually applied [162]. Several anti-viral treatments including lopinavir/ritonavir [163], chloroquine phosphate [164], and abidor are also suggested with different recommendations and prescriptions. Recent studies have reported that though CQ and HCQ have already been used to treat corona affected patients having a severe condition. But some side effects are also associated with their high dosage like some potential hazards when taken along with azithromycin and oseltamivir. So both of these should not be recommended for patients with critical conditions [165]. Remdesivir is also reported to be an effective drug against this disease. But despite its efficacy, the reported higher mortality rate shows that antiviral drug alone isn't enough for treatment. So future strategies should examine other therapeutic measures in combination with antiviral drugs to improve the treatment and patient outcomes [166]. Moreover, vaccination is highly recommended for the population acquiring poor immunity, especially for those with comorbidities. The development of vaccines is under process and many scientists around the globe are currently working on it. Moreover, it needs to be further tested for human trials. In addition to the stated therapeutic interventions, psychological interventions are also expected to be effective regarding infection control [14, 167].

8. Conclusion

The pandemic of COVID-19 has largely spread becoming a real menace all over the world. Characterization of this novel coronavirus has advanced; and therapies and vaccines are extensively being studied to fight against this virus. The whole knowledge about this novel coronavirus can be outlined as follows: It extends from asymptomatic to extremely severe health conditions collapsing the respiratory system and ultimately the deterioration of multi-organ systems. People with older age and other cerebrovascular diseases are more susceptible to this deadly virus. Molecular tests (i.e.; RT-PCR which is the primary diagnostic method) and chest X-ray are employed to diagnose the COVID-19. However, to distinguish COVID-19 from SARS CoV, MERS CoV, and other viruses, serological tests like ELISA are employed along with RT-PCR. SARS-CoV-2; being the causative agent of this COVID-19, manifests greater infectivity in comparison with other viruses like SARS and MERS considering mortality and morbidity. SARS-CoV-2, emanated from the reservoirs of bats, residing in an unidentified intermediate host, binds to the ACE2 protein (acts as virus receptor) present on lung epithelial cells with greater affinity and infects human beings.

Supportive treatments along with anti-viral drugs including lopinavir/ritonavir, chloroquine phosphate, remdesivir, and abidor are implied to treat the COVID-19 patients. Nonetheless, many queries remain unanswered and much research is needed to understand the transference and pathogenicity mode of this novel coronavirus. To limit its transference to animals or humans, the evolutionary pathway from its original host to cross-species transmission needs to be traced down. Besides this, the need of the hour is to implement the infection control strategies to limit the spread of coronavirus via human-to-human transmission. Public health authorities should keep monitoring the situation, as the more we learn about this novel virus and its associated outbreaks, the better we can respond. Moreover, this pandemic has accentuated the significance of evolving wide-spectrum antiviral factors to fight off the existent and future viruses.

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