Recent insights into clinical COVID-19 causing novel human coronavirus

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ABSTRACT

As everyone on earth came is panic about recent pandemic about coronavirus disease 19 (COVID-19) which is the most transmissible, contagious, deadliest and pathogenic viral infection that is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged from China (Wuhan city). The genomic sequence alignment analysis confirmed the phylogenetic origin of SARSCoV-2 from severe acute respiratory syndrome-like (SARS-like). This outbreak is suspiciously originated as zoonotic from the bats which might be act as primary reservoir. But, the major source of origin reason for conversion of this virus as transmitting agent from zoonotic condition to human to humans is still unclear. However, this kind of human to human rapid transmission, the clear pathogenesis, ambiguity with its clinical manifestation, non availability of rapid diagnostic tools, and either lacking of clinically approved proper anti-COVID-19 drugs or non existence of preventive vaccine for SARS-CoV-1 is available till date. Hence, in this review, we are summarizing the basic nature of pathogenic COVID-19 virus, its source of origin, pathogenicity, life cycle, infection, immunological invade in the host, diagnosis, clinical manifestations, possible therapeutic approaches and preventive measures of novel human coronaviruses severe acute respiratory syndrome coronavirus (SARS-CoV) in comparison with middle east respiratory syndrome coronavirus (MERS-CoV).

Keywords: SARS-CoV-2, severe acute respiratory syndrome, vaccine, COVID-19

How to cite this article: Jagadeesh C, Bose K, Mukherjee G (2020): Recent insight clinical COVDI-19 causing human coronavirus, Ann Trop Med & Public Health; 23(S15): SP231544; DOI: http://doi.org/10.36295/ASRO.2020.231544

Background

The viruses are extremely typical as well as critical objects in the world and regarded as the connecting link between the living agents and nonliving agents thus creating much more the ambiguity on biogenesis vs. abiogenesis theories of origin and evolution of life. Biologically these are obligate intracellular parasites as they exist as neutral lifeless entities when they occurs on the surface of any nonliving object but immediately they turn to pathogen once they adopt their propagation inside the host that may be animal cells, plant cells even in Microbial cells. Biochemically the viruses are nucleoproteins that have genome along with certain structural proteins. Certain viruses, exclusively...
animal and human viral pathogens, demonstrate structural complexity by exhibiting their surface outer envelope. This outer envelope of the virus was adopted from their host cell membrane and this was ornamented with some structural proteins which act as ligands, those are playing the vital role in the virulence by inducing the penetration of virus into the host cell via receptor-ligand interactions. Genetically the viruses adopted distinctive feature in terms of their genome by exhibiting their unique versatility by adopting even highly unstable RNA also as their genome. None other organisms in the world were found to be exist with RNA as genome as viruses. Microbiologically these viruses considered as infilterable agents that can pass even through minute porous sized filters range 0.2µm size and found to be living nanoparticles with a diameter of less than 200 nanometers (nm). These can exist as pathogens not only to plants, animals and human beings but also to bacteria, fungi and algae too and termed as bacteriophages, mycophages and phycophages respectively. The main intention of this review article on COVID-19 was to provide the preliminary view about COVID-19 disease, pathogenicity of corona virus, the ways of spreading, the modes of treatment, preventive measures and possibility of vaccines and therapeutics.

Introduction
In terms virulence the viruses express host specificity and generally their pathogenicity can be restricted within their compatible host genus. However, some vectors may not affect by viruses but carry out certain pathogenic viruses such as dengue, Chikungunya, Zika virus etc. Some animals including birds may sometimes hold certain harmful pathogenic viruses that can be spread to the public and cause severe illness leads to zoonoses such as rabies, avian influenza or bird flu subtypes of (H5N1) and (H9N2), swine flu subtypes (H1N1) and (H3N2) etc (Beard, 2011). There is wide range of human pathogenic viruses such as Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Hepatitis B virus (HBV), Human papilloma Virus (HPV) etc. classified under their taxonomical hierarchy(Kuchipudi and Nissly, 2018). Among them Human corona viruses are belong to family Coronaviridae, subfamily Orthocoronaviridae, order belongs to Nidovirales, and realm of Riboviria and first characterized in the 1960s as responsible for a considerable quantity of upper respiratory tract infections in human beings(Lefkowitz et al., 2018). The word "corona" is extracted from Latin literature where the term “corona” pertains to "crown" the same word in from Greek literature means "garland". This word Corona refers to the structural characteristic appearance of the viruses with scanning electron microscopy, which have an outer surface edge with huge, globular protrusions that creates an image that has resemblance with wither some crown or with solar corona(Li, 2016). This morphological character caused by the viral surface club like spikes called peplomers, those are the pin headed proteins on the surface of envelop of virus. These are certain group of viruses with positive sense RNA as their genome, which have broad host range of virulence leads to range of diseases ranging from enteritis to bronchitis both in mammals such as cows and pigs along with birds equally (Xu et al., 2020a). In humans, generally, Coronavirus cause infections that target the respiratory tract leading to the symptoms ranges from mild common cold to severe lethal symptoms that cause irreversible damage to respiratory tract. There are various corona viruses like Severe Acute Respiratory Syndrome (SARS), Middle Eastern Respiratory Syndrome (MERS), and corona viral disease in 2019 (COVID-19) those involves in the development of sudden epidemic to dangerous pandemic across the globe(Wang et al., 2013).

History of Human Corona Virus that cause COVID-19
At the end of December, 2019, numerous patients, during several weeks exhibiting with viral pneumonia due to mysterious viral agent, very first time in the world, were observed by an ophthalmologist Dr. Li Wenliang reported in city Wuhan, China. He shared the observations with his associated medical community as SARS-like infection may turn to epidemic and its high risk to the public. Later a novel corona virus was consequently detected as sole causative virus, provisionally reported in the name of 2019-nCoV (2019 novel corona virus). By the end of January 26, 2020, nearly 2000 sever cases with similar kind of symptoms as results of 2019-nCoV infection have been diagnosed and authenticated, mostly among the public of Wuhan, and transmissibility from human-to-human has been confirmed(Fan et al., 2020).

In courtesy of The Northern Times March 19, 2020

Fig.1 the structure of COVID-19 pathogenic virus and genomic arrangement of +ssRNA inside the virion.

Structure of COVID-19 pathogen
In 2019, novel Corona virus that caused pandemic COVID-19 disease is resultant of aggressive mutations of SARS-CoV-2 with pleomorphic positive sense RNA as genome encased within the envelop that harbors matrix (M-protein), Nucleoprotein (N-protein), Hemagglutinin esterase dimeric protein, envelop protein (E-protein) and the most critical spike glycoproteins that make the virus adherence to the mucosa of respiratory and intestinal tract and mobilization of virus into the host (Shang et al., 2018).

Epidemiology of COVID-19

Based on that epidemic outbreak, Chinese authorities publicized about this new isolate and this virus was called as 2019-nCoV as well as the disease name as COVID-19 (corona viral disease) by world health organization (WHO) in
(London., Jan 2020.). By February 12, 2020, more than 43,000 cases were diagnosed and confirmed and more
that 1000 deaths have been declared(data., 2020 February ). But the first case of the originated infection was
presumed through zoonotic agent as animal to human most likely through bats. There is drastic increment in the
figures of COVID-19 cases in China around Wuhan city and spread internationally after shutting down of the live
animal market and mass migration of these cases in China, has designated the subsequent transmission of the
COVID-19 from human-to-human. Primarily, new COVID cases were confirmed in other countries of Asian and
spread to many countries across the word and now it transformed into dangerous pandemic at global level
(Organization, 2020).

In January 22, 2020, officially, it has been proclaimed as Novel Corona Virus instigated from wild bats and this was
belonged to Group 2 of mutated β version of corona virus that was the resultant of Severe Acute Respiratory
Syndrome Associated Coronavirus (SARS-CoV) Even though, both COVID-19 and SARS-CoV are belonging to β-
corona virus subgroup, their genomic similarity after complete sequence alignment reports only 70%, and the new
COVID-19 causative viral group has been observed to express the genetic dissimilarity when compared with SARS-
CoV(10). As similar as epidemic created by Severe Acute Respiratory Syndrome (SARS), this COVID-19 outbreak
has emerged during Spring Festival, which is considered as the main well-known customary festival in China. As a
result, approximately 3 billion people travelled across the country. Both of these festival gatherings as well as
travelling conditions became most favorable for the spread of this potentially dangerous and contagious
disease(LGralinski, 2020). There were severe problems raised to implement preventive actions and controlling
measures of COVID-19 epidemic. The SARS epidemic hit the highest point ranging from January 17 and February
23, during the spring festival in 2003. In the similar way, during the same spring festival from January 10 to
February 18 in 2020, the epidemic COVID-19 cases were reached peak with 10 million cases as a results of mass
gathering, massive transport and massive celebrations. This extensive public travelling and gathering across the
world has also generated complimentary situations for the rapid spread of the difficult-to-control disease COVID-
19(Lu, 2020a). The asymptomatically infected Indians from different countries where COVID-19 turned epidemic
across the globe reached their homeland and government of India already taken the preventive and controlling
measures and strict quarantine was implemented across the country. Even after that, covid-19 cases are increased
day by day in India as per the table 1 as on 24-03-2020 (Ministry of Health and Family Welfare, 2020).

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Life cycle of Human Corona Virus:
SARS-CoV-19 is the structurally resembles a typical coronavirus with peplomeric spike protein on the surface of the outer envelope. These Coronaviruses include RNA (positive sense) that have precise genes those are in ORF1 will encode encodes some structural proteins like nucleoproteins, polyproteins, nucleocapsid and membrane proteins peplomeric spikes formation as well as the essential functional proteins that are participating in viral replication such as RNA polymerase, 3-chymotrypsin-like protease, glycoprotein, papain-like protease, helicase and accessory proteins(van Boheemen et al., 2012). Coronavirus peplomeric surface protein S has been identified as the most significant determinant of viral penetration into host cell (Wang et al., 2013).The globular peplomeric spikes called S protein which is glycoprotein in nature consists of receptor binding domain (RBD) and distributed over the surface of outer membrane of coronaviruses those are critically responsible for the anchorage by attachment to the suitable host cell and facilitates the entry of the virus into the host cells (Fig 2) (karen C. Carrol). The mechanism of the entry of a SARS-CoV-19 depends on the cellular protease enzymes, those includes, cathepsins, human airway trypsin-like protease (HAT) and transmembrane protease serine 2 (TMPRSS2). These can tear the peplomeric spikes of viral envelop and helps the virus particle to extend further by penetrating inside the host cell by allowing the host cell surface changes possibly by endocytosis. The peplomeric spike protein of SARS-CoV-2 consists of 3D structure in the receptor binding domain to keep up the vander Waals forces (Xu et al., 2020b). The glutamine residue playing unique role that is present in the receptor binding domain of peplomeric spikes of SARS-CoV-2 at 394 position will be able recognized the crucial lysine residue at 31 position in the receptor of human angiotensin-converting enzyme 2 protein (Wan et al., 2020). This receptor-binding domain (RBD) is freely attached on the surface of the virus, therefore, the virus possibly will distinguish diverse receptors like angiotensin-converting enzyme 2 (ACE2)
those are present on the host cells of human as well as bats. The entry of SARS-CoV-19 into human host cells was primarily recognized as proficient receptor mediated contact that favors the direct membrane integration between the viral envelop and host cell plasma membrane (Annan A, 2013; Simmons et al., 2004). It was observed that the critical proteolytic cleavage that carried S protein at position S2 that exist in the outer envelope of SARS-CoV-19 will facilitate the host pathogen membrane fusion and infectivity of the virus (Belouzard et al., 2009). The virus can penetrate by receptor mediated binding to infect numerous host range those are having the same kind of receptors (Chen et al., 2006; Wang et al., 2011). Mostly, the spikes of coronaviruses distinguish either the carbohydrates or the aminopeptidases as a receptor for their entry into the human cells, whereas SARS-CoV and MERS-CoV identify the exopeptidases as their receptors (E.de Wit, 2016). The entire life cycle mechanism of SARS-CoV-19, steps ranging from viral adhesion to release of progeny virions are well explained in figure 3.

Figure 3: The life cycle of SARS-CoV-19 in host cells; life cycle starts when Spike proteins on the surface of virus acts as ligand and interact with the host cellular receptor ACE2. After proper receptor ligand binding, there will be conformation change in the S protein of the virus that facilitates the fusion of viral envelope with the host cell membrane and viral penetration possibly through the endocytosis pathway. After that, SARS-CoV-19 releases its genomic RNA into the host cell cytoplasm. Then the SARS-CoV-19 genome RNA undergo transcription replication to synthesize multiple copies of genomic RNA and translation into viral functional replicase, structural proteins such
as polyproteins pp1a and 1ab, which are further cleaved into minute proteins by the action of viral proteases. The viral polymerase enzyme produces a multiple sequences of sub genomic mRNAs by performing discontinuous mode of transcription. These mRNAs ultimately translated into viral proteins. These viral proteins and genomic RNA will be fused together and consequently bring together to form new progeny virions migrated through the Endoplasmic Reticulum, Golgi apparatus and then transported by means of vesicles and finally released out of the cell as new progeny viruses that are ready to spread to the neighbor cells.

**Pathogenesis Mechanism of COVID-19**

Fortunately the genome of Corona viruses well documented and well studies among rest of RNA viruses. Major part of RNA nearly two by third of it encodes a fully functional viral polymerase enzyme (RdRp) (Drexler et al., 2010), RNA synthesizing enzymes, and two nonstructural huge viral polyproteins. These poly proteins are not involved in host response modulation. The other of part of the genome of SARS-CoV-19 (one-third) encodes majorly four structural proteins such as spike (S), envelope (E), membrane (M) nucleocapsid (N), and the other helper proteins those are involves in the assembly of the viruses(Luk et al., 2019). Even though, the span of the SARS-CoV-19 genome exemplifies elevated inconsistency for ORF1a or ORF1b and the four SARS-CoV-19 structural proteins, typically coupled with the quantity and volume of accessory proteins(https://viralzone.expasy.org/785). The primary step in the process of virus infection is the contact of sensitized and targeted human cells with peplomeric Spike Proteins that are occurring on the surface of the envelop of SARS-CoV-19. Genome of SARS-CoV-19 starts encoding immediately after entering into the host cell and facilitates repeated transcription and translation of their all sorts of proteins inclusive of useful accessory viral proteins, which go forward for the adaptation of SARS-CoV-19 viruses inside the human host. The SARS-CoV-19 will express high rate of genetic shift and drift. New SARS-CoV-19 viral strains continuously come up by two means that modify the genomic code of the virus. These are acknowledged as genetic drift and genetic shift. Genetic drift represents minute changes in genome that encode mRNA known as point-mutations which may take place in a single viral strain, where as Genetic shifts are when the genome of different strains of SARS-CoV-19 viruses mix up and form novel strains (Ren et al., 2015). Genomic variations in SARS-CoV-19 were raised as a result of genetic recombination, genomic exchange, insertion or deletion of nucleotides in ORF, which are very frequently, takes place those leads to outbreaks as similar as past epidemics. Consequently, the SARS-CoV-19 subfamily is very rapidly inflating with novel generations and genomics sequencing applications that facilitates the advanced diagnosis and description of novel CoV species. In summary, SARS-CoV classification is repeatedly altering. It has been identified that, there are four genera of thirty-eight unique species of SARS-CoV exist as per the most recent classification of International Committee on Taxonomy of Viruses (ICTV) (Subissi et al., 2014). SARS-CoV as well as MERS-CoV that make attachment with the host cell by binding with the cellular receptor SARS-CoV associated angiotensin-converting enzyme 2 and MERS-CoV associated dipeptidyl peptidase.

**Entry and replication of human Coronavirus**

After penetrating the virus into the host cell, the viral genomic positive sense RNA come out and exists in the cytoplasm and undergo encapsulation and polyadenylation, and encodes various structural and non-structural polypeptide genes. These SARS-CoV polyproteins are cleaved in to fragments and forms into complex by viral
specific proteases that demonstrate chymotrypsin-like activity (Lambeir et al., 2003). As a result of the formation of complex, the production of negative sense RNA through both replication and transcription and these copies are acts as templates for full length positive sense RNA genomes (Luk et al., 2019). A subset of 7-9 sub-genomic RNAs are produced during the viral RNA transcription, and ultimately translated into structural proteins such as viral nucleocapsid the collective form of genomic RNA along with R protein in the host cell cytoplasm. These are budded into the lumen of the endoplasmic reticulum. The newly created viral envelope glycoproteins are integrated into either the membrane of the endoplasmic reticulum or the membrane of Golgi, and the nucleocapsid will be generated by the combining the SARS-CoV genomic RNA along with nucleocapsid protein. Finally, new progeny viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Eventually, these vesicles those are containing the new virions then combine with the plasma membrane to release the virus(E.de Wit, 2016), released from the infected cell through exocytosis.

Clinical manifestation of COVID-19

The newly released SARS-CoV-19 viruses may spread systematically and infect complete lower respiratory tract, intestines, kidney cells, liver cells, and T lymphocytes as well as, where they can figure out the major signs and symptoms (Lambeir et al., 2003). Surprisingly, T-lymphocyte population will be lesser than 200 cells/mm$^3$ of blood in some patients with SARS-CoV-19 infection. Some viral strains are capable to affect even immunologically active human macrophages and dendritic cells. T lymphocytes are becoming the target for the SARS-CoV-19 pathogen owing to the characteristic CD26 rosettes. This SARS-CoV-19 virus may also affect the T-cell response and antiviral activities due to their capacity to stimulate T-cell apoptosis, thus causing a collapse of the immune system (Chu et al., 2014; Zhou et al., 2014). COVID-19 Patients with demonstrate clinical symptoms which are similar with SARS-CoV and MERS-CoV infections including fever, dry cough without sputum, dyspnea, fatigue, myalgia, decreased leukocyte counts, and pneumonia evidenced by radiographic investigations(Huang et al., 2020; J S M Peiris, 2004). Some time the patients are asymptomatic. Therefore, even though the exact pathogenesis of COVID-19 is poorly understood, they resemblance the similar mechanisms of SARS-CoV and MERS-CoV still can provide ample of information to understand the pathogenesis of SARS-CoV-19 infection as well as to make easy to diagnose the recognition of COVID-19.

Antigen presentation in coronaviral host interaction

When the extracellular pathogens like viruses enters in the reticuloendothelial system, its surface antigens will be processed and presented by circulatory antigen presentation cells (APC), which is a vital response generated by the host to achieve the anti-viral immunity. These processed antigenic poly peptides are generally presented by either human leukocyte antigen (HLA) or major histocompatibility complex (MHC) in human host and further these viral polypeptides to be identified by virus-specific cytotoxic T lymphocytes (CTLs). Therefore, understanding the mechanism of antigen presentation of SARS-CoV-19 virus will provide the comprehensive clues of COVID-19 pathogenesis. But, unfortunately non availability of information on this antigenic process and presenting phenomenon leads to much ambiguity in understanding the exact pathogenesis. Based on the previous research
reports on SARS-CoV and MERS-CoV, the presentation of SARS-CoV antigen primarily depends on MHC type 1 molecules (Liu et al., 2010), rather than MHC type 2 molecules even these are also have meager contribute in the presentation of SARS-CoV-19 viral antigens. Earlier investigations demonstrated abundant polymorphisms in HLA that was correlated with the susceptibility of SARS-CoV, like HLA-B\*0703, HLA-B\*4601, HLA-DR B1\*1202 (Keicho et al., 2009) and HLA-Cw*0801 (Chen et al., 2006), while the HLA-Cw1502, HLA-DR0301and HLA-A*0201 alleles are connected with the protection from previous SARS epidemic infections (Wang et al., 2011). Where as in MERS-CoV infections, MHC type 2 molecules like HLA-DQB1\*02:0 and HLA-DRB1\*11:01 are connected to susceptibility to MERS-CoV infection (Hajeer et al., 2016). In addition, genetic polymorphisms of mannose-binding lectin (MBL) linked with antigen processing and presentation is associated with susceptibility of SARS-CoV infection (Tu et al., 2015). These investigations may give the lead to understand the mechanism of COVID-19 pathogenicity to prevent and to treat as well.

**Immunological aspects of COVID-19**

Antigen processing and presentation consequently motivates the host immunity in terms of both cellular mediated immunity and humoral immune response and these are mediated by virus-specific T lymphocytes and B lymphocytes respectively. As similar as frequent acute viral infections, the development of antibody and their profile in response to SARS-CoV-19 virus posses the distinctive pattern of Immunoglobulins type M and type G. These SARS-responsive IgM antibodies vanished after a period of 12weeks, whereas the same SARS-responsive IgG antibody may be extend for a life time. This indicates that, IgG antibody generated against SARS-CoV-19 could be principally play the defensive role (Li et al., 2003), and these SARS-specific IgG antibodies are generated primarily against peplomeric S-specific as well nucleocapsid N-specific antibodies (E.de Wit, 2016). In comparison with the humoral immune responses, there are more investigations on the cellular mediated immunity of corona virus is most essential to understand the acquired resistance. The recent evidences demonstrates that, the number of both CD4\(^+\) specific and CD8\(^+\) specific T lymphocytic cells in the host peripheral blood of SARS-CoV-19 infected patients extensively reduced. Correspondingly, the acute phase response in SARS-CoV-19 patients is related with the severe diminishement of CD4\(^+\) T and CD8\(^+\) T cell populations. Even in absence of SARS-CoV antigens, both CD4\(^+\) and CD8\(^+\) memory T lymphocytic cells are able to persist for about four years in SARS-CoV recovered patients. In the recovered individuals, T cell proliferations, Delayed Type Hypersensitivity (DTH) response and interferon production (IFN-\(\gamma\)) will be successfully carry out (Fan et al., 2009). Even after six years of SARS-CoV infection, SARS-CoV specific memory T-cell demonstrated the immune responses to the library of surface S peptide in some SARS recovered patients(Tang et al., 2011). In the same way, the MERS-CoV specific CD8\(^+\) T lymphocytes are also confirmed a similar type of effect on MERS-CoV recovered mice (Zhao et al., 2014). These reports might provide precious information for the rational design of diagnostic tools, therapeutic as well as vaccines against SARS-CoV-19. The description in *Lancet* evidenced that acute respiratory distress syndrome (ARDS) is the major cause of deaths among COVID-19 patients (Huang et al., 2020). Among the population with SARS-CoV-2-infected patients in early stages of the epidemic outbreak, major patients were died from acute respiratory distress syndrome ARDS (Huang et al., 2020). Thus this is the common immunological as well as pathological incident for...
SARS-CoV-2, SARS-CoV and MERS-CoV infections (Xu et al., 2020c). One of the most important mechanisms for acute respiratory distress syndrome (ARDS) is the immunological cytokine storm, the deadliest, uncontrollable, systemic inflammatory response generated due to secretions of great quantities of pro-inflammatory cytokines such as IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc. as well as chemokines like CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc. by effector cells of immune system in SARS-CoV infection (Williams and Chambers, 2014) (Cameron et al., 2008). The patients with elevated MERS-CoV infections illustrated abnormal raised levels of IL-6, IFN-α, and CCL5, CXCL8, CXCL-10 in their blood serum as similar as severe SARS-CoV infections (Min et al., 2016). Hence, the cytokine storm determined the triggering of an aggressive attack by patient immune system to their own bodies leading to acute respiratory distress syndrome (ARDS), multiple organ failure, and lastly lead to death in severe cases of SARS-CoV-2 infections. SARS-CoV and MERS-CoV adopted multiple varieties of approaches for their better survival in the host cells and one of them is to evade immune responses. There are certain microbial structures known as pathogen-associated molecular patterns (PAMPs) which are evolutionarily conserved can be recognized by pattern recognition receptors (PRRs). On the other hand, SARS-CoV and MERS-CoV can be capable of inducing the construction of double-membrane vesicles which lack pattern recognition receptors and they can even replicate in these sorts of vesicles, thus stay away from the host detection of their dsRNA (Snijder et al., 2006). Both types of interferons such as IFN-α and IFN-β showed defensive effect on both SARS-CoV and MERS-CoV infections, but the type 1 interferon pathway was hampered in mice (Channappanavar et al., 2016; Channappanavar et al., 2019). Non structural accessory functional protein 4a of MERS-CoV could obstruct the stimulation of interferons at the stage of MDA5 activation by directly interacting with double-stranded RNA (Niemeyer et al., 2013). In addition, membrane proteins of MERS-CoV and ORF4a, ORF4b, ORF5 encoding proteins hinder both the transportation of interferon regulatory factor 3 (IRF3) to the nucleus as well as the activation of IFN β promoter (Menachery et al., 2018; Yang et al., 2013). The surface antigen processing and presentation can also be impaired by the corona virus. For instance, gene expression related to antigen processing and presentation will be down-regulated in the host after their infection (Menachery et al., 2018). Consequently, by targeting the destruction of the immune evasion pattern of SARS-CoV-2 is very important for treatment as well as precise drug development.

**Various Diagnosis Methods of COVID-19**

In general, nowadays, COVID-19 clinical diagnosis protocol is principally depends on epidemiological history, individual clinical manifestations of signs and symptoms. There are few secondary inspections also used to diagnose the COVID-19 such as chest X-ray, CT scan, immune identification technology Point-of-care Testing (POCT) of COVID-19 specific IgM/IgG, enzyme-linked immunosorbent assay (ELISA), COVID-19 RNA detection, and blood culture. On the other hand, the clinical signs and symptoms of the patients infected with SARS-CoV-19 are extremely sometimes atypical, together with abnormal respiratory symptoms with dry cough, dyspnea, moderate to severe fever, and viral pneumonia. Consequently, secondary investigations are indispensable for the proper and precise diagnosis of COVID-19 as it already turned to pandemic outbreak. There are two molecular diagnostic tools to confirm the SARS-CoV-2 in the samples, which regularly used in the detection technologies for nucleic acid, are
quantitative real-time polymerase chain reaction (RT-qPCR) as well as high-throughput sequencing technology. The reliable detection method for minimizing false positive problems in terms of q-RT-PCR is SARS-CoV-2 virus blood culture along with high-throughput sequencing of the whole genome (Zhou et al., 2020). On the other hand, the usage of high-throughput sequencing technology in medical diagnosis is inadequate because of its high cost. So RT-qPCR is the mainly widespread tool for effectual and uncomplicated method for detecting the COVID-19 viruses in the respiratory secretions as well as in the blood of the patients (Corman et al., 2020; Lu, 2020b). Although RT-qPCR technique is considered as most precise diagnosis method for COVID-19, this may lead to develop some false-negativity which should not be ignored since the severe consequences and complications of mis-diagnosis. Numerous clinical practitioners worldwide adopted usage of CT scans in their diagnostic procedures for patients with prominent clinical suspicious infection of SARS-CoV-2 with negative RT-qPCR screening, combination of frequent RT-qPCR tests as well as chest CT scan may be more helpful. The high-resolution CT (HRCT) scan for the COVID-19 patient chest is necessary for early diagnosis and evaluation of disease severity (Pan et al., 2020). The distinctive CT images will be evidence for bilateral pulmonary parenchymal ground glass and consolidative pulmonary opacities, from time to time with a rounded morphology and a peripheral lung distribution. Hence, CT scans encompass enormous value for clinical diagnostic of COVID-19 infection (Ooi et al., 2004). But, CT scans also demonstrates some disadvantages such as indistinguishability in terms of other viral pneumonia symptoms. Hence clinical laboratories must expand some concerns on serodiagnosis kits that may target viral structural antigens or SARS-CoV antibodies as soon as possible. Currently, Point-of-care Testing (POCT) of IgM and IgG based ELISA kits for SARS-CoV-2 were developed and pre-tested results are demonstrated higher rate of detection in comparative of nucleic acid detection. In terms of sensitivity of SARS-CoV N-protein based IgG detecting ELISA is having 94.7% is considerably higher than that of SARS-CoV S-protein based IgG detecting ELISA is having 58.9% only(Woo et al., 2005). Hence, there is a need of developing other specific and sensitive supporting methods on urgent basis for the diagnosis of COVID-19.

**Currently available therapeutic approaches for COVID-19**

Currently, there is no clinically demonstrated and proven précised antiviral drugs to control covid-19, just like SARS-CoV as well as MERS-CoV (E.de Wit, 2016). The drug regiments were based on the symptoms and aimed to target the relieving of bothered symptom. In India, COVID-19 patients were treated with anti malarial drugs like Chloroquine in combination with other antiviral drugs such as Lopinavir, Ritonavir, remdesivir and the results were significantly promising. In supportive of the primary treatment, oxygen therapy, body fluid management as well as to prevent the second line infections broad-spectrum antibiotics administration can be most significant management strategy (Huang et al., 2020). Based on the modern investigations and research on molecular mechanisms of COVID-19 infection as well as the genomic organization of SARS-CoV-19 (Lu et al., 2020), there are numerous prospective therapeutic targets to be developed for the efficient interventions against this current pandemic novel coronavirus. Remdesivir is potent antiviral agent considered to be adenosine analogue which targets the enzyme specifically RNA-dependent RNA polymerase as well as it block viral RNA synthesis in the host cytoplasm, So this can be used as most promising antiviral agent that can fight against a extensive array of RNA viral infections.
including SARS/MERS-CoV both in cultured cells (Lo et al., 2017), mice (Sheahan et al., 2020) as well as in primate models (de Wit et al., 2020; Lo et al., 2019). The intravenously administrated remdesivir might have potential protection from SARS-CoV-2 infection (Holshue et al., 2020) along with chloroquine and hydroxychloroquine regime revealed best and effective inhibition on SARS-CoV-2 in vitro (Wang et al., 2020). Therefore the nucleoside analogues like Favipiravir, Ribavirin and Galidesivir (De Clercq, 2019) may be potentially used to treat against SARS-CoV-2. There are certain non-structural proteins like Chymotrypsin-like (3C-like protease, 3CLpro) and papain-like protease (PLP) have a necessary function for replication and development of corona virus in the host cells and these protein actions may inhibit the host immune responses (Chen et al., 2020).

Hence, 3CLpro inhibitors like cinanserin and Flavonoids (Jo et al., 2020), and as well as PLP inhibitors like diarylheptanoids (Park et al., 2012) may be other effective alternatives to battle against SARS-CoV-2. The host receptor ACE2 mostly intervenes SARS-CoV-2 entry into the host cell as a by acting as functional receptor for coronaviral surface protein. By blocking the attachment of corona viral S protein with ACE2 is also a significant strategy to minimize SARS-CoV-2 infection. It has been described that there are numerous restorative COVID-19 patients are donating their blood plasma against SARS-CoV-2 for hyper immune serum treatment trials with preliminary obtained positive results in acute as well as highly severe SARS-CoV-2 patients. Furthermore, the generation of recombinant monoclonal antibodies (mAbs) which are humanized will be another clear-cut pathway to neutralize SARS-CoV. SARS specific human monoclonal antibody CR3022 has potential binding capacity with the receptor-binding domain (RBD) of Surface protein of SARS-CoV-2 as well as it has the potential therapeutics against SARS-CoV-2 infections (Tian et al., 2020). m396, CR3014 are also other type of monoclonal antibodies that can neutralize SARS-CoV might be another substitute to treat SARS-CoV-2 (Zhang and Liu, 2020).

Status of Vaccine Development for COVID-19
As SARS-CoV-2 became deadliest pandemic across the globe, it is very essential to develop a preventive vaccine against SARS-CoV-19 that may be used worldwide for reducing disease severity, viral shedding and to stop the viral transmission, thus facilitating the public to control the future outbreaks of coronavirus. Earlier, there are numerous vaccination strategies against both SARS-CoV as well as MERS-CoV were experimented in animals, including inactivated virus, live-attenuated virus, viral vectors, recombinant vaccines, proteins vaccines and subunit vaccines (Graham et al., 2013) . These investigations are in progress, but it may take some time to develop the potent vaccines against SARS-CoV-2.

Conclusion
In conclusion, the incidence and expansion of SARS-CoV-2 majorly depend on the interaction between the virus and the host immune system. Various viral factors such as type of virus, types of mutations, viral load, viral titer as well as viability of the virus in vitro along the side of host immune capacities will influence the pathogenicity and transmission. The host immune factors such as genetics, nutritional status of the individual, race, age, gender, neuroendocrine-immune regulation along with physical status might definitely influence the rate of incidence, the
duration of the disease, severity of the disease, reinfection as well as rate of surveillance. In the early stages of pandemic, precise diagnosis definitely helps to control the spreading of the disease among the community. It is very important to develop accurate, novel, safe, fastest and simple diagnostic methods to detect SARS-CoV-2. Certainly, physicians, clinicians, virologists and medical practitioners will deliberately contribute in these critical factors to make them expand into the beneficial path to human health care those might help the patients to recover as soon as possible.

References:


