CURRENT SCENARIO OF SARS-CORONAVIRUS 2: EPIDEMIOLOGY; POST-COVID-19 AND GLOBAL IMPACTS

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ABSTRACT
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly contagious strain of coronavirus that causes Coronavirus Disease 2019 (COVID-19) infection, which has distressed the world's health and wealth. This Global Pandemic outbreak has affected public health enormously at various customs. The investigation of SARS-CoV-2 is still at infancy; however, based on the available reports, this review gives an overview of the epidemiology, genomic landscape, diversity of SARS-CoV-2, viral genome pathogenic interactions, associating factors for COVID-19 infections, post-COVID-19, disease manifestations with their comorbidities, the major obstacles and the preventive measures along with current vaccine strategies of SARS-CoV-2. This review also summarizes all the relevant evidence of COVID-19 illness, which can provide valuable information on the SARS-CoV-2 genome and its mode of action strategies, thus delivering additional knowledge about COVID-19.

Keywords: SARS-CoV-2, COVID-19, Genetic factors, Post-COVID, Disease manifestations, Herd immunity, COVID-19 Vaccines

BACKGROUND
Virus life cycle mutation is one of the natural phenomena; perhaps not alter the virulence of the virus pathogenicity. The novel coronavirus (COVID 19; later named by WHO) is a pandemic disease caused by a family of the severe acute respiratory syndrome (SARS) in humans named SARS-CoV-2 (Coronavirus-2); the member of seventh RNA β coronavirus (Zhu et al., 2020). Furthermore, the genomic content of RNA is tightly packed and enclosed by a protein shell. RNA of COVID-19 has been mutating unconditionally based on physiological and environmental factors. Currently, researchers are working in the fields of epidemiology (Smith et al., 2013; Smith et al., 2014; Sanjuán & Domingo-Calap, 2016; Shen et al., 2004; Wang et al., 2020; Chan et al., 2013), molecular expression (Smith et al., 2013; Chan et al., 2013; Banu et al., 2020; Kaul, 2020), and clinical medical history (Zhu et al., 2020; Shen et al., 2004) of SARS-CoV-2, and were updated their consequences reported regularly. However, evaluation of these parameters is quite essential to track and solve this viral infection worldwide (Zhu et al., 2020; Chan et al., 2013). Even though, only a few studies were discussed about the genetics phenomenon of the host on COVID-19 infections. Additionally, the mutation rate of SARS-CoV-2 is very low compared to other viral mutations, even though these mutations haven't altered the functional characteristic of SARS-CoV-2. However, the functional characterization of specialized viral isolates was showed significant changes in the viral pathogenicity (Yao et al., 2020). Therefore, we are focusing on the SARS-CoV-2 genome; associated factors for host interactions with the mutational impacts of COVID-19 from the virtual investigation of genomic data were overviewed. Moreover, the perception of the noteworthy sceneries of the SARS-CoV-2 post-infection, disease manifestations, and deliberate features of vaccine development was highlighted.

THE GENOME LANDSCAPE OF SARS-COV-2

Strain Allelic diversity of SARS-CoV-2 genome

The evolution of SARS-CoV-2 exists in three distinct variants; based on their amino acid alignment, the genomic content of SARS-CoV-2 has been distinguished in three types A, B, and C (Forster et al., 2020). In type-A, nearly 96.2% of sequences are matched with bat coronavirus compared with the human virus (Zhou et al., 2020). Therefore, type A originated from Wuhan coming under the out-groups of ancestral prominent viral genomes and mutated in two clusters B and C. Briefly, identical mutation arose in T-allele T29025C, mutated into two sub clustered forms B and C. Moreover, in Wuhan (China), America and Europe consist of a significant level of type A and C (ancestral viral genome). Besides, type A predominant exists only in Wuhan, whereas type C existed only in Europe and America. A mutated genome of type B only found in East Asia derived from type A. Indeed, another interesting fact that the type B genome of SARS-CoV-2 not mutated inside and outside of East Asia may come due to tropical resistance power and immunological power (Forster et al., 2020). Additionally, scientists from the Peking University and Institute Pasteur of Shanghai reported that two strains of SARS-CoV-2 from 103 populations, S-type as original strain from Wuhan, and the L-type evolved from S-type, predominantly present in the US. The antagonistic L-type widely spread and act as a potent virulent than S-type. Moreover, the Wuhan strain of S-type was restrained to adapt and mutate. Further, these surface proteins emerged as L-type (Yang et al., 2020).

Recently, the unique cluster of the genome of CoV predominant clade I/A3i was identified in India, which clinically correlated with 41% of SARS-CoV-2 and in global genomes matched with 3.5%. It is suggested that the cluster of A3i were evolved from the common ancestor of SARS-CoV-2 on Feb 2020 during a pandemic outbreak, and the distinctive mutations have occurred on their viral genome were confirmed by epidemiological valuations. Additionally, the virulence clade I/A3i were isolated from the states of Maharashtra, Tamil Nadu, Telangana, and Delhi. However, presently A2a is the most predominant type of SARS-CoV-2 in India; A3i may evolve from A2a (Banu et al., 2020).

Host-COVID-19 interactions

The genome size of coronaviruses is 30-33 kb with 3'exonuclease activity during replication; trend to have the lowest mutation rate due to larger genome size compared to other RNA viruses. According to the Baltimore classification, the positive - strand of SARS-CoV-2 with RNA dependent RNA polymerases has the intrinsic polymerase fidelity activity to determine the initial mutation rate during the central dogma process (Smith et al., 2013; Sanjuán & Domingo-Calap, 2016). In the SARS-CoV-2 genome, a spike protein (S protein) diversity is responsible for host interactions, specificity, and pathogenicity. The occurrences of mutation in S protein induce the variety of mutations, which deals with host-specific interactions and functional expressions. Shen et al. (2004) reported that a single amino acid mutation in spike protein hampers its maturation, essential functions of cell-cell fusion, and virions assembly. However, the occurrences of these mutations aren't changing the virulence of the ancestral strain, the impacts SARS-CoV-2 virion are reflected in all the mutated strains. Therefore, these
mutualistic impacts of SARS-CoV-2 genome analysis are highly needed by utilizing submitted genomic variations, landscape variations with drug effectiveness.

**HOW CAN GENOMIC VARIATIONS IN SARS-COV-2 CONTRIBUTE AS A PATHOGEN?**

*Genomic organization of SARS-CoV-2*

The genomic structural characterization of coronaviruses (CoV) is 80-120 nm in size, single-positive stranded RNA viruses consist of four divergence groups, including α, β, δ, and γ-coronavirus (Wang et al., 2020). Among these four viruses, β-coronavirus of SARS-CoV-2 and MERS-CoV (Middle East Respiratory Syndrome) is responsible for pulmonary illness in humans (Zhu et al., 2020). The mechanism of SARS-CoV-2 is initiated by a binding receptor of angiotensin-converting enzyme 2 (ACE 2) through the S protein domain and causes infection to the target cells. The diagrammatic representation of SARS-CoV-2 interactions with host genome ACE 2 binding domain represented in Figure 1.

![Diagramatic representation of SARS-CoV-2 interactions with human host ACE2 receptors](image)

**Figure 1** Diagramatic representation of SARS-CoV-2 interactions with human host ACE2 receptors

The structural features of COVID-19 capped with 5' end and consist of a base of −26.2 to 31.7kb with ten open reading frames (ORFs). The replication proteins are located at the first part of ORF (nsp 1-16), and the last part of ORFs consist of structural genes in order of S-E-M-N and middle region accessory genes are located at a variable number of S-E-M-N. Frameshift occurs in ORF1a and ORF1b creates two polyptides: pp1a and pp1ab encode a viral chymotrypsin protease (3CLpro) / main protease (Mpro) with additionally papain hooked on 16nps.

![Genomic representation of SARS-CoV-2, (a) the coding and non-coding region of SARS-CoV-19, (b) Genomic characterization of COVID-19 and their similarity origin](image)

**Figure 2** Genomic representation of SARS-CoV-2, (a) the coding and non-coding region of SARS-CoV-19, (b) Genomic characterization of COVID-19 and their similarity origin (Adopted from Zhou et al., 2020).

**MEMBRANE ASSOCIATION WITH ACE RECEPTOR**

Inside the helical nucleocapsid, the RNA genome is packaged and covered by a lipid bilayer derived from the host. Furthermore, there are four membrane proteins involved for host-pathogen interactions; the spike protein (S), the envelope protein (E), the membrane protein (M), the nucleocapsid protein (N) are encrypted by ORFs10,11. Also, hemagglutinin esterase (HE) is present in some β-coronaviruses. The host interaction and virion releases are determined initiated through S protein and the viral assembly is carried out via M and E (Smith et al., 2013; Sanjuan & Domingo-Calap, 2016). The complete genome profile of SARS-CoV-2, and their similarity origin characterization were represented in Figure 2 (Zhou et al., 2020).

The membrane of SARS-CoV-2 consists of four membrane proteins; among that, the structural protein the glycoprotein present in abundantly; it extends to the bilayer membrane, while a small portion present in amino-terminal (NH₂) end and an elongated portion present in the cytoplasm at carboxyl-terminal (COOH).

The replication of SARS-CoV-2 comprises of the complex phenomenon of viral and cellular proteins, which take place in the cytoplasmic membrane and utilizes the host nucleus proteins for their replication process. N and 3b of SARS-CoV-2 proteins and two forms of N and nsp1 Arteriviruses being identified in the host nucleus of infected patients (Enjuanes et al., 2006; Hiscox et al., 2001; Wurm et al., 2001; Yuan et al., 2005; Tijms et al., 2002).

Furthermore, the peplomers are glycoprotein present in the S-protein, thus mainly neutralize the host antibodies and participates in molecular interactions. The assembly of viral particles is initiate by M-protein at the intracellular membrane (Mousavizadeh & Ghasemi, 2020; De Haan et al., 1998; Woo et al., 2010; Boekeen et al., 2012). The remarkable features of the SARS-CoV-2 genome comprise three important criteria: (i) human receptor ACE is optimized binder for SARS-CoV-2; (ii) the furin cleavage of S protein inserting 12 nucleotides at the peripheral membrane of S1-S2 cleavage site; (iii) the O-linked glycans at the site of membrane adherence on the peripheral membrane (Li, 2016; Andersen et al., 2020).

**REPLICATION MACHINERY MECHANISM**

The initial reorganization was carried by S-protein protease, named as TMPRSS2. The SARS-CoV-2 genome of RNA enters through the cytoplasmic
membrane, which ensued the central dogma events forming a large protein assembly encoded by the replicase gene (20-kb) made up of cellular and ~16 subunits of virus. The viral replication machinery and viral progeny releases were represented in Figure 3. The enzymes of RNA dependent RNA polymerase, RNA helicase, endo, 3’to 5’ exo-ribonucleases, 2’O-ribose methyltransferases, phosphodiesterases, ADP ribose 1’-phosphatase and proteases are involved in these events. The viral genome act as a template and utilizing a replicate enzyme for synthesizing their viral replicates to start via negative-strand intermediates to release viral offspring and their mRNA. The genomic mRNAs are further undergone translation events to synthesis structural and accessory proteins. Furthermore, these structural proteins are endured post-translational modifications in Endoplasmic Reticulum-Golgi Intermediate (ERGI). Moreover, N-protein produces nucleocapsid that is adhered to by viral offspring. In contrast, membrane-bound structural proteins are merged with viral progenies and further forming an assembly of virions released in the form of budding into ERGI complex. The latter viral progenies are discharged from affected cells via Golgi. However, part of SARS-CoV-2 directly extents to the plasma membrane without virion assembly. Simultaneously, the S protein surface initiates the union of the affected cell with neighborhood, non-infected cells, which form substantial multinucleated syncytia. Therefore, it facilitates the self-regulation of extracellular viral contagion spread and escapes from immune scrutiny (Hoffmann et al., 2020; Guo et al., 2020; Sola et al., 2015; Ziebuhr, 2002; Almazán et al., 2006; Peiris, 2016).

Transfigurations of the SARS-CoV-2 domain

In SARS-CoV-2 genome, S-protein is a variable portion consisting of six amino acids receptor-binding domain (RBD), which is a binding site for ACE2. The virus S1 receptor-binding domain (RBD) plays a key role in the binding of the ACE2 peptidase extracellular domain (PD) in the host. The host proteases cleave the S1-S2 cleavage site and fuse with the host cell membrane (Figure 3) (Andersen et al., 2020; Hoffmann et al., 2020; Lai & Cavanagh, 2006; Stawiski et al., 2020; Belouzard et al., 2009; Simmons et al., 2005). The interaction between RBD and PD was found to be 20-fold increased affinity, responsible for potential threat for high mortality (Shang et al., 2020; Walls et al., 2020; Wrapp et al., 2020; Yan et al., 2020). However, the phenomena of tropism and transferability were important criteria being analyzed (Walls et al., 2020).

Exploring the genetic and molecular factors can influence the COVID-19 for aggravating?

The concurrence with the clinical record, genomic expression, and ecological parameters were combined and recognized the impacts in host with COVID-19. Additionally, host genetic parameters are relatively given an idea for the SARS-CoV-2 risk factor analysis.

ACE variations

Mysteries are associated with the CoV genome influences of genetic and molecular factors linked with gene expression. The genetic polymorphism concomitant with tolerance deals with ACE2. The soluble membrane of surface protein contracts with the regulatory mechanism of blood pressure. The ACE2 enzymes play a receptor role for the binding of S protein of SARS-CoV-2 into the human cell surface. Similarly, MERS relatively binds with the dipeptidyl peptidase 4 enzyme expressed from a DPP4 gene integrated with human cells. Researchers are being focused on fining the integrator role of tissue-specific expression of ACE2 variation among individuals under S protein. Procko (2020) identified the polymorphism of ACE2 variants and interface interactions with S protein via site-directed mutagenesis. The mechanism of viral entry starts with the reorganization of S protein in human ACE2; and initiation of the molecular factors while releasing the RNA genome into the cells via intracellular (Figure 3). Moreover, the development of vaccine and potential therapeutics largely depends on the inhibition of SARS-CoV-2 entry in soluble ACE2. The ACE2 interactions with S protein induce the host susceptibility being investigated in the human population. Acquired mutations induced by SARS-CoV-2 towards ACE2, producing life-threatening infectious diseases because of the mutation in S protein augmenting the interface of ACE2.

![Figure 3 Diagramatic representation of SARS-CoV-2 surface proteins and their replication machinery](image-url)
The polymorphism of the ACE2 receptor predicts the SARS-CoV-2 pandemics, which modify the susceptibility of the CoV genome (Stawiski et al., 2020) (Figure 4). Furthermore, the ACE2 synthetic mutant map was constructed against S protein among a genomic database of 290,000 samples and identified >400 population groups. The virus-host interactions, ACE2 diversity linked with the susceptibility of the host. The increased susceptibility was found in ACE2 variants of S19P, 121V, K23E, K26R, T27A, N64K, T92I, Q102P, and H378R. The productive ACE2 variants of K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, and D509Y have tolerance ability against S protein adherence (Figure 5).

Moreover, the expression of ACE2 to individual cell types involves several challenges; ACE2 variants deteriorating the coding and non-coding expression part of the gene, tissue types, and the gene expression based on gender. Inversely, the permeation of SARS-CoV-2 is prevented by expression of ACE2 in candidate cell types, which includes nasal olfactory epithelium, tongue keratinocytes, mature enterocytes in the colon, and small intestine. Additionally, the asymptomatic persons possess a forfeiture of sensing is also additional cell types expression causes diarrhea. Furthermore, another interesting fact under manifestation based is the fecal-to-oral transmission of SARS-CoV-2 to susceptible individual cell types. There is lacking knowledge still existing regarding single-cell RNA-seq play a role to determine the cell type's expression, thus essential for qualifying an individual immunity based on SARS-CoV-2. These transcriptomic tools compiling the genomic expression data and quantifiable data of individuals may pave for designing effective therapeutics (Venkatakrishnan et al., 2020). Additionally, the ACE1-D allele may also involve in the S protein interaction and induces the regional level to increase the mortality rate in ecology (Kenyon, 2020). The expression of ACE1 variance is determined by insertion/deletion (I/D) polymorphism, 65% DD homozygotes, 31% ID heterozygotes are present in ACE1. The risk factors of hypertension, cerebrovascular disease, Cardiac arrest,
hyperglycemia, cancer, respiratory diseases (acute respiratory distress syndrome: ARDS) are associated with D-allele. Therefore, the association of D-allele in SARS-CoV-2 is another key factor for SARS-CoV-2 infection (Gard, 2010; Deng et al., 2015; Wu & McGoogan, 2020; Chan et al., 2005; Itoyama et al., 2004).

Figure 4 Polymorphisms of ACE2 receptor. (a) Protein mutation in ACE2 variation representation by Pie chart. (b) Polymorphisms of ACE2 protein binding domain (increased red line) to S-protein binding domain (decreased blue line) and the black vertical line represents the interaction of PD-ACE2 with S-protein (Adopted from Stawiski et al., 2020).

Figure 5 Mapping of ACE2-PD polymorphisms with SARS-CoV-2 RBD. (a) A systematic representation of predicted mutagenesis profile of ACE2 binding with RBD: 6VW1 of S-protein. (b) Structural domain interface interaction between ACE2 with RBD of S-protein. The represented codes are identical as in Figure 2b. (c) Recurrent polymorphism region of K26R and T27A. (d) Amino residual of lysine on ACE2 are highlighted in K31 and K353. (e) Polymorphism of ACE2 at E35. (f) Arginine residual mutation of ACE2 H34. PDB of 6VW1 (b, d) and 6LZG (c, e) (Adopted from Stawiski et al., 2020).
**HLA variation**

The genetic architecture of the host genome in response to infectious diseases is associated with the HLA region of an individual, polymorphisms of the protein domain in the epitope of infectious diseases (Tian et al., 2017). Human Leukocyte Antigen (HLA) genes are an alternative determining factor for individual immunity to distinguishing pathogens. The variation of this impact recognizes the foreign viral molecules, such as SARS-CoV-2 induces individual susceptibility towards the virus. Portland VA research foundation, the HLA variation among the individual, could recognize the COVID-19 infection severity from the affected populations. HLA alleles that regulate the prospective epidemiological consequences of SARS-CoV-2 infection. Briefly, the brutality of SARS-CoV-2 is analyzed by a genetic erraticism transversely HLA – A, B, C alleles are class I major histocompatibility complex genes. Additionally, HLA involves the viral recognition pathway; the 145 genotypes of HLA binds with S-protein were confirmed within silico studies (Figure 6) (Nguyen et al., 2020). The susceptibility of the individual is predicted by the lowest binding peptides of HLA-B (*46:01 exposure) for SARS-CoV-2 (Lin et al., 2003).

Inversely, the highly expressed conserved regions of HLA-B (*15:03) genotypes had the greatest resistance to SARS-CoV-2, which facilitates T-cell immunity (Nguyen et al., 2020). Similarly, the significance of HLA genes and their genomic expression additionally links with SARS-CoV-2 host immunity. The border based HLA variation was analyzed with five different populations of 21,546 individuals: Asian, South Asian, European, African, and Latino. The protein expression pattern of HLA allelic variations contributes to the SARS-CoV-2 threat (Nguyen et al., 2020; https://www.covid19hg.org/ (Accessed on 01 May 2020); COVID-19 Host Genetics Initiative, 2020; Godri Pollitt, 2020).

The viral protease of Mpro/3CLpro involved in the central dogma of the viral translation process was reported by Zhang et al. (2020). The polyproteins of the crystal structure of COVID-19 non-ligand and their potent inhibitor of α-ketoamide originated from the inhibitor of the P3-P2 amide bond present in pyridine ring to increase the compound life in plasma was revealed from X-ray structures (Figure 7) (Zhang et al., 2020). Therefore, for designing a vaccine, the inhibitor of α-ketoamide is suggested to be an inhalational mode of the administrated drug for lung tropism.

**Surface proteins of COVID-19 and host interactions**

The evaluation of spike protein linked vaccines, and antiviral drugs were reported in several studies (Chen et al., 2020; Du et al., 2009). The development of CoV vaccine production is purely dependent on the genome of S-protein, viral cloning vehicle, recombinant DNA, and recombinant S-protein (rS-protein). Besides, the evaluation of drugs activities in the in-vitro and therapeutic analysis is considered the major effectiveness of blockers for SARS-CoV-2; spike protein inhibitors, S1-S2 cleavage site (furin cleavage), ACE2-RBD inhibitors, S-protein–ACE2 fusion core blockers, counteracting antibodies, viral enzymes blockers, Small interfering RNAs activators (siRNAs), recombinant ‘interferon’s (rIFNs) are major drug designing zone for vaccine research. Noteworthy, the binding domain of RB of S-protein has strong empathy towards ACE2 (PD) than ACE1, and utility roles have differed. Therefore, the drug designing strategies mainly depends on the ACE2 blockers; e.g., administration of losartan blocks the angiotensin receptor 1 (AT1R). Currently, an Ebola virus drug of Remdesivir pooled with monoclonal antibodies are widely using to treat SARS-CoV-2. However, to determine the frequency of viral mutation and their transformation distribution in the highly challenging task of designing therapeutic drugs and vaccines (Chen et al., 2020; Du et al., 2009; Prabaharan et al., 2004; Gurwita, 2020; Sheahan et al., 2017; Martínez, 2020).

The surface proteins of S, M, and E of SARS-CoV-2 and their host protein interactions are involved in the maturation of viral protein and assembly into the host cell. The functions of post-translation machinery, mature proteins undergo protein folding and activate as functional proteins; its major functional mediated through glycoprotein maturation, ligand-receptor binding, oligomerization, and functional viral protein activations are the important modifications in host serum. In SARS-CoV-2, surface proteins of S, M, and E proliferation, maturation, and subcellular relocalization with their biochemical properties were discussed in the following sections (Nal et al., 2005).

**S-protein relationship in ER (Endoplasmic reticulum) to PM (plasma membrane) of the infected cell**

The trimers morphology of S proteins rich in glycosylating, with conserved 8–12mers from the SARS-CoV-2 proteome. (a) Scattering of HLA alleles of 8- to 12-mers from the SARS-CoV-2 proteome. (b) Scattering of HLA alleles highly conserved domains of SARS-CoV-2 peptides with latent to prompt cross-protective immunity. (c) Scattering of HLA allelic conserved 8- to 12-mers of general HLA alleles and independently for HLA-A, HLA-B, and HLA-C. (d) Heat maps of six HLA alleles frequency distribution globally (Adopted from Nguyen et al., 2020).
M-protein interactions with ER and Golgi of the infected host cell

The surface of the viral structural protein is enriched with M protein in mammalian cells, which is N-but not O-glycosylated. The leukocytes production is induced by interferon (IFN), which is stimulated by M-glycoprotein. However, this activity is influenced by the interferometric activity of the glycosylation status of M and N (De Haan et al., 2003; Baudoux et al., 1998). The infected host cell Golgi apparatus (GA) is highly concentrated with surface proteins of M. However, M-protein distribution differs from viral strains (Krjïne-Locker et al., 1995; Neuman et al., 2016). In addition, SARS-CoV-2 of M glycoprotein localizes with ER, endoplasmic reticulum-Golgi intermediate compartment (ERGIC), and cis-Golgi (Figure 3) (Nal et al., 2005; Appenzeller et al., 1999). Although, the expression of M-protein is not detected at the plasma membrane, which was accumulated and transported from the Golgi apparatus to Endoplasmic Reticulum.

Envelope protein assembly in the host cell

The viral assembly and accumulated of CoV at the minimum level in the viral envelope region are carried out by E-protein (Corse & Machamer, 2002; Lim & Liu, 2001). Although, E protein is co-expressed with M-protein for assembly of viral protein and expressed in a stable condition when combined with tiny envelope glycoprotein (Vennema et al., 1996; Raamsman et al., 2000). However, individual expression of E-protein lifetime is only 30 min. Therefore, the viability of E-protein regulation that occurred at post-translation events was reported by (Nal et al., 2005) (Figure 8). Additionally, the E-protein degradation phenomenon corresponds to the palmitoylated mediated regulation process, in which three cysteine residues were deduced in juxta membrane (Corse & Machamer, 2002; Arbely et al., 2004). The bend membranes structures are in the form of the tube and smooth is transported from ERGIC (Endoplasmic reticulum Golgi complex) to ER. The SARS-CoV-2 grows from the subcellular localization of ERGIC (Nal et al., 2005). The post-entry is present into the inside of ER and was present for 30mins, in Golgi, the high-mannosylated S, M proteins are assembled in the order of trimers with adherence of N-glycans. Although M localized in Golgi whereas S is sub-localized in ER to PM with a secretory pathway. The remaining non-glycosylated of surface envelope protein E localize at perinuclear patches with ER. Therefore, the differential variation in subcellular localization of surface proteins might be expressed along with factors associated with cellular and viral components, which is necessary for the transport of assembled budding viruses into the ERGIC (Nal et al., 2005) (Figure 3; Figure 8). However, the surface proteins biogenesis, variance of maturation, regulations of viral protein assembly with their host cell partner is still under at budding stage (Fischer et al., 2007).

![Figure 7](https://example.com/figure7.png)

**Figure 7** SARS-CoV-2 Mpro inhibition by α-ketoamide. (a) Inhibitors of α-ketoamide 11r, 15a, 13b, 14b chemical structure. The oval and circles represents their modifications. (b) The modified forms of Mpro three-dimensional views. Roman numerals indicated the domains. Yellow and blue spheres for catalytic site (Cys145), (His41), respectively. Location of Ala285 indicated by black spheres. N.C terminal for A domain (light blue) and N* and C* for protomer B (orange). (c) SARS-CoV-2 Mpro monoclinic crystal form binding with 13b compound of α-ketoamide. (d) the confirmatory study of 13b α-ketoamide inhibitor role in COVID-19 infected human Calu-3 lung cells (Adopted from Zhang et al., 2020).

![Figure 8](https://example.com/figure8.png)

**Figure 8** (a) SARS-CoV-2 surface S-protein interactions with host cell (BHK-21). (a1) SARS-S protein interactions from 0 to 12h. (a2) SARS-S treated to EndoH treatment. (a3) Better separation of S-protein bands for longer durations onto a SDS-PAGE, (1) Endoglycosidase – EndoH; (O) EndoH-resistant S glycoform in 180kDa; (+)50kDa EndoH-processed S glycoform;EndoH-sensitive trimer (+); EndoH-resistant S trimer (#1). (b) EndoH- resistant complex glycoform of N-glycosylated SARS-M protein and their maturity upto 0-12h on BHK2. (b) SARS-M protein interactions from 0 to 12h. (c) SARS-M treated to EndoH treatment (+, exposed), (-, non-exposed) to PNGaseF (peptide-N-glycosidase F). (b3) (Δ) Non-glycosylated of M; (1) sensitive M-glycoform of EndoH and PNGaseF; (O) M-glycoform of EndoH-resistant and sensitive PNGaseF. (c) Degraded E-protein of SARS-CoV-2 from 0-6h (Adopted from Nal et al., 2005).
POST COVID-19 AND OTHER DISEASE MANIFESTATIONS

Currently, there is an uncertain dispute about whether SARS-CoV-2 induces acquired immunity after SARS-CoV-2 infection? However, the respiratory infection of influenza and reinfected viral pathogens in humans didn't contribute to increasing immunity. Although the potential impact of post-infection immunity is to participate in the major consideration for the determination of individual immunity. The respiratory syndrome of SARS-CoV-2 infection increases the IgM and IgG antibodies in host immunity in severely infected hosts (Zhao et al., 2020; Wölfel et al., 2020; To et al., 2020). Besides, the antibodies evaluation in the host humoral system during post-SARS-CoV-2 infection was not detecting an anti-immunoglobulins in individual sera. The association between antibody titers and clinical applications is still unclear. Furthermore, the IgM and IgG antibodies were increased during higher viral loads of COVID-19. The viral load is typically higher in early infectious status and declined in when antibody titers develop probably within 3 weeks. However, the presence of the SARS-CoV-2 genome at higher concentrations without the release of symptoms is detected in post-SARS-CoV-2 individuals and acts as non-transmitters (Wölfel et al., 2020). Even though a clear sign of the presence of viral load in host sera during the post-SARS-CoV-2 infection is uncertain. However, the presence of neutralizing antibodies in individual sera is persistent for more than a month. Especially, the concentration of IgG is higher – half of the year (Wu et al., 2007). Similarly, MERS- CoV neutralizing antibodies persisted until 34 months in post-MERS-CoV individuals (Payne et al., 2016; Bao et al., 2020). Cavanagh et al. (2004) reported that the respiratory illnesses caused by the other four human coronaviruses of 229E, NL63, and OC43 were developed during re-infection; the protective immunity lived for the minimum period in infected persons, and also the post-exposed strains were genetically identical.

Up to date, there is no evidence of reported cases of re-infected SARS-CoV-2. Although, the culturing of the re-infected individual host has not shown distinct results. A recent report states that the recovered SARS-CoV-2 healthy individual samples of polymerase chain reaction (PCR) indicate the negative, which was collected from the upper respiratory tract of the individual after 24h. Similarly, the genome was collected in throat swabs and nasopharyngeal swabs for 20 days after discharge of SARS-CoV-2 patients, although the test results are negative (Xiao et al., 2020). Additionally, the post recovered patients were radiographically inspected, and the results show a stable improvement (Xing et al., 2020; Young et al., 2020). Moreover, the transmission of SARS-CoV-2 in post carrier is not clinically proven yet (Kirkcaldy et al., 2020).

Xing et al. (2020) reported, among 62 medical supervisors were affected by SARS-CoV-2 and recovered in Zhongnan Hospital in Wuhan, China. The post-recovery surveillance of two asymptomatic cases shown swabs test are positive and the disease manifestations are shown mild symptoms. It confers that a small fraction of discharged patients might test positive and they are non-transmitters. A minimum quantity of SARS-CoV-2 symptoms from recovered patients is difficult to isolate and detect the virus proposition. The current detection tool of RT-PCR, sensing 97% of accuracy, even though the remaining 3% diagnostic specificity is showed false-positive because of random sample analysis (or) specificity of sample collection and methods of sample processing durations (Xie et al., 2020). Besides, after recovery from SARS-CoV-2, the host body requires some duration to eliminate the viruses from their immune system (Shen et al., 2020). Moreover, it may combine with the host immune system and exhibit as positive and the clinical manifestations of asymptomatic ‘patient’s chest CT showed no evidence of virus survival. However, in some cases reported in Hunan Province, China the post-SARS-CoV-2 patient exhibit cough and fever for 2 days after discharge from hospital, and the disease manifestations showed deteriorated grade of the chest while CT investigation, it might be the decline of patient immune power (Xing et al., 2020; National Health Commission of Change, 2020) (Figure 9). Even though, at present, it is highly critical to find a clear justification for the above manifestations. Also, some clinical implications of SARS-CoV-2 have some clear clarification regarding the false-negative. It was presumed that the viral location at the initial stage could detect easily at the upper respiratory tract. Moreover, the proliferation and maturation of viral detection appear likely in the lower respiratory tract, intestines, and blood (Zhang et al., 2020). In such cases, the detection of viruses in the swab test showed negative. Therefore, it may elucidate false-negative at the preliminary stage of QRT-PCR but positive in manifestations of CT-chest (Xie et al., 2020; Fang et al., 2020).

Figure 9 COVID-19 post-discharge surveillance and re-infection status of two medical staff’s case history profiles from January to February and re-infected cases investigation profiles of KCDC. (a) Case 1 details of throat swab virus detection and chest-CT, Critical status of Chest reflected in CT scan shown worst morphology of SARS-CoV-2 virus’ detection on 18,20,23 and 29th January and followed by improved status on 4th February. (b) Case 2, throat swab test and CT-scan details of chest shown normal views on 2, 4, and 12th February. (On throat swab test colour indication denotes; red: Positive virus presence; pink: faintly positive; green: negative virus detection; asterisk: negative virus detection in stool) (Adopted from Xing et al., 2020). (c) KCDC discharge summary re-positive initial symptomatic average of 44.9 days from 226 cases in the range of 8-82 days from primary symptom commencement date. (d) Discharged positive cases on bases on 285 cases in the range of 1-37 days (Adopted from KCDC, 2020).

The epidemiological analysis and communication examination of re-infected cases of 285 patients were identified out of 447 patients and a sum of 790 peoples have contacted members of 285 re-infected peoples, out of them the 351 members are closely related to family members and remaining 439 members are non-related, reported by KCDC-2020 on 15th May 2020 (Korea Centers for Disease Control & Prevention, 2020). From this above investigation, there have been no cases reported as positive from re-infected carriers even though they have coughs, sore throat, etc (Korea Centers for Disease Control & Prevention, 2020) (Figure 9). Experimental evidence from Bao et al., (2020) showed the re-challenged Rhesus macaques with SARS-CoV-2; an initial recovery stage from the early stage of infection was evaluated by loss of weight, viral propagation, and respiratory diseases in pneumonia were identified in the lungs and intestine. Furthermore, the re-exposure of infection not produce viral colonies was evaluated from the clinical manifestations and host-pathogen studies. The presence of neutralizing antibodies present in the Rhesus monkeys might be the reason for viral protection in their body (Bao et al., 2020; Yu et al., 2020). Therefore, SARS-CoV-2 induces immunity in the host system and protects the host from subsequent re-infection (Figure 10 & 11) (Bao et al., 2020).
It is highly difficult to evaluate the frequency of SARS-CoV-2 infections, even in asymptomatic via serological assays. However, the individual re-infection determination at an early stage is also essential for the COVID-19 assessment. Although, the specificity, sensitivity and cross-reaction latent is also be required factor for SARS-CoV-2 determination (Kirkcaldy et al., 2020). The COVID-19 recovered individual’s population and a healthy population of the non-affected individual population may produce false-positives. Therefore, the above issues are highly complicated to correlate the medical and epidemiologic analysis with serological results. Furthermore, the dispute between the releases of IgG, IgM ‘immunoglobulin’s under SARS-CoV-2 and posts SARS-CoV-2 infections (Bao et al., 2020). However, inadequate supporting data are available for IgG, IgM ‘immunoglobulin’s production against SARS-CoV-2, and post-COVID potential to confer resistance for re-infection (Kirkcaldy et al., 2020). Therefore, it is necessary to evaluate the phenomenon of SARS-CoV-2 immune responses is highly required for further investigation to prevent viral transmission and which may help to save public health in a current scenario.

Comorbidities of COVID-19 positive during pregnancy

The pregnant ladies are in a highly risky zoon for SARS-CoV-2 infection: which causes health defects in both maternal and neonatal (Liu et al., 2020). A sum of 13 Chinese pregnant ladies was infected with SARS-CoV-2; the maternal age of between 22 to 36 years was admitted to the hospital in Wuhan, China, on 8th December, 2019. The gestation period of two women is below 28 weeks, and others are below third trimesters. All of them are healthy other than SARS-CoV-2 complications. Their body temperature range between 37.3-39.0°C, the symptoms like fever and fatigue was observed in ten maternal along with three of them noted like dyspnea. The epidemiologic history of 12 members had close contact with infected peoples. Out of 13 maternal, three of them are improved their health conditions and discharged. From the remaining 10 maternal, five of them are undergoing emergency cesarean because of fetal distress (in three), premature rupture of uterus membrane (in one), dead of the fetus (in one). During the hospitalization of the 6th patient condition worsened, she was suffered from multiple organ dysfunction syndromes (MODS), acute respiratory distress syndrome (ARDS), acute hepatic, and renal dysfunction with septic shock. Hence the patient was provoking to the intensive care unit (ICU) with ventilator support. The remaining 12 patients were discharged healthy without any clinical complications on 25th February, 2020. Therefore, an investigation of the above case history proven the complications of SARS-CoV-2 increased the susceptibility of infection in both maternal as well as fetus health. Furthermore, severely complicated patents had a cytokine storm because of the maximum production of plasma induces the hyperactivity of various cytokines (Huang et al., 2020). The most complicated three of them had dyspnea; it may due to the late pregnancy causes hypoxia during viral infections to promote maternal distress (Assiri et al., 2016). However, these viral complications may not affect the fetus asphyxia except abortion (in one) (Liu et al., 2020).

Figure 10 Investigation of prolonged infectious status of early SARS-CoV-2 infection and re-infection tracks identified in Rhusus macaques. (a) Chinese-origin of six rhesus monkeys were selected (3-Kg, 3-5 years old), labelled M0-M6 and surveillance (Adopted from Bao et al., 2020).

Pathophysiology of COVID-19 with an acute kidney infection (AKI)

Remarkably, the transcriptome studies reveal that the degree of kidney cells in ACE2 expression ligand with SARS-CoV-2 receptors and TMPRSS2 proteases association were identified and the mechanism of infection in kidney cells was diagnosed. The expression of kidney regulation genome function was higher in individual populations than Asian donors. Furthermore, it's suggested that occidental donors are more susceptible to SARS-CoV-2 infection, especially in renal failure fairly than Asian origin (Batlle et al., 2020; Pan et al., 2020). Significance observation reported in medRxiv, among 85 patients 23% is the prevalence of AKI. Epidemicology of renal failure from post-mortem reports declares that the occurrences of severe acute tubular necrosis (SATN) consist of lymphocyte and macrophages accumulation on their kidney region (Diao et al., 2020). Another autopsy investigation of COVID-19 patients showed acute proximal tubular damage with erythrocyte clumping and glomerular fibrin thrombi (Su et al., 2020). Remarkably, SARS-CoV-2 impacts in China and the United States endorsed that aggregation of clotting factors, scattered intravascular coagulation, tiny vessel thrombosis with a respiratory infraction were noted on autopsy reports. In some cases, additionally exhibits low platelet counts were found in autopsy patients (Tang et al., 2020; Zhou et al., 2020). Furthermore, Zhou et al. (2020) the manifestations of SARS-CoV-2 substantiation of myocarditis and microangiopathy in multiple organs, such as splenic infarction, hematuria, myocardial infarction initiates to cortical necrosis and renal failure.

Mechanism of SARS-CoV-2 on Kidney infection

Notably, the genome of SARS-CoV-2 not present in the kidney of infected persons, although it is believed that the SARS-CoV-2 might affect directly to the renal tubules and causes inclusions in renal tubules, nephropathies. Although, the feature aspect of SARS-CoV-2 infection, the genome of SARS-CoV-2 recognizes the ACE2 receptors in the kidney rather than in the lungs (Batlle et al., 2020; Serfazio et al., 2020; Ye et al., 2020). The expression of ACE2 is originated in the proximal tubule of the brush border apical membrane surface, where it recognizes the ACE enzyme. The invading viruses adhere to podocytes and utilize the tubular fluid machinery, followed by binding with a proximal tubule. Moreover, the ACE2 expression is present in the apical surface of epithelia in humans; however, the occurrences of infection are noted on the basolateral membrane with minimal potency (Jia et al., 2005). Additionally, SARS-CoV-2 infection is also associated with the proteases in host cells: TMPRSS2 is expressed initially in distal nephron (Batlle et al., 2020; Wu et al., 2018; Wilson et al., 2019). Although the biogenesis of viral manifestation is initiated by S-protein furin cleavage (Walls et al., 2020). The additional manifestations of AKI with SARS-CoV-2 infection are caused by proteinuria, excessive hemophagocytic macrophage stimulation, microangiopathy, and glomerulopathy.
In addition, the level of ACE2 is downregulated during AKI, which leads to activation of the ACE enzyme with low angiotensin accumulation causes of AKI damage (Su et al., 2020; Bhatraju et al., 2020). Moreover, the higher risk factor linked with AKI is diabetic kidney disease (DKD) due to the up-regulation of ACE as well as ACE2 down-regulations.

Figure 11 Investigation of prolonged infectious status of early SARS-CoV-2 infection and re-infection tracks identified in Rhesus macaques. (b) Detection of viral RNA in internal organs of M0 and M1 were early infected with SARS-CoV-2 and re-challenged profiles of M3 and M5. (c) Histopathology studies of M0 and M5 shown that the re-challenged thesus viral load. (d) The evaluation and score details under immunohistochemistry (IHC) of CD4, CD8 for T cell, CD20 for B cell, CD68 for macrophage and CD138 for plasma cells (Adopted from Bao et al., 2020).

Manifestations of SARS-CoV-2 on acute cardiovascular disease (ACV)

Understanding the phenomenon between SARS-CoV-2 with cardiovascular (CV) and acute cardiovascular (ACV) is an additional requirement for disease management. The clinical manifestation of SARS-CoV-2 causes pulmonary infections, although the CV illness is not much more common. The cardiac illness is measured by increasing the troponins in the cardiac region leads to ACV; almost 8-12% of people are affected with ACV. The mechanism of cardiac damage occurred due to viral attachment in cardiomyocytes and caused systemic inflammation (Bansal, 2020). Moreover, direct myocardial infection, transformed myocardial demand, plaque rupture, coronary thrombosis, imbalances of electrolyte, antagonistic effects of various drugs are risk complications associated with SARS-CoV-2 (Bansal, 2020).

Acute myocardial damage (ACD) is one of the commonly found complications associated with SARS-CoV-2 infection. The rising of the cardiac enzyme of troponin I (cTnI) has one of the reference markers to identify the ACD (Zhou et al., 2020; Lippi & Plebani, 2020). The comparative role of viral myocarditis and systemic inflammation induces the direct myocardial injury. The pandemic outbreak of SARS-CoV-2 in Toronto has confirmed the observations as mentioned earlier in autopsy patients (Oudit et al., 2009): 35% of the viral genome was found in autopsy patients of heart samples. Similarly, Zhou et al. (2020) observe the SARS-CoV-2 complications with ACD is minimum percentage compared to recovered patients (12%). In addition to the cTnI, other biomarkers of the brain-type natriuretic peptide, arhythmias, myocardial infarction, and heart failure are likely to be used to access the ACD (Akhermov & Marbán, 2020). However, the markers, as mentioned above, the detailed mechanism of ST-segmental myocardial infarction, left ventricular systolic dysfunction, acute left ventricular failure, and acute cardiac shock has not been reported elsewhere (Bansal, 2020).

COVID-19 interactions in the respiratory tract

The infection status from pre-symptomatic (first 3 days) to post-symptomatic (8 weeks) via early symptomatic stage (4 weeks), hence the incubation period is signified as 14-28 days. The lower respiratory tract as a moderate infection center for SARS-CoV-2. Noteworthy, the higher viral load is defected by an asymptomatic patient (Vardhana & Wolchok, 2020). The S-protein binding in the ACE2 cell surface receptors regulates the renin-angiotensin-aldosterone system (RAAS), which function as regulations of blood-pressure, vasoconstriction, vasodilation (Hoffmann et al., 2020). Furthermore, the expression of ACE2 in macosal epithelium covered by the nasal, nasal cavity, and lung infection mediates the respiratory tract infection. In addition, the expression of ACE2 also been found in the endothelium, cardiac, gut linings, and renal tubes spread the viral load unconditionally (Subbarao & Mahanty, 2020).

Moreover, the post- SARS-CoV-2 induces the release excess of cytokine secretion. The infection in the lung epithelial cells stimulates the monocytes, macrophages, interleukin-6 (IL-6), dendritic cells to secrete vast pro-inflammatory cytokines. The release of IL-6 initiates the proliferation and differentiation of lymphocytes regulation in T-helper cells (T_h7). Consequently, IL-6 stimulates the release excess of immune cells, which results in cytokine storm, which initiates blood pressure deviation, acute respiratory distress syndrome (ARDS). Therefore, to suppress the hyperactivity of immune cell secretion due to IL-6 in SARS-CoV-2 necessary, currently, immunosuppressive drugs, such as Tocilizumab, Situximab, and Sarilumab are clinically used for treating infected patients (Moore & June, 2020). Additionally, the amplified production of cytokines induces the massive secretion of fibrinogen and coagulation pathways on surfaces of endothelial cells, which is confirmed by the presence of D-dimer released from a fibrin cleavage. Moreover, the RAAS additionally prompts blood vessels shrinking and dyspnea. Similarly, the event was reported SARS-pneumonia tempts to reduce the oxygen supply in blood vessels but does not dyspnea (Subbarao & Mahanty, 2020). SARS-CoV-2 induces the obstruction of oxygen uptake due to the clogging of blood vessels in pulmonary tracts leads to the accumulation of coagulated small blood vessels induces severe dyspnea. Henceforth, for the treatment of severe dyspnea, anticoagulants, such as Coumadin, Xarelto, Eliquis, Pradaxa, and Savaysa, are highly recommended in SARS-CoV-2 patients (Subbarao & Mahanty, 2020).

COVID-19 manifestations in Liver

Viral infection in liver cells directly causes impairment of the liver organ. Notably, 2-10% of infected patients had liver damage causes diarrhea and diagnosed with the presence of viral RNA in their stool and blood specimens (Yeo et al., 2020). However, the absence of viral inclusions in liver tissue displays a lower titre value after the histopathological studies (Zhang et al., 2020). Liver biomarker of gamma-glutamyl transferase (GGT), alkaline phosphatase used to estimate the expression of ACE2, and it is higher in cholangiocytes to find the regulation of liver activity (Chai et al., 2020). The autopsy investigation of SARS-CoV-2 patient's proven the non-exhibit the viral load in the infected liver may due to hepatotoxicity induced by various drug intake (Xu et al., 2020). Moreover, in critical cases of SARS-CoV-2 patients associated with systemic inflammation, cytokine storm, and hypoxia as well as induce liver damage. The clinical manifestation of ACE2 in cholangiocytes determined by cholestasis aggregations with proliferated biliary cholangitis, GGT, and elevated levels of alkaline phosphatase. The comorbidities of liver cancer and liver cirrhosis induce the immunosuppression in severe infected CoV.
cases. Additionally, these comorbidities contribute to the additional impediments to the infected patients, such as hepatic encephalopathy, hemorrhage in the gastrointestinal tract, re-infection, liver failure, and mortality. The negotiated stage of the immune system is further required to find suitable immunotherapies for the surveillance of immunodeficient patients (Zhang et al., 2020).

Post COVID-19 impact in cerebrum

The SARS-CoV-2 infection induces the neurological impairment in the cerebrum, directly affects the neurotropic constituents in the brain, and the damages were confirmed by the presence of viral load in the cerebrospinal fluid (CSF) of patient’s autopsy. However, the progressive disease phenomenon in the cerebrum is not well known. Recently, neurological symptoms such as cephalgia, chronic coma, and paresthesia were observed in SARS-CoV-2 infected patients (36.4%) with SARS symptoms (Mao et al., 2020). Furthermore, systemic edema and degeneration of neuronal tissue in the brain were examined in the ‘patient’s autopsy (Xu et al., 2020). The detrimental impacts of viral infections affect the central nervous system (CNS) causes cerebrum encephalitis reported in Beijing in March 2020 (Wu et al., 2020; Xiang et al., 2020). Additionally, the entry of the SARS RNA gene through the olfactory nerve, thus distributes the viral population in the bloodstream and neurological system, consequently induces CNS disorders. The pathogenic interactions towards SARS-CoV-2 induce infectious, toxic encephalopathy, viral encephalitis, acute cerebrovascular disease, which existed through direct infection injury in the cerebrum, hypoxia damage, and ACE2 (Wu et al., 2020; Chau et al., 2004). However, the timely prevention and neurologic complications in cerebrospinal fluid is an important key factor for early prediction, which certainly helps for severely complicated ICU patients.

SARS-CoV-2 entry assist via Neuruplin-1 transmit the infection pathway to CNS

Noteworthy, the possible way of SARS-CoV-2 entry is mediated through the cellular ligand of neuruplin-1 (NRPI) penetrate via furin-cleaved S1-S2 subunits (Cantutti-Castelvetri et al., 2020). Moreover, the expression of NRPI was found in endothelial and epithelial cells of the respiratory, and olfactory region that confirmed in autopsies patient. Furthermore, the higher tropism is regulated by NRPI, which allows the penetration of SARS-CoV-2 infection to the CNS proven in in vivo studies (Mao et al., 2020; Cantutti-Castelvetri et al., 2020; Teseau et al., 2020; Pang et al., 2014). The associated symptoms of SARS-CoV-2 viz., vascular endothelitis, angiitis, and thrombotic microangiopathy might be the up-regulation of NRPI creation in capillary veins (Ackermann et al., 2020). The action of extracellular b1b2 domain NRPI is inhibited by administering the monoclonal blocking antibody to prevent the viral colony entries (Cantutti-Castelvetri et al., 2020).

The herd immunity role in SARS-CoV-2

Recently, to evaluate the seroprevalence of SARS-CoV-2, Pollan et al. (2020) stating that among 5% of people had developed the immunity against SARS-CoV-2. To acquired herd immunity, the virus spread should reach the 70-90% to protect the infected people. The nationwide study conducted by Spain, which proven the significant development of herd immunity, should reach 70-90% of the population to protect uninfected people (Pollan et al., 2020). Additionally, the prevalence of T-cell mediated antibodies was found higher in major affected areas compared to the coastal regions. However, the results mentioned above are not enough to determine herd immunity because of the lower estimated level of SARS-CoV-2.

MAJOR OBSTACLES IN COVID19

Approximately in the wide global population, the infection led by the 4 most common comparatively gentle human coronaviruses strains such as OC43, 229E, NL63, and HKU1. The respiratory flu-type origin of these strains like regular illness in the spring and winter months, during moderate climates. These SARS-CoV-2 seroprevalence data suggest that exposure is common in early childhood, with approximately 90% being seropositive for 229E, OC43, and NL63 strains and HKU1 sera 60% being seropositive (https://www.covid19india.org). In December 2019, no account recognized before the novel coronavirus (nCoV) strain founded rigorous respiratory associated illnesses identified in Wuhan, China. There has been the commencement of this epidemic. Contrasting with additional nCoVs, this nCoV2019 has a much bigger global spread and has been contrasting more with cytokine storm. SARS-CoV that causes the MERS and SARS. These prior nCoVs were confirmed to have been invented in bats, and nCoV2019 is also suspected. The WHO declared SARS-CoV-2 as a worldwide epidemic on 11 March, 2020. As first such description, since 2009, the H1N1 influenza is a deadly disease. The novel SARS-CoV-2 has been spreading at a supersonic rate as a rigorous deadly disease, causing significant anxieties at all stages and now stated on every continent, not including Antarctica. In addition, to treat the SARS-CoV-2 dangerous effects, currently, there are no proven therapeutic options or other drugs are available. Existing clinical managing includes disease obstacle, kind medicinal concern including automatic ventilator support, and supplemental oxygen. The number of people infected with SARS-CoV-2 continues to rise at a disturbing speed globally, the full amount and strictness of this outbreak remain uncertain and will continue to ruin toxins even more tedious, and it will burn itself remains to be seen. The developments were continuously monitored by the World Health Organization (WHO). As of 20th June 2020, India had 4,11,750 confirmed tainted folks with 1,70,239 active SARS-CoV-2 cases admitted in hospitals, 13,277 deaths, and 2,28,183 recovering cases discovered and improved at home. Several other countries now have even more tedious, pandemic, or it will burn itself remains to be seen. Healthcare and research workers at all extents are hard-working to identify appropriate handlings and 'vaccines'-prevention' steps to control this deadly epidemic. SARS-CoV-2 is a novel; therefore, humans have no innate resistance to it, and researchers must begin from square one to develop a vaccine to instruct the immune system to defend itself from the virus. The vaccine will target various pharma companies and chemical professionals the battle to a grow vaccine against SARS-CoV-2.

There are some most important obstacles to defeat to produce a vaccine against SARS-CoV-2. Conventionally, vaccines would be made from a destabilized or destroyed virus. Newly, there has been a hub using one to three molecules from the surface of a virus, rather than injecting whole virus in a person. Researchers are performing clinical trials with a range of targets and formulations, few of which have never been used before in a licensed vaccine. At least six groups have already begun injecting their formulations into volunteers in safety trials, while others have in progress with the first more established testing stage. The entry assist via Neuruplin-1 (NRPI) transmit the infection pathway to CNS the virus itself, in a weakened form. Many available vaccines are made in this approach, for example, those against poliovirus and measles virus. Still, these types of vaccines require broad protection testing. Remarkably, in humans ongoing to test an inactivated version of SARS-CoV-2 by Sinovac Biotech, Beijing.

A virus such as an adenovirus or measles is hereditarily engineered so that it can make coronavirus proteins in the body. These viruses cannot cause disease because they are weakened. There are two types: those that can still reproduce within cells, and other is those that cannot because key genes have been disabled. The protein from the COV stimulates the immune response aiming to use genetic instructions viz., DNA or RNA, respectively. The nucleic acid is inserted into human cells, which then mix out copies of the virus protein-normally, these vaccines program the 'virus' spike protein.

Numerous researchers want to add coronavirus proteins directly into the body. Proteins fragments or protein shells that copy the coronavirus external coat can also be used. There is subjective evidence that the BCG vaccine offers some protection against nCoV. At present, scientists are trying to attain something unimaginable a decade ago-creating a vaccine in opposition to a previously unknown virus rapidly enough to help end an existing occurrence. The current trials have been accelerated in unusual ways. However, even if we get a clear answer in the coming months, there is still this huge problem of manufacturing and distributing. Scientists have fast-tracked each step in the detection and examining process and wish to have a vaccine against nCoV2019 ready in 10 to 18 months. Even this seemingly long timeline does not guarantee safety or efficacy in the larger human population. In the interim, we will need to keep on to stick on to social distancing, wearing of surgical mask with practice personal hygiene heightened to contain the virus load spread (https://health.economictimes.indiatimes.com/news/industry/scientific-challenges-for-a-safe-covid-19-vaccine/75595176).

The novel coronavirus is pandemic and severely affects the lower respiratory tract, which is an acute respiratory syndrome (Tufan et al., 2020). The viruses and other infections involve suppressing the innate immune responses of the host to replicate the viral infections (Zhou et al., 2020). Pattern recognition receptor (PRK) is a surface receptor to recognize microbe-specific molecules that are called pathogen-associated molecular patterns (PAMPs) and include nucleic acids (such as bacterial or viral DNA or RNA). And viral infection in nonspecific immune responses. For example, a surface receptor of inflammasome Toll-like receptor (TLR), which are involved in recognition of pathogen-associated molecular patterns (PAMPs) molecules (Zhang & Mosser, 2008). The effectiveness of innate immune response against viral infection is mainly involved in the production of interferon (IFN) type I responses (Prompetchara, 2020) and also other pro-inflammatory cytokine including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a). SARS-CoV-2 directly enters the lungs through the alveoli epithelium type II receptor (ACE2). The ACE2 receptors are found in monocytes and macrophages when the SARS-CoV-2 enters the host, and it will infect the monocytes and macrophages, which lead to affect the phagocytosis. The main characteristic function of viruses is to manipulate the host microRNAs (miRNA), which plays a critical role in the replication of viral particles and immune responses. Recent studies have published that retinoic acid-inducible gene 1 (RIG-I) is found in the cytosol.
to recognize and binds to RNA viruses that initiates the signaling cascade and induces type-I IFN expression in the infected host which may help to reduce the severity of infection (Li et al., 2019). The main burden has been associated with social distancing, increased pressure on families and reduced access to support services. The risk of economic recession, consequent social stress and violence exposure may be predominant issues to meet in child and adolescent psychiatry (CAP) care (Fegert et al., 2020; Lambert et al., 2020; Hashem et al., 2020).

TREATMENT

The Indian Council of Medical Research (ICMR), from the Ministry of Health and Family Welfare (MHWF), has recommended chemoprophylaxis and hydroxychloroquine (0.4 g twice on the first day, after that 0.4 g once a week) for non-severe COVID-19 patients (pregnancy, personal or family history of severe COVID-19, suspected COVID-19, and for asymptomatic household confirmed cases peoples). Chloroquine (CQ) is a drug broadly used in the treatment of malaria and autoimmune diseases, also gives significant wide spectrum antiviral effects even against SARS-CoV-2 (Keyaerts et al., 2004; Savarino et al., 2006). A study reported that in vitro study CQ has anti-SARS-CoV-2 activity (Wang et al., 2020). Treatment with intravenous Remdesivir successfully improved the clinical state of the first U.S. COVID-19 patient (Holshue et al., 2020). Remdesivir is now being tested in several clinical trials planned to assess its effectiveness and protection for the treatment of COVID-19. An Israeli biotechnology company has claimed a 100% success rate in the first 10 patients treated with its drug as part of an early-stage clinical trial at Rambam Health Care Campus in Haifa (https://www.jpost.com/health-science/10-serious-covid-patients-given-israeli-drug-leave-hospital-in-one-day-69564/ from group message).

VACCINES

There were six vaccines candidate namely adenoviral vector 5 (NCT03413127); mRNA (NCT04283461); chimpanzee adenoviral vector ChAdOx1 (NCT04324066); DNA (NCT04336410); a lentiviral vector (NCT04276896) and another RNA vaccine (NCT04276896). CQ has been included in the first phase of clinical trials for presenting SARS-CoV-2 antigens to assess their immunogenicity and safety. Even though the reality that most of these SARS-CoV-2 vaccines contestants are being examined in the first phase of the clinical trial, few are under experimental (DNA/RNA vaccines) and may have a longer expedition ahead to reach licensure. Existing information specifies that many vaccines express the SARS-CoV-2 spike (S) glycoprotein to deactivate the virus and prevent addition to the human angiotensin-converting enzyme II (ACE2) receptor, called co-receptor for viral entry of SARS-CoV-2 (Zhao et al., 2020).

The WHO reported the pneumococcal vaccine and Haemophilus influenza type B (Hib) vaccines do not protect against the new coronaviruses. These two vaccines were not efficient against the novel SARS-CoV-2. Bacillus Calmette-Guerin (BCG) is a live attenuated vaccine, which is used against TB infection and is stated to produce antiviral activity by interfering with RNA replication (Agostini et al., 2010). The BCG vaccine stimulates the production of cytokines to protect the host from infections. The BCG vaccine response has changed through epigenetic modification through innate immune responses as antiviral responses against the viral infection (Arts et al., 2018). Hence, WHO recommended that to continue the BCG vaccine for neonatal, which helps to protect and prevent the newborns against SARS-CoV-2. Through adaptive memory recognition, the BCG vaccine may help to protect against SARS-CoV-2 infection for older peoples. BCG vaccine has a role against to protect against the non-specific infection, which plays a protective role against the host (Moore et al., 2019; Shann, 2010).

DIAGNOSTIC APPROACH

In India, the SARS-CoV-2 virus provoked coronavirus disease 2019 has already infected close to six lakh peoples, causing the death of above 17,000 peoples. While these numbers are not comparable with values observed for the developed countries viz., USA, Spain, or Russia given the population of India, and the fact that the deadly disease is now in the USA, Spain, or Russia given the population of India, and the fact that the deadly disease is now in the USA, Spain, or Russia given the population of India, and the fact that the deadly disease is now in the
Indirect method of confirmation

In early disease, chest X-ray regularly shows bilateral infiltrates but may be normal. By using X-ray, lungs infection stage can be determined. The CT is more specific and sensitive. CT imaging generally shows ground-glass opacities, infiltrates, and subsegmental consolidation. It is also abnormal in patients with no clinical evidence of lower respiratory tract involvement or non-symptomatic patients. Abnormal CT scans have been used to identify SARS-CoV-2 in suspect cases with the negative molecular diagnosis; on repeat testing, many of these patients had positive molecular tests (Hui et al., 2020).

A recombinant protein expressed the full-length SARS-CoV2 S1 protein was synthesized using 6x his tag by expressing them in human 293F cells and Chinese hamster ovarian cells to obtain the glycosylation S1 surface protein of virus in its native conformation. The SARS-CoV2 6Xhis tag is purified using S1-His protein with a molecular weight of 70 kDa glycosylation helps in protein folding correctly but also contribute greatly to protein affinity of the receptors. A Chinese patent technology was used to increase the expression level of the full-length recombinant SARS-CoV-2 S1 proteins up to 70 mg/L. Using this expressed recombinant protein as the capturing antigen, they were able to perform a serology ELISA Kit on 412 normal human serum samples and 69 SARS-CoV-2 patients serum samples with a 97.5% specificity and 97.1% sensitivity. The antibody levels were increased for two weeks in hospitalized and discharged patients. Out of 276 asymptomatic medical staff, 28 were detected using this kit. The ELISA kit would help in screening health care to reduce hospital transfected SARS-CoV-2 virus (Zhao et al., 2020). China introduced the rapid test kit to detect the SARS-CoV-2 virus for less time consumption compared to the qPCR technique. This test is very easy for the testing and diagnosing of SARS-CoV-2, i.e., need drop-off patient’s blood, whereas other diagnosis methods are not easier and time-saving. Hence India procured the rapid test kit from China, and they diagnosed the symptomatic and asymptomatic patients, but the results were false positive or negative. False-positive results were due to Indian populations were endemic, whereas Chinese populations were non-endemic. Hence kit results were not confirmatory and consistent. Further, the Indian Council of Medical Research (ICMR), New Delhi has banned the rapid test kit for diagnosing the SARS-CoV-2 patients in India. However, the rapid kid test was refused globally due to false positive effects.

Recently, visual naked-eye and selective detection of SARS-CoV-2 causal virus using nucleocapsid phosphoprotein (N-gene) of SARS-CoV-2 targeted antisense oligonucleotide capped plasmonic nanoparticles without the necessity of any sophisticated instrumental techniques (Moltra et al., 2020).

PREVENTION

“Prevention is better than cure” is the proverb that is evocative for the current SARS-CoV-2 pandemic disease. Preventive measures are few who may need to pursue by the peoples to fight against the SARS-CoV-2. COVID-19 infected patients should be self-quarantined for 14 days from healthy peoples and family members. People should wear masks and wash their hands with sanitizer or soap often at least for 20 seconds. In the present scenario, peoples should avoid unnecessary travel to other countries/states that were SARS-CoV-2 pandemic. School and college administrations should support online classes to avoid this deadly virus spread in the current situation. The most favorable situation would be COVID-19, automatically petering out as was the case with SARS in 2003 if nature gives us a chance.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The novel SARS-CoV-2 has challenged the economic, medical, and public health infrastructure worldwide. This review describes the broad investigations of the SARS-CoV-2 genome, pathophysiological mechanism, and the fundamental aspects of the viral genome. Additionally, the inferences of post- SARS-CoV-2 and clinical manifestations of vital organ disease transmission strategies with their comorbidities are highlighted. Scheme 1 provides an elaborate illustration of the SARS-CoV-2 inferences, major obstacles in therapeutic strategies, and various methods of vaccine development. The list of recent vaccines and their respective role in the stimulation of immune responses were additionally discussed in Table 1. Finally, the preventive measures of SARS-CoV-2 have an important phenomenon through inhibiting the role of surface proteins, and dysfunctional immune system status regulation may harmony to inhibit the infection transmission at the primary stage.
### Table 1 Recent vaccine profiles for COVID-19

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Vaccines</th>
<th>Type/Technology</th>
<th>Phase</th>
<th>Country</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sputnik V and Gam-COVID-Vac Lyo</td>
<td>Adenoviral-based vaccine (Adv5). CanSinoBIO's adenovirus-based viral vector vaccine technology. Ad5-CoV vaccine is genetically engineered with defective adenovirus type 5 vector to express SARS-CoV-2 spike protein. Developed based on a chimeric adenovirus called ChAdOx1.A single dose of AZD1222 resulted in a 4-fold increase in antibodies to the SARS-CoV-2 virus spike protein An inactivated new crown candidate</td>
<td>Completed and released</td>
<td>Russia</td>
<td><a href="https://www.coronavirustoday.com/coronavirus-vaccines">https://www.coronavirustoday.com/coronavirus-vaccines</a></td>
</tr>
<tr>
<td>5</td>
<td>CoronaVac SARS-CoV-2</td>
<td>Completed and released</td>
<td>China</td>
<td><a href="https://www.coronavirustoday.com/coronavirus-vaccines">https://www.coronavirustoday.com/coronavirus-vaccines</a></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>BNT162b2</td>
<td>Completed and released</td>
<td>Pfizer and BioNTech's USA</td>
<td><a href="https://www.coronavirustoday.com/coronavirus-vaccines">https://www.coronavirustoday.com/coronavirus-vaccines</a></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Moderna/mRNA -1273 SARS-CoV-2</td>
<td>Completed and released</td>
<td>Massachusetts, USA</td>
<td><a href="https://www.precisionvaccinations.com/vaccines/new-crown-covid-19-vaccine">Jackson et al., 2020</a></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>NVX-CoV2373</td>
<td>III</td>
<td>Maryland, USA</td>
<td><a href="https://novavax.com/download/files/2020.08.04NVXCoV2373PhaseIClinicalResults.pdf">https://novavax.com/download/files/2020.08.04NVXCoV2373PhaseIClinicalResults.pdf</a></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sanofi and GSK</td>
<td>II</td>
<td>USA-GSK</td>
<td><a href="https://www.coronavirustoday.com/coronavirus-vaccines">https://www.coronavirustoday.com/coronavirus-vaccines</a></td>
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<tr>
<td>14</td>
<td>UQ COVID-19</td>
<td>I</td>
<td>USA</td>
<td><a href="https://www.coronavirustoday.com/coronavirus-vaccines">https://www.coronavirustoday.com/coronavirus-vaccines</a></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Beijing BBIBP-CorV</td>
<td>I</td>
<td>China</td>
<td><a href="https://www.coronavirustoday.com/coronavirus-vaccines">https://www.coronavirustoday.com/coronavirus-vaccines</a></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Covaxin</td>
<td>Completed and released</td>
<td>Bharat Biotech, Pune, India</td>
<td><a href="https://www.coronavirustoday.com/coronavirus-vaccines">https://www.coronavirustoday.com/coronavirus-vaccines</a></td>
<td></td>
</tr>
</tbody>
</table>
18 CVnCoV  CureVac’s is an mRNA vaccine candidate that utilizes nucleotides without chemical modifications in the native mRNA. Combination of Medicago’s recombinant Coronavirus Virus-Like Particles (CoVLP) with GSK’s pandemic adjuvant system. CoVLP mimics the SARS-CoV-2 structure. Corvus is candidate for an agonized humanized monoclonal antibody, named as CPI-006 will be a potential immunotherapy Altrimmune, Inc.’s AdCOVID is designed to protect the pulmonary from viral attack and protect from spreading of viral colony. Valneva's VLA2001 is a Vero-cell, inactivated whole virus vaccine candidate targeting particles of SARS-CoV-2 with high S-protein density, combined with two adjuvants, alum and CpG 1018

19 CoVLP  III USA https://www.coronavirustoday.com/coronavirus-vaccines

20 CPI-006 Novel Immunotherapy  I Burlingame, California-USA https://www.coronavirustoday.com/coronavirus-vaccines

21 AdCOVID  I Maryland, United States https://www.coronavirustoday.com/coronavirus-vaccines


23 CovIVac  Completed and released Russia https://www.coronavirustoday.com/covid-19-vaccines

24 Covishield  Completed and released Serum Institute, Hyderabad, India https://www.coronavirustoday.com/covid-19-vaccines

25 EpiVac  Completed and released Vektor State Research Center of Virology and Biotechnology, Russia https://www.coronavirustoday.com/covid-19-vaccines

26 KCONVAC  III and released Shenzhen Kangtai Biological Products Co., Ltd., China Zhang et al., 2020

27 Sputnik Light  Completed and released Russia https://www.coronavirustoday.com/covid-19-vaccines


29 AG0301  III AnGes Inc. and Osaka University, Japan https://www.precisionvaccinations.com/vaccines/ag0301-covid-19-vaccine

30 Soberana 02  III Cuba https://www.coronavirustoday.com/covid-19-vaccines

31 Brilife (IBR-100)/VSV  II Israel Institute for Biological Research Indiana, Israel https://www.coronavirustoday.com/covid-19-vaccines

enhancing COVID-19 disease. Elixigen Therapeutics's EXG-5003 is a temperature-sensitive self-replicating RNA vaccine expressing the receptor-binding domain of the SARS-CoV-2 spike protein. ImmunityBio hAdS COVID-19 vaccine candidate targets the mucosal immune system. Virus-Like Particle (VLPs) of the coronavirus just 20 days after obtaining the SARS-CoV-2 (virus causing the COVID-19 disease) gene Prophylactic vaccine based on optimized epitopes selected to induce a lasting sentinel T lymphocyte immune response against SARS-CoV-2, the virus that causes COVID-19. The Receptor Binding Domain of the Spike Protein of SARS-CoV-2 at three dose levels adjuvanted with CpG 1018 plus alum

33 EXG-5003

34 hAdS-COVID-19

35 bacTRL-Spike

36 CoVepiT

37 COVID-19 Subunit Vaccine

SARS-CoV-2

Moreover, the viral pathogenicity and the resulting immune mechanism it elicits is an important measure for vaccine expansion. Currently, researchers are focusing on the study of correlation of the immune dysfunction in severely infected as well as healthy individuals, which is highly recommended for determining the SARS-CoV-2 responses. These studies will assist in finding the biomarkers to define an individual's health to preclude the viral infection progresses.

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REFERENCES


