Insights on Epidemiology, Pathogenesis, Diagnosis and Possible Treatment of COVID-19 infection

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Running title: **Current perspectives on biology of COVID-19: A review**

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Abstract

COVID-19, SARS-CoV-2 virus of the coronavirus family, created worldwide infectious outbreak affecting millions of people across the globe showing mild to severe symptoms of pneumonia and acute respiratory distress. Absence of precise information on primary transmission, diagnosis, prognosis, and therapeutics for patients with COVID-19 makes prevention and control tough. Treatment of millions of COVID19 patients without any specific drug is one of the biggest challenge, many existing antiviral drugs are in use as an alternative treatment and hunting is still on the way to develop COVID19 specific drug and vaccine. Being the world second largest populated country, fluctuating climatic condition at every 4 months, India is also at the high risk for spread of COVID19 infection. This review article has been intended to discuss biology of COVID-19, mechanism of COVID-19 infection in humans, epidemiology, possible effect of COVID19 infection on pregnancy, nervous system, individuals diabetes and cardiovascular disease, drug repurposing strategy as an alternative line of treatment and clinical practices recommended by World Health Organization (WHO) and other government agencies followed by situation and measures taken by Indian government to minimize the spread of COVID19 in India.

Keywords: COVID-19, Coronavirus, Acute respiratory illness, Repurposed Drugs

Introduction

Recently in December 2019, patients were presented with symptoms of fever or dry cough having either usual or reduced count of white blood cell from Wuhan city of China. They were classified bearing ‘Fever of Unknown Origin’ along with pneumonia [1]. Later on, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) identified as causative agent, potentially having human-to-human transmission [1]. The World Health Organization (WHO) stated ‘Public Health Emergency of International Concern’ at the outbreak of infection induced by COVID19 on 30th January 2020. On 12th January 2020, WHO termed the virus as ‘2019 novel coronavirus’ (2019-nCoV) and subsequently on 11th February 2020, the disease was designated as ‘coronavirus disease’ (COVID-19). The pandemic of COVID-2 has already been diagnosed in more than 10,021,401 people from 115 countries worldwide (Figure 1). It has caused nearly 4,99,913 deaths as published on 29th June, 2020 [4]. The genome analyses of SARS-CoV-2 have shown the evolution of these viruses into L- and S- types [2]. The prevalence of S-type (~ 30%) is reported to be less than that of L-type (~ 70%). Further, the S-type is evolutionary older and less aggressive while the L-type, being more contagious, showed higher frequency during early stages of COVID outbreak in Wuhan. Nonetheless, its frequency declined after early January 2020.

Coronaviruses (CoVs) are a group of varied and large enveloped viruses enclosing non- segmented and positive-sense single-stranded RNA. They have been observed to cause enteric and respiratory diseases. Besides, they also affect liver and neurological system with varying severity among animals and humans [3]. Human corona virus subtypes like HCoV-HKU1, HCoV-229E, HCoV-NL63 and HCoV-OC43 lead to mild respiratory sickness [4]. However, worldwide spread of two novel corona viruses namely SARS-CoV and Middle East Respiratory Syndrome CoV (MERS-CoV) in last 20 years has attracted global attention due to their high lethal potential. More than 8,000 people with around 10% mortality rate worldwide occurred due to widespread SARS-CoV infection. However, the MERS-CoV was infested in around 857 patients with a high death rate (35%) [5]. A recent outbreak of SARS-CoV-2 in China got rapidly spread throughout the world. Genome analysis revealed that, like SARS-CoV and MERS-CoV, the SARS-CoV-2 also falls in the same beta-corona virus (β CoV) clade and shows high homology with SARS-CoV [6]. Consequently, SARS-CoV-2 shares analogous pneumonia pathogenesis as instigated by SARS-CoV or MERS-CoV infected cases and its entrance into the human host cells has been recognized utilizing a

similar receptor as SARS-CoV. Since most CoVs have almost same viral structure and infection pathway, observations related to mechanisms of infections may also be applicable for SARS-CoV-2 [7].

The SARS-Cov-2

SARS-CoV-2 belongs to Sarbecovirus subgenus of the genus Betacoronavirus [6]. It possesses 29.9 kb long RNA consist of 5' untranslated region (5' UTR), replicase gene, S gene (for Spike protein), E gene (for envelope protein), M gene (for Membrane protein), N gene (for Nucleocapsid protein) and 3' poly (A) UTR with unknown open reading frames [8]. It is surrounded by envelope and spikes with spherical, oval, or pleomorphic shapes of 60-140 nm diameters. Although SARS-CoV-2 has distinct gene sequences from other corona viruses, it exhibits high sequence identity (80.26%) to the human SARS-CoV genome [7]. As per WHO, it appears as a chimera of coronavirus of a bat and of an unknown origin. Nevertheless, snakes are considered possible source for SARS-CoV-2 after comparing with other animals. Another research group reported that Chinese chrysanthemum-headed bats is closely related to SARS-CoV-2 and transmission to humans could have started from bats [9]. However, SARS-CoV-2 transitional animal host is still not clear.

Route of Infection of SARS-CoV-2 in Humans

The envelope spike (S) protein has been observed to shape host tropism and transmission capacity. It also facilitates receptor binding and membrane fusion. Structural analysis revealed two domains (S1 domain and S2 domain) of S protein. The S1 domain facilitates binding to the receptor, whereas S2 domain aids in fusion of virus with the cell membrane. Like SARS-CoV, the SARS-CoV-2 also employs angiotensin-converting enzyme 2 (ACE-2) receptor for entering into the host cells [10]. The ACE-2 have high expression in lungs alveolar cells, upper epithelial cells in esophagus and absorptive enterocytes cells of ileum and colon. This indicates that along with respiratory system, digestive system could also act as a probable route of entry for CoV-2 [6]. The binding of SARS-CoV-2 to its receptor promotes expression of ACE-2 that leads to alveolar cell damage that in turn activates a sequence of reactions leading to death. As compared to European and American populations, the expression level of ACE-2 was observed significantly higher in Asian populations and that too in males than females. The differential expression pattern of ACE-2 may form the basis of high rate of infection in male and in Asians [11]. However, cases in Europe and America may have additional sensitivity or genetic predisposition.

Epidemiology, Clinical features and Pathological conditions of COVID-19 infection

The COVID-19 has caused global pandemic (WHO Media Briefing held on 11th March, 2020). The global reports have suggested that the individuals infected with SARS-CoV-2 had average age of 59 years, among them males represents 56% of cases. The median incubation period of the virus was observed around 5 days. Also, the proportion of male to female mortality was observed to be high (3:1) with 75 years as the median age. Further, median time between the onsets of symptom to death is reported as 14 days that varies for patients with ≥ 70 years of age (11.5 days) from the subjects ageing < 70 years (20 days) [13]. About half of the patients contracting COVID-19 infection were seen to have other diseased conditions, mainly hypertension, diabetes or cardiovascular disease. With regard to children of age less than 15 years, comparatively less number of cases has been reported. Also, the clinical course was generally milder in children than adults infected with COVID-19 [6].

The COVID19 infected patients showed fever with dry cough and fatigue as common clinical symptoms. Some patients were presented with upper respiratory symptoms, gastrointestinal symptoms such as vomiting, diarrhea and abdominal discomfort [5-7] and they were categorized into mild, severe, and critical medical conditions. The patients with mild symptoms were reported to have non-pneumonia or mild pneumonia. In severe condition, observations suggest that oxygen saturation and partial pressure ratio of oxygen in arteries to inspired oxygen fraction decrease whereas lung infiltrates may increase within a short span of 24-48 hours [5]. The laboratory observation showed lymphopenia (low levels of lymphocytes) in the blood as cardinal feature of COVID-19. Apart from this, the elevated levels of lactate dehydrogenase and creatinine kinase relate abnormal myocardial zymogram. The patients also showed altered liver function with increased levels of alanine or aspartate aminotransferase [14]. Also, the levels of interleukins (IL10, IL9, IL8, IL7, IL1B, IL1RA), granulocyte-macrophage colony-stimulating factor (GMCSF), granulocyte colony-stimulating factor (GCSF), , fibroblast growth factor (FGF), interferon gamma-induced protein 10 (IP10), interferon-gamma (IFN- γ), macrophage inflammatory protein 1 alpha and beta (MIP1A, MIP1B), monocyte chemoattractant protein 1 (MCP1), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNF α) concentrations were reported up in COVID-19 patients compared to healthy adults. They also noticed that plasma concentrations of TNF α and interleukins (MIP1A, IP10, MCP1, GCSF, IL10, IL2, IL7) were higher patients admitted in intensive care unit (ICU) indicating damage to the host lung due to the production of chemokines and cytokines upon initiation of

immune response on COVID19 infection [16]. The reactome analysis (<https://reactome.org>), a high throughput in silico approach, was done in subset of COVID-19 clinical data. The upregulated proteins predicted 25 biological pathways that may get affected in the COVID19 infected patients (Figure 2). These pathways are related to signaling of interleukin and cytokines, inflammasome pathway, and chemokine receptors. The ATF4 activates genes in response to endoplasmic reticulum (ER) stress, regulation of gene expression by hypoxia inducing factor (HIF), VEGF-ligand receptor interaction and dimerization, Dectin-1 signaling, cell recruitment (pro-inflammatory response). Further extensive studies are needed to identify specific molecular targets and trace critical molecular pathways to better understand the transmission and pathogenic nature of this pandemic infection.

The radiologic display observed using chest computed tomography (CT) scan of SARS-CoV-2 infected patients revealed patchy ground glass opacities (GGO) with condensation in the middle and outer zone of the lungs. Based on chest CT scan, four stages of abnormalities observed in patients. The GGO appears in the lower lobes of either one or both the lungs in early stage. In progressive stage, GGO appear bilateral, diffused and condensed in more than two lobes. However, diffuse GGO and compact consolidation developed more dominant in peak stage whereas widespread GGO and condensation was progressively absorbed in last or absorption stage [5, 15].

The lung biopsy reports of few patients showed bilateral diffuse alveolar destruction with cellular fibromyxoid dislodge and interstitial mononuclear inflammatory penetration mainly by lymphocytes [5]. The SARS-CoV2 viral cytopathic-like changes i.e. multinucleated syncytial cells with unusual magnified pneumocytes identified in the intraalveolar spaces were similar to observation among patients infected with MERS-CoV and SARS-CoV. Further, liver tissue showed adequate microvascular steatosis, mild lobular, portal activity and heart tissue showed few interstitial mononuclear inflammatory infiltrates [15]. However, due to limitation of biopsies and autopsies, the pathological finding of human SARS-CoV-2 are very minimal.

Effect of COVID 19 infection on pregnancy

In two reports describing 18 pregnancies with COVID-19, all were infected in the third trimester, and clinical findings were similar to those in non-pregnant adults. Fetal distress and preterm delivery were observed in few cases. Out of all, two pregnancies were cesarean deliveries, and SARS-CoV-2 was negative on all babies tested. Based on these limited reports, and the available data from other respiratory pathogens such as SARS and influenza,

it is unknown whether pregnant women with COVID-19 experience more severe disease [16]. Therefore, further case studies are of utmost importance on large number of pregnant women affected with COVID19 infection throughout the world to understand the probable effect of COVID19 on neonate health.

Effect of COVID 19 on nervous system

The exact route of by which coronavirus enters the CNS remained matter of debate. The presence of SARS-CoV has been confirmed in brain (specifically in neurons) of patients infected with SARS. Reports suggest that SARS-CoV or MERS-CoV mainly through olfactory nerves enter the brain and spread rapidly in thalamus and brain stems. The HEV 67N uses clathrin-coating-mediated endocytotic/exocytotic pathway to get transferred between neurons in the porcine brain. The CoVs proposed to conquer the peripheral nerve terminals and enter the central nervous system through interconnected synapse. It has been observed that viral antigens infects specifically nucleus of the solitary tract and nucleus ambiguus in brain stem. Likewise, SARS CoV-2 may also possesses a similar potential for invading brain because of its high similarity with SARS-CoV. The latency period of COVID-19 virus as reported according to epidemiological studies may be sufficient for the virus to reach brain and effect the medullary neurons. However, some of the patients displayed neurological manifestations like headache, nausea, vomiting and even acute cerebrovascular diseases and impaired consciousness in few cases [17]. It will be interesting to investigate whether COVID19 spread across the brain or get localized at specific brain region. Likewise, COVID-19 related neurological pathologies should also be investigated mainly in asymptomatic infection population. Like any other neurovirulent virus, COVID19 may also effect brain specific immunity and cross the blood-brain barrier or reach directly to brain through olfactory bulb (Figure 3). The microglia are innate immune cells of the brain, perform regular immunological surveillance of brain and regulates brain immunity. Thus, microglia may be having protective function coordinating the innate immune response like other microorganisms, however the above underlying mechanisms still remains unclear.

Effect of COVID 19 on individuals having diabetes and cardiovascular disease

Diabetic individuals are at greater risk of infections and are highly prone to influenza and pneumonia like MERS CoV, SARS CoV and Pandemic Influenza A 2009 (H1N1). It is suggested that the presence of medical conditions like diabetes and cardiovascular disease with SARS-CoV2 infection can increase the mortality risk in population

[18]. It has been hypothesized that pneumonia can potentially cause low level of oxygen in the blood due to gas exchange obstruction, which will adversely affect the cell metabolism, increased anaerobic fermentation, intracellular acidosis and oxygen free radicals which will further damage the phospholipid bilayer of cell membrane [19]. At the same time, calcium ions influx due to hypoxia can damage cardiac muscle cells. In such stress conditions and due to medication, release of neurotransmitter mainly, catecholamines in excess amount can cause myocardial damage. It also suggested that cardiac diseases, hypertension, or diabetic patients are prone to severe COVID-19 infection when treated with ACE2-increasing drugs [20]. Thus, ACE inhibitors or ARBs (angiotensin II type-I receptor blockers) has been proposed to modulate ACE2 medications in such patients. Further based on patients with COVID-19 studies, Chen et al., 2020 suggest that COVID-19 can significantly affect the heart function and lead to myocardial injury [21].

Diagnosis of COVID19

The general approaches to detect COVID-19 are molecular and serological tests. Currently, the standard diagnostic test for SARS-CoV-2 infection using samples taken from respiratory tract by PCR techniques such as RT-PCR, RT-insulated isothermal PCR, RT-LAMP, and single-step rRT-PCR assay based on specific TaqMan probes. The whole genome sequencing may also be carried out on positive samples to aid understanding of transmission and mutations. Serological markers have also been identified but are not currently useful for clinical diagnostics. On comparison (Table 1) molecular tests (RT-PCR) have shown higher sensitivity than serological (ELISA) tests. For improving sensitivity of the test, additional sensitive molecular marker i.e. *N* gene has been incorporated in nested PCR [22]. However, efforts are still going on development of diagnostic kit to detect COVID-19 infection even at the early stage in minimum possible testing time with high sensitivity.

Drug repurposing strategies for COVID-19

The James Black, Nobel laureate excellently quoted that “The most fruitful basis of the discovery of a new drug is to start with an old drug.” [23]. Thus, the concept of Drug repurposing which also coined as Drug repositioning or Drug reprofiling developed and helped bring new therapies to the world (Table 2). Drug repurposing is basically defined as the reapplication of the approved drugs or failed drugs to target new indication(s). Three R’s (Repositioning, Reprofileing, and Repurposing) strategy serve as an important part of drug development process

pharmaceutical business from the last few decades. It helps to adjust or develop the multiple application of an active molecule. The advantage of using the existing drugs is that they have known pharmacokinetics, pharmacodynamics, clinical history and safety profile data for human use. Thus, repurposing may reduce early testing and clinical trials and dramatic dropping development times and cost.

Recently, compassionate use of anti-viral drug Remdesivir (RDV) has been suggested shown to be effective in severe COVID-19 infected individuals [24]. In another study, open label non-randomized clinical trials showed that hydroxychloroquine treatment significantly reduce the viral load in COVID-19 patients, where providing azithromycin along with hydroxychloroquine enhanced its antiviral effect [25]. However, efficacy and safety of hydroxychloroquine is still under investigation. Another protease inhibitor, lopinavir/ritonavir, conventionally used for HIV-1 treatment, have showed potential to act on SARS-CoV-2 and is advised to high risk group of COVID-19 pneumonia in Korean population. However, controlled clinical trials suggest no effect of lopinavir/ritonavir on COVID-19 [26]. Repurposing strategy has highlighted many other potential candidates also such as leronlimab, a CCR5 antagonist with the potential for multiple therapeutic indications, and galidesivir, a nucleoside RNA polymerase inhibitor, favipiravir, darunavir, immunoglobulins, arbidol hydrochloride combined with interferon atomization and others [7] (Table 3). The BCG vaccination has also been proposed as an alternative treatment strategy in reducing COVID19 infection mortality rate [27].

COVID19 infection in India

Humans serves as a host to number of respiratory viruses. Respiratory transmission from human to human is one of the preliminary cause of viral infections including measles and COVID19. Due to large population size (approximately 1.38 billion) Indian live closer that is easier for pathogens to jump from one host to another via air or surface transmission. Their reservoir is also facilitated due to the 4 climatological seasons of about three months each.

The first case of COVID19 in India was detected on 30th January, 2020. Soon after quarantine centers were established and admitted for monitoring for citizens from travelling to china and other part of the world (Source: PIB Daily Bulletin on COVID-19 matters, Government of India, <https://pib.gov.in/newsite/bulletinn.aspx>). Due to proactive measure of complete lockdown and monitoring, the spread of infection came under control as compared to

other countries [4] (Figure 4). Meanwhile, based on whole genome sequence of first Indian COVID19 case, gene-specific *in vitro* transcribed RNA for all the gene targets i.e. *N*, *E* and *RdRp* as in-house positive control for laboratory diagnosis of SARS-CoV-2 by National Institute of Virology, Indian Council of Medical Research, Pune, India [28]. The genome sequences of Indian SARS-CoV-2 showed approximately 99.98% similarity with that of (accession number: NC 045512) but belongs to different cluster in phylogenetic analysis [29]. Due to non-availability of any specific treatment for COVID19, lopinavir/ritonavir combination therapy has been approved for COVID-19 under restricted public health emergency by Central Drugs Standard Control and Indian Regulatory Authority [30]. The proactive preventive majors, life style and genetic composition of Indian helped to restricted transmission of COVID19 infection.

Conclusion

COVID-19 infection is causing major public health problem across the globe. Apart from severe respiratory illness, COVID-19 infection seems to affect multiple organs. Some drugs have shown promising results, however novel standard treatment regime and potent interventions are the need of hour. An original immunization against the pandemic by precisely targeting COVID19 is urgently required to boost our immune response against such infections in a much more generalized way. These comprehensive studies, genomic data, epidemiology data and clinical details positively supports for a novel and comprehensive diagnosis and treatment options in upcoming days to beat this coronavirus disease 2019 (COVID-19).

Significance Statement

The review article will provide basic understanding on the biology of COVID19 and effect of its infection on humans. It will also provide an insight on use of anti-viral and anti-malaria drugs as possible alternative treatment strategies.

Conflict of interest: SKM, AB, PS and RM declare no conflict of interest

Author's contributions: SKM conceptualized the manuscript. SKM, AB and PS wrote the manuscript. SKM, AB and RM reviewed and edited the manuscript. All the authors approved the manuscript before submission.

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Ethics approval

Not applicable

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Figures legend:

Figure 1: Geographical region showing countries, territories or areas with confirmed cases of COVID-19 as on 29th June, 2020 (Image Source: WHO Situation Report 161 (1)).

Figure 2: *In silico* analysis of proteins through neural network (Reactome analysis, <https://reactome.org>) indicates COVID19 infection may trigger innate and adaptive immune response, leading to activation of signaling pathways and signal transduction mechanisms.

Figure 3: Diagrammatic representation showing possible site of entry of COVID19 infection, either directly from the nose through olfactory bulb into the brain or directly into the lungs and then migrate through peripheral nervous system into the brain. Further the underlying mechanism whether microglia will be neuroprotective in nature if COVID19 virus enters through olfactory bulb or it will initiate neuroinflammation cascade still remains elusive. The status of neurons and astrocytes at the site of viral entry remains unknown till date.

Figure 4: Graphical representation of the number of COVID-19 positive cases in India, United States of America (USA), Italy, Spain, Iran, Germany, France and Canada (Data compiled from Statistical report of WHO on COVID-19 infection across world, as on 29th June, 2020).

Tables:**Table 1: Some of the classic examples of repurposed drugs**

Drug	Original Indication	Repurposed Indication
Thalidomide	Sedative	Leprosy and Multiple myeloma
Ropinirole	Parkinson's disease	Restless legs syndrome, sexual dysfunction induced by selective serotonin reuptake inhibitor (SSRI)
Pregabalin and Gabapentin	Anti-epileptics	Neuropathic pain and anxiety disorders
Minoxidil	Anti-hypertensive agent	Topical treatment for hair re-growth.
Methotrexate	Chemotherapy drug	Autoimmune disorders including arthritis
Gemcitabine	Antiviral	Anticancer
Raloxifene	Breast cancer	Osteoporosis
Bupropion	Depression	Smoking cessation
Dapoxetine	Analgesia	Premature ejaculation
Dapsone (DDS)	Antileprosy drug	Antimalarial
Fluxetine	Depression	Premenstrual dysphoria disorder (PMDD)
Doxepin	Antidepressant	Antipruritic
Bimatoprost	Glaucoma	Eyelash growth

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Figure 1

Figure 2

Figure 3

Figure 4