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A Systemic Review of COVID-19, Epidemiology, Virology, Pathogenesis, Diagnosis and Clinical Management

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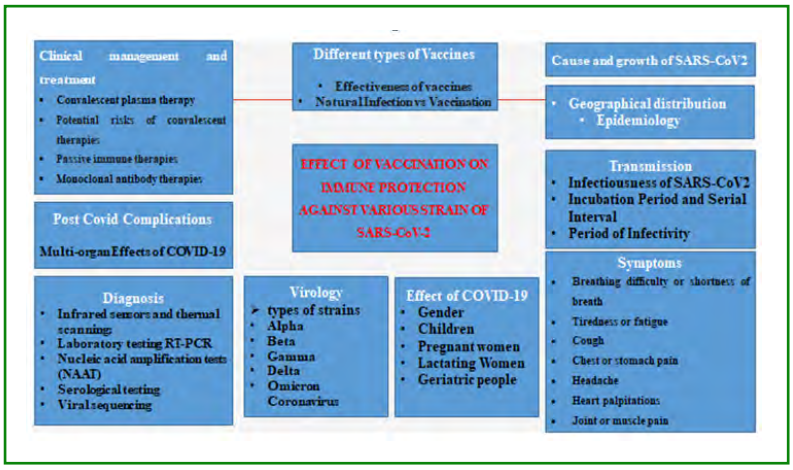
Abstract

Globally, corona virus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome Corona virus-2 (SARS-CoV-2) is the biggest and devastating public health challenge of the century. With a current tally of about 761 million of caseload with death count of around 6.8 million, the pandemic of COVID-19 had ravaged the mankind in last three years. The comprehensive understanding of the causes, the mechanisms, and the pathology of COVID-19 are still insufficient. The development of new drugs and therapeutic strategies for COVID-19 is still underway. Vaccines had been developed and are considered as the crucial weapon to counter with. However, the virus has been continued to mutate yielding various strains causing formidable counts of breakthrough and reinfection cases. This implies the importance of additional health metrics like timely detection and treatment to prevent transmission. SARS-CoV-2 rapid evolution threatens vaccine- and natural infection-derived immunity. Thousands of mutations have occurred in the SARS-CoV-2 genome as the pandemic has proceeded. Understanding the importance of mutations in spike proteins, particularly those of relevance for antiviral immunity, is important to allocating preparedness efforts. This review summarizes the comprehensive information of SARS-CoV-2 variants, pathogenesis, diagnostics, prognostics and management. Further we discussed recent progress on the conventional therapeutics strategies and challenges in COVID-19 management. Conclusively, the present review encompasses the COVID-19 related information and emphasizes the need for early prevention and clinical management.

Keywords: COVID-19; Epidemiology; Immunity; Pandemic; SARS-Cov-2; Vaccines

Abbreviations: COVID-19: Corona Virus Disease 2019; WHO: World Health Organization; MIS: Multi System Inflammatory Syndrome; ACE2: Angiotensin Converting Enzyme 2; SAR: Secondary Attack Rate; RBD: Receptor-Binding Domain; FCS: Furin-Cleavage Site; VUMs: Variants Under Monitoring; RT-PCR: Reverse Transcription Polymerase Chain Reaction; HFNC: High Flow Nasal Cannula; FDA: Food And Drug Administration; CCP: COVID-19 Convalescent Plasma.

Graphical Abstract



Introduction

The 2019 novel coronavirus (2019-nCoV), also known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for more than 761 million infection across the world [1,2]. It is responsible for severe respiratory disease, known as coronavirus disease 2019 (COVID-19), the virus's most common fatal effect. SARS-CoV2 has outspread across the globe since its outbreak, and the World Health Organization (WHO) declared it a pandemic on March 11, 2020 [3,4]. As of March 21, 2023, it has resulted in over 76,10,71,826 confirmed infections and 68,79,677 deaths reported to WHO (WHO Coronavirus Dashboard, 2023). There were a series of pneumonia episodes in late December 2019 instigated by a novel virus, which was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 11 February 2020 [5]. Despite, many countries of the world widely adopted three vaccine doses the COVID-19 infection enters its fourth year with several mutations, differential transmission and immune invasion [6]. However, SARS-CoV-2 continues to evolve and spread due to rapid mutations and emergence of the new Omicron and its descendant sub variants [7]. SARS-CoV-2 subvariants rapidly expanding because of vaccination or preinfection antibody evasion qualities obtaining from the rapid spike protein mutations [8,9].

In the Coronaviridae family, Coronaviruses (CoV) are a subgroup of viruses. Alphacoronavirus, betacoronavirus, and gammacoronavirus are the three genera that make up the Coronavirinae subfamily. There are two genera in the subfamily Torovirinae, torovirus and bafinivirus. These viruses are zoonotic, can be transferred between animals and humans [10].

As well as the normal cold, fever, and cough, tiredness. Initial symptoms may also include loss of taste and smell [11]. SARS-CoV-2 can also lead to pneumonia, respiratory distress and kidney failure or even death if left untreated for a long time [12,13]. The severity of symptoms can vary from mild to severe. A number of people may have no symptoms, although can infect others (asymptomatic transmission). Some infected people may have merely little symptoms. Some group of people may experience massive complications like, breathlessness or difficulty in breathing and pneumonia, chronic obstructive pulmonary disease (COPD) serious heart diseases, Type 1 or type 2 diabetes etc [14]. Some people experience post COVID-19 conditions for more than four weeks after they're diagnosed [13,15]. Many children suffered from multi system inflammatory syndrome (MIS), a syndrome that can disturb some organs and tissues, several weeks after COVID-19 infection. Elderly infected people had suffered from serious sickness including organ failure in several organs. The risk of serious health problems and the incidence of hospitalization increases with age. Patients who have existing medical conditions also may have a higher risk of serious illness [16].

However, a large group of patients infected with SARS-CoV-2 suffered prolonged effects of COVID-19, also referred as the "long-COVID" [17]. Almost 150 million of cases of long covid create a huge burden on society [6,18,19].

The pathological mechanism of the SARS-CoV-2 virus in developing various manifestations have been extensively observed. Many studies reported that SARS-CoV-2 triggers a "cytokine storm," that leads to an hypercytokinemia or excessive release of pro-inflammatory cytokines. The magnitude of inflammation is clinically related to the severeness of the infection. COVID-19 aggravated the activity of immune systems which can induce various signal transductions, that trigger cytokines release [20,21].

This review provides an overview of this novel corona virus.

We have discussed in a widely disseminated review the epidemiology, virology, pathophysiology, diagnostics as well as disease control measures and prevention methods in the current review.

Cause and Growth of SARS-CoV & SARS-CoV2

There has been an increase in severe pneumonia cases among adults in the Wuhan city, since December 2019. The World Health Organization activated the strict surveillance and sent biological samples from patients to the laboratory for analysis. A coronavirus was found in the Huanan Sea food market [22]. The virus is similar to the SARS-CoV, which was discovered on January 7th. Bats are considered to be the origin of HCoV-NL63, SARS-CoV, and MERS-CoV [23]. Some scientists believe that HCoV OC43 and HCoV-HKU1 evolved from rodents. The most common CoV in them is human CoV-OC43. Since the SARS-CoV-2 outbreak in China, the clinical features of Coronavirus Disease 2019 (COVID-19) have evolved. With pulmonary and flu-like symptoms, the disease is now subclinical or even asymptomatic [24]. Domesticated animals may play an important role in coronavirus transmission; they can be infected by bat-borne or thoroughly connected coronaviruses. Bats are thus the most important natural repositories of alpha and beta-CoVs [25]. Many coronaviruses that are phylogenetically connected to SARS-CoV (SARSr-CoVs) have been found in bats from China's, as well as European, African, and Southeast Asian countries. Bats may be usual hosts for SARS CoV, according to the research [26]. The finding of the S protein in Coronaviruses may have ramifications for the ongoing epidemic. The importance of recombination events in the evolution of the S protein is especially relevant now. The viral genome's S gene and upstream areas are thought to be critical breakpoints for viral RNA recombination. SARS-CoV is believed to have emerged due to bat SARS-CoV recombination. Journal of Clinical Microbiology published the research [27]. Human angiotensin converting enzyme 2 (ACE2) is bound to the S protein of SARS-CoV-2, allowing it to enter the human body. CoVs undergo frequent RNA recombination and have a large genetic diversity, which is believed to be a factor in the creation of new coronaviruses [23,28].

Epidemiology: The epidemiology of HCOVs is discussed in the subsequent sections and is briefed in (Table 1) [29,30].

HCoV	Symptoms	Case Fatality Rate	Incubation Period (days)
OC43	Fever and cough (10–20% of patients), Nasal discharge, Headache, Sore throat, Sneezing	NA	2-5
229E	Fever and cough (10–20% of patients), Nasal discharge, Headache, Sore throat, Sneezing	NA	2-5
NL63	Rhinorrhea Tachypnea Fever, Cough, Obstructive laryngitis (croup), Hypoxia	NA	2-4
SARS-CoV	Respiratory distress, Diarrhea (30–40% of patients, Headache, cough, Malaise, Fever, Dyspnea	9%	2-11
MERS-CoV	Sore throat, Cough, Fever, Arthralgia, Myalgia, Pneumonia, Dyspnea, Diarrhea and vomiting (one-third of patients) Acute renal impairment	36%	2-13
HKUI	Running nose, Dyspnea, Cough Fever	NA	2-4

Table 1: The epidemiology of HCOVs is discussed in the subsequent sections.

Transmission: Since most initial cases had a history of wet market exposure, zoonotic transmission appeared to be the most likely explanation. By the conclusion of January 2020, the number of people who contracted the disease without being exposed to the marketplace or another individual with breathing symptoms had increased. Those who never travel to Wuhan and healthcare professionals were infected, suggesting a one-on-one spread [5].

Infectiousness of SARS-CoV2

Based on a single case in a susceptible population, one can expect to see a certain number of secondary cases R0. As the name suggests, R0 is used in the communicable disease epidemiology and specifies the risk of an epidemic spreading. According to the studies, the R0 for SARS–CoV2 is somewhere between 2.0 and 3.0. Other factors affecting infectivity include the secondary attack rate (SAR). Possibility of an infection happened in a group of vulnerable individuals exposed to a primary case [31].

Incubation Period and Serial Interval

As a rule of thumb, it takes between five and six days for the disease to develop. 2.5 percent of patients had developed symptoms within 2.2 days (95% CI, 1.8 to 2.9 days), and 97.5

percent of patients had advanced symptoms within 11.5 days (95 percent CI, 8.2–15.6 days). About 4 to 5 days is estimated as the average interval between two consecutive events. In a study of 468 infector-infected pairs, 59 secondary cases showed symptoms before than their prime case. This raised the possibility that the disease was transmitted throughout the asymptomatic phase of infection [32].

Period of Infectivity

There is no way to tell how long a COVID-19 patient will be contagious. Onset of symptoms increases viral load in the oropharyngeal secretions. Patient's virus can be shed for a long time after symptoms have subsided. Surviving patients in a Chinese study had a median virus-shedding period of 20 days (IQR 17.0–24.0) [33]. A study of viral dynamics in moderate and severe cases exposed that mild cases tend to clear the viruses quickly, while severe cases can have lengthy viral shedding. Viral shed can continue in stool for more than 4 weeks even when respiratory samples are negative, according to research using twin respiratory and stool sampling. Asymptomatic transmission has also been documented. The transmission of COVID-19 during the asymptomatic phase was found to be responsible for 6.4% of the 157 locally developed cases in Singapore [30].

Virology

Virion Structure & Genome and Replication

Crown-shaped peplomers, positive sense single-strand RNA viruses, are Coronaviruses. There are no segments in this RNA virus, which has a size of 26 to 32kb. An RNA containing matrix protein is found in the capsular membrane, which is usually glycoprotein-protruding. In the body's outer envelope, it is known as the capsular membrane. The genome has a 5′ cap construction and a 3′ poly (A) tail, allowing it to function as an mRNA for replicase polyprotein translation. Hemagglutinin esterase (HE) and spike (S), small membrane (E), membrane (M), and nucleocapsid make up the structure (N) [12]. Coronavirus is classified as a member of the order nidovirus, family coronaviridae, subfamily coronavineae, and genus coronavirus. The human population is mostly affected by and genus of Coronaviruses. HKU1, 229E, OC43, MERS-CoV, SARS-CoV, and SARS-CoV-2 are all members of the genus, which also includes HCoV-229E (Human Coronavirus) and NL63 [34,35]. Cryo-electron tomography and cryo-electron microscopy experiments have revealed that Coronavirus virions are spherical with sizes of approximately 125 nm. Single-strand RNA, nucleocapsid protein, envelop protein, membrane protein, spike glycoprotein (S), and other components of coronavirus have been identified. Because it produces the crown-like construction on the virus's outer surface, the spike (S) glycoprotein is responsible for the virus's distinguishing feature. The spike S-protein undergoes structural change in order to facilitate the synthesis of the virus's outer membrane with the host-cell membrane. S1 and S2 are two components of the S-protein. In addition, the S1 subunit is divided into three domains, namely domains A, B, and C. Domain A of CoV-OC43 and CoV-HKU1 subunit S1 binds to host receptors. Researchers have also discovered that the membrane exopeptidase ACE enzyme (angiotensin-converting enzyme) acts as a COVID-19 receptor to enter the human cell. MERS-CoV binds to the DPP4 (Dipeptidyl peptidase-4) receptor via both A and B domains [36]. In contrast, SARS-CoV-2 and SARS-CoV penetrate target cells through direct interaction with domain B. And this is then bound by angiotensin converting enzyme-2 (hACE). Both the SARS-CoV and the novel SARS-CoV-2 viruses have a similar structure, with only a few changes. Coronavirus replication usually occurs in the cytoplasm and is tightly connected with the endoplasmic reticulum and other cellular membrane organelles. hACE-2 and CD90L (L-sign) in the case of SARS-CoV and SARS-CoV-2 and DPP4 receptor in the case of MERS-CoV allow the coronavirus to enter the host cell [37]. The SARS-CoV-2 has four unique amino acids on its S1 and S2 subunits, resulting in the insertion of furin cleavage sites. Furin cleavage sites enable a highly strong interaction of the S-glycoprotein with the hACE-2 receptor of SARS-CoV-2. Resulting the translation and assembly of viral replicase complexes, viral RNA synthesis takes place. In the viral RNA synthesis process, both genomic and sub-genomic RNAs are harvested and processed. Structural and accessory genes downstream of polyproteins are encoded by sub-genomic RNAs, which serve as mRNAs [38]. The genome is transcribed and then translated after the virus goes in the host cell and the uncoating process happens. Replication is characterized by the formation of an enclosed group of typical 3′ ends, with only the distinct portions of the 5′ ends being translated as mRNA. About seven mRNAs are produced in total. A nucleoprotein can be synthesized from another genome segment using the short mRNA and the others. Cell membranes collect these proteins, and genomic RNA emerges as a mature element type from the cell membranes [39].

Unique Features of SARs-CoV-2 Genome

SARS-CoV-2 differs from SARS-CoV in that it has mutations in the receptor-binding domain (RBD) of the S protein, as well as O-linked glycans & a polybasic furin cleavage site [34].

Mutation of the RBD of S Protein in SARs-CoV-2

RBD of the S1 subunit of the "S" protein is accountable for binding with ACE2 (Angiotensin-converting enzyme) receptors, according to recent literature. Coronaviruses have a highly variable RBD. As a result of recent research six RBD amino acids that keep on the S1 subunit are very important for receptor binding. SARS-CoV and SARS-CoV-2

have distinct residual proteins. SARS-CoV-2 residues in RBD (L455, F486, Q493, S494, N501, and Y505) and SARS-CoV (Y442, L472, N479, D480, T487, and Y4911) have only five distinct residues in common, with the exception of Y4911. SARS-CoV-2 may have a high attraction for receptors because of these differences [40,41].

Polybasic Furin Cleavage Site & O linked Glycans

In Spike protein's S1 and S2 subunits, there is a polybasic cleavage site (RRAR). SARS-CoV-2 has a proline residue added former to this cleavage site, resulting in the sequence becoming PRRA (Unique protein sequencing in SARS-CoV-2) [3]. SARS-CoV-2 is structurally similar to earlier pandemic coronaviruses, particularly SARS-CoV-1, with which it has 79.5 percent genomic and protein homology (95-100 percent). The addition of the polybasic cleavage site makes it easier for furin and other proteases to effectively cleave S-protein, which reduces viral infectivity. Furylation of the host cell membrane and virus infection are regarded as critical processes. At the S1/S2 intersection of the viral spike protein, a furin-cleavage site (FCS) containing multibasic amino-acids (PRRAR) distinguishes it from SARS-CoV-1 and other related viruses. Viruses with FCS are well-known for their pathogenicity. It's unclear whether it contributes to the virulence of SARS-CoV-2 [42]. In addition to the S1/S2 site, many other proteases can efficiently cleave this site. Due to this feature, O-linked glycans are added to S673, T678, and S686, among others. MERS-CoV and influenza viruses can be transformed into highly pathogenic forms. The purpose of the O-linked glycans is still indistinct, but they may form a mucin-like domain that aids in immunoevasion. The 'S' trimers exist in a partly open state in highly human pathogenic Coronaviruses [34,42].

SARS-CoV2 and its Variants

B814 was the first human Coronavirus (HCoV) strain reported in 1965. In the years since, roughly 30 new HCoV strains have been discovered. Seven HCoV strains, including two alpha-CoVs (HCoV-229E; HCoVNL63) and five beta-CoVs (HCoV-OC43; HCoV-HKU1; MERS-CoV; SARS-CoV including novel SARS-CoV-2) are commonly socializing in the human population and are primarily in control for cold symptoms and other respiratory diseases in healthy people. Middle East respiratory syndrome CoV and severe acute respiratory syndrome CoV are two zoonotic viruses that are linked to severe inferior respiratory tract infections and pose considerable public health risks [28].

In contrast, a variant form when a virus undergoes any type of mutation, not just one that alters its behavior. As a result of their rapid spread and potential to replace the previously dominant variants, a handful of the variants are of particular concern [43].

Variants of Concern (VOC) - Alpha, Beta, Gamma, Delta and Omicron

Alpha Coronavirus: The HCoV-229E & HCoV-NL63 strains belong to this CoV genus. NL63 is mostly seen in young children, the elderly and immuno-compromised people with respiratory diseases. Like animal alpha-CoVs, HCoV-229E uses aminopeptidase N (APN) as its principal receptor for entering the host cell, while HCoV-NL63 uses angiotensin-converting enzyme-2 (ACE-2) receptors to enter the host cell, similar to SARS-CoV, which is otherwise a beta-CoV. This strain first appeared in England in September 2020, triggering a winter spike in cases that pushed the U.K. back into lockdown in January. Alpha became the prevalent strain in the United States in early April and has been reported in at least 172 countries, according to the WHO. Flu-like symptoms such as coughing, rhinorrhoea, tachypnea and hypoxia are prevalent with NL63 infections. Laryngitis with obstruction, or croup, is a common side effect of infections caused by the virus, NL63 [44].

Beta Coronavirus: Two bat viruses, MERS-CoV and SARS-CoV, fall under this genus. New COVID-2019 virus is likewise a beta-CoV & has been dubbed SARS-CoV2. ACE2 is one of SARS-main CoV's receptors for entering the host cell, whereas DPP4 (also known as CD26) is the predominant receptor for MERS-CoV. HCoV-OC43 and HCoV-HKU1 are two more non-SARS CoV species in this genus that use sialic acid residues as receptors and have hemagglutinin-esterase activity. When it comes to symptoms of HKU1 respiratory infections, they can't be distinguished from those of other respiratory viruses. Fever, runny nose, and cough are the most common upper respiratory tract infection symptoms, while fever, productive cough, and dyspnoea are the most mutual lower respiratory tract infection symptoms. A recurrence of Covid cases, which began in August 2020 in South Africa, swept through across the world. At least 120 countries have reported it [44].

Gamma Coronavirus: This genus consists primarily of Avian Coronaviruses, with the infectious bronchitis virus of chickens being the most prominent. This variation, first discovered in the Amazonian city of Manaus in December 2020, has contributed to a spike in cases that has stretched Brazil's health system and led to oxygen shortages. At least 72 countries have reported it [44].

Delta Coronavirus: Bird and porcine Coronaviruses make up this new genus. An outbreak of Covid cases in India was sparked by this strain, which has subsequently spread to at least 96 countries. Public Health England reported in June that data from both England and Scotland suggest a higher hospitalisation risk associated to alpha, which has been related to a larger range of Covid symptoms, including hearing impairment [45]. Another study indicated that delta has a tendency to avoid antibody-based treatments, and that it could increase the likelihood of reinfection in persons who have improved from Covid caused by another strain of the

virus [43]. It is also 1.45 times more likely to see patients seeking emergency care in A&E. Scientists argue that there is additional evidence that the same characteristics that cause the variation to spread quicker also raise viral levels in persons infected.

Omicron Coronavirus: On the suggestion of WHO's Technical Advisory Group on Virus Evolution, WHO recognized the variety B.1.1.529 as a variant of concern, termed Omicron, on November 26, 2021.The Omicron lineage first identified on November 8 in South Africa has now split into two sub-lineages –BA.1 and BA.2.Omicron is more transmissible than other variations, such as Delta. The omicron variant of Covid-19 is 4.2 times more transmissible in its early stage than delta, according to a study by a Japanese scientist, a finding likely to confirm fears about the new strain's contagiousness [46,47]. All Covid-19 variations, including the globally widespread Delta variant, can cause serious sickness or death, especially in the most susceptible persons. The RT-PCR test is unlikely to identify the Omicron (B.1.1.529) sub-lineage BA.2. Since BA.2 does not have the S gene dropout unlike the main sub-lineage BA.1, it escapes identification through RT-PCR tests [9]. Study re [ported the reduced risk of hospitalization and associated risk as compared to Delta variants [48]. Recently new descendant of the Covid-19 XBB variant XBB1.16 is prevalent in India and is responsible for the recent surge in COVID-19 cases in India and South East Asia. As of 22nd March 2023 WHO has declared it as a variants under monitoring (VUMs). Genetic feature is recombinant of BA.2.10.1 and BA.2.75 sublineages, i.e. BJ1 and BM.1.1.1 XBB + S: E180V, S: K478R and S: F486P [49].

Pathogenesis

Coronaviruses are known to cause nasal oedema, sneezing, and breathing difficulties. The drug was developed in the late 1990s by the Department of Health and Human Services. Infection is spread through large droplets formed by symptomatic patients while coughing and sneezing, but it can also occur from asymptomatic people and before the onset of symptoms. When these viruses are released, they primarily affect the lower respiratory tract, with clinical signs and symptoms. In addition, the virus affects intestinal lymphocytes, renal cells, liver cells, and T-lymphocytes. Furthermore, the virus induces T-cell apoptosis, resulting in erratic T-cell responses and the immune system's complete collapse (Singhal, 2020). SARS-CoV poisons cells by binding to angiotensin-converting enzyme 2 (ACE2). The degradation of ACE2 is important in the pathogenesis of severe lung failure following a viral infection. The capacity of ACE2 is closely related to the severity of the virus infection.According to experts, a lower level of ACE2 and a weaker binding capacity with SARS-CoV-2 should be a major factor in the absence of clinical manifestations for asymptomatic infections [50]. Patients can be contagious for as long as their symptoms last and even after they recover.COVID-19's high pathogenicity and transmission capacity may be due to modified RBD residues in the S1 subunit, the presence of RRAR, and a partially opened state of the 'S' trimer. This could result in increased angiotensin-2 production by the related enzyme ACE1.SARS-CoV-2 contains antigen-presenting cells that attach to a host's dendritic cell, activating macrophages and causing a severe immunological reaction [51]. Increased AT2 production may increase pulmonary vascular permeability and cause lung injury. ACE2 is an inflammatory mediator that damages the epithelial cells lining and travels through the bloodstream, causing damage to other organs. More clinical samples should be poised, and an ACE2 relative analysis should be executed for different types of COVID-19 cases [1,50].

Mode of Transmission

Coronavirus transmission is primarily carried by respiratory droplets. Droplets of this type can either remain in the nose or mouth or enter the lungs via inhaled air. Touching an infected surface or object is another, more minor method of transmission of COVID-19 [12]. Droplet transmission occurs when people in the vicinity consume or inhale respiratory droplets (produced when an infected person coughs or sneezes).Many governments have recommended aerial safety measures with a high-risk method due to the current lack of awareness of transmission systems [52]. A person's risk of contracting an illness varies depending on where they live and whether or not they are involved in infection prevention. SARS-CoV2 can be transmitted even by asymptomatic persons or those in the incubation period. According to the CDC's data and evidence, the typical incubation period is 3 to 7 days, with some cases lasting up to 2 weeks, and the typical symptom manifestation from growth to infection takes an average of 12.5 days [53,54]. The rapid transmission, replication, and infectivity of this virus may be due to the furin cleavage sites and changed receptor binding sites of the S1 subunit. Infectivity is the same for asymptomatic and symptomatic infections. These asymptomatic patients may play a role in transmission, posing a serious infection control issue [50].

Alpha (B.1.1.7) was the first dominant variant travelled across UK and US and classified as a variant of concern by CDC. Mutations in Alpha's spike protein were responsible to make it more infectious. The B.1.1.7 lineage was believed to be 30 to 50% more contagious than the original SARS-CoV-2 strain. According to CDC beta variant was 50% more infectious than the original corona virus strain. It has been observed that Delta was 80 to 90% more transmissible than the Alpha variant. Delta AY.4.2 also referred as Delta plus was thought to be 10 to 20% more contagious than Delta. The

Omicron strain was more transmissible than Delta variant. Omicron and its variants B.1.1.529, BA.1, BA.1.1., BA.2, BA.3, BA.4, and BA.5. have been found efficient spreaders of the disease [55,56]. Omicron variant was even able to evade protection provided by vaccines and earlier infection [57-59].

Diagnosis

COVID-19 symptoms are very similar to those of previous respiratory epidemics such as SARS and MERS, but here the symptoms range from slight rhinitis to septic shock. There were some reports of intestinal disturbances with the other epidemics, but COVID-19 was free of them. Specific molecular tests on respiratory samples (throat swab, nasopharyngeal swab, sputum, endotracheal aspirates, and bronchoalveolar lavage) are used to make a diagnosis [60]. The virus can also be found in the stool and, in the most severe cases, the blood. Patients with viral pneumonia had unilateral or bilateral involvement, while patients in the intensive care unit had bilateral numerous lobular and sub-segmental consolidation areas. The clinical course of comorbid individuals was more severe than indicated by prior epidemics [61]. The whole history of travel and touch, as well as laboratory testing, are all part of the COVID-19 diagnosis. Serological testing, which can assist diagnose even silent infections, is preferred; various serological diagnostics for SARS-CoV-2 are currently being developed [52,57].

Infrared Sensors and Thermal Scanning

Thermal cameras were first used to identify patients with varying body temperatures at hospital entrances and in the emergency room. They're a good way to separate the affected people from the rest of the population. Such cameras require a scanning distance of 10 metres (62). It's also necessary for pre-diagnosis screening for auxiliary diagnoses. In comparison to Infrared (IR) scanners, thermal cameras are a better alternative for large-scale screening. They use longer wavelength IR energy, however screening a huge population takes longer. For public safety reasons, it is possible to infer that thermal cameras are safer than IR scanners [63].

Laboratory Testing RT-PCR

One of the most important ethics for controlling and dealing a disease outbreak in a country is the collection and testing of specimen samples from suspected individuals. To detect the virus, suspect cases must be thoroughly screened using nucleic acid amplification tests such as reverse transcription polymerase chain reaction (RT-PCR). If a country or region lacks the capacity to test the specimens, the suspected individual's specimens should be sent to the nearest reference laboratories on the WHO list [64].

Nucleic Acid Amplification Tests (NAAT)

NAAT is being utilized to confirm COVID-19 disease utilizing a real-time fluorescence polymerase chain reaction (RT-PCR) on a nasal swab or blood sample, as per the WHO recommended procedure [42]. It involves detecting the unique sequences of virus RNA using reverse transcription polymerase chain reaction (RT-PCR) and, if necessary, nucleic acid sequencing. So far, virus genes have been identified as N, E, S (nucleocapsid protein, envelope protein gene, spike protein gene), and RdRP (RNA-dependent RNA polymerase gene). Recently, the US-FDA and other regulators granted emergency use approval for diagnostic kits based on RT-PCR technology to detect COVID-19 [65].

Serological Testing

Also, serological surveys are measured one of the most effective tools for enabling epidemic inquiry, as well as a tool for measuring the disease's attack rate in retrospect [57,66].

Viral Sequencing

Aside from confirming the presence of virus in specimens, viral sequencing is also useful in monitoring viral genomic mutations, which has a significant impact on the performance of medical countermeasures, including diagnostic tests. The virus's genome sequencing can also aid in the development of several molecular epidemiology studies [59].

Effect of COVID-19

Gender

According to the clinical severity classification, men are more serious than women. The susceptibility of males and females to various viral pathogens differs. Females usually mount stronger immune responses than males. In the current study, males and females were found to be equally vulnerable to SARS-CoV-2 in 1019 survived patients (50.0 percent males) collected from a public data set and in a case series of 43 hospitalized patients (51.2 percent males). The number of men is 2.4 times that of women in the deceased patients. Men were more prone to dying from Covid-19 than women. Females are more resistant to infections than men, possibly because of sex hormones [67]. Women are more responsible than men when it comes to the Covid-19 pandemic. Women are also more likely to be able to detect and respond to a future outbreak of the disease [33]. The current COVID-19 pandemic appears to have both primary and secondary effects related to sex and gender, according to evidence. Prime effects include differences in incidence and case fatality between males and females, while secondary effects include differences in social and economic consequences as a result of the pandemic, such as increased risk of domestic violence, monetary and job uncertainty, and increased

internal workload [4].

Effects on Children

The pandemic's massive economic and societal disruptions put children at risk for serious consequences. There is little doubt that children tend to be healthier and live longer than other age groups, but they are nonetheless at risk for unfavourable outcomes [68]. About 50% of children and adolescents had asymptomatic COVID-19. Children with COVID-19 suffered with upper respiratory symptoms, fever, vomiting, and diarrhea etc. Associated medical complications increased the risk of severe disease with COVID-19, such as obesity, diabetes, asthma, congenital heart disease, genetic conditions.

Throughout the COVID-19 pandemic, several studies reported that children were experiencing psychological difficulties. For younger children, the most severe symptoms were fear, clinging, inattention, and irritability [69]. COVID-19 symptoms do not differ between adults and children. Although children's symptoms are milder than adults, they do not have a high mortality rate. It has been found that children and adolescents experience anxiety and depressive symptoms during COVID-19 [70,71]. Recent studies also reported that on COVID-19 pandemic led to mental health problems and fast brain maturation and aging in youngsters. It was also observed that after the pandemic adolescent had more severe mental health problems, low cortical thickness, higher hippocampal and amygdala volume, and developed brain age [72,73]. Although the prevalence and severity of COVID-19 in children and teenagers is relatively less, there are incidences on inflammatory disease. While rare, some children develop multisystem paediatric inflammatory syndrome (MIS) during or after COVID-19, also known as MIS-C associated with COVID-19. MIS-C is thought to be caused by an excessive immune response related to COVID-19. It can develop serious illness and prolonged adverse effects [74]. MIS is a condition in which various body parts get inflamed. The clinical symptoms range from the upper respiratory infection, continuous fever and inflammation, Kawasaki like disease, dermatologic, muco-cutaneous, cardiac dysfunction. It is a severe situation in which several vital organs such as the heart, lungs, brain, blood vessels, kidneys, digestive system, skin and eyes are severely inflamed. Severity of MIS-C may lead to multi-organ failure, it can also be life threatening. Rare blood disease including increased risk of coagulopathy, venous thromboembolism, also reported in children suffered from COVID-19 with markedly high D-dimer level.

Effects on Pregnant women

During the current 2019-nCoV outbreak, pregnant women appear to have a higher risk of infection & consequences. Pregnant women are more sensitive to respiratory infections than the general population; therefore they may be more prone to COVID-19 infection. Furthermore, owing to the unique immunological responses that occur during pregnancy and the potential dangers posed by COVID-19 infection's cytokine storm, pregnant women with COVID-19 infection may experience significant morbidity and even death [75]. There is a scarcity of information and data about COVID-19's effects on pregnant women. This hypothesis was built on previously published scientific findings on coronaviruses and pregnancy (SARS-CoV and MERS-CoV), as well as of COVID-19 instances. The clinical features and outcomes of ten newborns in China whose mothers are confirmed COVID-19 cases revealed that perinatal infection with 2019-nCoV can result in adverse results for the neonates, such as earlylabour, respiratory suffering, thrombocytopenia with abnormal liver function, and even death. COVID-19 infection can be transferred to the fetus via the transplacental pathway during pregnancy [67]. Although there is no evidence of intrauterine vertical transfer, the maternal infection and inflammation caused by COVID-19 might have an impact on the growing fetus and even the postnatal life. With the ongoing COVID-19 epidemic, additional measures to safeguard both mothers and fetuses should be done [33].

Effects on Lactating Women

The information currently provided is insufficient to determine if COVID-19 may be transferred through breast milk. The CDC advises that in the event of a long-established or alleged COVID-19 infection, the mother should decide whether or not to initiate or pursue breastfeeding in consultation with her family and healthcare providers. The woman must take extra care to avoid passing the illness to her baby through respiratory droplets during nursing. Before feeding the infant, mother should put on a facemask and wash hands. Furthermore, breast pumps should be cleaned thoroughly after each usage, and a healthy human should be accessible to give the expressed breast milk to the child if feasible [69,76,77].

Effects on Geriatric People

The Covid-19 epidemic significantly altered geriatric people's lives. The consequences of Covid-19 on older people's general health were severe, with significant mortality; however, the trend toward mental health is different. Surprisingly, geriatrics reported much lower levels of anxiety, sadness, and trauma or stress-related disorders such as drug abuse and suicide risk than younger persons [78]. Older adults beyond the age of 65 are at a greater risk for a severe development of sickness, according to published studies. In the United States, between the ages of 65 and 84, roughly 31-59 percent of people with confirmed COVID-19 required hospitalisation, 11-31% required intensive care unit admission, and 4-11 percent died. According to research, 53 percent of persons

over the age of 60 perished in India as a result of the Covid-19 epidemic, compared to just 10 percent of younger people. Preliminary findings show that male older individuals and patients with immunological dysfunctions may be more prone to the worst viral illness, but additional research into the virulence variables is needed [36,57,79,80].

Post Covid Complications

Post-COVID-19 syndrome includes a range of new, persistent or ongoing symptoms that people suffer more than four weeks after infection of COVID-19. In some cases, post-COVID-19 syndrome persists few months or years or leads disability [57]. Long Covid is post-infections, with large number of patients reported respiratory or gastrointestinal illnesses in the 6 weeks preceding presentation, which are considered to induce an immunological respond that results in neuropathy. COVID-19 viral pneumonia, about one week after the onset of the cough and myalgia was found prevalent. Various studies revealed that coronavirus disease 2019 (COVID-19) can develop neurological problems. It increases risk of stroke, muscle and nerve damage, dementia, vascular disorders, epilepsy, Alzheimer's disease, encephalitis etc (NIH report 2023). It occur due to the direct impact of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the nervous system or because of indirect effect of immune-mediated post-infection [81,82]. Although the actual neurotoxic mechanism of COVID-19 is not yet completely explored; however, a number of clinical and experimental reports proposed that neuroinvasion, endothelial dysfunction, neuroinflammation, immune-pathogenecity, and hypoxemia may be responsible for the development of neurological manifestations. The symptoms of COVID-19 and post-COVID-19 syndrome overlapped in some patients. The most frequent symptom was post-viral tiredness, which was followed by persistent cough, exertional dyspnoea, sleep problems, adjustment disorders, and headache [83]. Heart problems including chest pain, tachycardia has been reported by the patients [84]. Digestive problems including diarrhoea and stomach pain. Post-COVID-19 syndrome was shown to be linked to female sex, respiratory discomfort, a protracted recovery period, and illness severity. As a result, even after appearing to heal clinically, the patients did not fully recover. In over half of the patients, the COVID-19 produced long-term side effects and discomfort. COVID-19 patients require long-term monitoring and care of their post-COVID symptoms, even after they have recovered [85,86].

New or Ongoing Symptoms

After getting infected with the virus that causes COVID-19, few people had experienced different type of new or persistent symptoms that continued for months [87]. Unlike certain other post-COVID disorders that only affect those who have had a severe sickness, these symptoms can affect anybody who has had COVID-19, even if their disease was mild or they had no disease at all. Different of symptoms or disease are often observed like breathing difficulty or shortness of breath, tiredness or fatigue, cough, chest pain, cardiac problems, palpitations, liver problems, stomach pain, headache, joint or muscle pain etc. [57,88,89].

Multi-Organ Effects of COVID-19

Some patients who had severe COVID-19 sickness experienced multiorgan effects or autoimmune disorders for a prolonged period of time, with symptoms extending few weeks or months following the sickness. Most, if not all, including the heart, lungs, kidneys, skin, and brain, can be affected by multiorgan effects. Autoimmune diseases occur resulting in inflammation or tissue damage in the afflicted areas. If someone continues to have multiorgan effects or other symptoms, Multisystem inflammatory syndrome (MIS) can develop to post-COVID problems [57,90].

Vaccines

The current covid-19 pandemic has exhorted the scientific community internationally to find therapeutic interventions and vaccines to control SARS-CoV-2 virus (corona virus) and save the human lives. Certainly, Covid-19 vaccines are one of the greatest public health interventions [91]. There are several COVID-19 vaccines validated for use by World Health Organization (WHO). The Pfizer/BioNTech, AstraZwneca / AZD 1222 vaccines, Moderna, Janssen /Ad26.COV2.S, COVISHIELD, Sinopharm, Sinovac-CoronaVac vaccine, COVAXIN, Covovax (NVX-CoV2373), Nuvaxovid (NVX-CoV2373) vaccines are the WHO validated leading vaccines helped to control the pandemic (WHO, 2022). WHO has also recommended some of the vaccines for children [40,57,92].

Various types for components are used to make vaccines such as whole inactivated virus vaccines, live attenuated virus vaccines, mRNA vaccine, virus vectored vaccines, protein sub unit vaccines, DNA vaccines and monoclonal antibodies for non-resistant immunization, plant based viral like particles etc [57,93].

Different types of vaccines exert different mode of actions to offer protection against COVID-19 disease. These provide instructions to cells in the body to generate immune response. The non-invasive intranasal inhalable vaccines [94], nanovaccines have been invented and received a lot of attention. Second generation vaccines like patch vaccines is developed by using high density microarray patch (HD-MAP) technology. This type of vaccines can be administered simply attaching in the arm [93,95].

The vaccinations are effective against the Alpha version, and they are likely effective against the Gamma and Delta forms

as well, according to WHO. They also appear to be capable of lowering the risk of severe and mild to moderate sickness caused by the Beta version [87,91].

Clinical Management and Treatment

COVID-19 clinical characteristics span from asymptomatic to acute respiratory distress syndrome and multi-organ failure. Fever (not always), cough, sore throat, headache, tiredness, myalgia, and dyspnea are frequent clinical symptoms. Conjunctivitis has also been mentioned. As a result, they are indistinguishable from other respiratory illnesses. By the end of the first week, a fraction of patients may develop pneumonia, respiratory failure, and mortality [96]. This development is accompanied with an increase in inflammatory cytokines such as IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF [97]. Acute lung damage, ARDS, shock, and acute renal injury were all seen complications. In the 2nd or 3rd week of recovery, it began to feel better. In those who recovered, the median length of hospital stay was ten days. Death and adverse outcomes are more prevalent among the old and those with having co-morbidities (50–75% of fatal cases) [98]. In hospitalized adult patients, the mortality rate varied from 4% to 11%. The overall case mortality rate is expected to be amid 2 and 3%. This might be attributed to selection bias, as the cases reported from Wuhan only comprised the most severe cases, or to the Asian population's susceptibility to the virus because of greater expression of ACE2 receptors on the respiratory mucosa [1].

To avoid transmission to other patients, and healthcare staff, the first step is to establish sufficient isolation. Mild illnesses should be treated at home with education on warning signals. Maintaining hydration and nourishment, as well as managing fever and cough, are common concepts. In confirmed instances, antibiotics and antivirals such as oseltamivir should not be used routinely [91]. Establishment of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC), or non-invasive breathing is recommended in hypoxic patients. Mechanical ventilation, as well as supplementary corporeal membrane oxygen support, may be necessary in case of serious conditions. Some people may require renal replacement treatment. If co-infections are suspected or confirmed, antibiotics and antifungals are necessary. While the current worldwide consensus and WHO suggest in contradiction of the use of corticosteroids. Chinese recommendations do recommend short-term treatment with low-to-moderate dosage corticosteroids in COVID-19 ARDS [99].

Convalescent Plasma Therapy

Blood from patients who have recovered from disease is used in convalescent plasma therapy to aid others recover. The Food and Drug Administration (FDA) in the United States has granted emergency approval for COVID-19 convalescent plasma treatment with high antibody levels. It might be utilized to treat some COVID-19 patients in hospitals who are either early in their disease or have compromised immune systems. Antibodies to the virus that causes COVID-19 can be found in blood given by patients who have recovered from the disease [100]. These can be given to persons who have COVID-19 to help them fight the virus more effectively. People with COVID-19 who are in the hospital and are early in their disease or have a low immune system may be offered convalescent plasma treatment. It has the potential to reduce the brutality of the disease or decrease its duration [101].

Small case series results from previous MERS and SARS coronavirus epidemics showed that CP is safe and may have clinical advantages, such as quicker viral clearance, when given early in the illness phase [102]. As early as 1-3 weeks after infection, the gigantic majority of patients who recover from COVID-19 illness produce circulating antibodies to various SARS-CoV-2 proteins, which can be detected using ELISA or other quantitative assays and often correlate with the presence of neutralising antibodies. COVID-19 convalescent plasma (CCP) has been used to treat COVID-19 patients in many studies without any unexpected or major side effects.

Although, many early studies were observational and nonrandomized, and they were conducted in patients with severe or critical disease. They were complicated by the evolution of supplementary treatment interventions over time, such as steroids, antivirals, and other drugs; patient heterogeneity; and a lack of detailed analyses of neutralising antibody content of infused units. While many individuals recovered clinically, the function of CCP remained unclear after therapy with antivirals and/or corticosteroids. The relative risk of death was reduced in hospitalised but non-ventilated patients getting high-titer vs low-titer CPP in a retrospective investigation of a subgroup of these patients having data on the titer of neutralising antibodies in the given CPP [103]. However on 7th December 2021 in news release WHO has updated the living guidelines on COVID 19 therapeutics to include convalescent plasma therapy.

Allergies, transfusion-related circulatory overload, and transfusion-related acute lung damage are among known general dangers of plasma transfusion. Prior to deployment, other concerns about CCP included increasing immune-mediated tissue damage via antibody-dependent augmentation, blunting of endogenous immunity, and SARS-CoV-2 transfusion transmission. With CCP, none of these have been demonstrated [103].

Other passive immune therapies are available for COVID-19: For COVID-19, a number of passive antibody treatments

are available, including hyperimmune globulin (which can tenfold the neutralising antibody activity) and tailored monoclonal antibodies. Passive antibody therapy reduced virus shedding, symptoms, and hospitalizations, according to interim evaluations of early-phase clinical studies. The first, bamlanivimab, is a single antibody, while the second, casirivimab and imdevimab, is a grouping of two antibodies directed against the SARS-CoV2 spike protein [104]. However, NIH guidelines presently advise against using bamlanivimab and etesevimab owing to their ineffectiveness against developing SARS-CoV-2 virus strains now circulating throughout the world, and instead propose casirivimab, imdevimab, or sotrovimab, which are also licensed in the US under an EUA.

Monoclonal antibody treatment therapies: In a study found that giving bamlanivimab to senior nursing home patients and personnel quickly after being exposed to an infectious agent reduced the risk of illness and mortality. Further clinical trials of these and other purified or engineered antibody therapies are currently underway, with the majority of them concentrating on the treatment of very high-risk individuals who have not yet been PCR-positive, immunocompromised patients, or high-risk patients soon after a confirmed infection — settings more likely to benefit from any passive antibody therapy. The EUA for monoclonal antibodies in the United States restricts their use to non-hospitalized individuals who are at risk of severe illness or those who are hospitalised for other reasons and get sick. The use of intravenous antibodies in SARS-CoV-2 infected outpatients has been restricted due to logistical obstacles [105-107].

Conclusion

COVID-19 has not only created severe panic among the people but also challenged the social culture and healthcare infrastructure of the entire world. In order to fully understand the spread and evolution of the SARS CoV-2 virus, and to tackle its future spread, sequencing and analyzing the genomic data of SARS CoV-2 is essential. Prevention of transmission is seemed to be quite challenging with a population of India with deep dearth of preliminary awareness for disease identification followed by appropriate medical advice. In the last three years, clinically validated vaccines have exhibited potent efficacy in decreasing severe COVID-19 and mortality. Nevertheless, effective vaccines are still inadequate worldwide to stop the ongoing SARS-CoV-2 pandemic. Despite enormous efforts have been taken to provide efficient vaccines against SARS-CoV-2 and new variants, there are many difficulties to be resolved to arrest the pandemic. The regular mutations bring immune-escaping and breakthrough infection and less affected by presently available vaccines. Further follow up studies and more efficient vaccines are required to fight against the COVID-19. In this review we have discussed in detail the cause of COVID-19, virology, symptoms, diagnostic approaches, post COVID complications, different range of treatment regimen etc., and diverse vaccines for COVID-19 [108-118].

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