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Evolution and Virology of Coronavirus: An overview

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ABSTRACT: The present scenario clearly emphasizes the rapid emergence and transmission of the deadly virus named novel severe acute respiratory syndrome coronavirus-2, which has killed more than six million people and triggered profound disruption in the last two years. This review paper aims to analyze the complete morphology and the target sites of coronavirus-2019. Brief knowledge of the biological features of nCoV-2019 is essential with time because it helps to optimize the therapeutic care of infected patients. The collected information from the literature review about history, evolution, taxonomy, morphology, genome organization, pathogenesis, clinical manifestations, and risk factors of the coronavirus disease-2019 infection gives knowledge about drug target site and development of new chemical entities against coronavirus infections. The single-stranded RNA-based virus penetrates the host cell through transmembrane serine protease 2 (TMPRSS2) and Angiotensin-Converting Enzyme 2 (ACE2) receptor proteins, commencing transgression and exocytosis with the proprietor cell. The prime pathogenesis of Coronavirus-2019 targets and affects the breathing system and precipitates pneumonitis and RNAaemia in association with ground-glass attenuation and cardiac arrest. The membrane, spike, nucleocapsid, envelope, and hemagglutinin-esterase proteins act as target sites for natural products and synthetic drugs. The future research will be interdisciplinary and supranational. This review gives brief knowledge about pathogenesis and virus target sites, which we have more concentrated to discovered new chemical entities against various mutate variants of coronavirus and its infection.

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INTRODUCTION:

The prevailing pandemic of COVID-19 has affected the entire world in an invasive manner for the last two years. The first recognition of the pandemic was from the Wuhan city of China and witnessed the first case reported to WHO (World Health Organization) on 31st December 2019 of unidentified bronchopneumonia by the Municipal Health Commission of Wuhan to observe the growing infection deeply. The collected data submit, to WHO on 11th and 12th January 2020. There was a link between the seafood market and wild animals selling,

and it terminated on 1st January 2020 [1]. The beginning of the prominent symptoms took place on 1st December 2019. The manifestations of this disease are fever, dry cough, malaise, and shortness of breath which are identified as viral pneumonia and referred to as Wuhan pneumonia. The root cause of the infection was a novel coronavirus and confirmed by the research on the genetic sequences of the virus. It is the seventh member of the generation of coronavirus. On 12th January 2020, the virus was named novel coronavirus 2019 by WHO, followed by its standard or official nomenclature of COVID-19 (Coronavirus Disease-2019, on 12th February 2020). Afterward, the research on all its evolution, morphology, and accepted practice of viruses, according to ICTV (International Committee on Taxonomy of Viruses), termed Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [2]. The disease has announced as a Public Health Emergency of International Concern on 30th January 2020 and as a pandemic on 11th March 2020 by the World Health Organization (WHO) [1]. An overall analysis made by the WHO to reach one conclusion on 11th March 2020 that COVID-19 is a pandemic after 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 Pandemic flu (H1N1), leading to approximately the mortality of 50 million, 1.5 million, 1 million, and 300,000 humans, respectively [2]. The objective of the review paper is to analyze the complete pathogenesis, morphology, genome organization, clinical manifestations, and the target sites of coronavirus-2019. Brief knowledge of the biological features of nCoV-2019 is essential with time because it helps to optimize the therapeutic care of infected patients.

Evolution of Coronavirus:

The late 1930s mark the history of coronavirus. Avian coronavirus, known as avian infectious bronchitis (IB), is a respiratory disease of chickens. The house-trained hens were majorly affected by this virus and were first identified in the 1930s along with two other coronaviruses caused by animals. Enterotropic coronavirus is known as mouse hepatitis virus (MHV) [3] called B814, which is associated with the common cold in adults, identified in 1965 by Tyrrell and Bynoe [4-7]. Hamre and Procknow collected the fluid sample from medical students who were suffering from cold, and they initially cultured a virus and named given as 229E. The fluid on organ culture, Almeida & Tyrrell was prepared electron microscope, affected with organism B814 and noticed microbes which look similar to the contagious chickens (pathogenic virus of chicken causes bronchitis. In the year the 1960s, Tyrell and their Co-worker established a morphological resemblance between the zoonotic viral species and a novel coronavirus [1]. The virus infected the bronchial and gastrointestinal parts of humans and animals. From 2002 to 2003, the SARS (severe acute respiratory syndrome) seriously affected the humans in Guangdong territory, China. The virus produced minor complications for those who had strong immunity against the virus. After ten years of the interval of identification of SARS, another species of coronavirus known as Middle Eastern Respiratory syndrome was detected. The recognition of the pathogenic virus leading to SARS, afterward, the extended analysis of plants, animals, and wild civets, it has observed that the coronavirus strain was present in the wild civets and transferred to other animals. The two groups of SARS-CoV in humans are SARS-CoV-related viruses or SARS-like coronaviruses found in horseshoe bats (genus Rhinolophus). The discovery implicated those animals such as bats and civets could be the inherent and intermediate anchors for SARS-CoV respectively [8]. Successively, many coronaviruses having a phylogenetic connection with severe acute respiratory syndrome coronavirus were found in China and other countries through bats [9]. Based on the International Committee of Taxonomy of Virus (ICTV), the viral strains exclusively originate in several countries such as Southeast Asian countries, European countries, and China through Rhinolophus bats, which are SARS-CoV related viruses. The information implicates that SARSr-CoVs have a broad geographical span and may have retained a long period of 5 years in bats, explaining the presence of great divergence of SARSr-CoV in populations of bats in an antre of Yunnan territory of China. This place is a hub of the genetic heterogeneity of the SARSr-CoVs found in other regions of China. Even after 15 years of investigations, no direct progenitor of SARS-CoV was found in bat populations and as RNA recombination is common amongst coronaviruses, it becomes obvious that SARS-CoV has elevated via rejoin SARSr-CoVs in bats with other bat centers which are still there to be discovered [8].

Taxonomy of Coronaviruses:

The name “Coronavirus” has derived from the term ‘Crown-like or Corona-like morphology of the virus

exhibited under an electron microscope in 1968 [9]. The Coronaviruses (CoVs) belong to the family *Coronaviridae* and order *Nidovirales* according to the ICTV (International Committee on Taxonomy of Viruses) and two subfamilies *Coronavirinae* and *Torovirinae* [8, 10]. Based on their genomic arrangement and genealogical correlation, coronaviruses have been classified into the subfamily *Coronavirinae* that comprises of various genera such as Alpha-coronavirus (αCoV), Beta-coronavirus (βCoV), Gamma-coronavirus (γCoV) and Delta-coronavirus (δCoV) [9]. αCoV comprises human coronavirus NL63 (HCV-NL63), porcine transmissible gastroenteritis coronavirus (TGEV), porcine epidemic diarrhea virus (PEDV), and porcine respiratory coronavirus (PRCV). Beta coronaviruses comprises of severe acute respiratory syndrome- coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), bat coronavirus HKU4, mouse hepatitis coronavirus (MHV), bovine coronavirus (BCoV), and human coronavirus OC43. Gamma-and delta coronaviruses comprise avian infectious bronchitis coronavirus (IBV) and porcine delta coronavirus (PdCV). Presently seven Coronaviruses have been identified to infect humans. Specifically, these viruses are Human CoVs (HCoVs) which are HCoV-NL63, and HCoV-229E derived from alpha-coronavirus genera and HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 derived from beta-coronavirus genera. Excluding SARS-CoV, MERS-CoV, and SARS-CoV-2 the rest four out of these seven HCoVs lead to mild respiratory complications in humans [11, 12]. Evolutionary pattern studies of coronaviruses have shown that αCoV and βCoV have an animal origin from bats and rodents, while γCoV and δCoV have their beginning from avian species. The potential of CoVs to overcome the species barrier has produced few pathogenic CoVs [10]. HKU1, NL63, OC43, and 229ECoVs are linked with mild manifestations in humans, whereas severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) lead to serious illness [9].

Structure and genome organization of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2):

The virus is spherical shaped, non-segmented, possesses an envelope, and has a small size, and the range of diameter is 65-125nm possessing a positive-sense single-stranded RNA genome [2, 13, 22]. The virus contains uniform and a linear-shaped single strand of RNA with a length of 29 903 base pairs [14]. The virus on its surface contains spikes and has a large genome among all RNA viruses, characteristically in the range of 27 to 32 kb genome and a distinctive method of replication [1, 12]. The viral units of SARS-CoV-2, structurally similar to RaTG13-coronavirus [15]. The genomic RNA consists of structural proteins such as membrane proteins (M), spike proteins (S), nucleocapsid (N) proteins and envelope (E) proteins, and hemagglutinin-esterase (HE). All the proteins have specialized and specific roles. S proteins are the most significant proteins, which give rise to homotrimeric spikes (S1 and S2) that promote pathogenesis after attaching to the Angiotensin-converting enzyme 2(ACE2) receptor present on the type II pneumocyte. Membrane and E proteins combined to give the configuration of the viral structure and arrange the viral congregation. The hemagglutinin-esterase protein has similar features to influenza virus hemagglutinin and maintains the acetyl esterase activity. This protein is also responsible for the entrance and pathogenesis of CoVs. The genomic studies reveal that these proteins have encrypted at the 3' end of SARS-CoV-2 RNA [11]. The coronavirus gene contains 6–11 open reading frames (ORFs) encrypting 9680 amino acid polyproteins. The first ORF spans have about 67% of the genome that encrypts 16 nonstructural proteins, and the rest of the ORFs encrypts accessory and structural proteins [15]. The genome of SARS-CoV-2 is devoid of the hemagglutinin-esterase gene [10]. But it contains two fringing untranslated regions (UTRs) at 5′ end of 265 and 3′ end of 358 nucleotides. Genomic interpretation of SARS-CoV-2 shows that it has a zoonotic emergence (Fig 1) [9].

Morphology of SARS-CoV-2:

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) is a beta-coronavirus that is the causative agent for Coronavirus disease. The seventh number coronavirus infects human beings throughout the world, and it follows SARS-CoV-1 and MERS, which boosted to produce both the epidemic and had pandemic situations [15]. SARS-CoV-2 extracted from nasopharyngeal and oropharyngeal samples were inoculated on the Vero cells. For the recognition of SARS-CoV-2, the inoculated cells are adhered by using 2 % paraformaldehyde and 2.5 % glutaraldehyde, and transmission electron microscopy has been executed. The structures of SARS-CoV-2 has noticed by testing

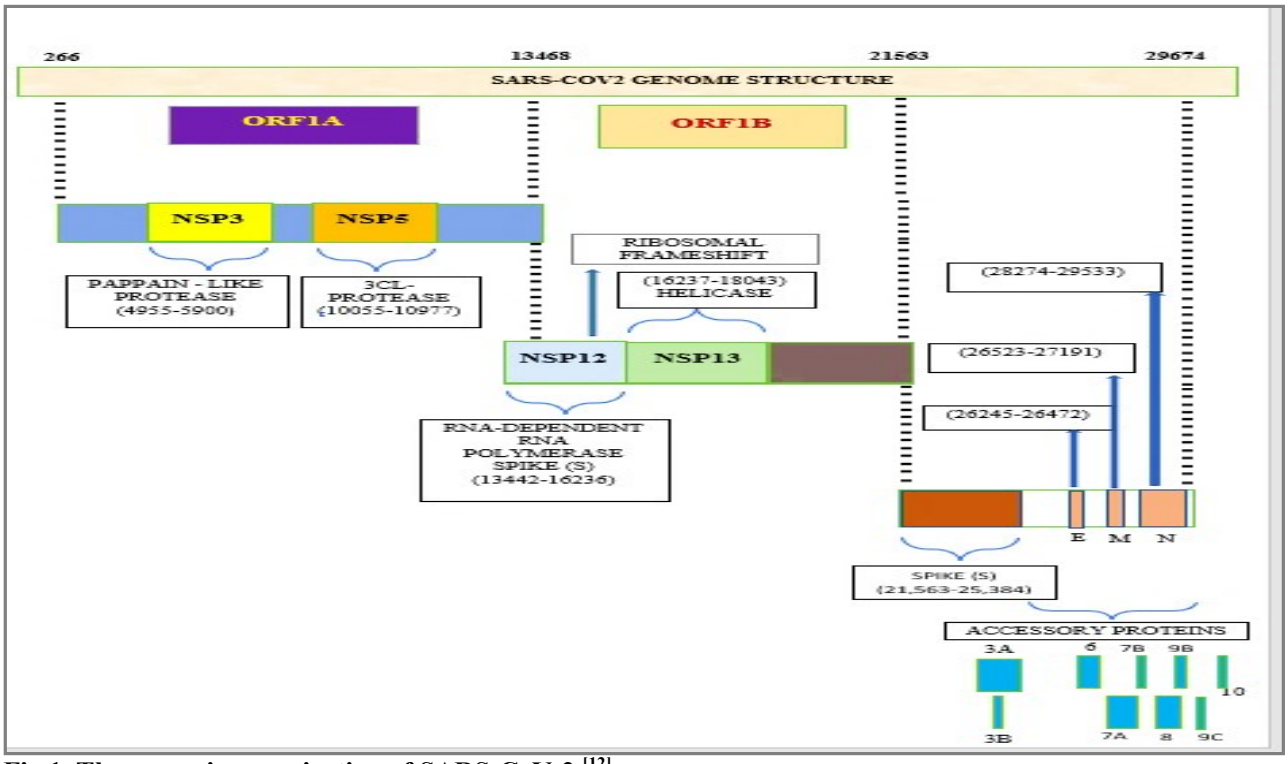

Fig 1. The genomic organization of SARS-CoV-2 [12].

the infected cells after three days of the occurrence of the infection. Electron microscopy depicted the coronavirus-specific morphology of SARS-CoV-2 with virus particles that had sizes in the range of 70 to 90 nm visible under different types of intracellular organelles, more particularly in vesicles. With the highest sequence resemblance, the structure of SARS-CoV-2 has anticipated to be the same as SARS-CoV. The viral proteins of the coronavirus spike, membrane, and envelope are incorporated into the host membrane-derived lipid bilayer enclosing the helical nucleocapsid constituting viral RNA [9]. Each viral transcript consists of a 5′-cap structure and a 3′ poly (A) tail [15]. One single virion has a diameter of 50 to 200 nm [18]. Generally, the virion of coronavirus-2 possesses around structure along with ductal and ovate shapes are also found (Fig 2) [9,10].

Replication mechanism of severe acute respiratory syndrome coronavirus-2:

COVID-19 virus is an intracellular microbe whose replication and development are happened in the host cell. The virus enters the host cell through the transmembrane S glycoprotein. The pathogenesis of SARS-CoV-2 depends on the host cell containing receptors and protease enzymes. The ACE-2 is the responsible receptor for the development of viral activity [15]. COVID-19 is a beta coronavirus that exhibits approximately eighty percent sequence similarity with Severe Acute Respiratory Syndrome Coronavirus and fifty percent with the Middle East Respiratory Syndrome coronavirus.

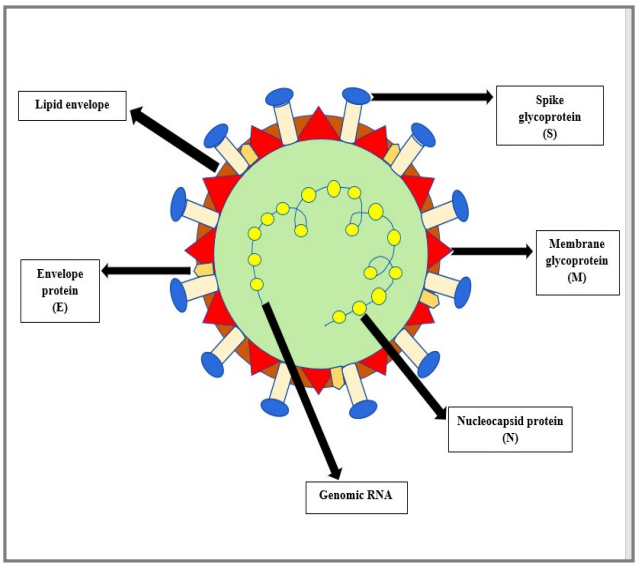

Fig 2. Structure of SARS-CoV-2: SARS-CoV-2 comprises surface viral proteins, which are: spike glycoprotein (S), the viral membrane glycoprotein (M), an envelope protein (E), and nucleocapsid protein (N) and lipid envelope encapsulating the viral genomic RNA of SARS-CoV-2 [9].

The angiotensin-converting enzyme-2 (ACE-2) is the cell surface receptor of epithelial, alveolar, endothelial, kidney cells, monocytes, neurons, and neuroepithelial cells where SARS-CoV-2 is attached and enters the host body [16]. Substantially the human angiotensin-converting enzyme 2 (hACE2) receptor is the receptor for SARS-CoV-2 via identification of its 'spike' (S) glycoprotein, with successive priming by the transmembrane serine protease-2 and lysosomal cathepsins [17]. The viral spike (S) protein is attached to ACE-2 host cell surface receptor and separated by Cathepsin or furin, transmembrane protease serine-2, which facilitates endocytosis and produces endosome through SARS-CoV-2 translocation otherwise, the viral envelope is directly merged into the host cell membrane [16]. ACE-2 is a carboxypeptidase (zinc metalloprotease) and an analogy of dipeptidase angiotensin-converting enzyme (ACE) [15]. This surface protein contains a unique furin-cleavage site between the S1 and S2 subunits and corresponds to a homologous domain in the human epithelial sodium channel α-subunit [17]. As the SARS-CoV-2 S protein is very much glycosylated and resides mainly in a closed perfusion configuration, pre-activation of the S protein by furin protease is known as the receptor-binding domain [18]. Virus receptor binding affinity is essential due to spike (S) glycoprotein and ACE2 receptor [11]. Research work has proved that SARS-CoV-2 has a higher affinity to ACE-2 than SARS-CoV [29]. Spike (S) glycoprotein splits into two sub-units, S1 & S2, which help ACE2 for viral fusion via cell membrane [9]. After pathogenesis within the host cell, RNA is synthesized and translated into polymerase proteins. Eventually, negative-sense RNA is generated and acts as a template for the genesis of sub-genomic positive-sense RNA. RNA and nucleocapsid (N) proteins replicate and translate within the cytoplasm, and other proteins such as S, M, and E undergo translation in the endoplasmic reticulum (ER) and subsequent translation and transit to the Golgi apparatus. These, S, M, and E proteins are then assembled in the ER-Golgi intermediate region (ERGIC) to generate fully developed virions, which are liberated from the host cell [11].

Pathogenesis of SARS-CoV-2:

The virus is the primary causative organism for the pathogenesis of COVID-19 infections. It affects the respiratory system and precipitates severe pneumonia and RNAaemia, the combinations of ground-glass opacities, and acute cardiac injury. The pathological study of SARS-CoV-2 gave information that it affected patients more seriously than SARS-CoV and MERS-CoV. The COVID-19 infected patients manifested with high leukocyte counts, unusual respiratory results, and elevated levels of plasma pro-inflammatory cytokines. The peripheral blood samples were analyzed by flow cytometric. The decreased level of CD4 and CD8 cell counts with hyperactivated as a large amount of dual positive (HLA-DR and CD38) was observed. The laboratory investigations revealed leucopenia with leukocyte counts of 2.91 × 109 cells/L, out of which 70.0 % were neutrophils. Liver biopsy of patients infected with SARS-CoV-2 displayed moderate microvascular steatosis and mild portal and lobular activity, implicating that the injury may be due to the virus or drug potentiated. Remarkably increased blood levels of cytokines and chemokines in patients with COVID-19 infections are IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some interstitial mononuclear inflammatory infiltrates are found in the heart tissue. Furthermore, an unusual level of 16.16 mg/L of blood C-reactive protein was more than the usual level (0 to 10 mg/L). Increased erythrocyte sedimentation rate and D-dimer were also observed. These pathological findings may give new cognizance about the pathogenesis of pneumonia caused by SARS-CoV-2, which would benefit doctors and health care professionals were successfully handle the COVID-19 infected patients [9, 30].

Clinical Manifestations of COVID-19:

The clinical manifestations of COVID-19 pneumonia in adults include fever, dry cough, sore throat, headache, fatigue, myalgia, and breathlessness. The overall incubation period of about five days (range: 2-14 days) follows the onset of characteristics of COVID-19 infection with dry cough and low-grade fever (38, 1 to 39 °C or 100, 5 to 102,1°F) often accustomed to depletion of smell and test. The disease complications in the infected patients vary from mild pneumonia (81 %) to moderate pneumonia (hypoxia that needs hospitalization, 14 %) and severe complications (leading to invasive mechanical ventilation, multi-organ malfunction, and probably death, 5 %). The infection of COVID-19 is mild to moderate in some patient cases. In most patients, the effect of COVID-19 is mild to moderate, and symptoms are observed within a week. The patient's recovery at home is possible with proper

care. The more the time the manifestations retain, the greater the possibility of developing critical COVID-19 that needs hospitalization, intensive care, and invasive ventilation [19, 20].

Many symptomatic patients have influenza-like symptoms such as fever, respiratory symptoms (cough, sore throat, and nasal discharge), headache, and malaise. The olfactory and gustatory disturbances, influenza-like symptoms, may represent coronavirus disease 2019 [21, 23]. The various co-morbidities such as cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, and malignancy lead to the severe threat of COVID-19 infection [24]. The clinical manifestations of infection are arthralgia, olfactory disturbances, chest pain, dry eyes and mouth, conjunctival hyperemia, rhinitis, phlegm, anorexia, dizziness, diarrhea, etc. [18]. The severe respiratory complications precipitated as alveolar and intestinal pneumonia [19, 20]. The COVID-19 Registry-Japan (COVIREGI-JP) registry of COVID-19 patients with hypertension, diabetes, liver disease, renal dysfunction, obesity, and hyperlipidemia produced more harmful health conditions in inpatient cases than patients without co-morbidities [25]. Neuroinvasive propensity has been displayed as a common characteristic of human coronaviruses. There are various sequences of discrete neurological complications like Guillain–Barré syndrome, myasthenia gravis or Miller Fisher Syndrome, and polyneuritis cranialis (PNS) [20]. The cardiovascular system is also targeted, with conditions like myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events [22]. Patients might also suffer from a hyper-inflammatory condition that can cause multi-organ failure [23]. Anomalous coagulation and microthrombi are a characteristic of COVID-19 infections in as many as 31% of ICU patients suffering from thrombotic complications that may cause a stroke. Hepatic complications like acute hepatic injury have also been critical of the risks and lethal consequences (Fig 3) [24,25].

Modes of transmission of Coronavirus:

The COVID-19 virus is chiefly conveyed between people using respiratory droplets and contact routes [26] SARS-CoV-2, the virus that leads to COVID-19, is transmitted from an infected individual to others by respiratory droplets and aerosols when an infected person inhales, wheezes, sternutate, sings, screams, or speaks [27]. Respiratory infections can spread through droplets of various sizes: droplet particles having diameters more than 5 to 10 μm are called respiratory droplets, and those with diameters less than 5μm are called droplet nuclei [28,29]. Air can be an essential source of spreading the SARS-CoV-2 virus, particularly in hospitals, shops, schools, and public transport. Some individuals are “super spreaders” who generate overall aerosol particles than others. The micro range diameter of the particles is very minute, and they are taken away by airflow and scattered through air turbulence and diffusion process [30]. The danger of transmission is influenced by various factors such as contact mode, surroundings, the infectiousness of the host, and socioeconomic attributes, as explained anywhere [31]. Airborne spreadability of SARS-CoV-2 can arrive during medical operations that produce aerosols (“aerosol-generating procedures”) [28]. Its contact spreadability from surfaces and objects infected by the virus, where these can stay for many hours and days and can cause contamination [29]. Most transmissions are carried out by proximity, within households, and through the congregation of family and friends [28]. Moreover, Penghui Yang and Xiliang Wang, on 11th February 2020 submitted that the severe acute respiratory syndrome of coronavirus-2 has been identified in the fecal matter of infected patients, which polluted aquatic environment and leads to a fecal-oral mode of spreadability (Fig 4) [32,33].

Risk factors for developing COVID-19 infection:

The risk of manifestations of covid-19 infection might get elevated in elderly persons or any age group suffering from other critical health conditions like cardiovascular and pulmonary complications, debilitated immune systems, obesity, or diabetes [34]. The highly recurrent demographic factor contributing to the development of criticality of the disease is increased age, male gender, post-menopausal, and age factor in females [35]. Smoking, high body mass index (obesity), and a prolonged waiting duration for hospital admission are lifestyle factors concerned with a greater possibility of suffering many complications [36]. Alcohol damages the body’s potential to combat infections such as COVID-19, and even a single large amount of drinking can significantly decrease the proper working of the immune system [34]. The incidence of lymphopenia and eosinopenia are laboratory indicatives of COVID-19. Severe hepatic and renal complications, cancer, and the profession of healthcare workers are considered risk elements of criticality [37].

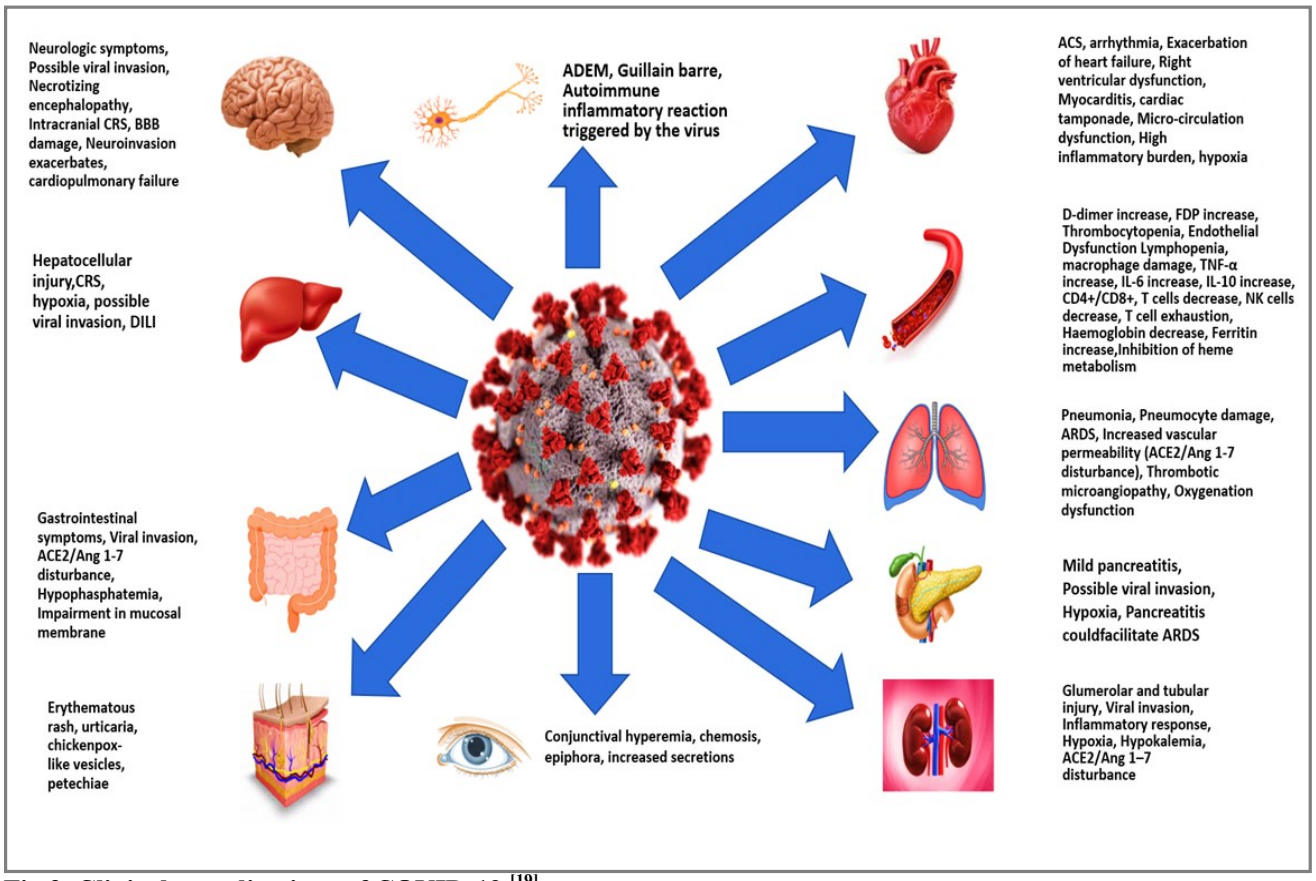

Fig 3. Clinical complications of COVID-19 [19].

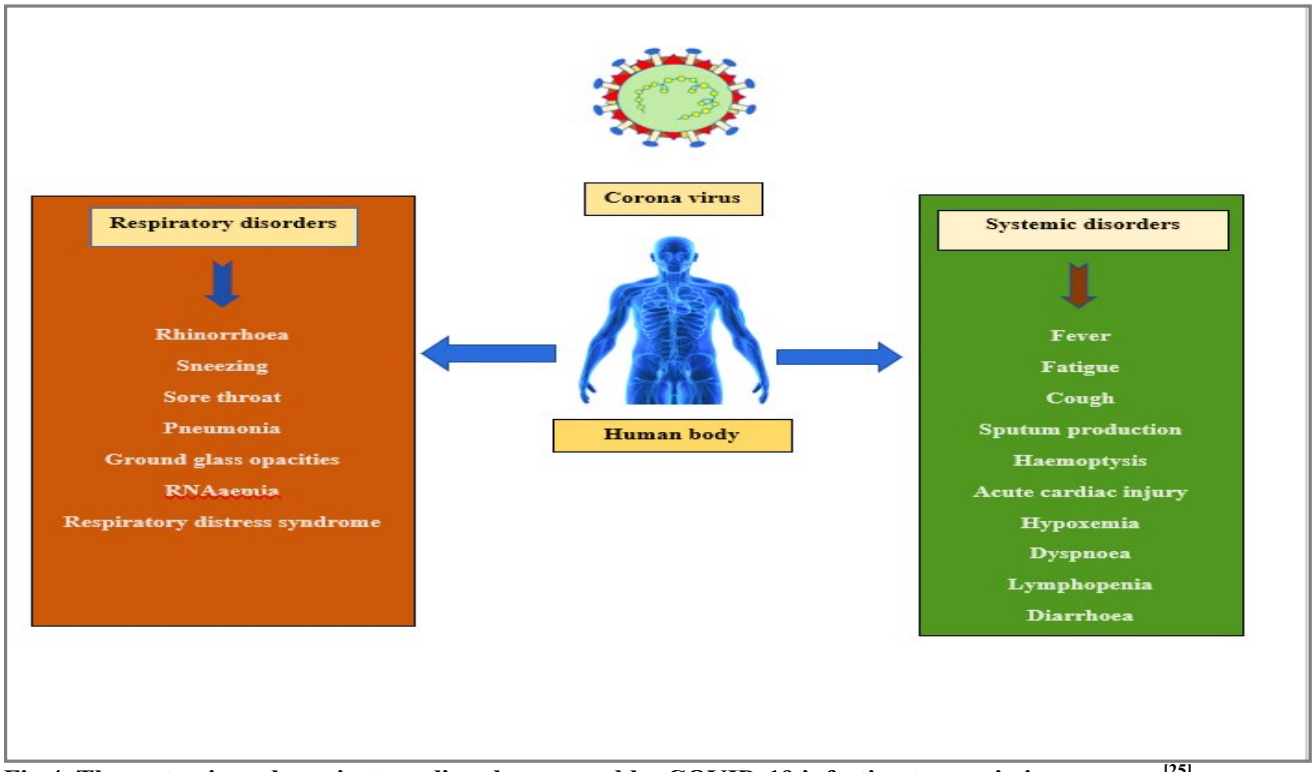

Fig 4. The systemic and respiratory disorders caused by COVID-19 infection transmission process [25].

CONCLUSION:

The viral respiratory infection continues to be one of the most common human illnesses and concentration on new drug development for contagious viral infection is a challenging task today which is to be addressed with regular and dedicated approaches. The above information about the history, evolution, taxonomy, morphology, genome organization, pathogenesis, clinical manifestations, risk factors, and symptoms of the coronavirus disease-2019 infection gives knowledge about pathogenesis and virus target sites and we have to more concentrate to develop new chemical entity against various mutate variant of coronavirus and its infection.

The coronavirus is a very deadly and dangerous virus that is infecting people at a very rapid rate and has proven to be fatal to human life. The studies regarding the morphology, pathogenesis, and genome organization are still being performed to explore new facts regarding this virus and develop effective measures to treat COVID-19 infections. The virus has still not been completely eradicated despite the treatment and therapies given to the patients. So, we need to follow certain precautionary measures like wearing masks, using sanitizers, and maintaining social distancing in order to protect ourselves from the harmful effects of this disease. We need to be socially and medically aware of this and should not delay visiting the doctor if we face any of the symptoms like prolonged coughing, breathlessness, loss of taste and smell sensations, fever, etc.

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