

Available online at [GSC Online Press Directory](https://www.gsconlinepress.com/)

GSC Biological and Pharmaceutical Sciences

e-ISSN: 2581-3250, CODEN (USA): GBPSC2

Journal homepage: <https://www.gsconlinepress.com/journals/gscbps>

(REVIEW ARTICLE)

A review on SARS-CoV-2: the origin, taxonomy, transmission, diagnosis, clinical manifestations, treatment and prophylaxis

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Publication history: Received on 27 May 2020; revised on 09 June 2020; accepted on 11 June 2020

Article DOI: <https://doi.org/10.30574/gscbps.2020.11.3.0156>

Abstract

Coronavirus disease 19 (COVID-19) pandemic, caused by highly contagious SARS-CoV-2 that infects the respiratory system. COVID-19 started in Wuhan, south China, in December 2019, and spread to all other parts of the world. SARS-CoV-2 has +ssRNA genome (29,844bp) enclosed in an enveloped capsule (60 to 140 nm) and showing high genome homology (96%) with coronavirus of its potential natural reservoir Horseshoe bats. Two types of SARS-CoV-2 were detected: type L (70%) and type S (30%). SARS-CoV-2 spikes have very high binding affinity with all cells expressing ACE2 receptor. Nasal swabs and bronchoalveolar lavage samples were used by reverse transcriptase rtPCR for detection of SARS-CoV-2. ELISA can detect anti-SARS-CoV-2 IgM and IgG antibodies five days post infection. COVID-19 infection is confirmed by clinical signs and symptoms and CT thoracic images. Patients typically present with fever (87.3%), cough (58.1%), dyspnea (38.3%), muscle soreness or fatigue (35.5%), chest distress (31.2%) and expectoration (29.4%). The fatality rate of the infection approaches 7%. Hundreds of lungs micro clots were reported to occur causing heart failure and death. Fatal consequences were reported in older patients and those with chronic diseases. There is no specific medicine, but supportive treatment and anticoagulants are in use. Chloroquine and azithromycin have fatal consequences in 50% of patients, while Remdesivir did not show significant clinical or antiviral effects. Plasma convalescence clear the infection within three days. There is no vaccine for SARS-CoV-2 due to its mutations. Social isolation and countries lockdown measures exert catastrophic negative impact on health and economy worldwide.

Keywords: Coronavirus; SARS-CoV-2; COVID-19; Spike S; ACE2; Horseshoe bat; rtPCR; transmission; fever, lungs micro clots; acute respiratory distress; plasma convalescent; Chloroquine.

1. Background

1.1. Coronaviruses epidemics and pandemic

1.1.1. SARS – severe acute respiratory syndromes-2002—2003 SARS-CoV

SARS epidemic started in Guangdong, southern China November 2002. The epidemic was caused by a newly emerged Betacoronavirus SARS-CoV. During that epidemic, ≥8000 patients were infected, and 774 of them died in 37 countries. Horseshoe bats and civets (*Paguma larvata*) were the natural reservoirs [1, 2, 3, 4, 5].

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1.1.2. MERS- Middle East Respiratory Syndrome 2012- MERS-CoV

MERS-CoV was first diagnosed in September 2012 in Jeddah at Kingdom Saudi Arabia. It infected 2494 patients and killed 885 patients, 38 of them were from South Korea. MERS was regarded as being more fatal than SARS (37% versus 10%). Its reservoir was widely believed to be the bats and the Arabian dromedary camel-*Camelus dromedarius* [6].

1.1.3. COVID-19 Pandemic – Coronavirus Disease 2019 -2020- SARS-CoV-2

COVID-19 is pandemic because it is infectious and occurring on a huge scale that crosses international boundaries and continents and affects large numbers of people. This pandemic started in China in 15 December 2019. COVID-19 pandemic is escalated exponentially, as it spreads like iceberg. The Phylogentic analysis of the virus genome suggested that it is zoonotic and that bats might be the original reservoir host of this new Betacoronavirus - 2019-nCoV - as it is more genetically related to Betacoronaviruses of horseshoe bats [7]. This coronavirus spread swiftly to all nations of the world, and still continues in spite of all isolation and controls measures. By April 18, the pandemic had infected 2,250,119 patients and killed 154,241, and overwhelmed Europe and the USA. One month later on 23 May the numbers doubled 5,080,000 infected and 332,000 deaths. On 8.6.2020 the number reached 7,148,341 with 407,436 deaths. COVID-19 has exciting disastrous negative impacts on human health and world economy.

2. Emergence and epidemiology of Coronavirus

Emergent viruses appear to have mysteriously altered or changed their behaviours with time, with significant effects on their pathogenesis. New pathogenic viruses emerge as a result of changes in human activities and direct contact with wild animals. Zoonotic emergent viruses breached or broke through the interspecies transmission barrier and transmitted from animals to human [8]. This could explain the potential disastrous consequences of epidemics and pandemics. Massive and unexpected epidemics have been caused by certain viruses over past decades; examples: SARS, Bird Flue-H1N5, Swine Flue –H1N1, MERS, Ebola, etc.

2.1. COVID-19

The current Coronavirus pandemic (SARS-CoV-2 or COVID 19 (respiratory pneumonia), started on December 15, 2019 in Wuhan City, Hubei Province, south of the People’s Republic of China. It is associated with Huanan seafood and live animal wholesale markets such as bats in Wuhan. COVID 19 is a zoonotic disease transmitted from animal to animal, from animal to human and finally from human to human. Underestimation and lack of information, recognition and treatment experience delayed the control measures in the World resulting in the current devastating pandemic. On March 11, 2020, WHO declared COVID 19 caused by SARS-CoV-2 outbreak as a pandemic [9]. Within 70 days the disease overwhelmed the entire world occurring in about 210 countries. The number of victims approached 458,000 patients by the end of March 25, 2020; most of the patients were from Europe (Italy, Spain, Germany and UK), China and USA. Two weeks later on 6th of April, Wikipedia showed that confirmed COVID-19 cases worldwide (208 territories) reached 1,272,737 cases of which 69,418 died and 261,485 recovered. The pandemic cases reached 336,537 in USA, 131,646 in Spain, 128,948 in Italy, 100,123 in Germany, 81,669 China, 70,478 in France, 58,226 in Iran and 47,806 in the United Kingdom. On 20th January the first SARS-CoV-2 (COVID-19) case was confirmed in USA. On 10th April 2020, the number of cases reached 469,121 with 16,688 deaths [10]; on 18th April the number rose to 2,250,119 with 154,241 deaths and on 29th April 2020, it reached 3,138,115 patients with 217,970 deaths (7% fatality rate). On June 7, 2020, the number reached 6,731,793 with 393,721 deaths.

3. Taxonomy of Coronavirus

3.1. Coronaviridae

"Corona" in Latin means "halo" or "crown". The diameter of the Coronaviruses' capsid envelope ranges from 50 to 200 nanometres. Its enveloped surface is covered with crown -like spikes or petal-like projections (peplomers), 12-24nm long, arranged in a characteristic fringe giving the appearance of a crown (corona), from which the family derives its name [11]. The Family Coronaviridae of the order Nidovirales (nested viruses) is composed of +ssRNA enveloped spherical viruses, and comprises four major genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus [12,13,14]. Six Human Coronaviruses – HCoV - were identified. The most important ones belonged to genus Betacoronavirus (order Nidovirales; suborder Cornidovirineae; family Coronaviridae; subfamily Coronavirinae; subgenus Sarbecovirus; SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East Respiratory Syndrome) [5,15,16].

3.2. SARS-CoV-2

Chinese researchers sequenced the complete genome of this novel human coronavirus and named it 2019-nCoV. The International Committee on Taxonomy of Viruses (ICTV) designated the aetiology of COVID 19 as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [11, 12, 13, 17, 18, 19, 20, 21, 22]. SARS-CoV-2 is a strain of the species SARSr-CoV (Severe acute respiratory syndrome-related coronavirus, previously known as 2019-nCoV novel coronavirus [23, 24]. The genome of SARS-CoV-2 (29,844bp) has the closest similarity (96.2%) to SARS-like bat CoV (RaTG13), this confirms the virus origin [18, 7]. Comparative genome sequence analysis showed that SARS-CoV-2 is not genetically engineered or a laboratory construct or manipulated [25]. Genotypic analysis of 558 SARS-CoV-2 revealed that the virus evolved through frequent multiple specific mutations in gene encoding; the S proteins, replicase, RNA polymerase and nucleoproteins [26, 27].

4. Virus genome, replication and assembly

Human Coronaviruses (HCoVs) have the longest complex RNA genome (26 to 32Kbp). Coronaviruses have a linear, non-segmented, positive sense single-stranded RNA genome (group IV +ssRNA) [8]. Their genome encodes 15 genes for structural (n, 4) and non-structural and accessory proteins (n, 11). The structural genes encode four viral proteins; S (Spike), E (Envelope), M (Membrane) (the three together create the viral Glycoprotein envelope) and N (Nucleocapsid; Phosphoprotein hold the +ssRNA genome) proteins. The non-structural open reading frame genes ORF encode these proteins: ORF; 1a, 1b, 3a, 3b, 6, 7a, 7b, 8a, 8b, 9b, 10 [28, 29, 30]. Orf1ab encodes replicase/transcriptase, which replicates its genome and may have effect on virus pathogenicity and virulence [31, 32]. Non-structural proteins were encoded by SARS-CoV-2; papain-like protein, 3Cl-protease, replicase, Helicase, and spike.

Coronaviruses did not pack their replicative enzyme - replicase – RNA polymerase (RdRp) [33, 13]. Replicase did not have proof reading and induces error borne mutations during replication throughout the genome [27]. Its genome with 5' terminal cap and a 3' terminal poly A-Adenine end functions as mRNA. Their +ssRNA genome is translated in the cytoplasm by cell ribosomes into replicase and other viral replicative proteins. Coronaviruses are assembled in the cytoplasm, mature and bud from the lumen of the endoplasmic reticulum and Golgi apparatus intermediate compartments - ERGIC [34,4,11,8]. HCoV genome evolves through recombination, mutation, and gene gains and losses and adaptive events that emerge new viral species and strains and contribute host shifts [13, 33]. For recombination to occur, the two divergent viruses must have infected the same organism simultaneously. The genome of the new coronavirus is highly similar and homologous to bats coronavirus, and also to other human SARS viruses in homology [7]. The diameter of SARS-CoV-2 virus particle ranges from 60 to 140 nm, its distinctive spikes are about 8 to 12 nm in length [31,35]. NSPs data showed that two SARS-CoV-2 types may coexist: the more prevalent (70%) or major type - L (Leucine) with highly faster transmission rate and the minor (30%) ancestral type –S (Serine) [31].

5. SARS-CoV-2 receptor binding domain-RBD and host cell receptor- ACE2

COVID-19 etiological viral agent evolved through many pathways as frequent mutations. SARS-CoV-2 pathogenicity, virulence and uncontrolled spreading and transmission from human to human might be related to its proteins Spike glycoprotein, ORF8 and ORF3 that have some variations from other SARS –like CoV [36]. The spike surface glycoprotein S of SARS-CoV-2 has two domains S1 and S2. S1 subunit for binding with ACE2 and S2 subunit for fusion of virus and cell membrane [27, 7].

Spike receptor binding domain-RBD was optimized for virus attachment and more than 10 to 20 times stronger binding than other SARS-CoV, with receptors on epithelial host cell membrane ACE2 - Angiotensin Converting Enzyme 2 receptor [37,38,39,40,41,42]. ACE2 is expressed in lungs (type 2 alveolar cells), heart, kidneys, gastrointestinal tract (ileum), bladder and immune cells [43, 44]. The SARS-CoV-2 spikes contain a mutated variable receptor-binding domain (RBD) that binds with ACE2 facilitating viral entry into target cells [43]. ACE2 is also expressed more in males than females and in smokers than non-smokers [41]. The virus S protein determines host tropism and transmission as a result of natural evolutionary selection via recombination and mutation [45, 17, 46, 25, 47]. Spike glycoproteins promote entry and invasion into the cell and are the main target of antibodies [50]. The cells of the respiratory tracts show very high expression of ACE2 in addition to salivary glands epithelial cells [48, 36].

SARS-CoV-2 is attached to ACE2 and effectively uses it for fusion and endocytosis of pulmonary cells. SARS-CoV-2 has a very high binding affinity with ACE2 [44, 49, 50]. The ACE2 encoded by a gene in the X chromosome in locus Xp22.2 [51, 52]. ACE-2 is a type 1 transmembrane metallopeptidase that normally degraded angiotensin II to modulate rennin-angiotensin system (RAS). The viral S protein binding with ACE-2 receptor is dependant on S protein priming by a serine protease -TMPRSS2 [50].

6. SARS-CoV-2 natural and intermediate reservoirs

Reservoirs are wild animal species, which naturally carry one or several viruses asymptotically due to their effective immune system. Coronaviruses infect humans and vertebrates, especially their respiratory tract, gastrointestinal organs and neurological tissues. SARS-CoV and MERS-CoV were transmitted directly to human from bats, civet and dromedary camels, respectively [43, 53].

6.1. The horseshoe bats - *Rhinolophus affinis*

Genomic and proteomic analysis data confirmed that this aggressive fast spreading virus emerged from wild animals' reservoir in nature. The Coronaviruses in bats are diverse. Moreover, 96% of horseshoe bats tested positive for Coronaviruses [54]. The genome sequence of SARS-CoV-2 was very similar to three Coronaviruses isolated from certain cave species of bats in Yunnan – China [44, 20, 21]. These three strains of bat viruses (Bat-SL-CoVZC45, bat-SLCoVZXC21 and Bat-CoV RaTG13) were isolated from the horseshoe bats *Rhinolophus affinis*. The Horseshoe bats were incriminated as the potential reservoir for SARS-related Coronaviruses [54]. The genomes of these bats' Coronaviruses were highly similar (88—92%) to SARS-CoV [44, 54, 55].

6.2. Malaysian pangolins - *Manis javanica*

The Malaysian Sunda pangolins are scaly long-snouted ant-eater mammals- Order Pholidota- Family Manidae. Their delicacy meat is used in China as food and their keratin scales for traditional medicine virtues (600US Dollar per kilo). *Manis javanica* was incriminated as the intermediate host for SARS-CoV-2 [56]. The genome sequence of one β CoV (Pangolin CoV), isolated from pangolin, is 99% similar to SARS-CoV-2 genome [57, 44, 32]. The highest genome homology of SARS-CoV-2 spike was confirmed to be with Pangolin CoV; GD Pangolin SARSr-CoV, then GX Pangolin SARSr-CoV [32]. The genomes of Coronaviruses Pangolin- CoVs, demonstrated a high homology with Bat CoV - RaTG13 (90.55%), and with SARS-CoV-2 (91.02%) [32].

6.3. Masked palm civet - *Paguma larvata*

COVID-19 epidemic was linked to bats and pangolin, and other wildlife such as snakes may also have a role in this pandemic [3]. Another small cat-like mammals closely related to the mongoose, the masked palm civet (*Paguma larvata*), may also be involved. The virus might be transmitted to humans as they raised and slaughtered these civets rather than by consumption of their infected meat. The civet cat might be an intermediate host between man and bats [32].

7. Diagnosis of COVID-19

Diagnosis is very important to identify persons infected with SARS-CoV-2 and to control the pandemic. Diagnosing the disease in asymptomatic carriers is also essential to prevent unchecked social transmission in the community and to treat carriers. Isolation of persons returning from COVID infected countries is also important. The magnitude of this pandemic is still unknown due false negative diagnostic results that may lead to a false sense of security. Diagnosis is the rock stone in the identification of patients, treatment follow up and proof of cure. Mass testing may have mitigated the pandemic in South Korea [58]. On the other hand, some cured patients in China were re-infected, which may suggest that no immunity was acquired and shed double on vaccination usefulness [31].

Real time reverse transcriptase rtPCR is the most sensitive automated RNA-based molecular diagnostic method for the detection of SARS-CoV-2 RNA [59]. Its results are totally dependent on the quality of the right clinical respiratory sample collected (e.g. oro/nasopharyngeal swab (60 to 75% sensitive), sputum or BALF- bronchoalveolar lavage [60]. PCR calibration, operation and interpretation of results should be adopted with great care by highly experienced staff [61].

ELISA could be used to detect antibodies (IgG and IgM) against coronavirus in whole blood, plasma or serum samples. It will give positive results 5 to 10 days post infection. IgM appears first after initial exposure, and IgG appear later in abundance [62, 63].

Many people with negative results might actually get sick later, and those people may be more infectious before becoming ill. No diagnostic test has 100% reliability or sensitivity and specificity; hence false results may occur and should be handled with great care. The test should be done at least twice a week apart with many samples; also the results should be verified by other confirmatory tests. Clinicians should rely mainly on patient's symptoms, exposure history and imaging, in addition to other lab work [62].

8. Transmission

8.1. Means of transmission

During winter SARS-CoV-2 (COVID-19) spread in the northern hemisphere, where it overlapped with influenza-like illnesses, which highly complicated and increased uncontrolled pandemic transmission. Patients shed viruses in all body secretions. Now SARS-CoV-2 is more transmissible from human to human and may continue to evolve to become even more virulent; currently, its fatality rate has reached around 7% [63]. COVID-19 is a highly infectious pathogenic airborne disease that spreads through the respiratory system, from direct contact with patients or via their respiratory droplets and excretions; biological aerosols, droplet inhalation, itching [64], cough, sneeze, mucus, saliva, nasal discharge, fomites, ocular fluid and through breathing and talking, or touching virus contaminated surfaces. Cough and sneezes create turbulent clouds of gas that can propel respiratory particles forward. Other probable sources are contact with oral, nasal, and eye mucous membranes (conjunctiva and eye-lid), faecal contamination and urine. The asymptomatic incubation for COVID 19 ranges from 5 to 14 days and the patients may have high viremia and spread the disease. The patients (10% tested positive) and asymptomatic cases (50%) are highly infectious. The basic reproduction number (R_0) was estimated to be 2, meaning that each infected person transmits the virus to an additional two persons [65].

8.2. Healthcare providers

Healthcare providers are highly exposed to risk, thousands of them being infected, and hundreds die due to shortage of personal protection equipments even in Europe. Dental professionals are at great risk, due to frequent direct or indirect contact with human fluids, patient materials, and contaminated dental instruments and surfaces making possible routes to the spread of viruses [66]. Clean dry dental clinics will minimize virus persistence. Personal protective measures for the dental professionals, mouth rinse before dental procedures, rubber dam isolation, anti-retraction hand-piece, disinfection of the clinic settings, and management of medical waste are important [67].

8.3. Community transmission

To minimize the impact of the pandemic, and to prevent community transmission, stringent public measures should be set up to stop coronavirus such as self-isolation or quarantine, social distancing, curb travel in addition to complete public curfew and large geographical and country lockdown and tracing and isolation of those with travel history and their families [68]. WHO indicated that the virus remains viable and infectious from 2 to 9 days (in stainless steel, glass and plastic surfaces) at low temperature and high humidity (RH: 30% - 50%). Protective and strict control measures should be enforced with all patients during pandemic including hand hygiene, wearing mask and gloves, isolation, quarantine, social distancing and community containment [69]. Staying home and wearing cloth masks in public will help slow the spread from actually infected asymptomatic persons.

8.4. Susceptible and at risk populations

COVID susceptible or at risk populations show more severe fatal complications. Older patients' ≥ 50 years have weak immunity (immunosenescence). Patients with chronic conditions such as hypertension, vascular diseases, diabetes, obesity, renal failure and respiratory complications may have vascular damage, pro-inflammatory state or reduced immune response. High incidence of COVID-19 in males may be due to over expression of ACE2 receptors, lack of protection by oestrogen, X chromosome. Females' immune system is very strong. Children are less likely to be infected, may have less ACE2 receptor in their airways, or may harbour mild infections and distribute the virus to adults. Children may be less exposed to COVID -19, but may have cross protection, or higher baseline levels of antibodies, against viruses' even coronas, or from successive infections or vaccination programs. However, the symptoms are mild in children and they don't have cytokine storm that leads to multi organ failure. COVID-19 susceptibility may be related to high expression of ACE2 and higher binding affinity of ACE2 with SARS-CoV-2 [70, 71]. In densely populated areas, people exposed to air pollution who suffer from damage of respiratory cells will be subjected to severe and fatal COVID-19 infections. Air pollution in industrial cities weakens and damages the ciliated mucosal cells lining of the lung bronchioles, thus providing a suitable environment for virus reproduction. Hundreds of thousands of persons with mild symptoms moved from China during the onset of the pandemic to various other countries throughout the world. In the USA, the virus hit black Americans harder than other ethnic groups (14% infected and 42% die) (CNN 8.4.2020) These patients might be tenfold those positively diagnosed and presented in hospitals, and, with time, they will have full blown disease. They are responsible for uncontrolled spread of the epidemic.

9. COVID-19 symptoms, clinical manifestations and laboratory indices

SARS - Severe acute respiratory syndrome - is a type of viral pneumonia, with symptoms including fever, dry cough, shortness of breath and headaches. Death may result from progressive respiratory failure due to lung damage. Epidemiologically SARS-CoV-2 has a very fast and powerful transmission rate, but with less pathogenicity with a fatality rate of about 6% [27].

9.1. Clinical manifestations – first meta-analysis study from China

A meta-analysis study based on 30 scientific papers from Wuhan in China was published [72, 73, 64]. In Wuhan, COVID-19 is more common and severe in older (≥ 55 years) males (60%). The dominant symptoms are fever (80%), cough (58%), diarrhoea (6%), nausea or vomiting (2%). About 54% of the cases are severely affected. COVID-19 is more severe in patients with hypertension (19%), diabetes (8.2%), cardiovascular diseases (2.7%), cerebrovascular diseases, chronic obstructive pulmonary disease, chronic kidney diseases and renal failure and smokers [72]. COVID-19 has longer latent period (7 days). Respiratory syndromes are the cardinal sign (79.1%), followed to a lesser extent by gastrointestinal disorders (7.7%) and neurological symptoms (6.1%). COVID-19 patients often present initially with lower respiratory signs including fever, coughing and fatigue. Later, they show progressive breathing difficulty, tachypnea, acute respiratory distress syndrome, or life-threatening complications [71, 72].

9.2. Neurological findings and cytokines storm

In addition to the lungs many organs are involved such as heart and blood vessels, kidneys, gut, and brain. In a case from Japan, the International Journal of Infectious Diseases reported that the virus can penetrate the CNS where ACE2 is present, and COVID-19 patients may present with encephalitis, seizures, sympathetic storm, and some patients lose their consciousness. Chemosensory dysfunction, due to damage of nasal nerve endings, could be used as a screening test because it is associated with COVID-19 patients; Loss of smell or hyposmia (68%) and of taste (hypogeusia) in 71% of the cases, as well as head and body aches may occur [74].

Clinicians in USA noticed cytokine storms that trigger immune cells (Th1/Th7) to attack healthy tissues, as a result of which there is blood vessels leakage, drop in blood pressure, clot formation and catastrophic organ failure. The disastrous overreaction of the immune system, the cytokine storm, triggers the immune cells to backfire or attack healthy tissues. This leads to the afore-mentioned complications.

9.3. Blood analysis

Analysis of patients' blood samples reveals elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH) and D-dimers (coagulation disorders). Reductions below the normal levels in albumen, lymphocyte count (lymphocytopenia, 55%) especially CD4 and CD8 and platelets count (thrombocytopenia, 13%), were noticed [71, 41]. High levels of protein (59%) and blood (44%) were reported from Chinese patients, suggesting kidney damage.

9.4. Clinical manifestations – Second Meta-analysis study from China and other countries

Another clinical meta analytic study based on 31 papers from China (n, 21) and other countries (n, 10) and including 46959 COVID-19 patients was reported by Cao [75]. The patients most commonly presented with; fever (87.3%), cough (58.1%), dyspnea (38.3%), muscle soreness or fatigue (35.5%), chest distress (31.2%), sore throat (12%), expectoration (29.4%), headache (9.4%) and diarrhoea (6.8%). This was followed by dyspnea (38.3%), myalgia or muscle weakness (35.5%), and chest tightness (31.2%). The main imaging findings were bilateral pneumonia (75.7%) and ground glass opacification (69.9%). Some patients presented with chills, conjunctivitis (pink, watery eyes, with sand like secretions) or discomfort, headache, shortness of breath, and joint pain. A smaller number of patients had nausea, vomiting, diarrhoea and other abdominal discomfort symptoms [75]

9.5. Hospitalization and fatality rate

Most COVID-19 patients require hospitalization; of them 29.3% require intensive care (ICU). The main complications are respiratory failure, acute respiratory distress syndrome- ARDS (28.8%), multiple organ failure syndromes - MODS (8.5%), heart failure, shock, renal injury, sepsis, striated muscle lysis and disseminated intravascular coagulation. COVID-19 fatality rate in China was about 3.8%, however, in other parts of the world it was 6.8% [75].

Case fatality varies from country to country and age-wise. On 6th April 2020, the numbers infected were 1,324,000 and the deaths 74000, accordingly the fatality worldwide were 5.6%. On April 21, 2020, the total number of patients was

2,536,577 of whom 175,759 died and the fatality rate rose to 6.93%. Case fatality also varies with age: 14.8% in patients aged ≥ 80 years, 8.0% in patients aged 70-79 years, and 49.0% in critical cases [29]. The highest fatality rate - about 18% - was reported from USA.

10. Recent clinical findings on COVID-19

10.1. Pneumonia and micro clots in lungs

Pneumonia (cough, fever, rapid and shallow respiration) and death occurred in patients as their alveoli were stuffed with stew of fluids, WBC, mucus, pus and detritus of destroyed lung cells. Deep lung damage is caused by the virus and the immune cells. Other patients die suddenly due to acute respiratory distress (ARDS) as their oxygen levels plummet. Their lungs are riddled with white opacities (pulmonary opacification) and the alveolar walls break down. Still other patients die suddenly due to acute respiratory distress (ARDS) as their oxygen levels plummet. The cytokine storm by interleukin 6 results in extensive tissues damage [76].

The virus may directly attack the alveoli, blood vessels and heart lining which are ACE2 rich sites. The virus enters the body through nose and throat and multiplies and sheds copious virus copies during the first week. Then the virus marches down to the pulmonary alveolar cells rich in ACE2. COVID-19 patients suffer from very low oxygen levels and gasp to breathe as oxygen uptake is impeded by constricted blood vessels and hundreds of micro clots throughout the lungs or ruptured alveoli. This may be due to deadly blood micro clots that move from the legs to the lungs and damage the heart. In Spain, clotting cases were more prevalent than elsewhere, and required therapeutic anticoagulant therapies. The abnormal clotting in COVID-19 patients leads probably to heart attacks and stroke. An over-activated immune system can cause clots, or the virus triggers clot formation in these unwell immobile patients [76].

Some COVID-19 patients have been crashing, hard and fast, from sudden events as pulmonary embolism, cardiac arrests, and respiratory failure. A new pattern of clotting tendency called COVID-19-associated coagulopathy, or CAC, was recognized and notably associated with high inflammatory markers in the blood, like D-dimers and fibrinogen. Damaged cardiac muscles, with swelling, scarring, and weak left ventricle, in 20% of the patients was documented [77]. Klok reported that unstable micro blood clots are a major player in the disease severity and mortality and can land in lungs, blocking vital vessels (pulmonary embolism) and causing strokes, seizures and mental confusion [78]. The virus may attack kidney cells which have abundant ACE2 receptors, leading to kidney failure due to plummeting or reduced blood pressure. Using EM, viral particles were observed in kidneys. Kidney damage was reported in Chinese patients with (59%) protein in their urine, and blood (44%).

10.2. SARS-CoV-2 attacks haemoglobin

A new research pointed out to a mechanism whereby SARS-CoV-2 non-structural proteins (ORF10, ORF1ab and ORF3a) attacked heme and generated porphyrin. Then ORF6 and ORF7a sent the porphyrin to form stable complex with ORF8 (Lui and Li, 2020). Therefore, less haemoglobin can carry oxygen and carbon dioxide, and the lungs are unable to exchange carbon dioxide with oxygen, which results in ground glass like lung image, causing respiratory distress. Chloroquine and Favipiravir may prevent heme attack and inhibit formation of porphyrin ORF8 complex [79].

11. Treatment and prophylaxis

There is yet no prophylaxis vaccine or specific antiviral medicine for COVID-19. Supportive care such as oxygen therapy, treatment with antibiotics and antifungal, in addition to extra-corporeal membrane oxygenation, are given to the patients. Many antiviral agents have been proposed, but their efficacy and safety are under investigation.

11.1. Chloroquine and hydroxychloroquine

Chloroquine is an old Chinese medicine. Since seventy years ago, Chloroquine (CQ) and hydroxychloroquine (HCQ) have been used for treatment of malaria, autoimmune diseases, arthritis, SARS and recently in AIDS [41, 80, 81]. The French scientist Raoult Didier explored a promising potential antiviral property of CQ and HCQ. These two medications showed an ability to inhibit spread of SARS-CoV-1 [82, 83, 84]. Yao reported that Hydroxychloroquine is more potent than Chloroquine (83). Chloroquine may reduce glycosylation of ACE2 preventing the virus binding and entry of host cell (EC50 0.77 μM) [35]. It also inhibits viral release into the intracellular space endosome where it replicates [85]. CQ accumulates in lysosome and interrupts lysosome-endosome fusion that inhibits release of virus contents. CQ may block synthesis of interleukin-6 and cytokine that mediate acute respiratory distress syndrome (ARDS) [84]. Chloroquine was used at 400mg for 5 days and there are no significant differences between treatment and control groups [21]. Insufficient

in vivo and *in vitro* trials were published with large numbers of patients to evaluate its safety, efficiency and side effects if any [84,83].

11.2. Heart failure due to combination of hydroxychloroquine and azithromycin

Michael Ackerman, a genetic cardiologist, reported that a combination of hydroxychloroquine and azithromycin results in heart failure one month later. Treating COVID-19 patients (n, 81) with hydroxychloroquine, combined with the antibiotic azithromycin, as suggested may have antiviral effects. This combination was used in a controlled study in Brazil for treatment of COVID-19; however, more deaths were reported among these patients and there was increased arrhythmia in the high dose group. Another study in the USA in 368 patients, found that the risk of death was greater in patients who received this combination, than those who didn't. Both medicines were documented to block channels on heart muscles that control the flow of ions which governs heart's electrical pattern and recharging between beats. Another study from Oxford found that in arthritis patients who received hydroxychloroquine and azithromycin, the risk of heart failure and cardiovascular death was more than doubled [86, 87].

11.3. Remdesivir (RDV)

Remdesivir which is used for treatment of Ebola, SARS and MERS has not been as promising as hoped. In Ebola patients it increased liver enzymes; that may indicate liver damage. Remdesivir works post-entry stages of SARS-CoV-2. It acts as nucleotide adenosine analogue targeting RdRp and results in premature termination during virus transcription. Remdesivir has powerful antiviral activities with low cytotoxicity, with effective concentration (EC₅₀) of 1.13μM [35,85]. A new study showed that, Remdesivir use was not associated with statistically significant clinical benefits in terms of time and improvement, or reductions in viral load, more over side effects were reported in 66% of the patients; anorexia, nausea, vomiting, aminotransferase or bilirubin increases, and worsened cardiopulmonary status [88].

11.4. Convalescent plasma CP, the last resort

Adaptive immunotherapy using convalescent plasma or immunoglobulins has been used to improve survival rate and to lower mortality rate of patients in many viral diseases [5, 89, 90]. WHO recommended using convalescent plasma for treatment of Ebola 2014, MERS 2015, HIV, and influenza A H1N1 pandemic-2009. Antibodies in convalescent plasma might suppress viremia and lower viral load and thereby reduce mortality within 5 days of symptom onset [91, 92, 93, 94]. The blood of selected cured patients with known blood groups and Rh, was screened for blood borne diseases (SARAS-CoV-2, HIV, HBV, HCV, Yellow fever, Syphilis, etc.) [95, 96].

In China one dose of 200 mL of inactivated cp plasma convalescent with neutralization activity of $1 \geq 6400$, was transfused into COVID-19 deteriorating patients (WHO transfusion protocol). It was found to be well tolerated by the patients, and their clinical symptoms significantly improved with the increase of oxyhaemoglobin saturation within three days, accompanied by rapid neutralization of viremia [96].

11.5. SAN-SC7

A Sudanese medicine SAN-SC7 (spray) that synthesized by Sanhorial Medical and Cosmetics, which formerly used for treatment of different types of flu and SARS was used for treatment of COVID-19. SAN-SC7, now it was under test as prophylactic and medicine for treatment of COVID-19. Preliminary good results that 90% of the patients cured without any side effects in comparison to controls (Professor Mohamed Alameer Sanhory personal communication).

12. Recommendations

- Funding of robust research on the development of new vaccines, medicines and sensitive tests for SARS-CoV-2
- Search for effective medicines against SARS-CoV-2 from traditional herbs used for treating respiratory diseases.
- Utilization of biotechnology to provide advanced solutions for developing VLPs vaccines or therapeutic proteins effective against SARS-CoV-2.
- Search for a natural enemy virus that may infect or disable the SARS-CoV-2 virus or a harmless coronavirus that competes with it [97].

- Development of reliable, economical and rapid tests for mass screening of SARS-CoV-2 in the population and for monitoring probable emergent viruses, such as Ebola, Coronaviruses and Flu, and studying their basic biology and suspected reservoir.
- Avoiding human contact with wild animals to avoid their emergent zoonotic viruses.
- Identification of SARS-CoV-2 risk factors to predict progression or severity of the disease causes of complications and how to solve them and how the virus affect susceptible populations.
- Undertaking further, more detailed studies on SARS-CoV-2 infected patients, to understand the mysteries of the virus, its behaviour, symptoms, signs mild, and severe clinical and pathological manifestations, virulence outcome.
- Establishment of new epidemiological strategies to control virus transmission and avoid future pandemics.
- Study SARS-CoV-2 nature, biology, evolution, thermostability, efficiency, transmissibility, and epidemiology.
- Hard questions need to be answered such as why the disease is mild or even asymptomatic in some patients and severe and highly fatal in others, and which immune proteins promote immunity in patients with mild symptoms. Are they genetically resistant to COVID, and how to identify their genes and proteins products?
- Benefit from knowledge of Coronavirus vaccines already developed for some animals (like cats) and birds (like Infectious Bronchitis vaccine for poultry)
- Great lessons can be learned from SARS-CoV-2 pandemic. Genomic, epidemiological and clinical data from patients should be combined to explain the mysteries of the disease.
- Rapid detection and isolation of SARS-CoV-2 genotypes and isolates from different geographical sites and the mutations that control or govern virus transmission, pathology and virulence are important issues.
- Different phenomena have to be studied such as mechanism of transmission, reinfection, coinfection and super infection.
- More funding should be directed towards health sector and disease control centres.

13. Conclusion

The current overwhelming SARS-CoV-2 or COVID-19 pandemic caused by a new member of Coronaviridae (+ssRNA genome), infects the human respiratory system. The genome of the virus ($\approx 29,000$ bp) was found to be in high homology to coronavirus of its natural reservoirs, the Horseshoe bats, Malaysian pangolin and palm civet cats. Two types of SARS-CoV-2 were detected: a major type L (70%) and a minor S type (30%). The virus spikes S – RBD have very high affinity with ACE2 host cell receptor. Reverse transcriptase rtPCR uses nasal and bronchoalveolar lavage –BAL for detection of the virus. False negative results present a great problem in virus diagnosis and epidemiology. Therefore, so far the diagnosis of COVID-19 mainly depends on clinical confirmation not lab diagnosis.

The cardinal symptoms are fever, cough, and dyspnea and muscle fatigue. Lung embolism or micro clots lead to heart failure and death. The virus attacks hemoglobin and forms a complex with prophyrin, which prevents oxygen exchange and accumulates carbon dioxide. The disease is more severe in older patients, and those with chronic diseases. No reliable vaccine has been developed yet due to virus mutations. Besides, there is no specific antiviral treatment for COVID-19 except supportive oxygenation. Some medicines showed promising results e.g., plasma convalescent blood, Remdesivir and anticoagulants. Fifty percent of the patients, who received high doses of Hydroxychloroquine with Azithromycin, died of heart failure. The mortality rate of SARS-CoV-2 is about 7%. The pandemic resulted in lockdown of countries throughout the World and had catastrophic negative impacts on health and economy worldwide. The summer and increase in temperature may delay or even end up the current pandemic. However, no immunity could be acquired against SARS-CoV-2. A new COVID-19 may hit the world again next winter unless an effective vaccine or specific treatment becomes available.

Compliance with ethical standards

Acknowledgments

The authors thank Professor Mansour Faris Hussein and Dr. Hind Abbas Hilmi who review this article and for their insightful comments. Our thanks were also to all scientists whose papers cited in this review and those who contribute in combating COVID-19.

Disclosure of conflict of interest

There is no conflict of interests between authors.

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How to cite this article

Hilmi ZA, Aloufi Bandar H and Ibrahim Husam MA. (2020). A Review on SARS-CoV-2: the origin, taxonomy, transmission, diagnosis, clinical manifestations, treatment and prophylaxis. *GSC Biological and Pharmaceutical Sciences*, 11(03), 52-66.
