LONG COVID OR POST COVID SYNDROME

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Abstract: Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease that is of great global public health concern. Based on the large number of infected people that were exposed to the wet animal market in Wuhan City, China, it is suggested that this is likely the zoonotic origin of COVID-19. Person-to-person transmission of COVID-19 infection led to the isolation of patients that were subsequently administered a variety of treatments. Extensive measures to reduce person-to-person transmission of COVID-19 have been implemented to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. In this review, we highlight the symptoms, epidemiology, transmission, pathogenesis, phylogenetic analysis and future directions to control the spread of this fatal disease.

Keywords: COVID-19, SARS-CoV-2, RT-qPCR, RT-LAMP.

I. INTRODUCTION:

Coronavirus is an enveloped, positive single-strand RNA virus. It belongs to the Ortho corona virinae subfamily, as the name suggests, whose members show characteristic "crown-like" spikes on their surfaces coronavirus [1] (CoV) is among the main pathogenic organisms that affect the respiratory system in humans. An ongoing outbreak of pneumonia associated with a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported in Wuhan, Hubei province, China [2-4]in December 2019. On 11 February 2020, the novel virus began to cause pneumonia, and was named as coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO). In December 2019, the prevalence of the virus increased at an epidemic rate since its first occurrence in Wuhan [5].

Consistently, the international virus classification commission termed the virus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease does not manifest initially as a chronic disease of the respiratory system. In previous decades, coronaviruses have caused Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).

Currently, COVID-19 cases have been recorded globally. On the 1 March 2020, reports indicated that 79,968 individuals were infected with the disease of whom 41,681 were cured, and 2873 died. On 31 January 2020, COVID-19 was presented by WHO as a Public Health Emergency of International Concern (PHEIC). The coronavirus has a diameter of 80–120 nm and is single-stranded RNA.

Four types of viruses have been reported, which include α-coronavirus, β-coronavirus, δ-coronavirus, and γ-coronavirus. Infection in humans is caused by six coronaviruses, and the 2019 novel coronavirus (SARS-CoV-2) is regarded as the seventh member of the coronavirus family to induce infection in humans. The virus belongs to the beta coronavirus group like the MERS coronavirus (MERS-CoV) and SARS coronavirus (SARS-CoV) (which also cause disease in human). SARS and SARS-CoV-2 have approximately 79% genome sequence homology, and SARS-CoV-2 has a higher similarity to coronaviruses found in bats, causing SARS.

Intriguingly, many studies have revealed that SARS-CoV-2 binds with angiotensin-converting enzyme-2 (ACE-2), similarly to SARS-CoV; this is due to the similarity of the receptor-binding domain found on spike-proteins. Coronaviruses use the spike (S) protein found on their surface to recognize and bind to specific receptors on host cell surfaces, resulting in virus entry to the cell of host and causing diseases. SARS-CoV-2 forms a complex with ACE-2 more than ten times more significantly than SARS-CoV, greater than the threshold needed for the virus to cause disease, as revealed by the structure model procedure.

Comprehensive information on whether the 2019 nCoV causes disease in humans by the interaction of ACE-2 and its S-protein, how this interaction could serve as a means of disease transmission in humans, and how the virus causes damages to organs in patients remain unclear; thus, more detailed researches are necessitated. The coronavirus virion is shown in Figure 1, revealing its various components.

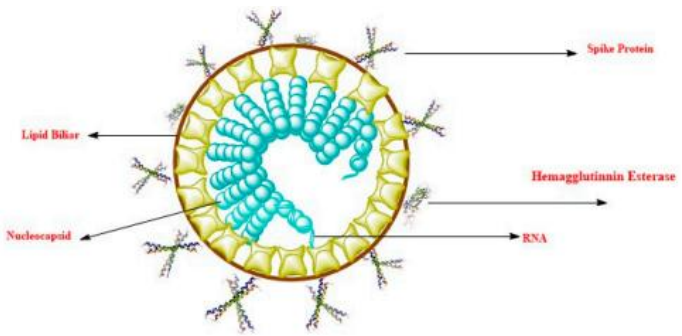

Figure 1: Structure of coronavirus virion showing the spike protein, membrane glycoprotein, lipid bilayer, nucleocapsid, envelope glycoprotein, RNA, an hemagglutinin esterase.

II. ETIOLOGY:

Complete viral genome analysis reveals that the virus shares 88% sequence identity with two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses, but is more distant from the severe acute respiratory syndrome coronavirus (SARS-CoV). Hence, it was temporarily called 2019-novel coronavirus (SARS-CoV-2).

Coronavirus is an enveloped and single-stranded ribonucleic acid named for its solar corona like appearance due to 9–12 nm-long surface spikes. There are four major structural proteins encoded by the coronaviral genome on the envelope, one of which is the spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell [4].

On 11 February 2020, the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses finally designated it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on phylogeny, taxonomy and established practice. Soon after, WHO named the disease caused by this coronavirus as Coronavirus Disease 2019 (COVID-19) [6]. Based on current data, it seems that bats might initially host COVID-19, which might have been transmitted to humans via pangolin or other wild animals sold at the Huanan seafood market, with subsequent spread via human-to-human transmission.

III. EPIDEMIOLOGY:

The first cases were reported in December 2019 [7]. From December 18, 2019 through December 29, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died. By January 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed COVID-19 infection, less than half of these patients had underlying diseases, including diabetes, hypertension, and cardiovascular disease. These patients were presumed to be infected in that hospital, likely due to nosocomial infection.

It was concluded that the COVID-19 is not a super-hot spreading virus (spread by one patient to many others), but rather likely spread due to many patients getting infected at various locations throughout the hospital through unknown mechanisms. In addition, only patients that got clinically sick were tested, thus there were likely many more patients that were presumably infected. As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (COVID-19) were reported in 25 provinces (districts and cities) in China.

The China National Health Commission reported the details of the first 17 deaths up to January 22, 2020. On January 25, 2020, a total of 1975 cases were confirmed to be infected with the COVID-19 in mainland China with a total of 56 deaths. Another report on January 24, 2020 estimated the cumulative incidence in China to be 5502 cases.

As of January 30, 2020, 7734 cases have been confirmed in China and 90 other cases have also been reported from a number of countries that include Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United States, The Philippines, India, Australia, Canada, Finland, France, and Germany.

The case fatality rate was calculated to be 2.2% (170/7824). The first case of COVID-19 infection confirmed in the United States led to the description, identification, diagnosis, clinical course, and management of this case. This includes the patient's initial mild symptoms at presentation and progression to pneumonia on day 9 of illness [8]. Further, the first case of human-to-human transmission of COVID-19 was reported in the US on January 30, 2020.

The CDC has so far screened > 30,000 passengers arriving at US airports for the novel coronavirus. Following such initial screening, 443 individuals have been tested for coronavirus infection in 41 states in the USA. Only 15 (3.1%) were tested positive, 347 were negative and results on the remaining 81 are pending.

A report published in Nature revealed that Chinese health authorities concluded that as of February 7, 2019, there have been 31,161 people who have contracted the infection in China, and more than 630 people have died of infection. At the time of preparing this manuscript, the World Health Organisation (WHO) reported 51,174 confirmed cases including 15, 384 severe cases and 1666 death cases in China. Globally, the number of confirmed cases as of this writing (February 16, 2020) has reached 51,857 in 25 countries.

TABLE 1: Updated COVID-19 cases as of 28 October 2020.

Regions	Total Cases	Total Deaths	Total Recovered	Total Active Cases
Asia	13,328,711	237,480	11,789,290	1,292,941
Europe	8,921,074	255,942	3,571,142	5,093,990
North America	10,822,292	346,631	7,204,179	3,271,482
South America	9,465,599	290,300	8,451,570	723,729
Africa	1,747,522	41,854	1,429,087	276,581
Oceania	36,585	967	31,776	3842

IV. PATHOPHYSIOLOGY:

The pathogenesis of SARS-CoV-2 disease is not documented, the similar mechanistic action of MERS coronavirus and SARS coronavirus could provide valuable information on SARS-CoV-2's disease pathogenesis to enable COVID-19 identification. The entry of the virus into the cell of the host organism is determined by the S protein found on the virus. The envelope S is constituted of glycoprotein binds to a specific receptor: CD209L (LSIGN also called C-type lectin) for SARS coronavirus, ACE2 for SARS-CoV-2 [9] and SARS-Co [10], and DPP4 for MERS cornavirus [11].

Initially, the movement of the virus into the cells of the host organism takes place through direct membrane fusion between SARS-CoV-2 and the host cell plasma membrane. Significant proteolytic cleavage process takes place at the position (S2´) of the SARS coronavirus S protein, controlling the viral infectivity and binding to the membrane.

An unusual activation of two-step furan for the fusion of the membrane is evolved in MERS coronavirus. Apart from the fusion of the membrane, the clathrin-independent and -dependent SARS-CoV cell entry is regulated by endocytosis. The virus's genomic material is released into the cytosol after entry into the cells of the host organism. Then the genomic material is transcribed into two polyproteins and structural proteins, followed by the replication of the RNA.

The envelope glycoprotein that was newly formed is transported into the Golgi apparatus membrane, or endoplasmic reticulum, and the combination of the nucleocapsid protein with the genomic material results in the formation of the nucleocapsid. Subsequently, the viral materials enter the endoplasmic reticulum-Golgi intermediate compartment (ERGIC).

The fusion of vesicles housing the viral materials results in their release. After the virus entry into the cells of the host organism, the antigen presentation cells (APC) recognize the antigen of the virus. This is vital for the anti-viral immunity of the host cell. The major histocompatibility complex (MHC) in humans, or the human leukocyte antigen (HLA), are involved in the presentation of antigenic peptides, followed by the recognition of the peptide by virus-specific cytotoxic T lymphocytes (CTLs).

Thus, knowledge of the presentation of SARS-CoV-2 will aid the understanding of coronavirus disease pathogenesis. Regrettably, information is still speculative, and However, MHC II also partake in the presentation of antigen. Previous studies demonstrate that many polymorphisms of HLA are similar in SARS-CoV susceptibility, including HLA-DRB1*1202, HLA-B*0703, HLA-B*4601 [12], and HLA-Cw*0801 [13], while, HLA-A*0201, HLA-DR0301 and HLA-Cw1502 alleles are linked to SARS disease prevention.

In regards to MERS-CoV disease, molecules of MHC II, including HLA-DQB1*02:0 and HLA-DRB1*11:01, are associated with MERS coronavirus infection susceptibility. However, mannose-binding lectin (MBL) gene polymorphisms linked to the presentation of antigen are linked to high chances of SARS coronavirus disease. Studies have shown that ARDS (acute respiratory distress syndrome) is the leading cause of mortality in coronavirus disease and, out of 41 patients infected by this virus in the initial phase of the outbreak, 6 died from ARDS. In MERS coronavirus, SARS coronavirus and SARS-CoV-2 diseases, ARDS is the prominent immunopathological feature.

Cytokine storm is an essential mechanism of ARDS along with chronic unregulated systemic inflammatory stimulus, which is an outcome of the release of many of the pro-inflammatory markers including IFN-α, IL-1β, IL-12, IL-33, IL-18, IL-6, TGF β, TNF-α, etc. and chemokines like CXCL10, CXCL9, CXCL8, CCL2, CCL5, CCL3, etc., by immune effector cells. Consistent with SARS coronavirus, patients with chronic MERS coronavirus disease display higher levels of IFN-α, IL-6 and CCL5, CXCL-10, and CXCL8 present in serum than those showing critical-moderate symptoms of the infection.

The cytokine storm stimulates an attack on the host body through the immune system leading to multiple organ failure and ARDS and eventually results in death in chronic cases of COVID-19, similar to cases seen in MERS coronavirus and SARS coronavirus diseases.

The MERS coronavirus and SARS coronavirus employ several methods to prevent the immune response of the host cell. Pathogen-associated molecular patterns (PAMPs), which is an evolutionary conserved microbial substance, can be seen by pattern recognition receptors (PRRs). However, MERS coronavirus and SARS coronavirus can stimulate double-membrane vesicle synthesis. The synthesized vesicle possesses no PRRs, causing it to divide in the vesicles, hence preventing host determination of their double-stranded RNA. IFN-β and IFN-α have demonstrated a protective role in disease caused by MERS coronavirus and SARS coronavirus; nevertheless, the pathways involving these cytokines is abrogated in infected experimental mice.

In MERS coronavirus disease, accessory protein 4a inhibits interferon (IFN) stimulation at melanoma differentiation-associated protein-5 (MDA-5) level induction, via the direct interaction with double-stranded RNA. However, ORF5, ORF4a and ORF4b, and MERS-CoV membrane proteins block nuclear transport of regulatory factor 3 of the IFN and IFN β promoter stimulation. Coronavirus can also influence antigen presentation. For instance, antigen presentation associated with gene expression is down-regulated after the infection of MERS-CoV. Hence, management and specific drug formation are based on the impairment of immune evasion caused by coronavirus, resulting in COVID-19.

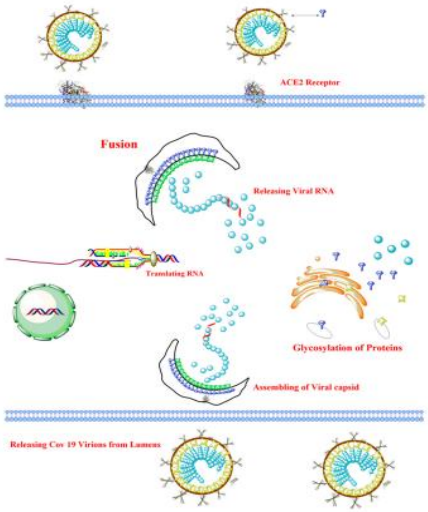

Figure 2: Scheme of Covid-19 pathogenicity mechanism.

V. SYMPTOMS:

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days [14]. This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients > 70-years old compared with those under the age of 70 [14].

The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia [14]. In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs that likely induced both systemic and localized immune response that led to increased inflammation.

Regrettably, treatment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities (Fig. 2). It is important to note that there are similarities in the symptoms between COVID-19 and earlier beta coronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans.

However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat. In addition, based on results from chest radiographs upon admission, some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnea with hypoxemia. Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress.

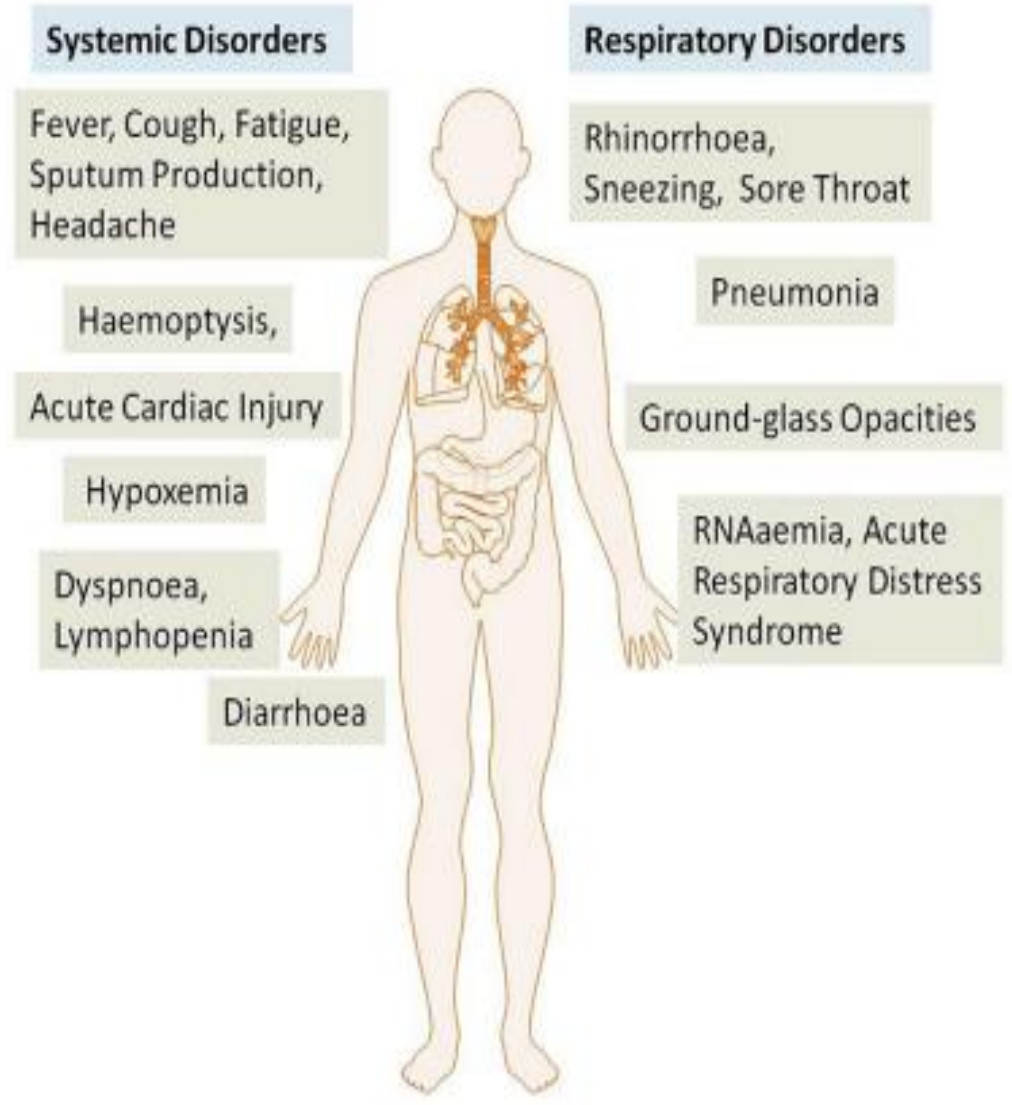

Figure 3: The systemic and respiratory disorders caused by COVID-19 infection.

VI. DIAGNOSIS:

In patients with clinical evidence of COVID-19 infection, laboratory tests may reveal lymphocytopenia, thrombocytopenia, elevated liver transaminases, elevated C-reactive protein and erythrocyte sedimentation rate, elevated serum lactate dehydrogenase and decreased or normal serum albumin. Elevated serum troponin-T may be present, indicating myocardial injury. The following tests are used in patients with symptoms suggestive of COVID-19 infection.

***VIRAL TESTING*:**

Viral testing is performed by the RT-qPCR test, used for qualitative detection of the nucleic acid for SARS-CoV-2. Swabs are usually taken from nasal, nasopharyngeal, oropharyngeal, sputum or lower respiratory tract aspirates or wash. Positive tests indicate

the presence of SARS-CoV-2 RNA, and together with the clinical picture support the diagnosis. Negative test results do not preclude SARS-CoV-2 infection, and shall be interpreted in light of the clinical picture and epidemiologic information [15].

SEROLOGY:

Serology testing for SARS-CoV-2 is now available. The test can assess prior exposure to virus and cannot be used in the diagnosis of current infection. Cross-reactivity with other human coronaviruses may occur. The serology test is particularly useful (i) when the viral test is not available.

Using the serology test together with the clinical picture could guide in decision making. (ii) Patients with late disease complications and their physicians need to make immediate decisions (the viral test takes more time to get the results). (iii) In some patients, virus shedding is reduced, making RT-qPCR results falsely negative. The serology test can detect IgM and IgG antibodies against SARS-CoV-2 in serum, plasma and whole blood.

RAPID ANTIGEN TESTING:

Rapid antigen testing is a monoclonal antibody test against the SARS-CoV-2 nucleocapsid protein (N). This protein is abnormally expressed in infected cells. Monoclonal antibodies are specifically directed against nucleocapsid protein, and by using enzyme-linked immunosorbent assay, it is possible to detect SARS-CoV-2. The test has a reported sensitivity of 84.1% and a specificity of 98.5%. No cross-reaction with human and animal coronaviruses in the assay were reported. There are no reports yet about applying this test to SARS-CoV-2[16].

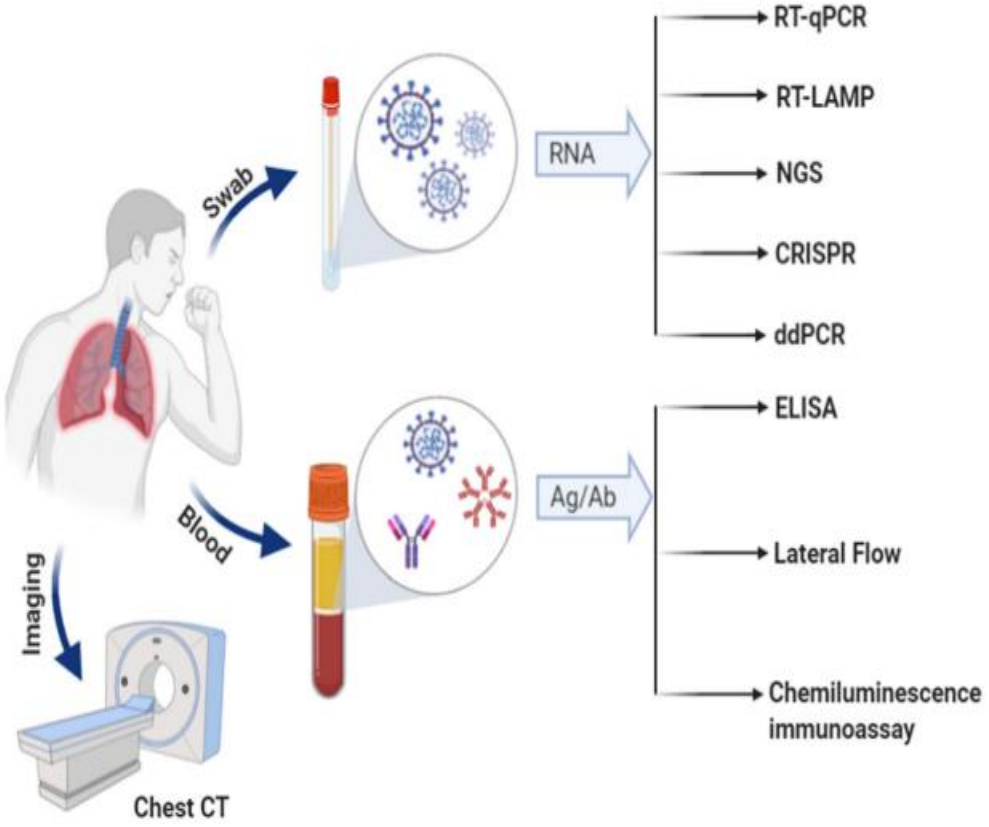

Figure 4: Schematic representation of various analytical methods available for SARS-CoV-2 detection.

ULTRASONOGRAPHY:

Whole-body point-of-care ultrasonography has been provided to COVID-19 patients. Ultrasonography is considered an essential modality to guide treatment in patients with cardiorespiratory failure. Current recommendations are to extend its use to multisystem and whole-body ultrasonography: thoracic, cardiac, abdomen and deep venous thrombosis.

CHEST COMPUTED TOMOGRAPHIC SCAN:

Earlier studies during the outbreak in China suggested that patients with and without SARS-CoV-2 can be differentiated by chest computed tomographic imaging, together with clinical presentation and the presence of pneumonia. The authors proposed that radiologic images and clinical features are excellent diagnostic tools for COVID-19.

Predictors of severe disease may include high virus load, elevated neutrophil-to-lymphocyte ratio, chest changes or changed extent of lesion on computed tomography, patient age and presence of comorbidities. Older age and neutrophilo-lymphocyte ratio are reported to be independent biomarkers for poor clinical outcomes.

VII. TREATMENT:

ANTI-MALARIALS & AMEBICIDES

Drug Name – Hydroxychloroquine phosphate [17,18].

Route – Oral

Mechanism of action: Inhibits autophagy and lysosomal acidification. Prevents virus entry *in vitro.*

Indications: Moderate to severe.

Side effects – QT prolongation,

headache
nausea
loss of appetite
vomiting
diarrhoea
rash.

ANTI-MALARIALS

Drug Name – Chloroquine [17,18].
Route – Oral
Mechanism of action – Not fully understood. Inhibition of viral fusion. Binds and inhibits glycosylation of virus proteins.
Indications – Moderate to severe
Side effects – QT prolongation,
headache
nausea
vomiting.

ANTIBIOTIC

Drug Name – Azithromycin [19].
Route – Oral
Mechanism of action – Azithromycin acts by binding to 50s ribosomal subunit of susceptible microorganisms.
Indications – Moderate to severe
Side effects – QT prolongation
Headache
Dizziness
Cholestasis
Hepatitis
diarrhoea

ANTIVIRAL AGENT

Drug Name – Remdesivir [20].
Route – Intravenous
Mechanism of action – Inhibits Rd Rp of RNA viruses.
Indications – Mild to moderate
Side effects – Elevated liver enzymes
Diarrhoea
Hypotension
acute kidney injury
atrial fibrillation
deep venous thrombosis.

HIV Protease inhibitor

Drug Name – Lopinavir/Ritonavir [21].
Route – Oral
Mechanism of action – Aspartate protease inhibitor. Lopinavir binds to site of HIV-1 protease activity and inhibits cleavage of virus Gag-Pol polyprotein precursors, hence interfering with HIV infection.
Indications – Moderate to severe
Side effects – Anorexia
Nausea
abdominal discomfort
diarrhoea
acute gastritis
liver dysfunction
thrombocytopenia
skin eruptions.

ANTI-PROTOZOAL AGENT

Drug Name – Nitazoxanide [22].
Route – Oral
Mechanism of action – Disturbs metabolism in anaerobic microbes and inhibits viral transcription factor.
Indications – Moderate to severe
Side effects – Nausea
Vomiting
abdominal pain
headache
dizziness
skin rash

IMMUNOMODULATOR

*****Drug Name – Tocolizumab [23].
Route – Intravenous
Mechanism of action – Monoclonal antibody; blocks IL-6 receptor and inhibits IL-6 pathway.
Indications – Severe
Side effects – Nasopharyngitis
Headache
Hypertension
elevated alanine aminotransferase
rash
dizziness
leukopenia
liver injury.
*Drug Name – Sarilumab [24].
Route – Subcutaneous
Mechanism of action – Monoclonal antibody that blocks IL-6 receptor and inhibitor IL-6 pathway.
Indications – Moderate to severe
Side effects – Allergy
thrombocytopenia neutropenia
elevated liver transaminases.

PLASMA, NEUTRALIZING ANTIBODIES

Drug Name – Convalescent plasma [25].
Route – Intravenous
Mechanism of action – Convalescent plasma contains specific IgG and IgM anti-SARS-CoV-2 antibodies, which can neutralize virus.
Indications – Severe and life-threatening
Side effects – Anaphylaxis.

VIII. CONCLUSION:

Currently, the SARS-CoV-2 pandemic has caused the main challenge to experts in the field of medicine for the development of drug/vaccine. Concerning its transmission rate, scientists around the globe are working up to their best knowledge to develop effective anti-SARS-CoV-2 therapies as early as possible. To date, various antiviral drugs have demonstrated potential in treating COVID-19 infection. Literature reveals that pharmacological drugs (Lopinavir/ritonavir, remdesivir, Chloroquine, Hydroxychloroquine, Tocilizumab, Nitazoxanide, Favipiravir (FVP) and Ivermectin), Corticosteroids, Convalescent plasma therapy, and traditional Chinese medicines (TCMs) are among the therapies possessing clinical significance against COVID-19. Although these therapies have shown certain therapeutic effects still COVID-19 remains a serious concern. Therefore, it is need of the time to conduct further clinical trials on a large scale to authenticate the effectiveness and safety of mentioned therapeutics in this review.

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