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A Review on Long Term Effect of Post Covid-19 on Endocrine System

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ABSTRACT

Since its emergence in late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused the COVID-19 pandemic has caused major health problems for people all over the world. In-depth discussions of the disease's genesis, epidemiology, transmission, pathophysiology, clinical manifestations, and diagnostic methods are provided in this study. Many symptoms, ranging from mild respiratory discomfort to severe consequences including acute respiratory distress syndrome (ARDS) and multi-organ failure, can be brought on by the virus. It is primarily spread via respiratory droplets. Diagnostic techniques such as RT-PCR, serological testing, and imaging modalities like CT scans have been instrumental in identifying infections. Treatment remains largely supportive, with oxygen therapy, mechanical ventilation, and anticoagulation therapy playing a crucial role in managing severe cases. Antiviral agents, corticosteroids, and immunomodulatory drugs have been explored, but their efficacy remains under investigation. The influence of COVID-19 on the endocrine system, including possible thyroid malfunction and hormonal abnormalities, is also highlighted in the report. Many facets of the virus's long-term consequences and interactions with the human body are still unknown, despite

tremendous progress in our understanding of it and how to treat it. To better understand post-infection problems, develop treatment strategies, and increase worldwide readiness for future epidemics, further study is required.

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INTRODUCTION:

Corona Virus disease 2019 COVID-19 is a novel disease caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). [1]. was declared a pandemic by March 2020 after being first identified in Wuhan, China, in December 2019. Most countries' healthcare systems are overburdened and have suffered large financial losses as a result of the COVID-19 pandemic. In most cases, SARS-CoV-2 is transmitted through respiratory droplets. The most frequent presenting symptoms were fever, cough, dyspnea, myalgia, or fatigue, and the incubation period lasted an average of 6.4 days. Only a small portion of people suffer from severe hypoxia, which requires hospitalization and artificial breathing; the majority usually have mild respiratory conditions.[2]

In response to the increase in positive infected cases in China, the WHO on January 30, 2020, declared the viral epidemic a public health emergency of worldwide concern. The coronaviridae family's beta coronavirus genus includes the enclosed, single-stranded, positive-sense Ribo Nucleic Acid (RNA) virus known as SARS-CoV-2.[3]

It was believed that the outbreak began as a result of a zoonotic transmission from the Wuhan, China, seafood market. Human-to-human transmission was later identified as the disease's widespread spread, with reports of it occurring in almost 200 nations globally.[4]

The **WHO** proclaimed COVID-19 a pandemic on March 11, 2020, following its transmission as a public health emergency on January 30, 2020. After first causing a serious pneumonia outbreak in China, SARS-CoV-2 is now quickly spreading throughout the world. Nearly 11.5 million cases were documented globally as July 6, 2020, with over 536893 fatalities.[4]

Moderate cases of COVID-19 require 7–10 days to recover, whereas severe cases require 3-6 weeks. A post-COVID-19 disease is characterized by a variety of new or recurring health issues that people may experience for longer than four weeks following their first COVID-19 infection, according to the Centers for Disease Control and Prevention.[1]

Introduction to Coronavirus Disease 2019:

The 2019 novel CoV is now known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. It belongs to the beta-CoV genus. Furthermore, Beta-CoV comprises Severe Acute Respiratory Syndrome CoV (SARS-CoV) and Middle Eastern Respiratory Syndrome CoV (MERS-CoV).[2]

The respiratory illness caused by the virus was dubbed coronavirus disease 2019 (COVID-19) by the World Health Organization. A wave of acute atypical respiratory infections struck Wuhan, in the Hubei region of China, in December 2019. The pathogen responsible for SARS-CoV-2, or severe acute respiratory syndrome coronavirus, was quickly determined to be a new coronavirus that is a member of the coronaviridae family. In 2002–2003, it was demonstrated to be strikingly similar to the respiratory pandemic-causing SARS coronavirus-2 (SARS-CoV).[4]

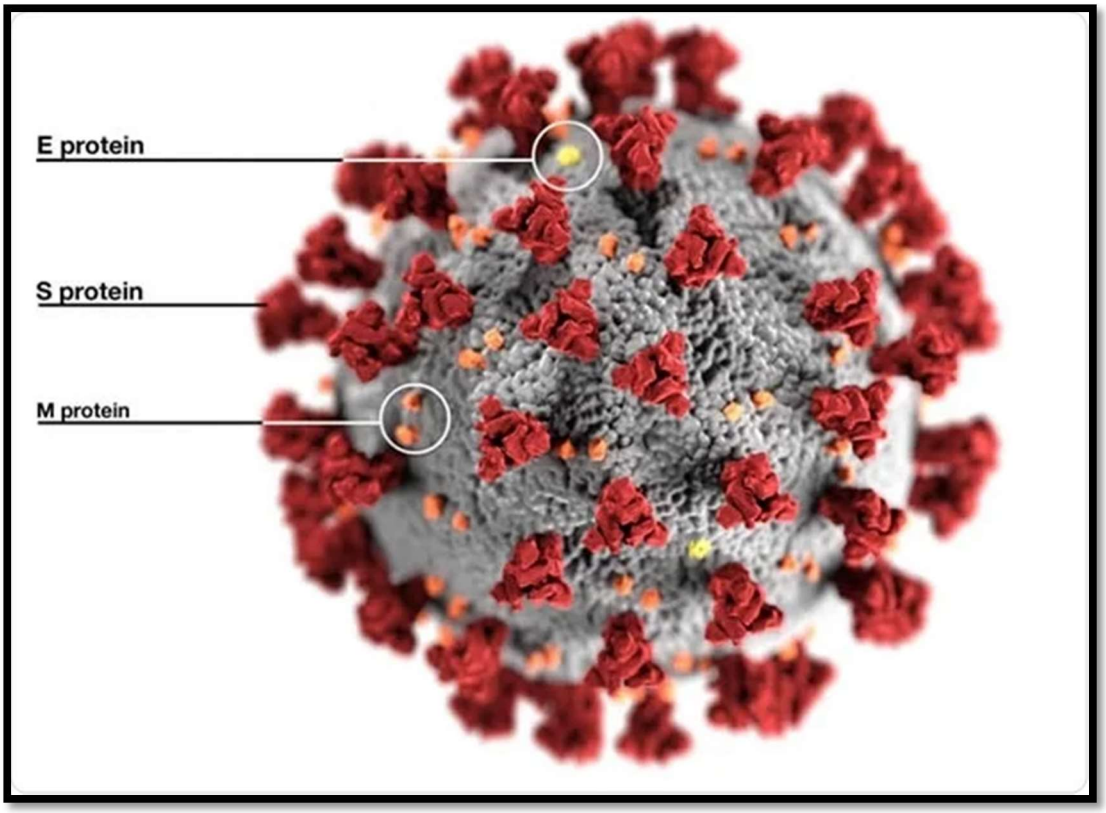

Fig. 1: Corona Virus.

It was believed that a zoonotic spread from Wuhan, China's seafood markets was the cause of the outbreak. Human-to-human transmission was later identified as the cause of the disease's community spread. Being reported in almost 200 countries throughout the globe.[4]

On February 11, 2020, the World Health Organization (WHO) announced that the disease caused by SARS-CoV-2 will now be referred to as COVID-19. As a public health emergency, COVID-19 was broadcast on January 30, 2020. The World Health Organization declared it a pandemic on March 11, 2020. Previously responsible for a severe pneumonia outbreak in China, SARS-CoV-2 is currently rapidly expanding globally. Almost 65 million cases and more than 536893 reported deaths occurred worldwide as of July 6, 2020. [2 4 7]

The WHO defines post-COVID-19 syndrome **(PCS)** as the continuation of symptom after three months following an infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). About 80 % of patient, both hospitalized and non-hospitalized, experience symptoms that last more than a year. Pre-existing risk factor for PCS, particularly cardiorespiratory, autoimmune and oncological prior conditions, as well as neuropsychiatric disorders.[7]

Coronavirus (CoV) structure:

29.9 kb SARS-CoV-2 strains were recovered from a sample of pneumonia patients who worked in Wuhan's seafood market. Spike (S) glycoprotein, membrane (M) glycoprotein, nucleocapsid (N) protein, and tiny envelope (E) glycoprotein are the four main proteins of SARS-CoV-2. There are several auxiliary proteins as well. A transmembrane protein with a molecular weight of roughly 150 kDa, the spike is frequently referred to as S glycoprotein and is present in the outer layer of viruses. By attracting the lower respiratory tract cells' angiotensin-converting enzyme 2 (ACE2) and forming homotrimers that protrude on the viral surface, the S protein helps encapsulated viruses adhere to host cells. [6]

The Furin-like protease in the host cell breaks this glycoprotein down into two smaller fragments, S1 and S2. Part S1 employs the composition of the receptor binding domain to ascertain the host virus's range and cellular tropism, whereas S2 promotes virus fusion in transmitting host cells. [6]

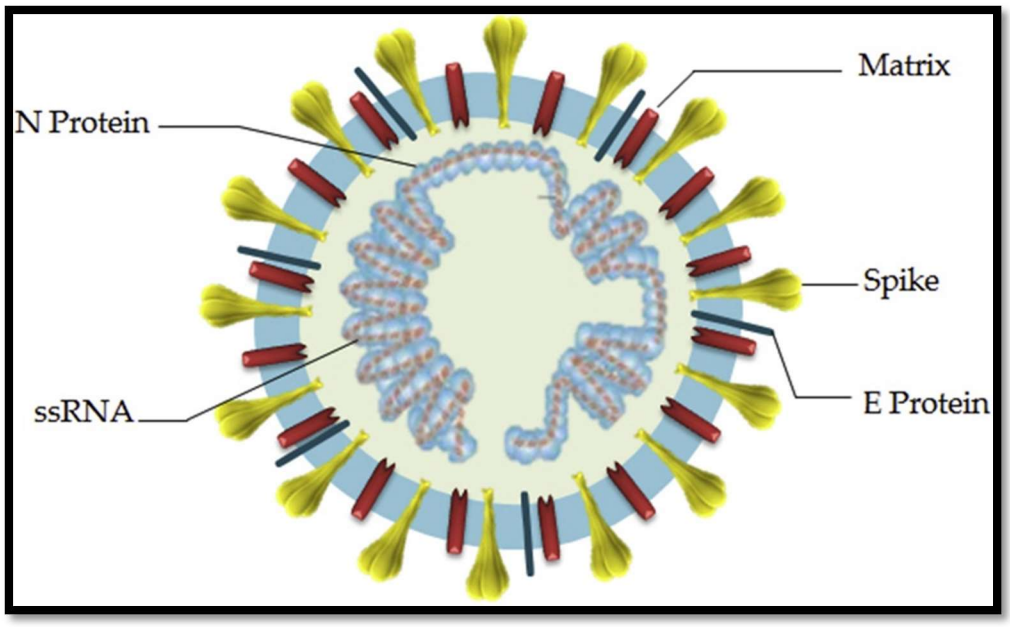

Fig. 2: Structure of corona virus.

CoV's structural component, the nucleocapsid, also referred to as the N protein, is located in the endoplasmic reticulum-Golgi area and is structurally connected to the virus's nucleic acid content. Due to its RNA-binding function, the protein is involved in the viral genome, viral replication

cycle, and host cell biology in response to viral infections. Additionally, the N protein's enhanced phosphorylation might result in structural alterations that boost its affinity for viral RNA.[6]

This virus's membrane protein, also known as the M protein, is another crucial component. This protein is the most organized and influences the structure of the virus envelope. The N protein-RNA complex within the internal virion can be bound by any structural protein; contact with the M protein facilitates the completion of viral assembly and stabilizes N proteins or nucleocapsids. The SARS CoV structure, sometimes referred to as the envelop or E protein, is the last element and is involved in the development and maturation of the virus. [6]

To aid in the virus's penetration into the host cell, SARS-CoV-2 binds to the ACE2 receptor, which is widely expressed in the lower respiratory tract and comprises cells such as the absorptive enterocytes of the ileum and colon, cholangiocytes, myocardial cells, bladder urothelial cells, type II alveolar cell (AT2) of the lungs, upper oesophagus, and stratified epithelial cells. Acute respiratory distress syndrome is caused by pneumonia, and patients infected with this virus also experience heart, kidney, and digestive tract problems.[6]

Epidemiology of Covid-19:

In December 2019, a new, infectious coronavirus disease (COVID-19) outbreak with an unknown etiology was centered in Wuhan City, Province of China. [5]

Coronavirus disease 2019 (COVID-19) is spreading quickly throughout China and is being exported to more countries, some of which have seen additional transmission.[5]

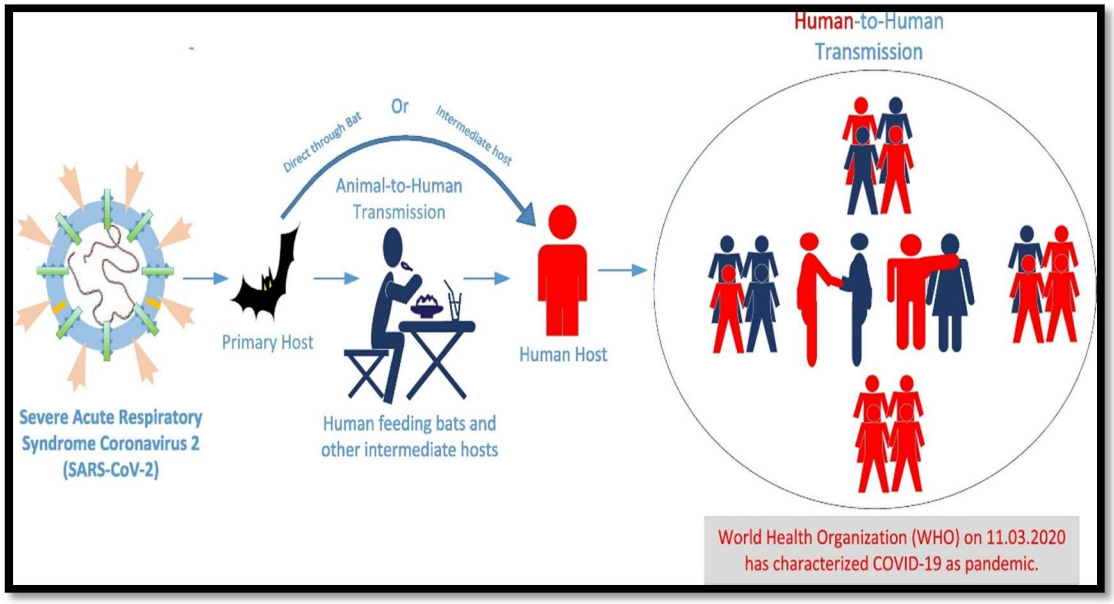

Fig. 3: Epidemiology of COVID-19.

An epidemiologist linked the initial outbreak to a seafood market where more wild animals were being sold for human consumption. Bats were believed to be a source of high-diversity CoV infection.[8]

In the first outbreak, the epidemiologist verified that there was person-to-person transmission via aerosols, droplets and close contact.[8]

In conjunction with the Chinese New Year celebration, the second and third phases of the mass march outside Wuhan city to other parts of China and other countries (more than 200 worldwide) took place.[8]

Recent research indicates that severe COVID-19 is more common in individuals over 60 and in those with diabetes, cardiovascular illness, cancer, chronic respiratory disease, and renal and hepatic failure than in children, who may be less susceptible to the virus. If they do, their symptoms can be minimal or non-existent.[5]

COVID-19 continues to pose a significant risk to public health, according to the World Health Organization (WHO). On March 11, 2020, the WHO declared this outbreak a pandemic because to the dramatic rise in patient numbers, and on January 30, 2020, it declared a public health emergency of global importance.[8]

Transmission of covid-19:

Following successful infection, SARS-CoV-2 is mainly transmitted horizontally between humans, either directly or indirectly through contact with contaminated surfaces.[2]

The host's mucosal surfaces, including the mouth, nose, and eyes, are exposed to respiratory droplets from the invasive disease. Additionally, stethoscopes, kitchenware, blankets, bedsheets, and thermometers are among the goods that the infected person uses or wears that might spread the virus.[4]

Furthermore, it has been found that SARS-CoV-2 can stay in the air for up to three hours. Raising the possibility of getting infected with the virus, there is little chance that maternal COVID-19 will be transmitted vertically to the newborn.[2]

The fecal-oral route is believed to be a minor part of SARS-CoV-2 transmission because the amounts of viral genetic material in urine and feces are significantly lower than those in nasopharyngeal fluids, even though the presence of SARS-CoV-2 RNA in urine and feces suggests that it may also be involved.[2]

The incubation period for COVID-19, or the interval between virus exposure and the beginning of symptoms, is typically 5–6 days, though it can extend up to 14 days. The infected person may spread the virus to healthy people during this time, which is frequently referred to as the "pre symptomatic" period.[4]

Even though patients may have mild, moderate, severe, or no symptoms, COVID-19 patients usually range in age from 40 to 70 and most commonly exhibit fever, body aches, dyspnea, malaise, and dry cough.[4]

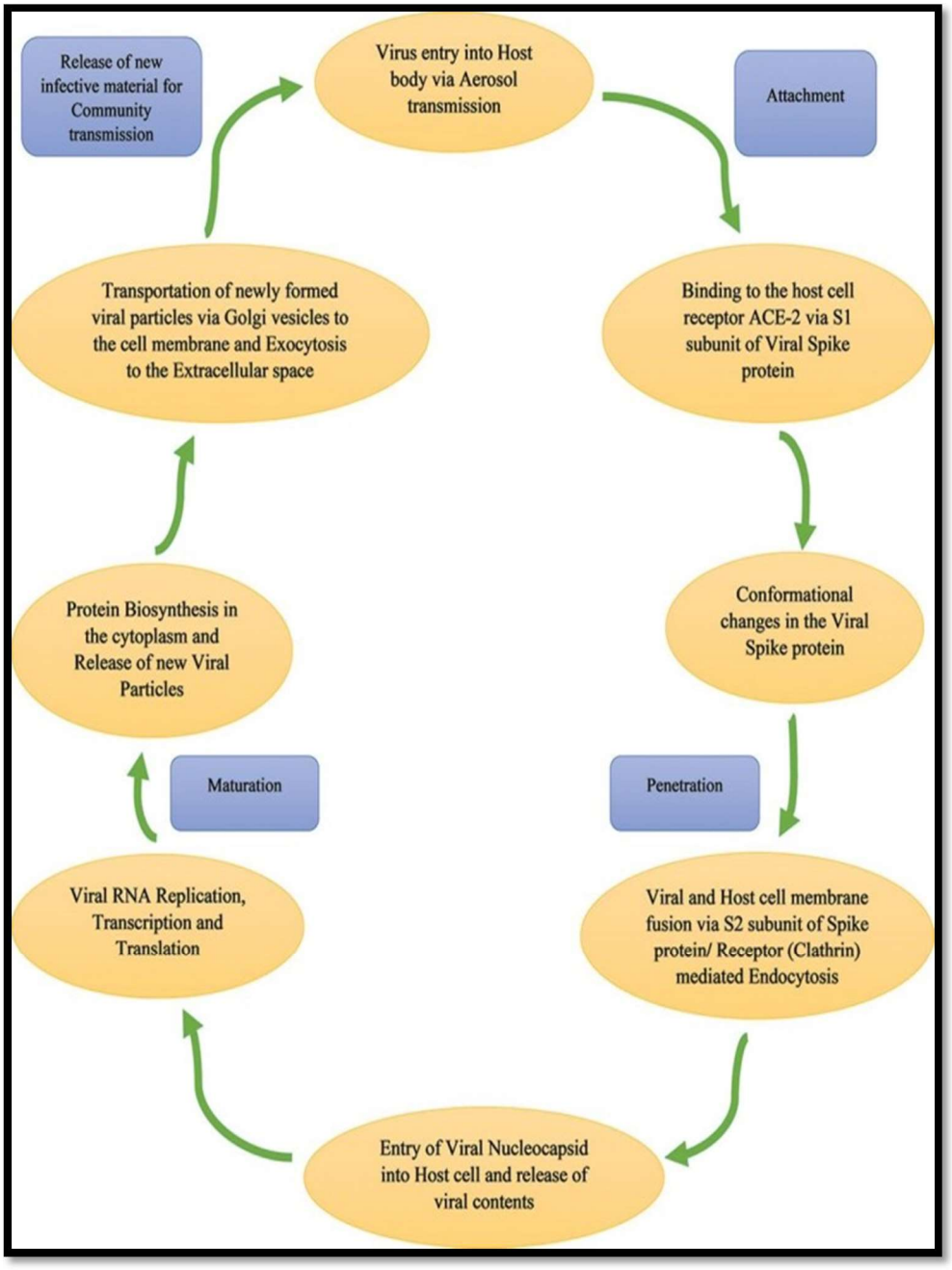

Fig. 4: Transmission of COVID-19.

Additionally, gastrointestinal symptoms such loose stools, vomiting and abdominal discomfort may be present in some people. Patient with COVID-19 infection often experience problem as a result of the "cytokine storm".[4]

Pathogenesis of Covid-19:

The COVID-19 pandemic has highlighted the complex interactions and balance between the immunological, hemostatic, and inflammatory responses. Moreover, genetic variation and acquired host immune systems may be the cause of the different symptoms and their intensity. Indirect markers that this infection has a significant immunological component include pathological characteristics like the presence of neutrophilia and lymphopenia on hematological testing and macrophage infiltration in the infected tissue.[9]

Any virus's attachment and subsequent penetration into the host cell are essential stages of its life cycle. Contact between the spike surface glycoprotein S and angiotensin-converting enzyme 2 (ACE-2), a member carboxypeptidase widely distributed in a range of human organs, is unquestionably what enables SRAS-CoV-2 binding.[9]

It is to be noted that the expression of ACE-2 dependent on age, sex and genetic variables, and that the affinity of the S protein for ACE-2 is reportedly much stronger (at least 10-20 times) than that of similar protein on SARS-CoV-1. This explains why juvenile patients have a relatively low compared to patients over 80 (CFR of 0% for those under 8 vs. 21.9% for patient over 80). Sadly, concomitant diseased like obesity, cancer disease, and immunosuppressive medication use also raise ACE-2 expression, making these patients more likely to suffer severe illness.[9]

The four proteins that make up CoV—S, N, M, and E—allow it to enter the host cell. The S protein is highly N-glycosylated, the M protein is present in the virion as a dimer that keeps its form, and the E protein, a transmembrane protein with ion channel activity, is crucial to viral pathogenesis. The virus can grow and exit the host cell more easily as a result. The nucleocapsid is the sole structure that has the N protein; it encapsulates during infection and aids in binding the viral DNA with the NSP3 protein of the RTC. The compound also acts as an antagonist of interferon (IFN), which seems to facilitate viral propagation.[2]

The ability of the virus to bind to S protein and proliferate across mucosa is finally facilitated by the HE. In human cells, the virus enters after the S protein's Receptor Binding Domain (RBD) first binds to its receptor. Different residues of the RBD of the S protein compared to SARS-CoV and the absence of the polybasic furin cleavage site (RRAR) from other coronaviruses may explain SARS-CoV-2's enhanced virulence and transmissibility. Furin and other proteases can more easily cleave the S protein as a result.[2]

Once in the cytoplasm of the host cell, the virus continues to replicate, transcribe, and translate its structural proteins, such as the M, E, and N proteins. After then, exocytosis is used to construct these proteins. Because the S protein can't assemble and guide cell-cell fusion between infected

cells, the virus can grow inside an infected host, forming large, multinucleated cells that are invisible to antibodies specific to the virus. The M, E, and N proteins are among the structural proteins that the virus copies, transcribes, and translates after entering the cytoplasm of the host cell. These proteins are then assembled and exocytosed.[2]

The virus can propagate within an infected host because the S protein, which controls cell-cell fusion between infected cells, does not assembled and forms huge, multinucleated cells that are invisible to virus-specific antibodies.[2]

Like the original SARS-CoV, the new SARS-CoV-2 enters target cells via using the ACE2 receptor, which downregulates these receptors and increases the production of angiotensin-2 (AT2). Increased pulmonary vascular permeability and lung injury are possible outcomes of elevated AT2 production. Type II alveolar epithelial cells are the primary sites of viral invasion because they express approximately 83% of the ACE2 receptors on their luminal surface. Furthermore, ACE2 receptors are widely distributed in extra-pulmonary tissues such as the gut, kidney, heart, and endothelium, which may be connected to the multi-organ dysfunction seen in these patients.[2]

Interstitial mononuclear inflammatory infiltrates named after lymphocytes were also shown to invade. The patient's acute immunological damage resulted from T cell overactivation, which raised the quantity of cytotoxic granules in CD8 T-cells and the quality of pro-inflammatory cytokines produced by CD4 T-cells. The SARS-CoV-2 virus infects alveolar macrophages and epithelial cells that carry these viral particles, causing lung inflammatory reactions.[2]

In the clinical phase of SARS-COV-2, there are three distinct phases: the "viremia phase," when the virus enters the peripheral blood from the lungs; the "acute or pneumonia phase," when the immune-compromised individuals become critically ill and their T and B lymphocyte counts drastically decrease; and the "recovery phase," when coagulation parameters, such as D-Dimer, and inflammatory cytokines, mainly IL-6, are abnormally elevated.[2]

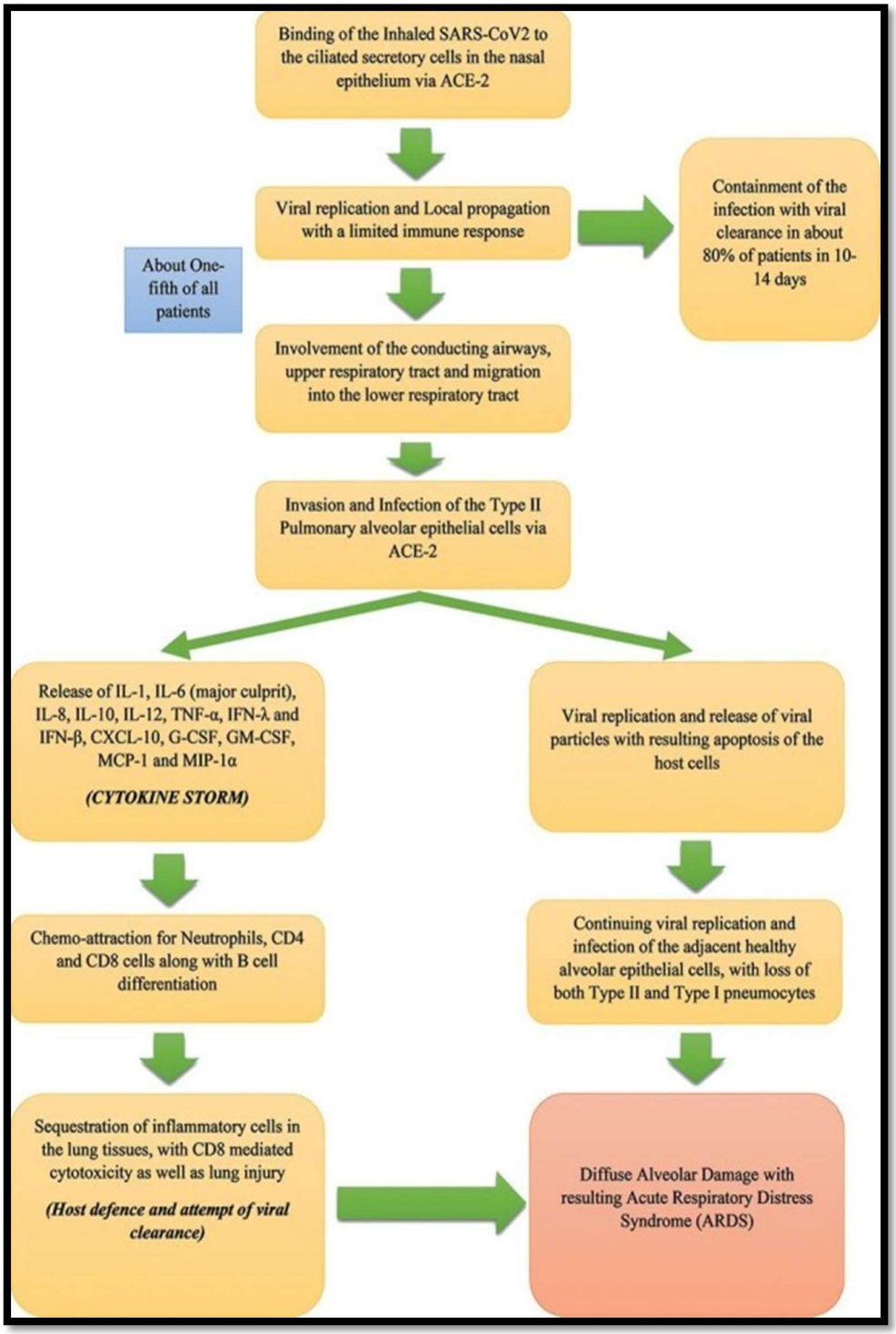

Fig 5: Pathogenesis of COVID-19.

Thus, infection and inflammation caused by an excess of coagulation cascade activation culminate in disseminated intravascular coagulation (DIC). It has been demonstrated that SARS-CoV-2

patients have greater initial plasma levels of inflammatory cytokinesis than do healthy persons. In patients with viral pneumonia, chest CT scans revealed ground-glass opacification with or without consolidative anomalies. The lower lobes of the lungs are involved in the peripheral dispersion of these anomalies, which are more likely to be bilateral. Additionally, there is isolated renal haemorrhage, splenic atrophy, liver enlargement with inflammatory cell infiltration, edema, hilar lymph node necrosis, and scattered neuronal degeneration in the brain.[2]

Additionally, COVID-19 individuals have also been reported to have olfactory dysfunction; however, it is yet unknown if the virus directly affects the olfactory bulb sensory cells.[2]

A pathophysiology of covid-19 is in to three phases,[4]

Asymptomatic phase:

The SARS-CoV-2 virus adheres to the nasal epithelial cells in the upper respiratory tract and is transported by respiratory aerosols. Mature nasal epithelial cells exhibit significant expression of ACE-2, the primary host receptor for viral cell entry. Ciliated cells in the conducting airways become infected, and the virus replicates and spreads locally. A modest amount of work is produced over the course of a few days. Despite having a low viral load at the moment, the patients are highly contagious, and nasal swab testing can detect the virus.[4]

Invasion and infection of the upper respiratory tract:

During this phase, the virus migrates across the conducting airways from the nasal epithelium to the upper respiratory tract. The condition appears as fever, lethargy, and dry cough because it affects the upper respiratory tract. Since the increased immune response is adequate to spreading, most patients do not advance past this stage.[4]

Involvement of infection in lower respiratory tract:

Approximately one-fifth of all infected individuals have severe symptoms at this stage. The virus replicates to create additional viral nucleocapsids after entering type 2 alveolar epithelial cells via the host receptor ACE-2.[4]

Pathogenesis of coronavirus Disease in different parts of the body:[9]

>Pulmonary pathology:

The lungs appear heavy, hard, and highly congested upon gross examination, with patches of firmness ranging from patchy to widespread. The most common histopathological finding in the

majority of patients' lungs is diffused alveolar damage (DAD), which responds to the exudative phase by displaying severe capillary congestion and eosinophilic hyaline membrane. The organizing phase of DAD has been observed in several individuals with persistent respiratory symptoms.

Other lung conditions that have been reported include alveolar haemorrhage and pulmonary edema. Additionally, the prevalence of central or peripheral pulmonary thrombi or thrombo-emboli in many COVID-19 patients may indicate a previous correlation between this infection and coagulopathies. Bacterial superinfection, which is frequent in viral pneumonias, has been linked to both focal and widespread bronchopneumonia.

>Cardiac pathology:

Heart involvement is quite common and severe as a prognostic factor in COVID-19, as evidenced by the elevated cardiac injury biomarker.

This behavior can be explained by a variety of ways. The first would be myocarditis, which would result from a direct infection of the cardiomyocytes. The consequences of the cytokine storm and stress brought on by hypoxemia may be linked to additional mechanisms of heart damage.

From modest symptoms like chest pain or dyspnea to more severe manifestations like arrhythmias, right-sided heart failure, or cardiogenic shock, the clinical presentation can vary widely.

>Hepatic pathology:

The liver specimens have shown nonspecific changes including micro vesicular and mild lobular tract infection.

>Gastrointestinal pathology:

The pathology data are limited, despite the fact that numerous clinical research on the gastrointestinal manifestation of COVID-19 have demonstrated the virus's presence in feces. There have been reports of endothelial and inflammatory cell death as well as endothelitis of the submucosal arteries with inflammatory cell buildup. It was also shown that there were virus particles inside the endothelium cells.

>Pathology in other organs:

Skin biopsies taken from COVID-19 patients have revealed thrombi in tiny dermal arteries, mild lymphocytic exocytosis, and superficial perivascular dermatitis.

Sign and Symptoms of Covid-19:

In addition to other nonspecific symptoms like headache, dyspnea, exhaustion, and muscular pain, coronavirus disease 2019 (COVID-19) patients most frequently experience fever, cough, shortness of breath, and other breathing issues. Additionally, gastrointestinal problems like vomiting and diarrhea may be reported by some individuals.[5]

COVID-19 takes three to seven days to incubate worldwide. About 80% of infected cases stay moderate or asymptotic, 15% become severe, and 5% become critical and need ventilation. Acute respiratory distress syndrome (ARDS) and multi-organ failure complicate severe pneumonia, non-severe pneumonia, and mild illness with upper respiratory syndrome as the three main infection courses.

COVID-19 was similar to SARS and MERS in some clinical manifestations.[5]

All patients eventually acquire varying degrees of lung anomalies, which are visible on chest CT (CT). Patients are given CT scans of their chests, which yield accurate information on the dynamic X-ray pattern. [5]

Aspartate aminotransferase **(AST)**, neutrophils, lactate dehydrogenase **(LDH)**, reactive protein C, inflammatory indicators, lymphopenia, platelet abnormalities, and a decreased level of albumin and platelets were seen in the majority of patients at admission. Furthermore, pleural effusion and bilateral pneumonia were more common in refractory patients.[5]

Generally, hospitalized patients fall into one of two categories: the general COVID-19, which is established using the following criteria: less than ten days in the hospital; a discernible improvement in respiratory symptoms (such as cough, chest pain, and dyspnea) following treatment; the capacity to sustain a normal body temperature for more than three days without the need of corticosteroids or antipyretics; and the subsequent resolution of radiological abnormalities in X-rays or the chest scanner.[5]

Fig. no. 6: Symptoms of COVID-19

A patient was deemed very ill if their respiratory rate was 30 beats per minute, their partial arterial oxygen pressure (PaO2) at the inspired oxygen fraction (Fio2) was 300 mmHg, and their oxygen saturation (Spo2) on a pulse oximeter was 93% at rest.[5]

Diagnosis of Covid-19:

The physical examination, symptom evaluation, and sometimes laboratory testing are used to diagnose corona virus disease 2019.

Molecular tests (RT-PCR):

Nasopharyngeal and oropharyngeal swabs are used to obtain samples from the upper respiratory tract, whereas expectorated sputum and bronchoalveolar lavage are used to obtain samples from the lower respiratory tract (only for patients on mechanical ventilation).[4]

Afterwards, it proceeds through Real-time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) in an automated thermocycler using a master reaction mixture that contains all the components required to generate complementary DNA that is amplified and identified by gel electrophoresis. However, this conventional method is laborious and necessitates highly qualified diagnostic personnel in outfitted lab settings.[4]

Numerous commercial and in-house assays have been developed using a broad range of target areas and gene targets. The COVID-19-RdRp/Hel RT-PCR assay is an example of the extensive research conducted to develop the RT-PCR assay. It has a lower limit of detection (LoD) and higher specificity than the well-known RdRp-P2 assay for the detection of SARS-CoV-2 RNA in vitro and in patient specimens.[2]

Fig. no. 7: RT-PCR TEST

It is recommended that the test be repeated for verification in the event of a positive result and to verify viral clearance in COVID-19 positive cases. While 53.3% of patients with COVID-19 had positive oropharyngeal swabs, approximately 71% of patients tested positive for RT-PCR utilizing sputum samples, indicating the low sensitivity of both assays. Usually, the results of the RT-PCR after two to eight days show positive.[4]

The CDC developed the Flu SC2 Multiplex Assay, a novel nucleic acid-based test that can identify SARS-CoV-2, influenza A, and influenza B all at once. SARS-CoV-2 testing and ongoing flu monitoring are made possible by this assay. [2]

Blood tests:

Frequently observed in conjunction with lymphopenia, a decreased or aberrant white blood cell count is also believed to be an indication of a worse prognosis.[4]

In addition to lymphopenia, a decreased or aberrant white blood cell count is frequently observed, and this is also believed to be an indication of a worse prognosis.[4]

Some patients have higher neutrophil-to-lymphocyte ratios and higher D-dimer levels.[4]

Fig.no. 8: Blood test

Severe cases may have coagulation problems, as evidenced by elevated prothrombin time and international normalized ratio.[4]

Chest X-ray:

A chest X-ray may not reveal any notable alterations and is typically inconclusive in the early stages of the disease. Bilateral multifocal alveolar opacities are seen when the illness worsens and could also be linked to pleural effusion.[4]

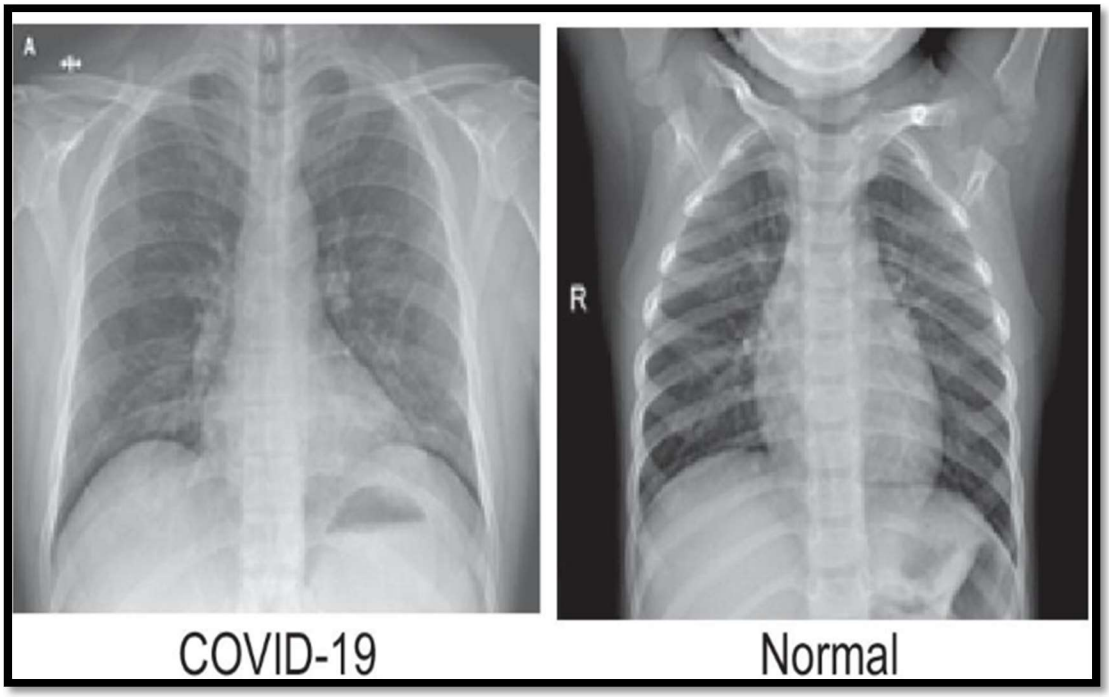

Fig. no. 9: Chest X-ray

Computer tomography scans (CT Scans):

Even in the early stages of COVID-19 pneumonia, high-resolution CT (HRCT) is the preferred diagnostic technique due to its exceptional sensitivity. With a higher involvement of the lower lobes, the most typical features are multifocal bilateral "ground-glass" patches and patchy peripheral dispersion linked to consolidation. Some individuals also exhibit the "reversed halo sign," which is a core region of patchy opacities encircled by a periphery ring that has consolidation. Pleural effusion, cavitation, calcification, and lymphadenopathy are further findings.[4]

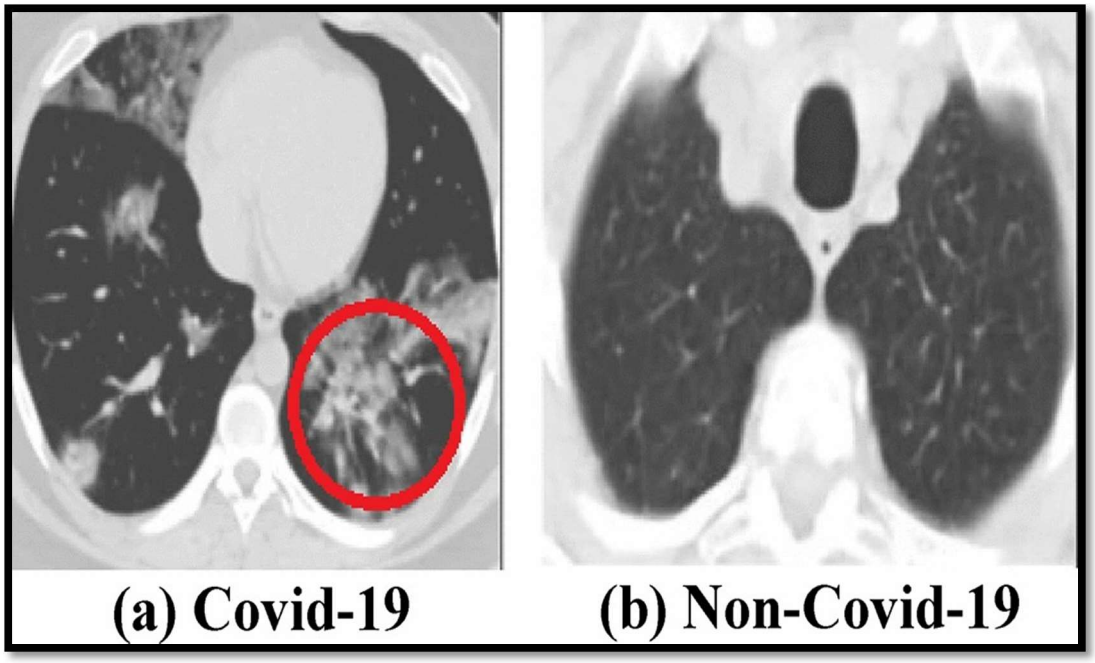

Fig. no. 10: CT scan

Serology testing:

The Enzyme-Linked Immunosorbent Assay (ELISA), which detects a rise in antibodies against specific strains of CoV in patient sera obtained during the acute or convalescent stages, is a rapid and secure method of diagnosing the illness. One day after the sickness began, N protein was discovered in the serum samples of SARS CoV patients. These N proteins can be used as antigens in ELISA to identify the SARS-CoV and a number of other animals CoV-specific antibodies. Variations in the sensitivity and specificity of serologic testing have been documented.[4]

Fig. no. 11: serology testing

However, the **FDA** has cautioned against using many of the currently available SARS-CoV-2 serology tests to rule out infection, implicate genuine infection, or determine protective immunity since they lack adequate clinical validation. Therefore, only sensitive molecular (PCR) studies of respiratory secretions can rule out an active infection. [4]

Treatment of Covid-19:

Supportive treatment:

The cornerstone of treatment for COVID-19 is still supportive care. For patients with serious infections, oxygen therapy is the main course of treatment. Mechanical ventilation is necessary when oxygen therapy is not working to treat respiratory failure, and hemodynamic support is necessary to treat septic shock. Controlling hydration and using antibiotics to treat subsequent diseases are examples of further supportive therapy. Antiviral medications are being used to limit SARS-CoV-2 reproduction, with some encouraging initial results, while a range of immunomodulatory medications are being studied in clinical trials to reduce cytokine storm and the resulting inflammation. Supportive care continues to be the cornerstone of COVID-19 care.[2] Supportive care is still the cornerstone of COVID-19 treatment. For patients with severe infections, oxygen therapy is the primary treatment. Mechanical ventilation becomes essential when oxygen therapy is unable to treat respiratory failure and hemodynamic support is required to treat septic shock. Two more supporting strategies include controlling hydration and utilizing medications to treat any infections that may arise. Clinical trials are investigating a variety of immunomodulatory drugs to limit SARS-CoV-2 replication and lessen cytokine storm and the ensuing inflammation, with some promising first results. Supportive care is still the cornerstone of COVID-19 treatment.[2]

Antiviral agents:

Chloroquine **(CQ)** and hydroxychloroquine **(HCQ)** were initially thought to be effective against SARS-CoV-2, but the WHO SOLIDARITY trial found no significant impact on mortality, leading to their discontinuation in treatment protocols.[2]

Remdesivir, an adenosine analogue, has shown promise in several clinical trials. It mimics natural nucleosides, inhibiting viral RNA polymerase and thereby reducing viral replication. Originally developed for Ebola, remdesivir demonstrated a reduced median recovery time in COVID-19 patients (11 days compared to 15 days for placebo) in preliminary studies, though overall survival benefits were not statistically significant. However, subsequent trials, including SOLIDARITY, indicated little effect in hospitalized patients, prompting the WHO to recommend against its use on November 20, 2020.[2]

In contrast, baricitinib, an anti-inflammatory drug that inhibits Janus kinase **(JAK)** 1 and 2, has shown potential when combined with remdesivir, resulting in shorter recovery times and improved clinical outcomes in patients requiring high-flow oxygen. This combination received FDA emergency authorization for treating severe COVID-19 cases.[4]

NIH guidelines now recommend remdesivir for hospitalized patients with low oxygen saturation and baricitinib in combination with remdesivir for those on mechanical ventilation or ECMO. Treatment durations are generally 5 days for non-intubated patients and up to 10 days for those who are mechanically ventilated.[2]

Other antiviral agents like lopinavir/ritonavir and oseltamivir showed limited benefits in COVID-19 treatment. Favipiravir, approved in India as 'FabiFlu' for mild-to-moderate cases, has demonstrated in vitro activity against SARS-CoV-2 and resulted in significant improvements in some patients.[2]

Overall, while individual antiviral drugs have shown some effectiveness, there is a need for further research on combination therapies to improve outcomes for critically ill COVID-19 patients.[2]

Corticosteroid:

Steroids can be administered for a short duration, such as three to five days, to patients who show gradual deterioration of oxygen saturation, acute worsening of chest imaging features, and enhanced activation of the pro-inflammatory response. Methylprednisolone, the first and only steroid initially recommended, should not be used in excess of 0.5–1 mg/kg/day for mild patients and 1-2 mg/kg/day for severe instances. As steroid-mediated immunosuppression delayed viral clearance, greater doses were not recommended. Recent research has also demonstrated that dexamethasone can help reduce mortality in cases of severe and extremely ill patients.[4]

Antibiotics:

While an effective antibiotic regimen is generally not recommended in cases of viral pneumonia, it does help prevent or manage sepsis and subsequent bacterial infections. Azithromycin and other macrolides have a potent anti-inflammatory effect on the airways and are effective in avoiding lung infections in patients with viral pneumonias.[4]

Immunomodulatory Drugs:

Research on the FDA-approved anti-IL6R medication tocilizumab has been extensive. A randomized controlled trial that was published in The New England Journal of Medicine looked at the effects of tocilizumab on 389 patients. Tocilizumab decreased advancement to the composite objective of mechanical ventilation or death, but it did not improve survival in COVID-19 pneumonia patients admitted to the hospital without mechanical ventilation, according to the trial's results. A French trial comparing tocilizumab plus standard treatment to standard treatment alone also found that tocilizumab decreased the rate of non-invasive or mechanical breathing as compared to placebo. 129 COVID-19 patients who were not in the intensive care unit and those who had moderate to severe pneumonia participated in the trial. Other potential drugs under investigation include anti-GM-CSF drugs, monoclonal antibodies specific to SARS-CoV-2, sarilumab (anti-IL6R), siltuximab (anti-IL6), and anakinra (anti-IL1)..[2]

Supplementary therapies:

Given the increased risk of thrombosis, patients with moderate anticoagulation (once daily) to severe anticoagulation (two daily) should receive prophylactic anticoagulation with low molecular weight heparin (LMWH) (enoxaparin 40 mg SC, for example). Comorbid conditions including diabetes, hypothyroidism, or related hypertension should be treated appropriately. Needful discussions with obstetric, neonatal, and critical care specialists should be sought when pregnant women exhibit severe illness. For individuals experiencing worry and fear after receiving a COVID-19 diagnosis, psychological counseling should be provided.[4]

ENDOCRINE SYSTEM:

The **endocrine system** is a complex network of glands and hormones that regulate various physiological processes in the body. It plays a crucial role in metabolism, growth, reproduction, and stress response. Below are key details about the endocrine system:

Major Endocrine Glands & Their Functions:

1. **Hypothalamus** - Communicates with the pituitary gland to regulate hormones.
   Pituitary Gland - referred to as the "master gland," it regulates other glands that produce hormones.
   - Generates prolactin, oxytocin, growth hormone (GH), and antidiuretic hormone (ADH).
2. **Thyroid Gland** - Regulates energy balance and metabolism.
   - Thyroxine (T4) and triiodothyronine (T3)are produced.
3. **Parathyroid Glands** - Control blood calcium levels.
4. **Adrenal Glands** - Control stress response, metabolism, and blood pressure.
   - Produce cortisol, adrenaline, and aldosterone.
5. **Pancreas** - control blood sugar levels.
   - Produces insulin and glucagon.
6. **Ovaries (in females)** – Production of oestrogen and progesterone, essential for reproduction.
7. **Testes (in males)** – Production of testosterone, essential for male reproductive functions.
8. **Pineal Gland** - Regulates sleep patterns via melatonin secretion.

How COVID-19 Affects the Endocrine System:

Thyroid dysfunction: COVID-19 survivors showed lower levels of T3 and T4 hormones and higher TSH and aTPO antibodies, suggesting a potential autoimmune thyroid condition.

Hormonal changes:

- Increased prolactin levels.
- Lower testosterone levels in males.
- No significant changes in cortisol and estradiol levels.

Metabolic Impact:

- No major changes in glycaemic control, body composition, or lipid profile, except for an increase in HOMA2-B index, indicating a potential alteration in pancreatic beta-cell function.

Conclusion:

The COVID-19 pandemic has had a significant impact on medical infrastructure, economy, and world health. Many elements of the virus's transmission, pathogenesis, diagnosis, and treatment are still unknown, despite extensive research in these areas. The need for more research is highlighted by the variation in symptoms, long-term problems, and the virus's effects on several organ systems, including the endocrine system.

The long-term implications of COVID-19, post-infection symptoms, and the complete effectiveness of existing medications are still unknown despite advancements in diagnoses and treatment approaches. Further investigation is needed into the ways in which SARS-CoV-2 interacts with the immune system and its possible contribution to the development of metabolic or autoimmune diseases. Additionally, thorough clinical trials are required to confirm the efficacy of newly developed immunomodulatory medications and antiviral medicines.

This review suggests to continue research is essential to better understand the virus's evolving nature, develop more targeted treatments, and improve prevention strategies. Future studies should focus on identifying long-term health risks, optimizing therapeutic approaches, and enhancing global preparedness for potential future outbreaks.

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