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Characteristics, Comorbidities, and Vaccination of COVID-19

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Abstract: ***COVID- 19 (Coronavirus disease 2019) is a quite contagious disease this is derived from Orthocoronavirinae family. SARS-CoV-2 viruses are single-stranded, plus-stranded RNA virus that infect numerous animal species, inclusive of humans, and cause respiration, neurological, and liver illnesses. SARS-CoV-2 is generally transferred through respiration droplets during close contact including speaking, coughing, sneezing, and shouting. Typical common symptoms of COVID-19 include respiratory symptoms like Fever and cough, diarrhea, nausea, vomiting, loss of appetite, and neurological manifestations. COVID-19 has currently been recognized using a viral nucleic acid RT-PCR test primarily based totally on affected person nasopharyngeal and throat swabs. The CT score could play a important function in the prognosis of COVID-19 infected patients if the RT-PCR test for swabs became negative at an early stage. COVID-19 patients with comorbidites like Diabetes Mellitus, Hypertension, Asthma, Deep Vein Thrombosis, Chronic Obstructive Pulmonary Disease (COPD), Cardio Vascular Disease, Obesity, Renal Disease, Liver Disease and other comorbidities can develope life-threatening situation. Remdesvir is the primary preference of medication, an antiviral agent that works via way of means of inhibiting viral replication in the body. There is a higher death rate in men while in comparison to women, hypothetically because of sex-based immunological or gendered differences. Vaccines are regarded as the maximum efficient way to halt the pandemic.***
Keywords: COVID-19, SARS-CoV-2, RT-PCR, comorbity, treatment, vaccine.

I. INTRODUCTION

COVID-19, a disease caused by infection with the SARS-CoV-2, was initially discovered in China in 2019 and has since spread throughout the world. World Health organisation (WHO), on March 11th in the year of 2020, labelled the Coronavirus disease (COVID-19) outbreak of 2019 a Pandemic [1]. SARS-CoV-2, a novel, positive-sense single-stranded, enveloped RNA virus with a close similarity to SARS-CoV, was identified as the pathogen [2]. The associated disease was then named Coronavirus disease 2019 or Covid-19. It rapidly spread through the World, becoming a pandemic and global health emergency, which affected over 10 million people with a death count of more than 5000 by July 2020 [3]. While the disease is under control in some areas, it is still progressing globally [3]. This virus genomic features were shown to be significantly different from human SARS-CoV and Middle Eastern Respiratory Syndrome (MERS) CoV [4]. SARS-CoV-2 virus are single-stranded, plus-stranded RNA viruses that infect a variety of animals, including humans, and cause respiratory, neurological, and liver problems [5]. Typical common symptoms of COVID-19 include respiratory symptoms like Fever and cough, diarrhea, nausea, vomiting, loss of appetite, and neurological manifestations [6]. COVID-19 disease can show in a variety of ways, ranging from asymptomatic or mild disease (up to 18%) to a severe life-threatening sickness with pneumonia. A small percent of individuals experience respiratory distress that necessitates Intensive Care Unit ventilation support (ICU; 3-5 percent). An exuberant immune response to the virus can sometimes induce a severe inflammatory response marked by high levels of IL1-, IL-6, TNF, and inflammatory chemokines such as C-C motif chemokine ligands (CCL)-2,3 and 5[7]. Increased pneumonia, myocarditis, and renal impairment, all of which can be fatal, can occur from an inflammatory response. The mortality rate in the general population is estimated to be between 1.4 and 8% [7]. To prevent the disease from progressing, mild or moderate patients should be admitted to the hospital and separated from the susceptible population to prevent further transmission [8]. Due to angiotensin-converting enzyme-2 (ACE-2), the intergrate site for SARS-CoV-2, which is widely indicated in proximal tubule cells and podocytes, the Renal might be a target organ for harm in COVID-19 patients [9]. Based on numerous case series and retrospective reviews, AKI has been recognised as the most severe COVID-19 blockage related to a extra threat of dying in significantly ill patients [9]. SARS-CoV-2 usually causes acute hypoxemic respiratory failure (AHRF) due to viral pneumonia in serious conditions. This could progress to ARDS, a prevalent but under-recognized cause of ICU admission that is linked to high fatality rates and considerable morbidity in survivors [10]. In the ICU, such patients are managed using standard methods, such as invasive mechanical ventilation (MV), in accordance with evidence-based clinical practise recommendations [11]. Despite the fact that COVID-19 or SARS-CoV-2 affects people of all ages, epidemiological research consistently shows that children have a less severe than adults [12].

II. CORONAVIRUS DISEASE 2019 (COVID-19)

COVID- 19 (Coronavirus disease 2019) is a quite contagious disease that is derived from Orthocoronavirinae family. The virus has a single-stranded RNA envelope and unique 'crown-like spikes' on its surface [13]. Coronaviruses (CoVs) are divided into four genera: α-CoV, β-CoV, γ-CoV and δ-CoV [14]. For certain SARS-CoV-2 isolates, the BinaxNOW limit of detection (LOD) [15], its ability to detect VOC-202012/01 or B.1.1.7 (α) was initially discovered in the UK, B.1.351 (β) in South Africa, P.1 (γ) in Brazil, and B.1.617.2 (δ) in India [15]. SARS-CoV-2 is a member of the β-CoV virus family, which is an enveloped virus with a positive-sense RNA genome that causes COVID-19 [16]. The genome of SARS-CoV-2 single-stranded positive-sense RNA enclosed in a membrane envelope approximately 75–150 nm in diameter. Coronavirus has a genome that is roughly 30 K nucleotides long. SARS-CoV-2 shares around 85 percent of its homology with SARS-CoV [17]. The spike (S) surface glycoprotein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein are the four major structural proteins encoded by the SARS-CoV-2 genome. RNA polymerase, RdRp; papain-like protease, PLpro; and coronavirus primary protease, 3Clpro are among the non-structural proteins encoded by the SARS-CoV-2 viral genome [18]. Coronavirus reaches the CNS via nerve olfactory with nasal infection, and then it can cause inflammation and demyelination [19]. Around the time when symptoms occur, the viral load in the upper respiratory tract of infected people reaches its highest [20]. The viral shedding is estimated to start 2-3 days earlier than the onset of symptoms [20]. This means that presymptomatic carriers can transmit the infection [21].

COVID-19 pathogenesis is based on the coronavirus (CoV) spike protein (SP) attaching to ACE2 receptors, where it is subsequently proteolytically cleaved into SP1 and SP2, leading in effective host cell infection [22]. Angiotensin-converting enzyme (ACE) is a protein that converts angiotensin 2 receptors are found in the lungs, various regions of the gastrointestinal tract (GIT), the heart, and the brain/central nervous system, among other organs. As a result, respiratory, cardiac, gastrointestinal, and neurological indications are the most common COVID-19 symptoms in symptomatic patients [23].

Severe Respiratory failure that results in immune dysfunction is observed in COVID-19 patients [24]. In acute respiratory failure, the macrophage activation syndrome was observed, as well as lower human HLA-DR expression and a lower number of CD4 lymphocytes, natural killer cells, and CD19 lymphocytes, as well as persistent TNF- and IL-6 production [25]. Plasma from COVID-19 patients inhibited the expression of Human Leukocyte Antigen-DR (HLA-DR), which may be partially restored with an IL-6 blocker. In this case, IL-6-based expression of HLA-DR is a distinguishing feature that deals with cytokine production and hyperinflammation. SARS-CoV-2 affects the host immune response, resulting in hyperinflammation and reorganisation of the RAAS. An imbalance in RAAS and high inflammation induced acute lung damage and coagulopathy. The RAAS system is an essential hormone system that controls blood pressure and helps the body's fluid equilibrium. It would also cause fibrinolysis, immunothrombosis, and damage to various organs [26]. Patients in the later stages of the disease have worsening symptoms and die quickly due to organ failure and acute respiratory distress syndrome (ARDS). All of these things happen as a end result of cytokine storms, and they play a big role in exacerbating symptoms. Clinical trials in severely unwell patients have also validated cytokine storm. As a result, suppressing the cytokine storm is another strategy to treat COVID-19-infected patients [27].

A. Replication of SARS-CoV-2

There are 8-10 open reading frames (ORFs) in SARS-CoV-2. ORF1a and ORF1b are transformed into polyprotein 1a (pp1a) and pp1ab, respectively, which are then processed by viral proteases to produce sixteen non-structural proteins containing RNA-dependent RNA polymerase enzymes (RdRp). The viral RNA is replicated by an RNA-dependent RNA polymerase enzyme that arranges a minus-strand transcription (RdRp). SARS-CoV-2 generates 6-9 subgenomic mRNAs (sg mRNAs) during replication, which result in the translation of extra and structural proteins from downstream open reading frames (ORFs) [28].

Spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, which are produced from sgmRNAs, complete the viral replication cycle [29].

B. Immune Response of SARS-CoV-2

A higher B/T cell ratio was seen in COVID-19 patients [30], [31]. ASCs are discovered after 7 days of post-admission in mild cases, and they have a link with viral clearance [31]. In severe cases, ASCs levels are increased than healthy controls, 7 days after the arrival of the symptoms [32]. In the case of SARS-CoV-2, no significant changes in IgM and IgG production were detected, with a peak from 7 to 40 days post-admission, regardless of clinical course [33], [30], [31].

Also, it shows that in asymptomatic patients their IgG was decreased while as compared to symptomatic patients, and their neutralizing antibody activity was also reduced [30]. As a result, only 19.3 percent of patients had a healthy level of neutralisation activity, which reduced up to twenty eight days after recovery, indicating that neutralising antibodies had a limited half-life [34].

C. Transmission

SARS-CoV-2 is typically transferred through respiratory droplets during close contact such as speaking, coughing, sneezing, and shouting [35]. The virus can survive for up to 7 days on impenetrable surfaces in laboratory circumstances, depending on the substance. Touching surfaces or items contaminated with the virus is another possible mode of transmission [36]. Despite the fact that large-scale vaccine manufacture is now regarded a dawn for civilization, the globalisation of vaccination [37] and virus mutation [38] make it difficult to eradicate SARS-CoV-2. After a 1-14 day incubation period, COVID-19 infected patients may develop symptoms [39]. In the blood of infected patients [40] and also in blood donars [41], RNA from SARS-CoV-2 has been found. However, there's no affirmation so far that it may be transmitted via blood transfusion [42].

D. Epidemiology

Elderly adults, men, and pre-existing diseases such as comorbidities are all characteristics that contribute to a worse COVID-19 outcome [43]. Patients with autoimmune diseases (AD) have additionally been discovered to have a higher threat of infection severity [43], because they have a typical immune response and are frequently treated with immunosuppressive drugs [44]. There is a higher death rate in men when compared to women, hypothetically due to sex-based immunological or gendered differences [45]. Some studies show a higher death rate in patients with COVID-19 due to renal involvement [46].

III. CLINICAL MANIFESTATIONS

Fever, tiredness, cough, anorexia, sputum production, shortness of breath, and other symptoms of COVID-19 disease vary from patient to patient, but the most prevalent symptoms during various stages of COVID-19 disease include fever, fatigue, cough, anorexia, sputum production, shortness of breath, and others [47]. There have also been reports of less common symptoms such as sore throat, headache, disorientation, shortness of breath, and chest tightness [48] there were additional reports of minor symptoms like nausea, vomiting, diarrhoea, and gastrointestinal complications [49]. COVID-19 symptoms were identical in adults and children, but the symptoms in children were milder than in adults [50]. At the beginning of the Pandemic, the Neurological clinical symptoms of COVID-19 were reported [51]. The viral infection syndrome is correlated with nonspecific symptoms like dizziness or headache [52]. In the early phase of COVID-19 infection, the common symptoms were Anosmia and Dysgeusia [53]. COVID-19 patients' neurologic consequences, such as CNS dysfunction, altered level of consciousness or stroke, encephalitis, seizures issues, or PNS and skeletal muscle complications, such as myopathy [51], must be addressed by neurologists [51].

Because they express the ACE2 receptor, the targets of SARS-CoV-2 infection includes CNS cells such as astrocytes and oligodendrocytes [54]. Previous studies showed that from deer mice coronavirus has been found in neurons and microglia after 6 days of infection [55]. As a result, 36.4 percent of patients exhibit a range of neurologic symptoms, such as headaches, altered consciousness, and Guillain-Barre syndrome [56]. Coronavirus reaches the CNS via peripheral nerves and the BBB, although it is unclear whether the virus uses immune cells to enter the CNS or to get past the BBB [57]. As a result, it has been demonstrated that COVID-19 infected patients have olfactory and taste problems (OTDs) [56]. Clinical symptoms are more frequent in women when compared to men [58]. Dysgeusia and Ageusia were the symptoms of taste disorder, while hyposmia and anosmia exist as olfactory disorders [59]. The coronavirus arrived at the olfactory bulb and enter the CNS then cause symptoms involving Olfactory and Taste disorders [60]. However, because the ACE2 receptor is not produced by olfactory sensory neurons, SARS-CoV-2 will not infect them unless it employs a receptor that has yet to be discovered [60].

IV. INTERPRETATION

High C-reactive protein (CRP), lymphopenia [61], increased fibrinogen, and D-dimer were the most prevalent laboratory markers in SARS-CoV-2 infections [62], [63]. Some comorbidities had been detected as prognoses like HTN, DM, obesity, cardiovascular and respiratory chronic diseases [63]. COVID-19 has recently been diagnosed using a viral nucleic acid RT-PCR test based on patient nasopharyngeal and throat swabs [64]. The clinical studies disclosed different clinical and laboratory characteristics between the non-severe and severe patients, and some prognostic risk factors were initially discovered, such as age and D-dimer [65].

A. D-Dimer

D-dimer derives from the development and lysis of cross-linked fibrin and reflex activation of coagulation and fibrinolysis [66]. Recent studies suggested that a prominent elevation in D-dimer levels as an indicator of adverse outcomes was constantly seen in COVID-19 indicating the presence of underlying coagulopathy [67].

B. Ferritin

Ferritin is a key acute phase promoter this produced in inflammatory diseases of the body such as infectious, neoplastic, hematologic, and rheumatologic [68]. Increased serum ferritin levels have been seen in COVID-19 infected patients, indicating that ferritin plays a defence role within the body by limiting the supply of iron. Ferritin limits the pathogen's access to iron, also regulates cytokine production and release, which is responsible for to produce cytokine storm [69].

C. C- Reactive Protein (CRP)

C-reactive protein (CRP) is responsible for inflammation or infection. The CRP is an acute phase promoter and proced in the liver. Most acute-phase proteins have substantial changes in plasma levels due to synthesis, consumption, and catabolism rates, but CRP levels are almost constant in plasma. Serum concentration is considerably raised during acute inflammation, and it is a more accurate measure for sepsis [70]. CRP also plays a role in proinflammatory cycle by activating the inflammatory cytokines in the body [71]. Both CRP and serum ferritin play important roles in the production of proinflammatory cytokines. Surprisingly, in COVID-19, the cytokine storm is the principle of immunopathology. When the virus replicates quickly in the body's endothelium and epithelial cells, the immune system produces a large number of proinflammatory cytokines and chemokines [72]. COVID-19 severity is still reflected in the generation of large amounts of proinflammatory cytokines, which can eventually contribute to ARDS and MOF [73]. Previous research has linked respiratory tract viral infections to worse clinical outcomes due to higher levels of immune responses like cytokines and chemokines generated during infection [74]. ARDS, sepsis, septic shock, coagulopathy, metabolic acidosis and MOF are also common consequences in severe COVID-19 cases [75]. The most serious consequences, such as sepsis, ARDS, respiratory failure, and heart failure, were identified based on the clinical characteristics of deceased COVID-19 patients [76].

D. Interleukin- 6 (IL-6)

Several investigations have found that COVID-19 patients with increased IL-6 levels require hospitalisation or present with abrupt respiratory failure [77], [78]. When compared to patients with non-complicated COVID-19 (i.e. ICU admission or acute respiratory failure), patients with complex COVID-19 [had about three times higher serum IL-6 levels p [79]. Clinical factors such as the highest body temperature or the presence of bilateral lung involvement on chest CT [78] were also linked to elevated IL-6 levels. Finally, IL-6 levels were higher in severe COVID-19 infected patients than in non-severe COVID-19 infected patients [80].

E. Lactate Dehydrogenase (LDH)

In COVID-19 patients, lymphopenia and elevated level of lactate dehydrogenase (LDH) were linked to a greater likelihood of ICU admissions [81].

F. RT-PCR and CT Scan

To detect SARS-CoV-2 [82], a real-time reverse transcriptase-polymerase chain reaction test (RT-PCR test) has been widely employed. The chest computed tomography (CT) scan is useful for illness staging and monitoring treatment efficacy, whereas RT-PCR is still the gold standard for COVID-19 diagnosis [83], though it is limited to identifying the virus, which has significant limitations [84]. When compared to RT-PCR, early chest CT aids in illness detection with improved sensitivity [85]. The diagnosis of COVID-19 pneumonia was made based on epidemiological factors, clinical symptoms, chest CT imaging, and laboratory data. The chest picture would play a significant role in the diagnosis of COVID-19 infected patients if the RT-PCR test for swabs was negative at an early stage [86].

G. Negative RT-PCR

A false-negative diagnosis is observed when RT-PCR testing results in negative after a positive test result in the early stages of the disease. Repeated RT-PCR testing is recommended by clinical practise guidelines and consent statements to confirm a clinical diagnosis, especially in the presence of symptoms related to COVID-19 [87]. Multiple pre-analytical and analytical factors, which includes loss of standardisation for specimen collection, postponement or poor storage conditions earlier than arrival withinside the laboratory, the use of insufficiently validated assays, contamination during the procedure, insufficient viral specimens and load, the disease's incubation period, and the sight of mutations that clear out detection, have been implicated in COVID-19 detection failures [88].

V. COMORBIDITIES

A. *Diabetes Mellitus (DM)*

COVID- 19 infected type 2 diabetes patients have a major risk of negative outcomes than non-diabetic patients [89]. Diabetes is a risk factor for structural and pulmonary ventilation abnormalities in severe COVID-19 patients [90]. Metformin may have a favourable effect on antiviral by reducing pro-inflammatory and pro-fibrotic states [91] and improving immune response, according to theoretical findings [92]. Due to reduced phagocytic cell capacities, people with diabetes are greater at a risk of infections. An elevated level of ACE-2 receptors has been linked to diabetes in Mendelian randomization research, which could contribute to SARS-CoV-2 infection in diabetics [93]. Furin is a type 1 membrane-bound protease that is increased in diabetes individuals [94]. When furin is linked to the entry of virus into the host cell, SARS-reliance CoV-2's on human proteases lessens. The SARS-CoV-2 spike (S) protein binds to ACE-2 receptors, which are triggered by high levels of furin. This pre-activation of the spikes (S) protein permits to enter the virus into the cell and avoid detection by the human immune system [95]. As a result, an aberrant immune response characterised by higher ACE-2 receptors and furin expression may result in greater lung inflammation and lower insulin levels. For diabetic patients, the virus's proper entrance results in a life-threatening situation [93], [94]. T-cell dysfunction and elevated levels of IL-6 are also important factors in the development of COVID-19 illness in diabetics [96].

B. *Hypertension (HTN)*

COVID-19 infection patients with uncontrolled blood pressure have a higher case fatality rate. COVID-19 cases were reported in China with 23 percent of hypertensive patients and 6% CFR, with the number steadily increasing due to pandemic anxiety [97]. ACE-2 inhibitors and ARBs are commonly used to treat hypertension in hypertensive patients. When ACE-2 and ARB inhibitors are taken in large doses, the ACE-2 receptors upregulate expression, resulting in greater exposure to SARS-CoV-2 infection [98]. The greater expression of receptor cells on the lungs makes infection more vulnerable, increasing the risk of serious lung injury and respiratory failure [100]. ACE-2 is a powerful anti-inflammatory medication that protects COVID-19 patients from serious consequences such as respiratory distress syndrome, lung injury, and renal injury. The use of Angiotensin converting enzyme inhibitors and ARBs, which reduce the inflammatory impact of angiotensin II [99], increases ACE2. Although it is unclear if using ARBs or ACE inhibitors is harmful or useful, it is recommended that these inhibitors be used to maintain normal blood pressure. Controlling blood pressure in COVID-19 patients is critical for reducing disease burden [100].

C. *Cardiovascular Disease (CVD)*

ACE2 is highly and intentionally expressed in pericytes [101], despite its modest expression in cardiomyocytes. The frequency of cardiac damage ranged from 2% in non-severe COVID-19 patients to 59 percent in severe COVID-19 patients [102], according to a meta-analysis. As a result, SARS-CoV-2 infection may assault pericytes in the human heart, causing capillary endothelial cell malfunction and microcirculation disorder [101]. ACE2 expression in the heart tissue is raised in numerous cardiovascular diseases, including ischemic heart failure, idiopathic dilated cardiomyopathy, and pulmonary hypertension, despite its favourable role in cardiovascular function [103].

D. *Pulmonary Disease: Chronic Obstructive Pulmonary Disease (COPD)*

Patients with comorbidities related with severe COVID-19 and ACE2 had been strongly expressed in over seven hundred lung transcriptome samples while as compared to control individuals. A lung RNA-seq dataset revealed a remarkable upregulation in the expression of ACE2 in patients with COPD when compared to normal spirometry subjects, and ACE2 was notably up-regulated in six out of seven lung transcriptome studies, suggesting that patients with COPD or PAH may have an higher risk of severe COVID-19 progression [104]. The discolouration of lung tissue slices from persons with Pulmonary Arterial Hypertension (PAH), a serious consequence of COPD, revealed elevated ACE2 protein in the endothelium of pulmonary arteries when compared to healthy controls [105]. Smokers and people with COPD have high levels of ACE2 in their airways, indicating the severity of covid-19 have a higher risk. in these groups and highlighting the necessity of quitting smoking [106].

E. *Asthma*

Asthma, which tends to increase during respiratory viral infections, was revealed to be a risk factor for COVID-19 severity [107]. In comparison to healthy participants, asthmatic and allergic rhinitis symptoms have reduced nasal epithelial cells of ACE2 expression [108]. IL-13 linked to allergic asthma and it is a cytokine. It has been observed that IL-13 reduces ACE2 expression in nasal and airway epithelial cells [108]. As a result, lower ACE2 expression in asthma patients is linked to lower COVID-19 severity [109].

F. Liver Disease

Liver damage and altered liver parameters have been seen in SARS, MERS, and COVID-19 infections. COVID-19 and abnormal liver enzyme production are linked in an indirect way [110]. The entry of SARS-CoV-2 inside the liver cell is mediated by liver cells ACE2 receptors [111]. Despite the fact that no patients with intrahepatic cholestasis or liver failure were reported [112]. According to other research, COVID-19 individuals have high ALT and AST values, as well as elevated bilirubin levels in 39% of cases [112]. Approximately 29% of COVID-19 patients experience liver impairment, which can have major consequences as the infection worsens [113]. In COVID-19, the release of elevated enzymes from cardiac and skeletal frame muscles, similarly to unusual liver function tests. The modifications in blood chemistry normally go back to regular without notable hepatic morbidity. As quickly as, ALT and AST level is elevated when the hepatic gets damage without hepatic failure in maximum of the patients; even though this may be lethal in serious cases of COVID-19. In COVID-19, the release of increased enzymes may be from cardiac and skeletal body muscles, in addition to abnormal liver function tests [114]. Recently, it is not clear that SARS-CoV-2 is related to pathophysiology of intrahepatic cholestasis or hepatocellular damage [100].

G. Obesity

Obesity (BMI 30 kg/m2) is linked to a reduced blood oxygen saturation because of the base of the lungs have lack of ventilation. Furthermore, some other characteristics of low-grade inflammation, such as aberrant cytokine, adipokine, and interferon productions, may emerge as a end result of obesity, resulting in a weakened immune response [115]. Unexpectedly, obesity was not a risk factor for COVID-19 in the early reports from China, Italy, and US [116]. However, the increasing number of COVID-19 cases reported with more obese people from Europe and North America [117]. As a result, research into the link between overweight and COVID-19 rate is required. Obesity is a relatively uncommon Comorbidity related to COVID-19 infections. Although obese people are infected with coronavirus illness in 47 percent of cases, 68 percent of these patients require emergency ventilation. As a result, a high BMI is linked to the severity of COVID-19 [118]. In the current pandemic situation, obese patients should take loyal care to prevent COVID-19 [100].

H. Renal Disease

Coronavirus causes a cytokine storm in the kidneys by causing direct cellular injury or sepsis. SARS-CoV-2 was recovered from the urine of COVID-19 infected individuals in China, indicating that the Renals are a likely target for SARS-CoV-2 [119]. AKI reported 4–8% of the COVID-19 cases, while it was observed in SARS (6%) and MERS (14%) patients with a 65%–85% death rate [119]. Moreover, studies show that when blood urea nitrogen levels rise, 26 percent of individuals develop haematuria, 33 percent albuminuria, and 64 percent proteinuria [120]. COVID-19 is more likely to harm people with kidney illness because ACE-2 expression is higher [100].

I. Secondary Infection and Co-Infection

In viral respiratory tract infections (influenza), bacterial co-pathogens are associated and are a most important cause of mortality and morbidity, making necessary timely diagnosis and antibacterial therapy [121]. Co-infection has been observed in patients with MERS and SARS, but there is limited knowledge on co-infection among patients with COVID-19 [122]. The most common co-infective virus was Influenza A. At an early stage of SARS-CoV-2, the RT-PCR test may result in false- negative [122]. The influenza bacterial coinfection causes severe complications and its mechanism is mainly due to a lack of effective immune response and pathogenic synergy [123]. Secondary infection and bacterial co-infections with pandemics and viral epidemics have irreversible outcomes, mainly in high-risk groups, including people with immunodeficiency or immunosuppression [124].

J. Deep Vein Thrombosis (DVT)

Deep vein thrombosis(DVT) and pulmonary embolism(PE) are notable indications of venous thromboembolism. DVT and PE are common risk factors and, in most cases, PE is an outcome of DVT [125]. Thromboprophylaxis seems to be related to lower mortality and is suggested for COVID-19 patients unless contraindicated [126]. An increased risk of VTE has currently been recommended in intensive care unit (ICU) patients with COVID-19 despite adequate thromboprophylaxis [127]. Hypercoagulability is a common haematological change in COVID-19 patients who are hospitalised, and it is a predictor of disease progression [128]. Even when indicated pharmaceutical thromboprophylaxis is taken, pulmonary embolism (PE) and venous thromboembolism (VTE) are more common in hospitalised SARS-CoV-2 patients than in patients hospitalised for other acute medical diseases [128].

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VI. PHARMACOLOGICAL TREATMENT

A. Remdesvir

Remdesivir, a newly discovered innovative antiviral medication in the nucleotide analogue family, has demonstrated to be most effective in treating Ebola and Marburg virus infections [129]. This medicine has showed antiviral action against a variety of single-stranded RNA viruses, including the Nipah virus, the Hendra virus, and coronaviruses (including MERS and SARS-CoV viruses) [130]. More recently, Remdesivir is analyzing the treatment of COVID-19 infections. Remdesvir rapidly recovered the COVID-19 infected patients at an early stage of disease [131]. In the month of May 2020, this drug was approved by Food and Drug Administration (FDA) [131]. Patients with confirmed COVID-19 infection were treated with compassionate use of Remdesivir for 10 days, it was confirmed in a recent clinical trial study [132]. Spinner et al [133]. conducted a randomised and open-label phase 3 clinical trial of Remdesivir on 584 patients with mild COVID-19 illness (ClinicalTrials.gov Identifier: NCT04292730). For SARS-CoV-2 infected individuals, Remdesvir is the medication of choice [134]. It is an antiviral agent that works by inhibiting viral replication within the body [134]. FAVIPIRAVIR: Favipiravir is an antiviral medication belonging to the pyrazine class that is mostly used in Japan to treat influenza [135]. The technique involves reducing the action of RdRp enzymes, a protein that is necessary for viral genome transcription and replication [136]. Favipiravir was also explored in the treatment of the Ebola virus, and it was recently discovered to be effective against COVID-19 [137].

B. Ivermectin

Ivermectin was observed to reduces SARS-CoV- 2 replication in vitro, which has been conducted to off-label use, but clinical uses have not been reported previously. Ivermectin was associated with a lower death rate during treatment of COVID-19 sufferers, mainly in patients who needed increased stimulated oxygen or ventilatory support [138].

C. Azithromycin

Azithromycin is a macrolide with a 15-membered ring that belongs to the azalide class [139]. It's safe, with very minor gastrointestinal side effects that are usually well tolerated. After oral administration, azithromycin is rapidly absorbed and has a lengthy half-life. Due to significant intracellular deposition, it has a vast volume of distribution, with tissue concentrations up to 100-fold higher than in plasma [140]. The uptake is particularly higher in leukocytes [141]. Azithromycin can cross the BBB and be centralized in CNS tissue [142]. This is significant since there is a greater knowledge of COVID-19 neurological results as a end result of inflammatory cell infiltration and activation, as well as direct viral neurotropism [143].

D. Inhalation Treatment for ARDS

Treatment of ARDS is associated with the virus and prevention of inflammation of lungs and fibrosis appears to be a good treatment technique that can supply and induced antiviral treatment while potentially improving the overall result. Furthermore, any treatment should be administered via local intrapulmonary medication delivery in patients with lung damage. Inhalation of Intratracheal transport of anti inflammatory drugs, hormones, antioxidants or other biologically active substances to the lungs, or even just to the dead cells, is critical for inducing the therapy of major lung injury, preventing drug enters into the systemic flow to some extent, and thus limiting possible side effects on healthy organs and tissues [144]. Previously, it was proposed, developed, and examined on animal models that inhalation and intratracheal treatment of extreme hypoxia-associated lung edoema, idiopathic pulmonary fibrosis, and lung manifestations of cystic fibrosis with nano carrier-based therapeutics such as alpha-tocopherol [145], prostaglandin E2 (PGE2) alone [146], or in combination with siRNAs for the suppression of inflammation and lung injury [147] using nano carrier-based therapeutics [148]. This treatment may be also effectively used for the prevention and treatment of patients with COVID-19 related to lung hypoxia, inflammation, and cystic and pulmonary fibrosis [149].

E. Ventilation

NIV is comparable to or better than MV in certain patients, which would support its usage as an alternative for MV in health-care settings with limited resources and staff [150]. The main-stay of treatment for COVID 19 patients is Supplying adequate oxygen, in mechanical ventilated (MV) patients, but fatality costs round 50% were reported [151]. Non-invasive ventilation (NIV) has been used as an alternative way for supplying oxygen to hypoxemic COVID-19 patients during spikes in COVID-19 cases, due in component to a restricted supply of mechanical ventilators [152].

VII. PREVENTION

The WHO (World Health Organization) is now working with countries all over the world to manage the pandemic crisis by providing guidelines for health personnel [153]. The current outbreak can also be prevented by preserving social distance and decreasing person-to-person transmission. The sudden step needed to maintain disease [154] outbreak like isolation, early diagnosis, and other supportive measure [155]. Also, be proactive by maintaining personal hygiene, avoiding congested areas, wearing fitted masks, and ensuring adequate ventilation [156]. Special precautions should be taken for children, the elderly, and immune compromised adults, as they are greater liable to COVID-19 [156].

VIII. VACCINE

The primary extremity is an immunity measurement or substitute marker which is known to be associated with protection against infection or a disease in a vaccine immunogenicity RCT [157]. A vaccination is viewed as the most effective way to combat the pandemic, with more than 100 COVID-19 vaccines in development around the world [158]. CEPI is believed to be needed to speed up the research and manufacture of vaccines against previously unknown infections within 16 weeks from antigen detection to vaccine candidate release for clinical trials [159]. The initiation of nine COVID-19 vaccine programs was announced by CEPI [160]. CEPI is being utilized by supporting the fast response platforms for vaccine development. CEPI is being used to support vaccine development platforms that are quick to respond. Platform technology takes the same fundamental parts as a backbone and adds new protein or genetic order to create changes for usage against different pathogens [161]. A DNA vaccine (administered via electroporation); a molecular-clamp vaccine (production of viral surface proteins, during the contamination that connects to the host cell and clamp them into shape, allowing the immune system to recognise them as the ideal antigen); recombinant protein nanoparticle generation to produce antigens acquire from the coronavirus spike (S) protein (proprietary saponin-based adjuvant); a recombinant protein vaccine such as two mRNA vaccine There will be a pandemic vaccine adjuvant to speed up development [160]. Some vaccination applicants were determined to protect against infection in laboratory animal models [162]. Most vaccine studies have focused on antibody responses developed against the S protein, which is also the most exposed protein of SARS-CoV-2 [163]. Antibody responses, however, are not found in all COVID-19 individuals, particularly those with milder strains of the virus [164].

A. COVID-19 Vaccines

Pfizer-BioNTech, commonly known as Comirnaty (BNT162b2), is an mRNA vaccine that codes for the P2 mutant spike protein (PS 2) and assembles as an RNA–lipid nanoparticle of nucleoside-modified mRNA (modRNA). This vaccine was the primary vaccine got authorize for regular use. This vaccine is presently being used in 99 countries. This is an mRNA type of vaccine and is administered in two doses that are given 21 days separately. Each dose contains 30 µg (0.3 mL) and the direction of administration (ROA) is through Intramuscular (IM)-deltoid muscle. This vaccine has effectiveness upto 95% in preventing symptomatic disease. Adverse effects include and not limited to pain, redness and swelling on the injection site, tiredness. It requires sub-zero storage and can be stored at room temperature for no more than 2 hours [165].

The LNP-encapsulated mRNA vaccine mRNA-1273 COVID-19 from Moderna reveals the prefusion-stabilized spike glycoprotein. This vaccine was developed in the United States through Moderna and the Vaccine Research Center on the National Institute of Allergy and Infectious Diseases (NIAID).By the usage of mRNA technology platform. Moderna vaccine is developed as the second vaccine approved for the emergency use in US on December 18, 2020 which is currently used in 47 countries. 0.5ml dose of Moderna vaccination path includes separate doses given through Intramuscular-deltoid muscle within the interval of 28 days. Moderna is 94.5% effective in excluding the SARS-COV-2 infection. Moderna vaccine are frequently shipped and reserved for a long-term storage under standard freezer temperatures, and kept in normal refrigeration for storage upto 30 days, it is easier to distribute and store when compared to Pfizer-BioNTech [165].

The Janssen vaccine (Ad26.COV2.S) is a retroviral vector vaccine was developed by Janssen Biotech, Inc, which is primarily based totally on the Ad26 vector platform that makes uses of human adenovirus to express the SARS-CoV-2 spike protein. A dose of 0.5ml is administered intramuscularly, currently being used in 24 countries and it was approved by FDA for emergency use on February 27, 2021. The vaccine could be stored for three months at 2°C to 8°C. Some studies showed that overall efficacy of 72% and 86% efficacy against severe SARS- CoV- 2 contamination in the U.S Fatigue, fever, headaches, injection site discomfort, and myalgia (muscle or group of muscle pain) are among of the side effects that usually go away after a day or two [165].

Covishield and Covaxin were manufactured in India and made available for use of Indian and western population [165]. On January 3rd, 2021 [166], Covishield (Astra Zeneca) and Covaxin (ChA-dOx1 nCoV-19) received emergency use approval.

Covishield is a nonreplicating viral vaccine based on an adenovirus vector that contains recombinant SARS-CoV-2 spike protein. In interim analysis of phase III trials, it had showed a satisfactory safety profile in phase I/II trials and an efficacy of 74% in avoiding infectious disease [167].

The Oxford–AstraZeneca COVID-19 vaccine (AZD1222) was produced by oxford university and AstraZeneca, a monovalent vaccine containing of a single remerging, replication-inadequateadenovirus vectors and pathogen-specific transgene. It was approved for use in UK on 20 December, 2020 and consists of two seperate dose of 0.5ml given intramuscularly within interval of 8 to 12 weeks. Studies shows that 76% effective in preventing the symptomatic SARS-COV-2 infection. The adverse reactions of this vaccine are mild to moderate in severity (injection site pain, fever) and commonly resolved within some days [165].

Sputnik V is named after the first Soviet space spacecraft and is primarily based totally on a well-studied human adenoviral vector-based platform. Sputnik V is the world's first coronavirus vaccine, with registrations greater than sixty five countries. The vaccine makes use of a heterologous recombinant adenovirus approach to specific the SARS-CoV-2 spike protein, with adenovirus 5 (Ad5) and adenovirus 26 (Ad26) as vectors. Specific serotypes are given 21 days apart to overcome any prior virus immunity in the population [165].

IX. CONCLUSION

Male patients and those who are older are much more likely to emerge severity, while comorbidities and clinical manifestations can have a big impact on COVID-19 prognosis and severity. Even with minimal protection against infection, vaccination can have a significant influence on reducing COVID-19 outbreaks. To accomplish this benefit, however, ongoing compliance with non-pharmaceutical measures is required.

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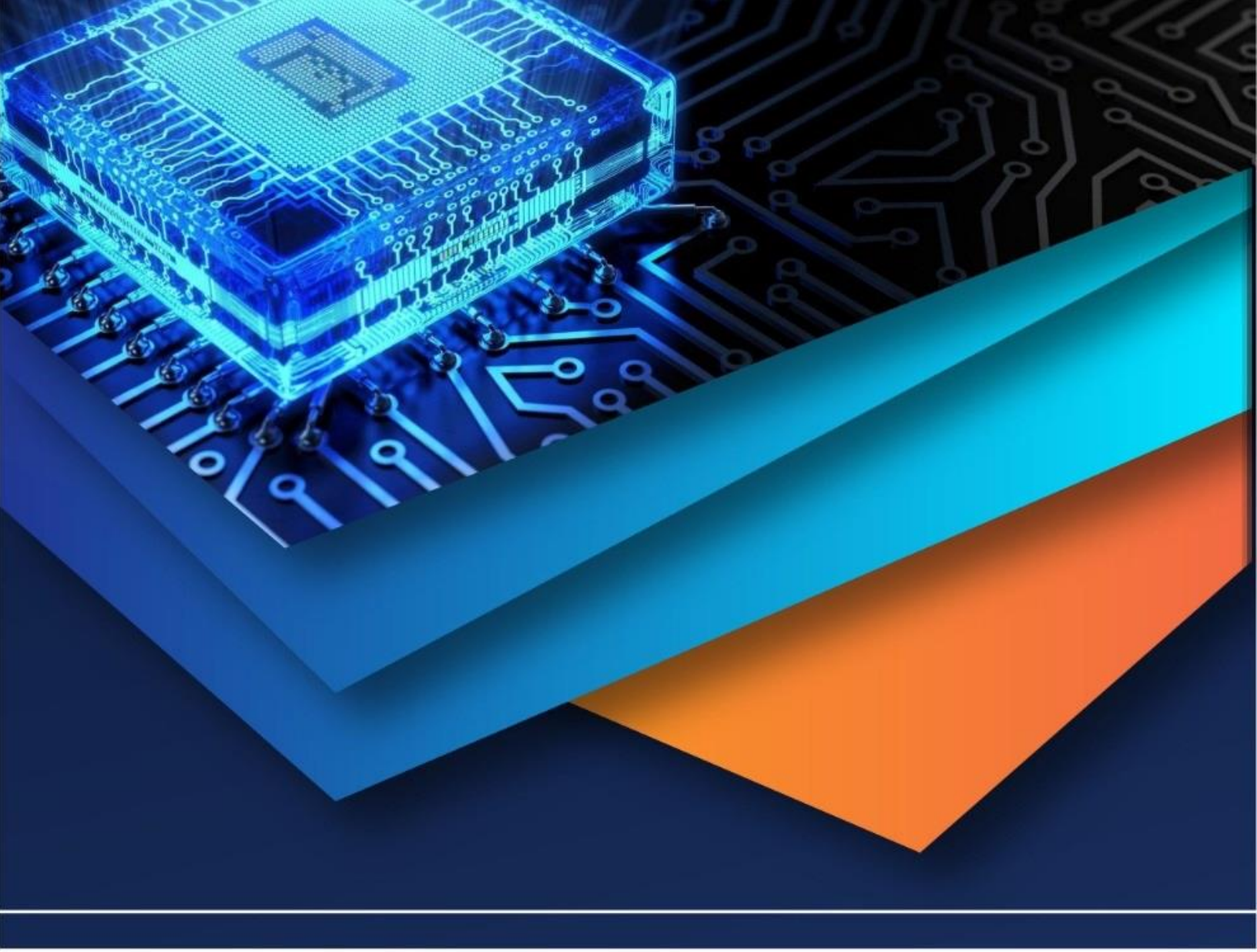

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