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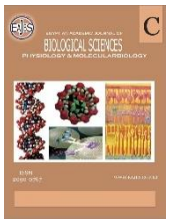

Human Genetic as Risk Factors for COVID-19 Progression

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ABSTRACT

Background: Thousands of people have already died as a result of the 2019 coronavirus disease pandemic (COVID-19), which was brought on by the SARS-CoV-2 coronavirus. There were many unimaginable cases of illness in Washington in 2020 as a first case, and then it was transmitted to Wuhan, Germany, France, Italy, Spain, the United Kingdom and China. The newly discovered SARS-CoV, MERS-CoV, and SARS-CoV-2 are believed to be natural and not laboratory synthetic. The COVID-19 pandemic may be due to the contamination of infected people and objects with infected materials that spread across the world.**Main body:** Human COVID-19 infection symptoms can range from being asymptomatic to being fatal, including respiratory failure, multiple organ dysfunction, and death. Large-scale genetic association studies have demonstrated that immune system components such as interferons, interleukins, toll-like receptors, and human leukocyte antigen as well as COVID-19 receptor variations (angiotensin-converting enzymes, transmembrane serine protease-2) are important host determinants of COVID-19 severity. **Conclusion:** The current review aims to demonstrate the human genetic factors that affect COVID-19 severity.

INTRODUCTION

There were many unimaginable cases of illness in Washington in 2020 as the first case was transmitted to Wuhan, Germany, France, Italy, Spain, the United Kingdom and China (Hosoki *et al.*, 2020), but cases have similar symptoms of illness severe acute respiratory syndrome coronavirus (SARS-COV) and MERS-COV. The Global Health Organization (GMO) called this epidemic a coronavirus disease (COVID-19) or SARS-COV2 (Tumban 2020 ; Halpin *et al.*, 2021). In 2020, the virus invades the whole world and leads to morbidity and mortality (Li *et al.*, 2020), so it acts as a reference of scientific passion for most researchers and scientists.

The structure of COVID-19 consists of an extracellular membrane that flanks the RNA genome of the virus and includes proteins that divide to spike glycol protein surface, nucleocapsid, and protein envelope (Hoffmann *et al.*, 2020). The genomic composition of COVID-19 includes genome sequences from 798 and 29,674 bases which contain different numbers of open reading frames (ORFs). The first ORF constitutes 67% of the entire genome that encodes two considerable polyproteins (PP1a and PP1ab), which are proteolytically divided into 16 non-structural proteins (NSPs) that contain papain-like protease, 3-chymotrypsin as a cysteine protease (3cLpro), RNA-polymerase, helicase and exonuclease (ExoN) (Tsai *et al.*, 2021). 96.2% of similar genomes of COVID-19 existed in SARSr-Ra-BatCoV-RaTG13 horseshoe bats which were discovered in Yunnan and China in 2013 (Novelli *et al.*, 2020).

Furthermore, all six residues of COVID-19's receptor binding domain (RBD) location, which may be found in CoVs in Malayan pangolins, have displayed high similarity to one another. (Manis javanica) (Hosoki e*t al.,* 2020).The virus COVID-19 is still unknown until now for scientists, and they have many questions and no one has any answers but another one can be identified as stages, causes and diagnoses.

The virus has a cycle that progresses the infection and it can be divided into 3 stages: the duration of incubation inside the host which can reach 5 days and that is called the first stage, the second stage which the infection can be remarkable by the patient but the virus has symptoms like mild flu including fever, Anosmia, dysgeusia, headaches, nausea, vomiting, muscle aches and pains, diarrhoea, dyspnea, and cough without phlegm (Halpin *et al* ., 2021), and the final stage which consider as highly progressive one that leads to severe failure of lung epithelial cells, thrombosis, hypercoagulation, mortality, and acute respiratory distress syndrome (ARDS) (Pollard *et al.,* 2020).

Main Text:

Classification of COVID-19:

The newly discovered SARS-CoV, MERS-CoV, and SARS-CoV-2 are believed to be natural and not laboratory synthetic. It is highly pathogenic, leading to upper and lower respiratory syndrome and extrapulmonary infection. The first coronavirus strain identified in 1996 was HCoV-229E, which was responsible for 10–20% of cases of fever, sore throat, coughing, and sneezing. (Hamre 1966; McIntosh *et al.,* 1967). Later, in 1976, a strain of HCoV-OC43 that caused symptoms identical to HCoV-229E was identified following organ transplantation in mice and later serial passage in lactating mice's brains. (DAJ *et al.,* 1993). The first human coronavirus is SARS-CoV. and it is about 98% like to SARS-CoV2. The incubation of SARS_COV2 is found between 4 to 7 days and then reaches the highest peak on the 10th day. In 2002, the first case of SARS was found, which led to 919 deaths (Cheng *et al.,* 2007; Peiris *et al.,* 2003).

From 2003 to 2004, five additional cases were discovered from zoonotic transmission from bats to men (Menachery *et al.,* 2015), causing cough, malaise and fever leading to an increase in macrophages, epithelial cell proliferation, and diffuse alveolar damage (To KK *et al.,* 2013). In 2012, MERS-CoV appeared which was discovered in the lungs of 60 years 60-year-old patient who suffered from acute pneumonia and renal failure in Saudi Arabia (Lu *et al.,* 2013). In 2019, an unknown etiology spread in Wuhan province in China and named as SARS-CoV-2 which is the factor of spreading COVID-19, and there was a lack of antiviral treatment and vaccines. In 2020, COVID-19 was considered a pandemic and extended to more than 100 countries and reached 6960,259 confirmed cases and 401,970 deaths (Gorbalenya, *et al.,* 2020; Wu *et al.,* 2020; Azamfirei 2020). Lots of reports believe that the pandemic may have a risk on the bloom (Azamfirei 2020). SARS is a spherical single strand with RNA, a glycoprotein that is projected over the coat in a crown-like fashion that's why it's called coronavirus and these proteins bind to the receptor found in human and animal bodies (Xia *et al.,* 2020; Xiao *et al.,* 2020). The dispersal of animals and the crossing of species barriers are caused by changes in receptor-binding ligands at the level of spikes. The high similarities in genetics detected that SARS-CoV-2 is produced from bats which are considered the ancestral natural host (Malik *et al.,* 2020; Riccucci 2012). The genetic research revealed that the only nucleotide variation between SARS-CoV and SARS-COV-2 is five, making SARS-COV-2 distinct from SARS-CoV. (Benvenuto *et al.,* 2020).

Three COVID-19 waves have affected South Africa: the ancestral variant wave from June to August 2020, the beta wave from November 2020 to January 2021, and the wave from May to September 2021. (Delta). Beginning on November 15, 2021,

when Omicron was discovered, the number of cases began to rise again; by December 7, 26% of the community had tested positive. In the prior waves (wave 1: June 14 to July 6, 2020; wave 2: December 1-23, 2020; wave 3: June 1-23, 2021), researchers determined the period when 26% positive rates. The latter was attained and compared to wave number four (November 15 to December 7, 2021). (Maslo *et al.,* 2022). In November 2021, the new variety, also known as B.1.1.529, was discovered. Since then, it has been found in more than 60 nations. There were 10 017 instances of omicron in the UK. (Burki 2022). In South Africa, Omicron (B.1.1.529) was found to be the source of a fourth COVID-19 wave.The spike protein's mutation in the receptor-binding region has drawn criticism. The alterations increase transmissibility and immune evasion after spontaneous infection and immunization. (Andrews *et al.,* 2022). Omicron may not considerably increase the risk of serious disease or death in populations that have had vaccines, according to data on vaccine effectiveness., "It appears that a three-shot omicron immunization program will be required. Compared to the delta version of the COVID-19 vaccine, the omicron variation may only offer 10% protection against symptomatic disease 25 weeks after two doses (Burki 2022). New laboratory findings show that vaccinated individuals had a significantly lower level of neutralizing antibodies to the omicron variation compared to the original strain of SARS-CoV-2 or the delta (B.1.617.2) variant, however, booster doses enhanced neutralizing efficacy. (Buchan et al., 2022). Omicron cases are doubling every two to three days, so it makes control efforts more difficult. Symptomatic Omicron or Delta infection and serious consequences (hospitalization or death) related to infection were the key outcomes (Buchan *et al.,* 2022).

The severity of the second wave in India was primarily due to the Delta variant, a subtype of COVID-19. The mutation was done in the genetic information of the virus due to repeated copying errors. New variants are produced by these mutations, some of which have the potential to spread more quickly, produce more severe COVID-19 disease symptoms, and have a higher mortality rate, these spike proteins open the cells, allowing the infection to propagate by replicating the virus' genetic material. The E484Q, L452R, and P614R modifications in the Delta form, among others, make it easier for the viral spikes to bind to ACE-2 receptors. This implies that it can proliferate and infect more quickly, as well as more successfully escape the body's built-in defenses against disease. (Alexandar *et al.,* 2021). The first signs of COVID-19 infection typically show up five to six days after exposure, however, they can also develop between two and 14 days later (Alexandar *et al.,* 2021). The most frequent symptoms reported by those with the Delta form are headaches, sore throats, and runny noses, which, for the most part, have replaced coughing and a loss of taste and smell. (Alexandar *et al.,* 2021).

A variant of Delta, known as Delta Plus (B.1.617.2.1/(AY.1)), is also considered a variant of concern. The K417N mutation in Spike protein that Delta Plus variants have distinguishes the two. Six Indian genomes were discovered to contain the new mutation. According to some, Delta Plus is very contagious. Concern is growing in some circles as a result of experts' warnings that Delta Plus may exhibit resistance against monoclonal antibody cocktail treatments (Alexandar *et al.,* 2021). The Deltacron super variant, which combines the Delta and Omicron, was discovered in January 2022. However, other experts contend that it never existed and that the sequences were probably contaminated. The World Health Organization decided to begin monitoring it in March 2022. (Maulud *et al.,* 2022).

More importantly, they have discovered two distinct incidences of infection with a recombinant Delta-Omicron virus. Deltacron is currently recognized as a novel strain. According to recent genetic studies, The Omicron variety of the virus serves as the virus' spike, which binds to the host cells' ACE2 receptors, while the Delta

strain serves as the virus' backbone (Maulud *et al.,* 2022). Three genomes obtained between 3 January and 16 February 2022 were phylogenetically related to Delta 21J/AY.4-Omicron 21K/BA. In one hybrid genome, one variant N-terminal domain (NTD) mutation was discovered. Without a doubt, the recombinant's receptor-binding domain (RBD) was taken from the Omicron 21K/BA.1 variant. (Colson *et al.,* 2022; Fantini *et al.,* 2022). More importantly, they have discovered two distinct incidences of infection with a recombinant Delta-Omicron virus. Deltacron is currently recognized as a novel strain. According to current genetic studies, Deltacron's backbone is derived from the Delta strain, while its spike—the part of the virus that binds to ACE2 receptors of the host cells—is derived from the Omicron variation. (Maulud *et al.,* 2022).

Over 527 million cases had been reported as of the end of May 2022, with over 6 million deaths (WHO 2022). The COVID-19-causing severe acute respiratory syndrome coronavirus (SARS-CoV-2) manifested a range of symptoms, from trivial to potentially lethal (Jin *et al.,* 2020; Weiss *et al.,* 2020). Non-pharmacological measures (like preserving social distancing, donning masks, and keeping track of close contacts) and the cornerstones of health policy initiatives to halt the virus' transmission and decrease its medical impact are COVID-19 vaccination campaigns. (Odusanya *et al.,* 2020).

Epidemiology of COVID-19:

Does the virus attack humans without any reason or have mystique causes that can be the first and most important reason for several infections with the virus in the whole world? This confusion leads scientists to do more examinations and more research, from their studies they found that many different causes and risk factors can lead to COVID-19. One of them is social communication among human beings, without regard for peace can cause many infections by the contact between infected and healthy individuals. The rate of morbidity is reduced with different and several amounts. Another reason is an impaired immune system which can have a great effect in several ways (Salzberger *et al.,* 2021) like the innate immune cells as macrophages that has a role in the development of virus by generating several IL-6, so it may lead to the increase the inflammation in COVID-19 (Paces *et al.,* 2020). The world's population's upregulation of its enzyme, caused by the angiotensin-converting enzyme-2 (ACE2) receptor's attraction to viruses, makes infection easier. (Pollard *et al.,* 2020).

Transmission of COVID-19:

COVID-19 has become a pandemic may be due to the contamination of infected people and objects with infected materials that spread across the world (Grennan 2019). The soldiers that came from the world war spread the H1N1 strain of influenza (Erkoreka 2009; Yan 2019), and then several mutations occurred causing pandemics such as Asian flu (1957-1958), also the swine flu in 2009 (Rajagopal 2007; Rewar 2018).

It was once believed that droplets or aerosols may spread an infection. The sneezing and dry coughing that COVID-19 patients experienced caused viral plumes of thousands of droplets (droplet sizes varying between 0.6 and 100 m per cubic centimeter) to be created (Jayaweera *et al.,* 2020). At first, it was believed that the viruses were spread by droplets that remained at the surface and were later conveyed to the host by rising dust.

By increasing the cough, the number of droplets increases (Yang *et al.,* 2020). Pre- or asymptomatic patients produce small droplets in large quantities through normal breathing and speech. These droplets are smaller than 1 μm (Asadi *et al.,* 2020), The particle size distribution becomes smaller during the evaporation of droplets generating droplet nuclei. Droplets that are less than 10 μm could become droplet nuclei. Due to the ambient airflow, these droplets remain suspended in the cloud of air. When the diameter of the droplets is less than 50μm, survival is increased in the plume without any evaporation (Han *et al.,* 2013; Johnson *et al.,* 2011).

SARS-CoV-2 is around 0.1 m in size. Exhalation, sneezing, and coughing cause

multiphase turbulent flow, which results in heated, damp air. (Jayaweera *et al.,* 2020). The droplet's lifetime is extended from a second to minutes by the presence of a moist, warm environment that helps the droplets resist evaporation for a longer period of time. (Bourouiba 2020). Coughing and sneezing cause aerosol plumes to build at a fast rate of speed, which is sufficient to infect everyone standing close to the sufferer.

At the optimal temperature and humidity, the aerosol droplets can travel up to 7−8 m (Bourouiba 2020; Bourouiba 2016). The human infection is brought on by COVID-19 aerosols, which have a half-life of around one hour and remain viable in the air for at least three hours. (Doremalen *et al.,* 2020). Wells and Riley model quantified airborne infection rates at close space (Keene 1995; Riley *et al.*,1978). According to the Wells-Riley equation (eq. 1), the number of new infections over time (t) depends on the number of infected individuals and the number of susceptible individuals in a room with a ventilation rate Q expressed in m3/S. Additionally, the amount of infected material may also be expressed as q, where the rate of pulmonary ventilation for the exposed individual is p m3/S. The spread of measles in schools and the impact of distribution and ventilation on diffusion rate were predicted using the Wells-Riley equation. (Noakes *et al.,* 2009). According to Wells et al. (1948), the Wells-Riley model serves as a representation of the quantum (q) of the infection or the number of infectious droplets that could be sufficient to infect 63% of those exposed. The interaction between physical, chemical, and biological agents that cause infection cannot be captured by this straightforward approach, which measures the quantity and virulence of infectious substances in the air. However, this limitation was addressed by the development of detailed dose-response models and stochastic modelling approaches. (Chen *et al.,* 2009; Huang 2009; Pujol *et al.,* 2009).

There is no indication that COVID-19 may spread through food or through the water when swimming, although it can be killed by high temperatures. Until now there's no evidence that proved that animals could transmit COVID-19 to people but there are some types of coronaviruses that can be transmitted from animals to people, but this is rare, Additionally, when there is close contact, COVID-19 can be transmitted from people to some animals.

Clinical Features of COVID-19 in Patients:

For example, asymptomatic infection, mild-to-moderate illness with fatigue, cough, and fever, and severe disease with acute lung damage are all included in the clinical spectrum (Guan *et al.,* 2020; Zhou *et al.,* 2020; Bhatraju *et al.,* 2020; Goyal *et al.,* 2020; Richardson *et al.,* 2020; Cummings *et al.,* 2020; Grasselli *et al.* Multiorgan failure and septic shock are the two main symptoms of the most serious illness (Zhou *et al.,* 2020). According to recent estimates, 80% of illnesses might be asymptomatic (Day 2020). A recent study found that 87.9% of pregnant patients who tested positive for SARS-CoV-2 were asymptomatic (Sutton *et al.,* 2020), accounting for 13.7% of all patients showing delivery. Most COVID-19 patients have a mild illness and fully recover to normal health. A study of 72,314 people showed that 81% were mild disease, 5% were critical, and 14% were severe (Wu and McGoogan 2019). The mortality rate is highest in people larger than the age of 70 years (8% to 14.8%) and (49%) in those with critical illness.

1.4% of the 1,099 Chinese patients with laboratory-approved COVID-19 died, 2.3% underwent invasive mechanical ventilation, and 5.0% were admitted to an intensive care unit (ICU) (Huang *et al.,* 2020). The most typical signs and symptoms were fever and cough. The typical incubation time was four days. Most of these individuals (50%) had a sudden comorbidity, with hypertension acting as the most prevalent, followed by diabetes and coronary heart disease (Zhou *et al.,* 2020). In a prior study with 191 patients, 54 patients died in the hospital. Older age, a higher score on the sequential organ failure test, and a D-dimer level of more than 1 lg/ml at admission were all associated with hospital death. The

average age of the 1,591 SARS-CoV-2 positive patients admitted to Italian ICUs was 63 years old, according to another study. and 82% were male (Grasselli *et al.*, 2020). The majority of the 1,300 patients receiving respiratory assistance (99%), including 88% of those receiving mechanical ventilation and 11% of those receiving non-invasive ventilation, expressed a preference for the support. Finally, in this situation, 26% of the patients were ICU morbid, and the majority were older men. Additionally, information from prior coronavirus infections, such as Middle East respiratory syndrome, severe acute respiratory syndrome (SARS), and information from the COVID-19 pandemic, suggests that SARS-CoV-2 infection may have significant fibrotic consequences. (George *et al.*, 2020).

A normal CT was also present in 56% of patients with early illness. prolonged after the onset of symptoms, aberrant CT findings such as consolidation, bilateral, peripheral, and linear opacities, prolonged total lung involvement, and the "reverse halo" mark were more prevalent. 88% of cases with advanced disease and 28% of cases in the early stages of the disease had bilateral lung involvement. Because RT-qPCR sensitivity can drop as low as 60%, CT scans performed when symptoms first appear may increase the likelihood of a correct diagnosis (Kanne *et al.*, 2020). Additionally, the results of chest X-rays in COVID-19 patients showed bilateral lower zone consolidation. (Wong *et al.*, 2020).

As seen in patients with disseminated intravascular coagulopathy (DIC), COVID-19-stimulated infection can be linked to coagulopathy with infection-stimulated inflammatory alterations (Connors and Levy 2020). Initial coagulopathy in COVID-19 individuals is associated with induced D-dimer and fibrin/fibrinogen breakdown products. For patients with sepsis-elevated DIC, COVID-19-linked coagulopathy should be managed as it would be for any very unwell patient, employing thromboembolic prophylaxis and normal supportive care measures.

Five to Fifty percent of COVID-19 patients experience hepatic enzyme induction. According to Cai *et al.* (2020), Xu *et al.* (2020a), and Xu *et al.* (2020b), the outlines of liver injury are primarily hepatocellular rather than cholestatic, with focal necrosis, hepatocyte degradation, portal region inflammation, and cholestasis in the capillary bile duct. The severity of COVID-19 has been correlated with the severity of liver damage. Acute chronic liver failure and COVID-19 patients could both be decreased by the presence of chronic liver illnesses (Ji *et al.*, 2020). About 50% of COVID-19 patients had the virus in their stool samples, and about 18% of them had diarrhea and abdominal pain (Cheung *et al.*, 2020b). It has been shown that ACE2-positive enterocytes can support COVID-19 replication. (Lamers *et al.*, 2020).

Clinically, both adults and children with similar incidences of COVID-19 struggle with gastrointestinal symptoms such as nausea, vomiting, anorexia, and diarrhea (Tian *et al.*, 2020; Mao *et al.*, 2020). The abundant mRNA expression of ACE2 and protein receptors on enterocytes may be related to the underlying mechanism (Jin *et al.*, 2020; Pan *et al.*, 2020). A response mediated by the immune system was suggested by histological alterations, such as lymphocyte and plasma cell infiltration into the lamina propria of enterocytes (Xiao *et al.*, 2020). In fact, several COVID-19 cases may have been spread by faeces (Cheung *et al.*, 2020a). The epidemiological management of the COVID-19 pandemic sickness is therefore greatly impacted by the presence of COVID-19 in the stool.

According to a study conducted in Wuhan (Li et al., 2020), the estimated average incubation period for COVID-19 is 1–14 days, with most cases lasting 3–7 days. However, a study on 1,099 cases revealed that the pandemic disease's incubation period was 3 days on average and varied from 0 to 24 days (Guan et al., 2020). According to the demographics of 8,866 patients, a prior study showed that the incubation time was 4.8 (3.0-7.2) days (Yang *et al.*, 2020). Health authorities must correct the effective

quarantine period in accordance with the most accurate incubation period in order to prevent the transmission of the virus to others by infected but asymptomatic individuals (Chang et al., 2020). Chest X-rays are the most common diagnostic tool for COVID-19. (Cenggoro *et al.,* 2023).

In comparison to healthy controls, patients with COVID-19 had reduced levels of the three microRNAs (miR) miR-146a-3p, miR-155-5p, and miR-146a-5p in their peripheral blood mononuclear cells. Notably, they found that COVID-19 patients had an overexpression of a number of miRNAs. Furthermore, levels of miR-29a-3p, miR-146a-3p, and let-7b-3p have been connected to post-acute sickness. The miRNAs miR-29a-3p, miR-155-5p, and miR-146a-3p were discovered to be accurate diagnostic biomarkers for COVID-19 through the study of their individual receiver operating characteristic (ROC) curves.

Since it was demonstrated that the levels of miR-29a-3p and miR-146a-3p varied during the acute and post-acute stages of COVID-19, these molecules have been suggested as markers for phase differences. (Donyavi *et al.,* 2021). Plasma miRNAs have also been suggested as a technique for determining the severity of COVID-19. MicroRNAs like miR-192-5p and miR-323a-3p, for example, may be expressed, which could be used to distinguish between ICU fatalities and successful recoveries. The quantity of these miRNAs expressed is directly associated with the length of time patients with COVID-19 spend in the ICU. (de Gonzalo-Calvo *et al.,* 2021).

Between COVID-19 and Influenza-ARDS patients, distinct variations in the expression of miR-155, miR-208a, and miR-499 were observed. Furthermore, COVID-19 patients were distinguished from those with influenza-related acute respiratory distress syndrome (ARDS) who required mechanical ventilation by their cardiovascular miRNA profile, pointing to very specific involvement of heart tissue in COVID-19 patients. (Garg *et al.,* 2021).In the serum and/or plasma of COVID-19 patients, large levels of GFAP have been discovered recently (Kanberg *et al.,* 2020, 2021; Frontera et al., 2022; Hanson *et al.,* 2022; Sahin *et al.,* 2022). Given that it was shown to be much higher in COVID-19 patients who died during hospitalization compared to those who survived, this supports the theory that GFAP levels correlate with illness severity (Frontera *et al.,* 2022). High GFAP levels have been linked to illness severity in other investigations, but not to the existence of neurodevelopmental abnormalities. (Sahin *et al.,* 2022).

According to one study, GFAP levels standardized in all COVID-19 patients regardless of the severity of their condition or the identification of their cognitive symptoms, proving that COVID-19-related cognitive impairment symptoms continue even in the absence of any active CNS injury. These results may further lend credence to the idea that reactive gliosis attempted to disseminate hematogenously, infected endothelial cells, and disrupted the BBB in order to generate COVID-19-related memory impairment. (Johansson *et al.,* 2021; Mohamed *et al.,* 2022).

Type IV intermediate filaments known as neurofilaments (Nfs) allow neurons to expand radially while maintaining cytoskeletal integrity (Yuan *et al.,* 2017; Gaetani *et al.,* 2019). Under normal conditions, neurofilament light chain (NfL), the most prevalent subunit of Nfs, is released into the blood in modest quantities, and this has been seen to rise with age. (Yuan *et al.,* 2017; Gaetani *et al.,* 2019; Zanella *et al.,* 2022).

Several COVID-19 patient populations studied (Ameres *et al.,* 2020; Kanberg *et al.,* 2020; Kanberg *et al.,* 2021; Aamodt *et al.,* 2021; De Lorenzo *et al.,* 2021; Prudencio *et al.,* 2021; Frontera *et al.,* 2022; Hanson *et al.,* 2022; Verde et al. Patients with COVID-19 encephalopathy who were hospitalized had higher levels of NfL and GFAP (Hanson et al., 2022). In COVID-19 patients who passed away while receiving medical care, NfL levels were discovered to be correlated with the severity of the disease (Aamodt *et al.,* 2021; Frontera *et al.,* 2022).

COVID-19 patients had higher levels of NfL in comparison to the non-COVID-19 AD patients in the control group (Frontera *et al.,* 2022).

Increased serum NfL levels were found in COVID-19 patients who had no overt symptoms or evidence of cognitive deterioration (Prudencio *et al.,* 2021; Verde *et al.,* 2022). Intensive care unit (ICU) patients with COVID-19 who did not recover from the infection exhibited higher levels of NfL than those who did (Aamodt *et al.,* 2021). In COVID-19 patients who continued to experience neurological symptoms, plasma NfL levels reportedly climbed steadily after 30-70 days and subsequently returned to baseline after six months (Kanberg *et al.,* 2021). From the first to the last follow-up, increased plasma NfL levels were also seen in the severe group. (Kanberg *et al.,* 2020).

Patients with severe COVID-19 delayed axonal damage, although astrocyte activation formed linkage and is not only present in patients with severe COVID-19 (Kanberg *et al.,* 2020, 2021). Further investigation is needed to determine whether the neuropathological mechanism producing neuroaxonal injury and whether the higher plasma NfL concentrations found in these COVID-19 patient populations can play a substantial role in the cognitive morbidities that develop in post-COVID-19 infections. (Alvarez *et al.,* 2022).

Soluble tau proteins support neuronal microtubule integrity by promoting assembly and supplying stability (Wang and Mandelkow, 2016). For the protein to modify its conformation and function under physiological circumstances, tau post-translational phosphorylation is necessary (Wang and Mandelkow, 2016; Kent *et al.,* 2020). Patients with COVID-19 had higher serum and/or plasma p-tau 181 (Sun *et al.,* 2021; Frontera *et al.,* 2022).

P-tau 181, NfL, and GFAP levels were elevated in COVID-19 individuals who developed COVID-19 encephalopathy or died from the virus. Hospitalized COVID-19 individuals with new cognitively associated symptoms exhibited higher levels of p-tau 181 compared to those who did not develop further cognitive sequelae (Frontera *et al.,* 2022). High amounts of p-tau 181 were discovered in a study that examined the contents of neuronal-enriched extracellular vesicles (nEVs) in the plasma of COVID-19 patients. Patients with neurological adverse effects also showed a high association between these levels and NfL. (Sun *et al.,* 2021). There is some indication that COVID-19 worsens conditions such as tau, -amyloid aggregation, neuroinflammation, cerebral ischemia, and blood-brain barrier (BBB) damage that have been connected to Alzheimer's disease (Miners *et al.,* 2020; Shen et al., 2022). Consequently, these findings imply that p-tau 181 is yet another neurological biomarker associated with the severity of COVID-19 disease. (Alvarez *et al.,* 2022).

As a component of the ubiquitin-proteasome system (UPS), ubiquitin is a protein regulator well-known for its role in DNA repair, proteolytic degradation of proteins, and cellular trafficking (Guo and Tadi, 2022). Different subgroups of COVID-19 patients have also been found to have elevated plasma UCH-L1 levels (Cooper *et al.,* 2020; Frontera *et al.,* 2022). This was shown to be significantly higher in COVID-19 individuals who had developed encephalopathy, suggesting a relationship between the two and the severity of the condition (Frontera *et al.,* 2022). As previously indicated, when compared to a control group of non-COVID AD patients, COVID-19 patients hospitalized with new neurological symptoms exhibited greater plasma levels of UCH-L1, p-tau 181, and NfL (Frontera et al., 2022). Higher levels of UCH-L1 were also found to be associated with delirium in a subset of COVID-19 patients who were hospitalized in the intensive care unit (Cooper *et al.,* 2020).

In a second cohort of COVID-19 patients, predictive values for the requirement for an ICU transfer were determined using UCH-L1 and NfL (De Lorenzo *et al.,* 2021). Therefore, when paired with other indicators to predict probable clinical outcomes, UCH-

L1 may be employed as a predictive biomarker in COVID-19 patients (De Lorenzo *et al.,* 2021). The homodimer S100BB or the heterodimer S100AB can be used to describe the levels of S100B, a member of this protein family that has received extensive research (Thelin *et al.,* 2017). Additionally, S100B's activity changes with serum concentration, becoming neuroprotective at low concentrations (nanomolar) but lethal at high concentrations (micromolar). (Lam *et al.*, 2013).

S100B levels in the blood have been discovered to be abnormally high in COVID-19 patients. (Sahin and others, 2022). Serum S100B has been connected to higher disease severity in COVID-19 patients, along with other brain injury biomarkers (Mete *et al.,* 2021). In patients with acute phase COVID-19, serum S100B levels were not substantially connected with neurological symptoms, but they were shown to be modestly increased in those patients who had more than one neurological symptom. (Sahin *et al.,* 2022).

There are no indications as to the clinical or long-term effects of increased S100B levels during the acute phase of COVID-19. S100B is a pro-inflammatory ligand that binds to the Receptor for Advanced Glycation End Products (RAGE) and has been associated with neuroinflammation following neurological injury (Michetti *et al.,* 2019). The association between higher S100B levels and deteriorating health and cognitive outcomes in COVID-19 infection may have some basis in these findings. It's still unclear if S100B is a direct cause of the neuropathological harm in COVID-related cognitive dysfunction or if it's a response to the downstream inflammatory processes. (Alvarez *et al.,* 2022).

Human Genetic Factors That Increase the severity of COVID-19:

The intensity of COVID-19 infection can change due to variations in human DNA.

1. ***Angiotensin-converting enzyme 2 (ACE2):***

After two different research teams characterized a carboxypeptidase homologue of the well-known ACE that could cleave angiotensin I and angiotensin II and was resistant to traditional ACE inhibitors like captopril, lisinopril, and enalaprilat, Angiotensin-converting enzyme 2 (ACE2) was discovered in the year 2000. The ACE2 gene has 18 exons and 17 introns and occupies a space of around 40 kb on chromosome X (Lima *et al.,* 2021). The N-terminal extracellular region of this type I transmembrane glycoprotein, which is 805 amino acids long, is where the peptidase domain (PD) of ACE2 is found. (Lima *et al.,* 2021). The level of ACE2 may be different for males and females (Cao *et al.,* 2020). The expression of this region is higher in males than in females in some tissues, but it has been reported that female cells can bypass X inactivation. In addition, several SNPs in the ACE2 gene have been identified (Itoyama *et al.,* 2005). Three hundred percent of the amino acids are identical between ACE2 and the testicular ACE, and the two enzymes share a region in their active sites that is conserved: the zinc-binding motif His-Glu-Met-Gly-His (Lima *et al.*, 2021).

ACE2 is a mono-carboxypeptidase since its first active site is a conserved cysteine (Lima *et al.,* 2021). Additionally, ACE2 can be detached from the plasma membrane by disintegrin and metalloproteinase domain-containing protein 17 (ADAM-17), which is produced in response to angiotensin II (Lima *et al.,* 2021). Angiotensin II and angiotensin I are broken down by ACE2 into angiotensin and angiotensin, with angiotensin I working much less effectively than angiotensin II. Because of how it works, ACE2 reduces the availability of angiotensin II and promotes the synthesis of angiotensin. (Hoffmann *et al.,* 2020; Phua *et al.,* 2020).

The presence of the ACE2 receptor in host cells is crucial for the entry of the virus into the host cell. Because T20, Y83, S218, A246, K353, P426, T593, N636, A714, R716, and A774 are present in the virus interface and allow the association with the receptor-binding domain (RBD) of the COVID-19 spike (S) protein, COVID-19 can recognize

the location of ACE2 in Xp22.2 (Hou *et al.,* 2020). According to Benetti *et al.* (2020), the ACE2 gene might be thought of as a genetic risk factor for the severity of COVID-19 infection. Due to the low level of ACE2 mRNA expression, it is possible that these conditions are connected (Yan *et al.,* 2020). In comparison to adults, children exhibit higher plasma levels of ACE2 (Choudhary *et al.,* 2020). Children (6 months to 17 years old) have plasma ACE2 levels between 13 and 100 U/L. However, ACE2 plasma levels in adults range from 9 to 67 U/L, therefore children have a limited capacity for viral infection. Only 0.9% of children with cases under nine years old and 1.2% of other children with cases between the ages of 10 and 19 were included in a recent study of 331,099 patients in China. (Guan *et al.,* 2020).

2. Angiotensin-converting enzyme 1:

The ACE gene is frequently polymorphized, and the variation in ACE levels is caused by the insertion (I) or deletion (D) of a 287-base-pair (bp) Alu repeat (Gemmati *et al.,* 2020). The development of COVID-19 has been linked to changes in the DNA sequence involving the insertion (I) or deletion (D) of a pair of nucleotides at position 287 (bp). Due to an Alu repeat polymorphism, the DD allele of the ACE gene is linked to elevated ACE levels (Gemmati *et al.,* 2020). An increase in tissue damage, proliferation, fibrosis, thrombosis, or inflammation may be brought on by an imbalance in the ACE/ACE2 ratio. Therefore, it was hypothesized that ACE genotype, in addition to ACE2, would influence the clinical outcomes of the COVID-19 study (Delanghe *et al.,* 2020b; Zheng & Cao, 2020). The number of COVID-19 infections decreased as the D allele's prevalence rose in 25 European countries (Delanghe *et al.,* 2020b). In 33 nations in Europe, North Africa, and the Middle East, the frequency of the D allele was inversely linked with death from COVID-19 (Delanghe *et al.,* 2020a). According to Yamamoto *et al.* (2020), there was an inverse correlation between the prevalence of the I/I genotype and susceptibility to COVID-19 infection and mortality in Europe and Asia. In a related ecological analysis, the frequency of the I/I genotype was found to be highly associated with a lower risk of COVID-19 mortality in 25 countries spanning all continents and seas. (Aung *et al.,* 2020).

3. Transmembrane serine protease 2 (TMPRSS2):

Chromosome 21 contains the gene for the serine protease enzyme known as transmembrane serine protease 2 (TMPRSS2) (Yildirim *et al.,* 2021). Because of an associated translocation, the ETS-family of oncogenes is expressed in most tumors where TMPRSS2 is present (Stopsack *et al.,* 2020). According to Choudhary *et al.* (2020), TMPRSS2 is linked to the endosome cysteine proteases CatB/L and is crucial for the entry and spread of viral diseases. According to Anastassopoulou *et al.* (2020), the COVID-19 virus receptor recognizes the location of TMPRSS2 on 21q22.3, making the gene a higher risk factor for the severity of the virus. However, this only occurred in a small number of cases. (Yu *et al.,* 2020). TMPRSS2 receptor can be targeted by numerous miRNAs such as hsa let7a 5p, hsa let7b 5p, hsa let7c 5p, hsa let7d 5p, hsa let7e 5p, hsa let7f 5p, hsa let7g 5p, hsa let7i 5p, hsa miR 98 5p, has miR 4458 and hsa miR 4500 (Katopodis *et al.,* 2022). The TMPRSS2 is regulated by the MR147 3p in the gut, and it promotes viral infection by boosting the COVID-19 spike protein (Abedi *et al.,* 2021). The ACE2 and TMPRSS2 genes are the targets of several cell host miRNAs that can stop COVID-19 from adhering to and entering different organs. Human lung microvascular endothelial cells (HMVEC L) and human umbilical vein endothelial cells (hsa miR 98 5p) have both been shown to directly target the 3' UTR of TMPRSS2; however, miR 98 5p can also inhibit the expression of TMPRSS2 in human endothelial cells. These miRNAs are necessary for the operation of ACE2 and TMPRSS2 because lysine-specific demethylase 5B can control them by downregulating miRs let 7e/miR 125a and

miR 141/miR 200. (Nersisyan *et al.,* 2020; Katopodis *et al.,* 2022).

4. The risk of allele GA:

CXCR6 expression is decreased by Allele GA while SLC6A20 expression is increased (Group 2020) by association with SNP rs11385942, SLC6A20 that share in the interaction of the coronavirus with ACE2 (Kuba et al., 2010; Vuille-dit-Bille *et al.,* 2014). Critical research on the impact of risk alleles was conducted, and the discussion's outcomes revealed that one viewpoint claimed that patients who underwent mechanical ventilation had higher risk allele levels than patients who merely got supplementary oxygen. Another stated that patients who were heterozygous or homozygous for the non-risk allele were more likely to be homozygous for the risk allele when they were younger. (Group 2020).

5. HLA-B 46:01 and HLA-B15:03*:*

The HLA class I heavy chain paralogues include HLA-B. A heavy chain and a light chain form a heterodimer in this class I protein (beta-2 microglobulin). The membrane serves as the anchor for the hefty chain. By presenting peptides obtained from the endoplasmic reticulum lumen, class I molecules play a crucial part in the immune system. They are present in almost every cell. The heavy chain has an estimated 45 kDa and has 8 exons in its genome. Exon 1 codes for the leader peptide, while exons 2 and 3 code for the alpha1 and alpha2 domains that bind the peptide, exon 4 for the alpha3 domain, exon 5 for the transmembrane region, and exons 6 and 7 for the cytoplasmic tail. Each class of one molecule's peptide binding affinity is done by polymorphisms in exons 2 and 3. It is standard procedure to type for these polymorphisms prior to renal and bone marrow transplantation.

Possible connections between different types of genetic diversity in MHC1 (human leukocyte antigen [HLA] A, B, and C) genes (Anastassopoulou et al., 2020). HLA-B 46 and HLA-B15 are common genes among human COVID-19. Suggesting that this allelic variant could enable cross-protective T cells (Nguyen *et al.,* 2020). The HLA-A*11:01, -B*51:01, and -C*14:02 alleles are studied in many ways and after some experiments which are done in China and the studies admitted that the alleles lead to the worst clinical result in patients (Wang *et al.,* 2020). The studies of them in Italy can illustrate another three types of HLA alleles that are called HLA-DRB1*15:01, -DQB1*06:02, and B*27:07 (Novelli *et al.,* 2020).

6. The X-chromosomalTLR7:

Rapid clinical whole-exome sequencing of patients and family members showed unusual, potential loss-of-function mutations in the X-chromosomal Toll-like Receptor 7 (TLR7) gene, which lowered type I and II IFN responses (Van Der Made *et al.,* 2020). Patients are distinguished from healthy people by transcriptional downregulation in primary peripheral blood mononuclear cells (PBMCs) for downstream type I interferon (IFN) signalling. On motivation, the TLR7 agonist imiquimod decreases IRF7, IFNB1, and ISG15 mRNA expression. Imigumod also reduced the production of type II IFN-. Thus, TLR7 appears to be a key component of innate immunity against coronaviruses, particularly COVID-19 (Channappanavar *et al.,* 2019), despite being subject to specific human evolution restrictions against the expected reduction of activity (Casanova *et al.,* 2011; Anastassopoulou, 2020). However, COVID-19 induces a weaker antiviral transcriptional response than other respiratory viruses, owing to low type I IFN levels and increased chemokine expression (Blanco-Melo *et al.,* 2020). TLR7 impairment and variants cause type I and II IFN response failure as well as antiviral transcriptional decrease. The latter occurs in more severe clinical patients and lonely people in their houses who opt to return home after being diagnosed with a positive virus (Made *et al.,* 2020).

7. Sex chromosome associated with immunity system*:*

Recent documents approved that males are infected by COVID-19 more than females. Sex chromosomes have polymorphism which have various effect on

the severity of infection. ACE2 is related to the X chromosome and this relation plays a critical role in infection in different ways between men and females (Anastassopoulou *et al.,* 2020.) which also can be identified by the hormones. Non-coding micro-RNA (miRNA) may be involved in innate and adaptive immune responses discovered on the X chromosome. The X chromosome, X-linked genes, and X chromosome work as stimulation mechanisms for sexual dimorphism especially in females who have 2 X chromosomes one of them can come from the mother and the second can originate from the father. When X chromosome inactivation occurs, it leads to functional mosaics and the development of immunological function. Previous studies found that the estrogen hormone stimulates the immune system by various mechanisms such as upregulating pro-inflammatory cytokines TNFα (Cutolo *et al.,* 2006; Klein *et al.,* 2015). The number of X chromosomes in males is only one which is received from the mother, if any disorders happen in it, it will affect the immunity system by higher effect which will happen in females who have the same disorder. Testosterone is a hormone specific for men that acts as an inhibitor of immune response by upregulation of anti-inflammatory cytokines IL-10 (Anastassopoulou *et al.,* 2020).

8. Apo lipoprotein E (ApoE):

Human apolipoprotein E (apoE) is an example of a soluble apolipoprotein. The apoE family, which is involved in lipid transport in the plasma and the central nervous system, interacts with members of the low-density lipoprotein receptor family. The effects of its three common structural isoforms on the risk of atherosclerosis and neurological disorders such as Alzheimer's disease are different (Hatters *et al.,* 2006).

The three major isoforms of the apolipoprotein E (APOE) gene are encoded by genotypes at the single nucleotide polymorphisms (SNPs) rs429358 and rs7412 on chromosome 19 (T-T, C-T, and C-C, respectively) (Anastassopoulou *et al.,* 2020). COVID-19 infection in older persons with ApoE gene differences is considered a risk factor for COVID-19 severity (Atkins et al., 2020). ApoE isoforms e2, e3, and e4 can encode APOE2, APOE3, and APOE4. The homozygous ApoEe4e4 genotype enhances the likelihood of severe COVID-19 and has been linked to other risk factors such as cardiovascular disease (Atkins *et al.,* 2020). Because the ACE2 receptor is extensively expressed in lung cells, it interacts with Apo lipoprotein E, increasing the severity of COVID-19 (Kuo *et al.,* 2020).

9. ABO blood group*:*

Group, 2020; Wu *et al.,* 2020; Zhao *et al.,* 2021). Several COVID-19-positive patients have B blood groups without taking the O blood group fraction into account. Not only does the type of blood group (A, B, and O) affect the infection, but so does RH. If RH is positive, persons are more likely to become infected with COVID-19, and in most cases, mortality occurs after infection (Zietz *et al.,* 2020). There was evidence for an association between ABO and Rh blood groups, with O blood group depletion and B blood group enrichment among COVID-19-positive patients; additionally, Rh(D)-positive blood types were associated with COVID-19 infection and death following infection, without confounding by demographics or other known risk factors (Zietz *et al.,* 2020; Anastassopoulou *et al.,* 2020).

10.Neuropilin-1 (NRPs):

NRPs are single transmembrane glycoproteins that are non-tyrosine kinase and function as co-receptors for a variety of substances. These molecules include semaphorins and vascular endothelial growth factors (VEGFs), both of which are important in a variety of physiological processes (e.g., neuronal development and axon control, immune function, angiogenesis, cell proliferation, and vascular (Davies *et al.,* 2020; Kielian., 2020). NRP1 increases the infectivity of COVID-19 by increasing virus entry into host cells (Cantuti-Castelvetri *et al.,* 2020; Daly *et al.,* 2020). NRP1 promotes infection by a clinical COVID-19 isolate and lentiviral particles pseudotyped with the COVID-19 S protein by binding to this Cend

R motif of the furin-cleaved COVID-19 S1 protein, according to human cell lines. The presence of acetylcholinesterase 2 (ACE2) and tyrosine methyl peptidase receptor-like sialoprotein 2 (TMPRSS2) appears to enhance NRP1-mediated COVID-19 infectivity rather than increased viral binding to the cell membrane (Katopodis et al., 2022). Overexpression of the NRP1 gene has been found in infected olfactory epithelial cells and lung tissue from COVID-19 patients; additional co-staining confirmed infection of cells positive for oligodendrocyte transcription factor 2, which is primarily expressed by olfactory neural progenitors (Cantuti-Castelvetri *et al.,* 2020). Because COVID-19 is frequently associated with extrapulmonary symptoms (such as gastrointestinal and neurological symptoms), and because NRP1 is a host cell infection mediator, much more research is required to determine the relationship between COVID-19 tropism and the mechanisms by which NRP1 is transported to different tissues and organs (Katopodis *et al.,* 2022).

There are about 27,000 alleles in the Human Leukocyte Antigen (HLA) system, which are split between three classes of genes (Class I, Class II, and Class III). The immune system can tell the difference between self and foreign proteins thanks to the presentation of antigenic peptides by class I and class II HLA molecules to T cells (Lorente *et al.,* 2021). HLA alleles that either increase or decrease COVID-19 severity and mortality have been discovered in multiple investigations. When the HLA binding affinity of all available 8-mers to 12-mers from the SARS-CoV-2 proteome was evaluated, it was found that three peptide-presenters (HLA-A*25:01, B*46:01, and C*01:02) were likely associated with severe infection (Nguyen et al., 2020). Due to its expected poor affinity for binding any of the viral peptides, the HLA-DRB1*08 allele has been linked to an increased risk of severe COVID-19 infection (Amoroso *et al.,* 2021). Multiple studies have linked the presence of certain HLA alleles to an increased risk of dying from COVID-19 (Novelli *et al.,* 2020; Wang *et al.,* 2020; Shkurnikov *et al.,* 2021). These alleles are HLA-A*11:01, HLA-B*51:01, HLA-C*1402, HLA-DQB1*06:02, and HLA-B*27:0.

However, having HLA-A*02:01, HLA-A*03:01, HLA-B*18:01, HLA-C*07:01, or HLA-DRB1*11:04 was associated with a lower risk of dying (Novelli et al., 2020; Wang *et al.,* 2020; Shkurnikov *et al.,* 2021). In one study, HLA-A*11 was found to be associated with a worse prognosis for patients with COVID-19 (Lorente *et al.,* 2021), whereas in another, HLA-A*11:01 was reported to trigger powerful antiviral responses (Tomita *et al.,* 2020). Using allele frequency data from 74 countries, researchers identified HLA-C*05 as the most influential allele in increasing COVID-19 mortality. KIR2DS4fl, expressed by NK cells, recognises viral peptides associated with HLA-C*05. The haplotypes HLAA*01:01, HLA-B*08:01, and HLA DRB1*03:01 have been associated with higher COVID-19 mortality in northern Italy. HLA-B*18:01, HLA-C*07:01 and HLA-DRB1*11:04 were all linked to a lower death rate in southern Italy (Pisanti et al., 2020). Data from 6,919 patients showed, however, that neither HLA genotypes nor viral T-cell epitopes were linked to COVID-19 disease severity (Schetelig *et al.,* 2021).

11.Other genetic variations:

Two single nucleotide polymorphisms (SNPs), rs35081325 and rs1024611, in LZTFL1, have been recently found to be strongly associated with more severe infections (Roberts *et al.,* 2022; Ruter *et al.,* 2022). Incorporating expression quantitative trait locus (eQTL) mapping, researchers at Kasela et al. 2021 identified SLC6A20 and CXCR6 as risk-associated genes for COVID-19. However, in a different study (Yao *et al.,* 2021), CCR9 and SLC6A20 were identified as potential target genes. More study is needed to definitively identify the effector genes at the 3p21.31 locus, any of which may play a role in the pathophysiology of COVID-19 (Ji *et al.,* 2022). Loci on chromosome 3p21.31 and chromosome 9q34.2 were associated with COVID-19 severity in two

different GWAS (genome-wide association study). In the first study of its kind, researchers in Italy and Spain found a high association between the genetic markers rs11385942 (at 3p21.31) and rs657152 (9q34.2) and severe COVID19 with respiratory failure (Ellinghaus et al., 2020). In addition, the second analysis (Shelton et al., 2021) revealed the risk alleles rs13078854 at 3p21.31 and rs9411378 at 9q34.2 for severe COVID-19 characteristics. The association signal at 3p21.31 influenced the expression of six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1) (Ji *et al.,* 2022).

11.1.Genetic variants of cellular proteases:

COVID-19 enters cells via membrane fusion after binding to a cell surface receptor and being spiked by cellular proteases. TMPRSS2 was the first pro tease implicated in the priming of S proteins. Subsequent investigation suggested that other proteases may be involved in the entrance processes of COVID-19 (Yildirim *et al.,* 2021).

11.1.1. Cathepsin B and L (CatB/L):

TMPRSS2 and the cysteine proteases cathepsin B and L (CatB/L) are both resident in endosomes. CatB/L and TMPRSS2 work together to activate the S protein, but CatB/L activity is not required for viral replication or pathogenicity (Hoffmann *et al.,* 2020b). Cathepsin L, on the other hand, is required for admission to COVID-19 (Ou *et al.,*2020). An extra protease cleaves the spike protein at the S1/S2 site and is essential for S protein-mediated cell-cell fusion and entry into human lung cells (Hoffmann *et al.,* 2020a). Variations in ACE2, ELANE, CTSL, TMPRSS2, and TMPRSS11A, all of which have a role in SARS-CoV entrance (Vargas-Alarcon *et al.,* 2020). These polymorphisms may be of interest in association studies for COVID-19 disease (Yildirim *et al.,* 2021).

11.1.2. Furin (paired basic amino acid-cleaving enzyme, PCSK3):

In silico analysis of the coding regions of proteases in a small Serbian cohort suggested two changes in Furin, p. Gly146Ser and p. Thr33Ala, with the potential to impact protein structure and/or function (Klaassen *et al.,* 2020).

The S protein of C COVID-19 can be cleaved by the host cell protease Furin at a multi-basic S1/S2 site (Hoffmann et al., 2020a). COVID-19 can be treated by inhibiting TMPRSS2 and Furin, two proteases important for the proteolytic activation of SARSCoV2 (Bestle *et al.,* 2020). Patients with diabetes mellitus may be more susceptible to COVID-19 and have poorer outcomes due to greater plasma Furin levels (Yildirim *et al.,* 2021). Despite the identification of six Furin gene mutations in a small COVID-19 cohort, no association with the disease was reported (Torre-Fuentes *et al.,* 2020).

11.2.Genetic variations of immunity components:

11.2.1.Interferons:

IFNs are a specialized cytokine family that initiates a cell signalling cascade that controls hundreds of interferon-stimulated genes. There are three types of IFNs (Types I, II, and III) that stimulate the host immune system in response to viral infections (Acosta *et al.,* 2020). In humans, but not mice, IFN- causes an increase in ACE2, which may protect lung tissue from damage (Ziegler *et al.,* 2020). IFNAR1 (p. Trp73Cys, p. Ser422Arg, p. Pro335del) and IFNAR2 (p. Glu140fs) variations were found in hospitalized patients with COVID-19-related pneumonia (Zhang *et al.,* 2020). The existence of the essential COVID-19 allele is significantly correlated with the IFNAR2 intron variant rs2236757 (Pairo-Castineira *et al.,* 2020). Transduction of IFN-stimulated phosphorylation signals from IFN receptors requires the cytoplasmic kinase tyrosine kinase 2 (TYK2) (Yildirim *et al.,* 2021).

The TYK2 coding locus has been recommended as a possible therapeutic target, and a single nucleotide polymorphism (rs74956615) in this region has been related to severe COVID-19 (Pairo-Castineira et al., 2020). Homozygosity for the C allele of rs12252 in the IFITM3 gene has been linked to more severe disease in COVID-19, and this association appears to increase with age (Zhang *et al.,* 2020). IFNs stimulate genes of the 2′,5′-oligoadenylate synthase (OAS)

family early in viral infection; this family destroys viral RNA signals (Yildirim *et al.*, 2021). Klaassen *et al.* (2020) postulated that the OAS1 coding region modifications p. Arg47Gln, p. Ile99Val, and p. Arg130His might be used as predictive markers for interindividual variances in the response to the Covid19. In a study conducted by the COVID-19 Host Genetics Initiative (HGI) (Yildirim *et al.,* 2021), an association area was identified on chromosome 12 close to the OAS gene cluster signals. A recent GWAS research (Pairo-Castineira et al., 2020) indicated that the rs10735079 mutation in the OAS gene cluster was related to crucial COVID-19.

11.2.2.Interleukins (ILs):

The discovery of interleukins and interleukin receptors has proven critical in regulating CD4+ T cell activity across illnesses. Interleukins control the presence, flexibility, differentiation, and proliferation of CD4+ T cells (Kubick *et al.*, 2021). According to a recent meta-analysis (Leisman et al., 2020), patients with cytokine release syndrome, sepsis, and acute respiratory distress syndrome not related to COVID-19 had significantly increased mean IL-6 concentrations. IL6 polymorphisms have not been definitively linked to the onset or severity of COVID-19. Understanding IL6 polymorphisms is critical for establishing focused pharmaceutical development against COVID-19 (Kirtipal & Bharadwaj., 2020). Three hundred thirty-two patients with Covid19 were categorized into five severity levels so that genetic variants could be studied (Wang *et al.,* 2020). Most strongly related to illness severity was a gene locus termed TMEM189-UBE2V1 (Yildirim *et al.,* 2021). This gene locus is a part of the IL-1 signalling system.

11.2.3.Toll-like receptors (TLRs):

Class of pattern recognition receptors (PRRs) are involved in innate immunity (Takeda & Akira, 2015; Yildirim *et al.*, 2021). It is possible that this class of receptors can recognize pathogen-associated molecular patterns and activate the host immune system. TLR3 is the most abundant and broadly expressed TLR and is responsible for the recognition of viral double-stranded (ds) sRNA. Virus ss RNA is recognized by toll-like receptors 7 (TLR7) and 8 (TLR8). Once TLRs have identified a pathogen-associated molecular pattern, they play a role in the production of Type I IFN and inflammatory cytokines. Both IRF3 and IRF7, IFN regulatory transcription factors, are involved in these signal transduction pathways (Lim & Staudt, 2013; Yildirim *et al.,* 2021).

Patients with a potentially lethal instance of COVID-19 have a type I IFN response that is regulated by tyrosine kinase receptor 3 and IFN regulatory factor 7. The authors of a serious condition found eight genetic loci (Yildirim *et al.,* 2021). Recessive (IRF7, IFNAR1) and dominant (TLR3, IFN3, IFNAR1, IFNAR2, TICAM1, TBK1, and UNC93B1) versions of the disease have been linked to mutations in these genes (Zhang *et al.,* 2020). TLR7 loss-of-function variants (c.2129 2132del; p. Gln710Argfs*18; c.2383G>T; p. Val795Phe) have been found in four young males from two unrelated families with severe COVID-19 infection (Yildirim *et al.,* 2021). These signalling cascades also involve IFN regulatory transcription factors such as IRF3 and IRF7 (Lim & Staudt, 2013; Yildirim *et al.,* 2021).

11.2.4.HLA LOCUS:

HLA proteins deliver antigens and preserve genetic diversity. HLA, the most variable genetic locus, allows the immune system to adapt to several illnesses. The region's 240 HLA genes are mostly class I, II, and III (Yildirim *et al.,* 2021). HLA peptides may boost T cell response to SARS-CoV infection by increasing their binding specificities. Covid19 patients have higher frequencies of the HLA-C*07:29 and B*15:27 alleles (W. Wang *et al.,* 2020). However, the HLA-B*15:03 allele can display the most highly conserved COVID-19 peptides (Nguyen et al., 2020), allowing bearers to develop cross-protective T-cell-based immunity. HLA alleles A*11:01, B*51:01, and C*14:02 strongly predict the worst COVID-19 outcomes (Wang *et al.,* 2020). GWAS of 1980 COVID-19 patients

with severe disease found no SNP association signals at the HLA locus (Yildirim *et al.*, 2021).

11.2.5.3P21.31 AND 9Q34.2 LOCI:

Genome-wide association analyses of severe COVID-19 and respiratory failure patients identified significant relationships with rs11385942 at 3p21.31 and rs657152 at 9q34.2 (Yildirim *et al.,* 2021). COVID-19 patients with respiratory failure had more GA variants in their gene pools (Yildirim *et al.,* 2021). The ACE2 receptor may relate SLC6A20 to COVID-19 (Vuilledit-Bille *et al.,* 2015). Expose this loci's COVID-19 role. Proteomic analysis and genetic data from three cohorts identified these loci's target proteins (Katz et al., 2020). CXCL16 and TGF-1 share a quantitative characteristic at the 3p21.31 locus (Yildirim *et al.,* 2021). IJCB | 1165 Three copies of CXCL16, a chemokine, and one of its receptors, CXCR6, occur on chromosome 3p21.31. CXCL16 and CXCR6 may mediate COVID-19 since they are associated with LPS-induced acute lung injury (Tu *et al.,* 2019; Wein *et al.,* 2019).

11.2.6.How micro-RNA can be a danger for the host:

COVID-19 targets 1,367 human genes and 479 human miRNAs involved in viral entry, replication, biosynthesis, and infection (Choudhary *et al.,* 2020). Some believe that 10 viral genes can bind to miRNA, affecting their function (Demirci *et al.,* 2020). By regulating cellular components, molecular functions, and biological processes, miRNA affects genes differently. Importantly, COVID-19 patients have different peptidases, protein kinases, and Ras GTPases than healthy controls.

COVID-19 infection relies on miRNAs (Li *et al.,* 2020). Since miRNA is too tiny for the immune system to recognize, it helps viruses infiltrate hosts better than proteins (Tycowski *et al.,* 2015). MR385-3p, a viral miRNA, binds to the 5′-UTR of TGFBR3, an immune system receptor. MR147-5p binds CXCL16 and ARRB2 stimulators. TNF-α stimulator MR147-3p binds to MR66-3p. They target TMPRSS2, MR198-3p, ADAR, MR359-5p, and MR328-5p, which bind to viral infection proteins MYH9 and RARA, MD2-5p, and MR147-3p. They cause apoptosis by targeting CHAC1 and RAD9A (Liu et al., 2020). MiRNAs target virus functional RNAs, including S (Spike), E (Envelope), M (Membrane), N (nucleocapsid), ORF1ab, ORF3a, ORF8, ORF7a, ORF10, and ORF6 (Demirci *et al.,* 2020).

Bioinformatics showed that host miRNAs may work with COVID-19's 3-UTR, 5-UTR, ORF1ab, and S gene (Khan et al., 2020). Scientists linked miRNAs to COVID-19 ORFs (miR-23a (1ab), miR-29a,-29c (1ab, N), miR-151a,-151b (S), miR-298 (5′-UTR), miR-4707-3p (S), miR-8075 (5′-UTR), ACE2 3′-UTR (miR-9-5p, miR-218-5p), miR-7851-3p (5′-UTR), and TMPRSS2 (3′-UTR) (let-7d-5p,-7e-5p, miR-8075). MiR-200c binds COVID-19 and ACE2 receptors in cardiomyocytes by targeting its 3′-UTR.Overexpression of miR-200c gene decreases mRNA and ACE2 protein expression (Lu *et al.,* 2020). According to earlier studies, miR-98-5p in 3′-UTR human endothelium cells decreases TMPRSS2 expression (Matarese *et al.,* 2020). Lysine-specific demethylase 5B (JARID1B) regulates ACE2 and TMPRSS2 via inhibiting the transcription of let-7e/miR-125a and miR-141/miR-200, which target 3′-UTR (Zhang *et al.,* 2021a). In pregnant women with PE, miR-126v is reduced, which strikes out an anti-viral miRNA and increases COVID-19 severity (Abel *et al.,* 2021).

COVID-19's micro-RNA genome affects host cell miRNA. Mi-RNA was increased or down-regulated. 35 micro RNAs may be upregulated, including hsa-miR-16-2-3P, hsamiR-142-5p, hsamiR-4685-3p, hsamiR-454-5p, and hsamiR-30c-5p. Compared to healthy controls, miR-16-2-3p is up-regulated 1.6-fold. MiR-6501-5p and miR-618 are 1.5-fold upregulated compared to healthy adults. Acute inflammatory responses can result from RSV-induced miR-155 upregulation (Inchly *et al.,* 2015; Li *et al.,* 2020). COVID-19 infection was especially dangerous in preeclamptic patients. Hsa-miR-183-5p, hsa-miR627-5p, hsa-miR-941, hsa-

miR-21-5p, hsa-miR-20a-5p, hsa-miR-146b-5p, hsa-miR-454-3p, hsa-miR-18a-5p, hsa-miR-340-5p, and hsa-miR-17-5p were downregulated. Compared to controls, miR-627-5p down-regulated the infection by 2.3-fold. Infection downregulated miR-183-5p, miR627-5p, and miR-144-3p by more than 1.3-fold compared to controls (Li et al., 2020). In vitro studies suggest COVID-19 may upregulate endogenous targets as a competitive RNA. After COVID-19 infection, epithelial cells up-regulate the CSF1 gene, which miR-1207-5p targets. CSF1 can attract and stimulate acute inflammatory macrophages during COVID-19 infection. COVID-19 may dysregulate miR-1207-5p targets, causing out-of-control inflammatory responses (Bertolazzi et al., 2020). A high-throughput peripheral blood sample investigation found 35 up-regulated and 38 down-regulated miRNAs in COVID-19 patients. Patients overexpress miR-16-2-3p the greatest. These patients have 1.5 times more miR-6501-5p and miR-618 than healthy donors. Patients underexpress miR-627-5p the most (Li *et al.*, 2020). COVID-19 patients who did not respond to one dose of this medicine exhibited decreased blood serum miR146a-5p levels. Non-responders with low miR-146a-5p expression have the worst outcomes (Sabbatinelli *et al.,* 2021). In COVID-19 patients' lungs, miR-146a regulates differentially expressed genes (Geraylow et al., 2022). In both cohorts, COVID-19 cases had higher serum miR-21, miR-155, miR-208a, and miR-499 than healthy subjects (Garg *et al.,* 2021).

The MiR-200c-3p expression is highest in COVID-19 patients with severe symptoms, followed by respiratory difficulties and mild symptoms (Geraylow *et al.,* 2022). Severe COVID-19 is linked to elevated miR-200c-3p and systemic arterial hypertension. MiR-200c-3p expression may predict COVID-19 progression (Geraylow *et al.,* 2022). COVID-19 cerebrovascular difficulties may be caused by miR-24 levels in endothelial cells/extracellular vesicles (Gambardella *et al.,* 2021b). Bloodstream miRNAs increase COVID-19 mortality. MiR-30b/c/e, miR-6080, miR-181a-5p, miR-199a-3p, and miR-339 are highly specific for COVID-19 disease severity and death (Gustafson *et al.*, 2022).

COVID-19 patients showed higher CCL20, IL-6, IL-10, and miR-451a, which enhanced their chance of death (Wilson *et al.*, 2022). COVID-19 patients with miR-133a and miR-122 have higher mortality after 28 days. Giuliani *et al.* found that miR-320b and miR-483-5p were up-regulated in deceased individuals. Hospitalized COVID-19 patients with 20% above-average serum miR-320b and miR-483-5p levels have a threefold greater risk of death (Giuliani *et al.,* 2022). Viral RNA interference and p53. RNAi is post-transcriptional gene silencing (PTGS) in plants, animals, insects, and nematodes. Previous study has shown that RNAi helps the body fight infections. SARS-CoV N-protein binds siRNA and shRNA to suppress RNAi. In a SARS-CoV-like hepatitis virus mouse model, Dicer and Ago2 knockdown boosted viral replication (Cui *et al.,* 2015).The "microbiome" of bronchoalveolar stem cells (BASCs) showed that SARS-nucleocapsid CoVs and spike protein suppressed miR-223. p53 is crucial to RNAi-SARS viral interaction (Ramaiahm 2020). Human-encoded microRNAs and COVID-19 infection. MiRs regulate viral infection and protect the host. Host miRs block translation or stabilise viral RNA, inhibiting replication. Human miRs may fight HIV-1, HCV, CMV, influenza, and dengue, according to studies (Trobaugh & Klimstra 2017). Multiple viral escape mechanisms cause problems.

For Example:

1) Prevent host miRs from working.
2) Avoid being targeted by host miRs by modifying your own 30 UTR sequence in a way that makes it mutated or too short to bind complementary.
3) Secondary structure is provided by a 30 UTR sequence that is far too lengthy.

Host miRs that have been hijacked can help viruses modulate cellular biological processes and change the activity of target genes. COVID-19 was projected to hijack 28 human miRs, generating alterations in over

800 genes. Most of these human miRs were anticipated to interfere significantly with the immune response in COVID-19 patients (Liu *et al.*, 2020).

Micro-RNA regulates ACE2 expression and is classified as follows:

1- Mi-200c-3p:

Mi-200c-3p has been discovered in a variety of cell types, including cell culture (HEK293T, THP1, A549), pneumonia, control patients, and C57Bl/6 mice. H5N1 virus, dsRNA, LPS, and LTA, as well as acute pneumonia patients, upregulate miR-200c-3p via NF-B. MiR-200c-3p suppression increases ACE2 expression, survival, and lung damage in H5N1-infected mice (Liu *et al.*, 2017).

2- Cell culture: neonatal rat cardiomyocytes (NRCMs), neonatal rat cardiomyocytes (NRCFs), HCFs, HUVECs, and hIPSC-derived cardiomyocytes (hiPSC-CM). With miR-200c-3p, NRCMs and hiPSC-CMs downregulate ACE2 mRNA and protein (Lu *et al.*, 2020).

2- Mir- 1246:

Mir-1246 has been discovered in a variety of cell types, including 1- In PMVEC cells from C57Bl/6 mice treated with LPS, miR-1246 is increased, resulting in lower ACE2 expression. Overexpression of ACE2 inhibits apoptosis, whereas LPS increases apoptosis, IL-1, and TNF-. After intrathecal LPS instillation, anti-miR 1246-injected animals improved in lung injury score, ACE2 expression, vascular permeability, and inflammation (Fang *et al.*, 2017).

2- A two-way comparison of small airway epithelial (SAE) cells from smokers and nonsmokers According to microarray and qRT-PCR investigations, smokers showed lower miR-1246 expression than nonsmokers. ACE2 mRNA was found to be higher among smokers, with similar results (Zhang *et al.*, 2020).

3- Mic- 125b:

Cell culture in the lab (HK-2 and HEK-293T) In cells treated with 30 mM glucose, miR-125b expression increased whereas ACE2 expression dropped. After inhibiting miR-125b expression, reduced reactive oxygen species (ROS) generation and apoptosis were reported in high hyperglycemia settings (Huang *et al.*, 2016).

4- MiR-421:

Mir-421 is present in a variety of cell types, including 1- MiR-421 overexpression specifically reduced the expression of the ACE2 protein in cell culture (HEK293T, Huh7, isolated cardiac myofibroblasts). The expression of miR-421 in the kidney is higher than in the heart, liver, or spleen. HEK293T cells had higher levels of miR-421 expression than Huh7 or isolated cardiac myofibroblasts (Lambert *et al.*, 2014; Lima *et al.*, 2021).

2- It has been demonstrated that serum miR-421 levels are higher in kidney disease patients compared to those on hemodialysis or as a control group. The expression of ACE2 in leukocytes is inversely related to miR-421 levels in the blood. In response to uremic toxins, miR-421 expression increases whereas ACE2 expression decreases (Trojanowicz *et al.*, 2019).

5- Mic-143 Mic-143:

It is present in a variety of cell types, including 1- miR-143 Females of the Wistar strain of rodents Mildly and highly trained rats had higher levels of ACE2, Ang (1-7), and the Ang (1-7)/AngII ratio in the heart's left ventricle, whereas highly trained rats had lower levels of miR-143 (Lima *et al.*, 2021).

2- Wistar and SHR male rats SHR rats with moderate training had increased ACE2 protein expression and decreased mi-143 in the aorta (Gu *et al.*, 2014; Lima *et al.*, 2021).

6- MiR-483-3p:

Mir-483-3p is found in a variety of cell types, including 1- MiR-483-3p, which was discovered to target ACE2 mRNA as well as other renin-angiotensin system genes after being identified from human embryonic kidney 293T cells. A reporter test using the ACE2 30 UTR revealed decreased luciferase expression. ACE2 mRNA levels were unaffected when miR-483-3p was expressed in cells on a long-term basis. Protein concentrations were not investigated (Kemp *et al.*, 2014; Lima *et al.*, 2021).

2- HTR-8/SVNeo cells developing in vitro. Cell growth was reduced by transfection of a miR-483-3p mimic (Arthurs *et al.,* 2019).

7- MiR-429 Mice: Mice lacking microRNA 429 (miR-429): FVB/NJ Mice fed a low-protein maternal diet (MLPD) exhibited higher miR-429 levels in their female offspring than mice on a standard mouse diet, but the inverse was true for male offspring. Female MLPD offspring had lower levels of ACE2 protein expression (Goyal *et al.,* 2015).

MiRNAs linked with COVID-19 infection include miR-146a, miR-155, Let-7b, miR-31, miR-16, and miR-21 (Alvarez *et al.,* 2022).

MiR-146a:

COVID-19 infection is associated with the downregulation of miR-146a expression (Keikha and Jebali, 2021; Roganovic, 2021; Sabbatinelli *et al.,* 2021). This increased the levels of IL-6, which causes resistance to various medications being tested against COVID-19 (Arghiani *et al.,* 2021; Sabbatinelli *et al.,* 2021).

MiR-155:

Thus, in the setting of COVID-19-associated cognitive dysfunction, upregulation of miR-155 in SARS-CoV-2 infection may explain a component of the enhanced immune response, which then leads to CNS damage (Alvarez *et al.,* 2022).

Let-7b (Rahman *et al.,* 2020; Yuen *et al.,* 2021) is a multifunctional miRNA whose expression changes between those with cognitive disorders and those who are healthy. Let-7b recognizes ACE2, inducing alterations in ACE2 gene expression; Let-7b is a clinical COVID-19 infection treatment target (Bellae Papannarao *et al.,* 2022). In the context of COVID-19 infection, Let-7b promotes apoptosis by reducing BCL-2, an anti-apoptotic protein, and regulating immunological responses (Islam *et al.,* 2021b).

MiR-21:

MiR-21 is an anti-neuroinflammatory miRNA, and its downregulation in COVID-19 patients promotes systemic inflammation via hyperactive immunological response, T-cell function loss, and immune dysregulation (Tang *et al.,* 2020).

Conclusion:

The current investigation examined the connection between the COVID-19 strain, human genetic characteristics that increase infection susceptibility, and the mechanism of harmful inflammation. Toll-like receptor, ACE2, Furin (paired basic amino acid cleaving Enzyme, PCSK3), HLA LOCUS, and ABO blood group are all examples. Therefore, there may be genetic risk factors for the development of COVID-19.

List of Abbreviations:

SARS-COV: Severe acute respiratory syndrome coronavirus; COVID-19: Coronavirus; ORFs: Open reading frames; 3cLpro: 3chymotrypsin as a cysteine protease; NTD: N-terminal domain; RBD: Recombinant's receptor- binding domain; DIC: Disseminated intravascular coagulopathy; ACE2: Angiotensin-converting enzyme2; Nfs: Neurofilament; PD: peptidase domain; ADAM-17: Disintegrin and metalloproteinase domain-containing protein 17; TMPRSS2: Transmembrane serine protease 2; HMVEC L: Human lung microvascular endothelial cells; HLA: Human leukocyte antigen; TLR7: Toll-like receptor 7; PBMCs: Peripheral blood mononuclear cells; mRNA: micro-RNA; SNPs: Single nucleotide polymorphisms; APOE: Apolipoprotein E; NRP1: Neuropilin 1.

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