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Review Article

Evaluating the Impact of Different Genetic Variants on the Prognosis of Patient with COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan (China). It soon became widespread so that the World Health Organization (WHO) declared the outbreak of COVID-19 as a pandemic crisis. This disease has caused significant morbidity and mortality in the world. Clinical studies reported that there is a significant correlation between genders, immunogenetic variants, serum levels of some circulating factors, blood groups, and different races with severity and mortality of COVID-19 patients. Hence, some studies have investigated the role of individual genetic background in the susceptibility and vulnerability to COVID-19 infection. It is proposed that host genetic polymorphisms affect the onset and progression of COVID-19 infection and could dramatically impact the virus life cycle. This paper aims to review the state-of-the-art research on the roles of genetic variants in host cell membrane proteins and blood circulation factors in the prognosis of patients with COVID-19.

Keywords: COVID-19; SARS-CoV-2; Polymorphism; Prognosis; Host Genetic Factors; Susceptibility

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Introduction

Coronaviruses are a species in the Coronaviridae family. They include human coronavirus 229E (HCoV-229E), HCoV-OC43, severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV), Middle East Respiratory Syndrome-CoV (MERS-CoV), and HCoV-NL63 in humans. A new coronavirus isolated from humans is now recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its similarities to SARS-CoV (1-3). SARS-CoV-2 emerged in December 2019 in Wuhan, China. It soon became widespread, so the World Health Organization (WHO) declared the outbreak of COVID-19 as a pandemic crisis (4, 5). The SARS-CoV-2 virus has infected approximately 30 million people in the US and about 540000 total deaths (https://www.cdc.gov/coronavirus/nov-

el-coronavirus-2019.html). Mortality and morbidity of infection with the virus are lower than with SARS-CoV due to less circulating neutralizing antibodies, inducing a high level of pro-inflammatory mediators and more chronic involvement (6, 7). To limit the pandemic created by COVID-19, knowing the molecular mechanisms of viral entry and replication will help design therapeutic interventions and preventive strategies. Molecularly, the entry of SARS-CoV-2 is led by binding the spike glycoprotein (S protein) to angiotensin-converting enzyme-2 (ACE2), the primary receptor for SARS-CoV-2. The S1 subunit of the S protein contains the receptor binding domain (RBD) that binds to two "hotspots" in the extracellular domain of ACE2: Lys31 and Lys353. After connecting the RBD to ACE2 on host epithelial cells, the following steps of virus entry require breaking the S1 / S2 connection. This process is driven by the function of host cell proteases such as transmembrane protease, serine 2 (TMPRSS2), and lysosomal protease cathepsins, which play a significant role in the spread of the virus throughout the body (8, 9). Moreover, some evidence indicates the involvement of other proteases in the process of virus entry, including the Furin protein that facilitates the virus entry into target cells that do not have significant expression of the main proteases TMPRSS2 and lysosomal proteases cathepsins (10). Various clinical studies during hospitalization of patients with COVID-19 have shown significant correlations between genders, serum levels of some circulating factors, blood groups, and different races, and severity and mortality of patients with COVID-19. Therefore, much attention is paid to the involvement of different genetic variants in the hosts susceptibility and vulnerability to COVID-19. This review aims to gather the genetic variants in the host cell membrane proteins and blood circulation factors suspected to be involved in the prognosis of patients with COVID-19.

Polymorphism in Proteins Involved in COVID-19 Primary Invasion

The main molecular interactions in the starting point of the SARS-CoV-2 entry into cells is handled by several molecular interactions (**Figure 1**), as mentioned below. Recent studies have shown that the principal core of this binding is the ACE2 protein, a type 1 membrane protein from the family of metallocarboxypeptidases that is structurally analogous to the serum protein ACE and tends to bind to the S protein (11).

ACE2 Polymorphism

For the first time, an association between ACE2 polymorphisms and serum levels of this protein with susceptibility to hypertension was reported by Rice, et al. in 2006 (12). Consequently, numerous studies have examined the types of polymorphisms within the ACE2 gene that could affect its protein expression level among different populations and races. One of the most well-known polymorphisms is the single nucleotide polymorphism (SNP) rs228566 (G>A). The AG genotype is associated with a lower risk of hypertension in women, while the AA genotype is associated with an increased risk of hypertension in different populations (13-15).

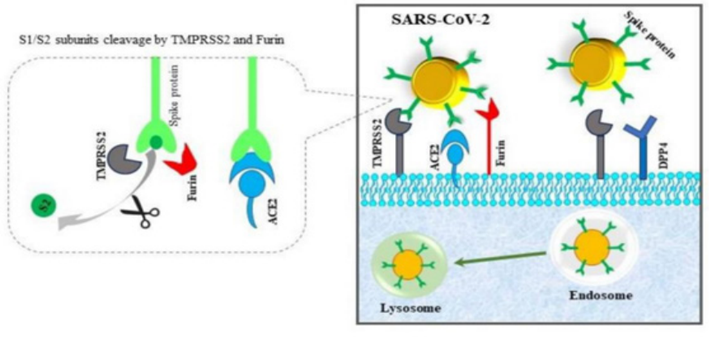

Figure 1. Molecular interactions in starting point of the SARS-CoV-2 entry into cells.

Various clinical studies have shown that COVID-19 patients with hypertensive manifestations have a greater risk of death. (16, 17). Further studies have shown a more precise association between ACE2 rs228566 polymorphism and hypertension in the elderly with COVID-19 (14, 15). However, Gómez, et al. reported that there is no association between the variants of this gene and the disease outcome (18). Studies have examined the effect of different variants such as K26R on its expression, activation, and binding affinity to S protein (20). Also, some variants like N720D in ACE2 as well as increased TMPSRR2 activity are suggested to affect the virus entry in European countries (19). In addition, in Middle Eastern countries, the variants rs769062069 (R708Q, p.Arg708Gln) and rs776995986 (R708W, p.Arg708Trp) have been found to affect the cleavage site between the S1 and S2 subunit that can consequently affect the severity and susceptibility to COVID-19 (19). These findings are consistent with a decrease in expression levels of ACE2 and an increased risk of complications and comorbidities such as hypertension and heart failure, which could increase the risk of hospitalization in patients with COVID-19 (17). In another study, Martínez-Sanz et al. reported two variants of ACE2 associated with increased risk of infection susceptibility. They showed that the minor T allele in the rs6629110 variant (TC and TT genotype) and the minor A allele in the rs2106806 variant could increase the risk of susceptibility to COVID-19 infection in highly exposed healthcare workers (20).

ACE Polymorphism

Contrary to what has been said about ACE2, increased ACE levels due to the Ang II / AT1R axis can increase the risk of cardiovascular or pulmonary manifestations in patients (18). Two of the most common polymorphisms in this gene expression, ACE insertion/deletion variant (I/D), have been widely studied. It has been demonstrated that it can increase the risk of several diseases (22 – 24). During the COVID-19 pandemic, some studies initially indicated the involvement of I/D polymorphisms in the circulating ACE levels. However, some studies declared no significant association between ACE (I/D) polymorphisms and susceptibility to COVID-19 (21-23). A recent meta-analysis reported that there is a significant association between ACE I/D polymorphisms and the risk of developing acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) in patients with COVID-19 infection (24). It has been shown that the D/D genotype is associated with increased expression of ACE and increased risk of cardiovascular disease as well as acute respiratory manifestations, including ARDS and the progression of pneumonia in patients with SARS (25, 26). A study demonstrated that patients with D/D genotype are at a 3.69-fold increased risk of COVID-19 severity (27).

Additionally, other studies reported a correlation between COVID-19-related mortality and D/D genotype (28, 29). More detailed statistical studies reported that the I/I genotype was inversely associated with COVID-19-related mortality. The frequency of ACE in patients with D/D genotype leads to increased Ang II levels (30). This factor increases platelet count, leading to their accumulation in lung tissue, which is similarly seen in patients with the COVID-19 virus (31, 32).

TMPRSS2 Polymorphism

TMPRSS2 and Furin are essential proteins that activate the virus. TMPRSS2 is one of the serine protease proteins that plays an essential role in the virus entry and invasion into the cells by cleavage of SARS-CoV-2 S protein units. In the expression of quantitative trait locus (eQTL), a variant of TMPRSS2, rs35074065, was associated with overexpression of this protein and reduced transcription of the MX1 gene, which could ultimately increase the susceptibility to infection and reduce cell anti-viral defense (33, 34).

Dipeptidyl Peptidase 4 (DPP4) Polymorphism

Dipeptidyl peptidase 4 (DPP4) was the main receptor for cell entry of MERS-CoV (35). A study by Vankadari et al. reported an interaction between the S1 domain of SARS-CoV-2 S protein and DPP4. Therefore, it could be considered another receptor for SARS-CoV-2 (36). Also, studies declared that DPP4 polymorphisms are associated with insulin resistance and obesity which are significant risk factors for COVID-19 infection and its severity (37, 38). Schlicht et al. reported that the serum levels of DPP4 were notably de-

creased in patients with COVID-19 compared to healthy controls (39). The results of this study were compatible with Posadas-Sanchez et al. study (40). The gene that encodes DPP4 is polymorphic, and there is a correlation between the levels of this protein and different genotypes. It has been reported that rs3788979 polymorphism is associated with an increased risk of COVID-19 infection, and patients with TT genotype had the lowest levels of DPP4 (40).

ABO Blood Group Type

Early reports from Wuhan, China, after the COVID-19 virus became a pandemic, showed a high risk of contracting the virus in a population with blood type A and vice versa with blood type O (41). Since then, many studies have tried to find a link between them. Despite the discrepancies in the results (42, 43), systematic and meta-analytical studies have found a significant correlation between blood type A group and predisposition to severe prognosis and outcome in patients afflicted with the COVID-19 virus (44). Jacques Le Pendu et al. (45) briefly discussed the mechanisms involved in ABO blood type and the results of COVID-19 virus infection.

ABO Blood Type and Furin Cleavage

The interaction mediates the entry of coronavirus into epithelial cells between the virus S protein, ACE2 receptor, and TMPRSS2 in the host cell. From a molecular perspective, the S protein comprises a receptor-bound N-terminal S1 subunit and a membrane-fusion C-terminal S2 subunit. After binding the virus to the receptor, morphological changes in its structure facilitate binding the S protein to other receptors. Then the cleavage stage occurs under the action of proteases including TMPRSS2, cathepsin CTSL, and trypsin (8). Furin is a proprotein convertase (PC) that converts precursor proteins into biologically active proteins. It is noteworthy that SARS-CoV-2, in this regard, has the cleavage site of the Furin surrounded by an O-glycosylation section (46, 47). This protein also plays an important role in infecting S protein-dependent entry precursors in other viruses such as infectious bronchitis viruses (IBVs) (48). The study by Abdelmassih, et al. provides strong evidence for an association between ABO blood groups and Furin plasma levels in patients with COVID-19. They hold this mention that its concentration might be reduced in patients presenting O blood group and less severity of affliction as a result (49). Despite the multistage mechanism of the S protein activation and cleavage in COVID-19, some studies support that Furin is significantly involved in the maturation and replication stages of the virus. It is suggested that its overexpression can increase the activity of the S protein but does not interfere with its cleavage and cell-cell and virus-cell fusion (8, 50).

ABO Blood Type and Gut Microbiota

Lockdown during the COVID-19 pandemic has led to increased consumption of home-cooked food compared to fast food and balancing and strengthening the gastrointestinal microbiota and symbiosis, consequently (51). On the other hand, the bacteria in the microbiota stimulate the synthesis of anti-A and anti-B antibodies (45). Numerous studies have evaluated the effect of blood groups A and B carriers on the gastrointestinal microbiota composition. Mäkivuokko H et al. (52) showed that the composition of Actinobacteria in A group carriers is much higher than that in other blood groups. This correlation is associated with an increased incidence of gastrointestinal inflammatory-based diseases such as Crohn's disease and ulcerative colitis and may enhance the inflammatory response of patients with COVID-19. Another investigation reported decreased levels of Blautia in blood type A carriers, associated with inflammatory and autoimmune conditions in these individuals (53, 54). As a result, an association between poor prognosis and severe inflammatory conditions can be inferred in people with blood type A and COVID-19.

ABO and Thrombosis

Severe COVID-19 disease is associated with manifestations of inflammatory conditions, including endothelial damage, interference with respiratory gas exchange, and thrombosis (55-57). Some studies have found a significant association between the high risks of these manifestations in people with non-O blood groups (58).

From a molecular perspective, the level of blood coagulation factors, especially von Willebrand factor (VWF) and factor (F) VIII are high in the serum of people with ABH antigens. Consequently, the presence of these antigens at the level of megakaryocytes and vascular endothelial cells is elevated (45, 59). In 1995, Koster T et al. showed that patients carrying ABH antigens and increased VWF and factor VIII levels were at higher risk for thrombosis (60). One of the mechanisms in this process is the increased risk of thrombosis in carriers of mutated versions of FV Leiden and ABH antigen. Since FV Leiden is an essential cofactor for activated protein C (APC) inducing inactivation of FVIII, adverse FVIII response to APC in the absence of FV Leiden function is common in these individuals (59). In addition, a significant increase in vascular adhesion molecules such as TCAM, P-selectin, and E-selectin in blood group A carriers may increase leukocyte-endothelial interactions and intensify inflammatory state mechanisms (61).

Anti-ABO Antibodies

In addition to being carriers of blood group antigens, ABH antigens are also produced in the cells to remove large amounts of viral particles from the respiratory and gastrointestinal tracts (62). Relevant antigens are divided into groups A, B, AB, and O. On the other hand, anti-A and anti-B are also found in the serum of B and A carriers, respectively (45). As mentioned above, the entry of SARS-CoV-2 into the cell is targeted by the transmembrane glycoprotein. Previous studies via the application of Cryo-electron microscopy (Cryo-EM) have shown the presence of 14-22 N-glycans at 22 different sites of protein S and the presence of O-glycans in its monomers. It is suggested that the former is a key factor for proper protein folding and the effective configuration of host cell protease (63, 64). Shajahan, et al. also studied the human embryonic kidney cells (HEK-239) infected with the SARS-CoV-2 virus and expressed the recombinant S protein subunits (65). As a result, it is hypothesized that blood type O carriers, due to the presence of both anti-A and anti-B antibodies, can effectively prevent the virus from attaching, entering, and initially invading cells that express protein S. These findings are consistent with the studies show the presence of anti-A antibodies in S protein-producing cells can prevent the binding to ACE2 receptors and other dependent proteins (66).

C3 Complement Polymorphism

The complement system is one of the critical components of the innate immune system for cellular homeostasis, apoptosis, and immune survival guided by three independent pathways that eventually lead to the common C3 component (67, 68). Stoermer, et al. noted the involvement of the complement system in the pathogenesis of viral diseases (69). The activated complement system results in large amounts of the C3 component, which cleaves to the C3a component and binds to the C 3aR1 receptors (70). Subsequently, the recruitment and activation of polymorphonuclear (PMN) cells and macrophages leading to the production of inflammatory cytokines, myeloperoxidase, and elastase (71), an essential role in the pathogenesis of SARS-CoV-2 cell damage. Also, in a study of mice lacking C3 complement and infected with the SARS-CoV virus, Gralinski, et al. found that the pathogenesis of SARS-CoV disease is immune-derived, and the studied mice had less weight loss, respiratory dysfunction, and pathology in their lung tissue (72). An epidemiological study based on data collected from different countries shows a correlation between blood group alleles and complement C3 polymorphism in the prevalence and mortality of COVID-19 patients (73). The replacement of a base in C3 results in the expression of two alleles “fast” and “slow” for this locus. The multivariate regression analysis demonstrated the notable correlation between C3 polymorphism with S alleles and blood group A antigen in patients with COVID-19 (73). The increased attachment of leukocytes to the blood vessel wall is cleared by antigen-A via the action of complement system C3. It indicates the effective role of the gene polymorphism of this protein in the clinical manifestations of COVID-19 (74).

TNF-α G-308 a Promoter Polymorphism

The entry of the virus into the respiratory tract cells will fire up the cascade of cytokines and pro-inflammatory factors exerted by the activation of Th1 cells and synthesis of large amounts of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-6, and tumor necrosis factor (TNF)-α in the inflammatory environment (75). The term “cytokine storm” refers to the high expression of significant proteins including IL-6 and TNF-α in the viral-inducing

inflammatory environment. The cytokine storm is an over-activation of white blood cells in responding to infectious agents, which release excessive amounts of pro-inflammatory cytokines into the blood. The cytokine storm is associated with severe inflammation at a local site and spreads to other organs via systemic circulation. During the cytokine storm, the immune reaction flares to persistent organ dysfunction. Acute lung injury (ALI) is a common consequence of the overactivation of immune cells in the lung alveolar environment and is commonly associated with respiratory infections. The complex and dynamic nature of a rapid overreaction of the immune response has been probably underestimated. Molecular genetics knowledge is necessary to formulate comprehensive views of the etiological agents triggering inflammation and the cytokine storm (76).

TNF-α is one of the fundamental factors for protecting cellular homeostasis and changes in its transcription can lead to contradictions in its role in the body (77). In the upstream start point of the TNF- α transcription site, at the promoter (G-308) location, the polymorphism of allele A can increase the serum level of this protein approximately 6 to 9 times (78, 79). It is noteworthy that the study conducted by Ahmed Saleh, et al. (80) showed a significant correlation between this polymorphism and adverse outcomes and prognosis in patients with COVID-19.

Gel-Forming Mucin 5B (MUC5B) Polymorphism

One of the most critical primary defenses against the entrance of pathogens into the respiratory tract is the innate immune system exerted via the secretion of mucus by the gene encoding MUC5B (81). This molecule is secreted by the salivary glands, nasal mucus, and the sub-mucus glands of the lungs (82). In vivo studies showed that the presence of this substance is a vital element for mucociliary clearance (83). The expression levels of MUC5B are affected by a promoter polymorphism located on its gene, rs35705950. Two common alleles of this polymorphism, the T allele, and the G allele are associated with increased and decreased secretion levels, respectively (84, 85). Despite studies that issued the overproduction of MUC5B as a trigger factor of idiopathic pulmonary fibrosis (IPF) (85), an observation by van Moorsel *et al.* (86) revealed a considerable low frequency of T allele in COVID-19 patients requiring hospitalization as an adverse prognostic factor for further comorbidities.

Glutathione S-Transferase Polymorphism

Glucose phosphate deficiency is the most common metabolic disease globally, which annually affects 400 million people. The role of this enzyme in the pathogenesis of viral diseases such as COVID-19 may be due to the presence of its effective intervention in the metabolism, oxidative stress, and glutathione, which is considered one of the most important antioxidants of the body (87). Previous studies suggest that viral infections can induce reactive oxygen species (ROS) production and reactive nitrogen species (RNS), which ultimately cause metabolic cell disruption. As a result, the lack of a mechanism that deals with oxidative stress can increase mortality, morbidity, and disability in COVID-19 patients (87, 88). The level of glutathione is significantly correlated with the level of active vitamin D (89, 90). According to several studies, normal or increased glutathione levels improve the patients' curability rate, surprisingly (91).

A study conducted by Wu et al. showed that glucose-6-phosphate dehydrogenase (G6PD) deficient cells derived from human epithelial lung tissue are more susceptible to getting infected with human coronavirus 229E (HCOV 229E), and the viral replication is more active in them (88). Moreover, other studies indicate that the polymorphisms involved in the path of glutathione superfamily gene expression could affect the prognosis of patients with COVID-19. The GSTT1 and GSTM1 genes show different tissue expression patterns, although both genes belong to a single superfamily. The expression profiling studies indicated that only GSTT1 is expressed in lung tissue (92). Investigations on the allele frequency of GSTT1 and GSTM1 polymorphisms in different countries and their relationship with prevalence, fatality, and mortality rate in patients with COVID-19 are interesting. Only a significant relevance was found between the null genotype of GSTT1 and the mortality rate in the patients. However, no significant association was found between the polymorphisms in the GSTM1 gene with disease prevalence (92).

Additionally, a study on the different polymorphisms of the GSTP1 gene shows that the Ile105Val variant may reduce the activity of this enzyme, which is extensively expressed on the membrane of the lung epithelial cells and its resident macrophages as well. This enzyme has a variety of properties, such as being a negative regulator in the TNF-α-induced mitogen-activated protein kinase (MAPK) signaling. Also, statistical surveys reported that the Ile105Val variant in the corresponding gene might be associated with increased prevalence and mortality of COVID-19 (93).

Methylene Tetrahydro Folic Acid Reductase (MTHFR) Polymorphism

The 5, 10-methylenetetrahydrofolate acid reductase enzyme plays a significant role in protecting cellular DNA (94). One of its known polymorphisms, C677T, has a protective role in several malignancies, including colon and leukemia. The level of its activity in the folate cycle is by the daily consumption of folate, proportionally (94). Limitation in folate intake reduces the activity level of this enzyme and prevents the conversion of cysteine to methionine, which later leads to hyper-homocysteinemia (H-Hcy). Hence, MTHFR C677T polymorphism is considered the most common cause of H-Hcy (94). An increased concentration of homocysteine results in the generation of a cellular messaging cascade that is mediated by nuclear transcription factor (NF-Kβ). This phenomenon leads to the production of ROS, which provides a critical point to advance pre-inflammatory reactions. The above process also occurs in acute inflammatory conditions such as viral respiratory infections (95). ROS produced by the NF-Kβ cascade can facilitate SARS-CoV replication (96). Hypothetically, reviews suggest synchrony of different DNA methylation as SARS-CoV-2 invades cells by angiotensin receptor II, modifying DNA methylation pattern (97). Alexander J. Nash et al. reported that hypermethylation of different loci positioned at chromosome 1 region is associated with changes in TNFRSF8 gene expression. This gene leads to the production of the intracellular protein that is mediated via the NF-Kβ cascade (98). As a result, through the analogy of the mentioned mechanism with the molecular interaction between C677T and homocysteine (HC), increased ROS production and exacerbation of clinical manifestations in patients with COVID-19 would be construed, interestingly (97).

Apolipoprotein E (ApoE) and Bridging Integrator 1 (BIN1)

Apo E belongs to the apolipoprotein gene family and is expressed extensively by various organs such as the brain, liver, macrophages, and lungs (99). While the virus SARS-CoV-2 modulates the ACE2 receptor to enter the alveolar type II cells, Apo E is abundantly expressed on the surface of alveolar cell type I and II (100). Consequently, besides the contribution of Apo E in lipoprotein metabolism and the process of atherosclerosis, it can effectively interfere in being afflicted with viral and bacterial diseases (101). Its polymorphic gene contains 3 common alleles, including ε_2, ε_3 , and ε_4 which encode E2, E3, and E4 isoforms, respectively (99). Several studies have investigated the effect of the diverse the Apo E4 copies on the aggravated progression of infections such as human immunodeficiency virus (HIV)-1 and hepatitis C virus (102, 103). The results reveal that having one or multiple copies of Apo E4 compared to two copies of Apo E3 may lead to a more enhanced cytokine level during disease (104). Moreover, the correlation between the genotype of the Apo E4 with both dementia and delirium related to Alzheimer's disease has been investigated in many studies (105, 106). Since these demonstrations are recognized as one of the most common morbidities in patients with COVID-19, studies have been raised to evaluate a connection between the Apo E4 genotype and the severity and progression of COVID-19 (107). In a study conducted by Chia Kuo, there is a significant correlation between the presence of the Apo E e4e4 allele and the risk of COVID-19 severity. This genotype affects lipoprotein function and may interfere with the inflammatory state by regulating the pro-inflammatory and anti-inflammatory roles of macrophages (107).

The SNP rs744373 in the Bridging Integrator 1 gene (BIN1) has an important role in developing sporadic Alzheimer's disease. A study by Lehrer, et al. showed that COVID-19 patients with ho-

Table 1. The polymorphisms that incline patients with COVID-19 to severe prognosis.

Gene or Protein	Polymorphism or allele	Probable effects/mechanisms
***ACE2* (13-15, 19)**	rs228566	- AA and AA + GA genotypes are associated with an increased rate of hypertension
	rs4646116 (K26R)	- ACE2 activation and increased binding of spike virus protein to receptors
	rs41303171 (N720D)	- Increased TMPSRR2 activity and virus entry
	rs769062069 (R708Q, p. Arg708Gln) and rs776995986 (R708W, p. Arg708Trp)	- Affect the cleavage site due to the interaction between ACE2 and TMPRSS2
***ACE* (25, 26, 30-32)**	I/D	- Increased circulating level of ACE
	D/D	- Increased expression of ACE protein and increased risk of cardiovascular disease as well as acute respiratory manifestations including ARDS and the progression of pneumonia - Increase in Ang II level that increases platelet count
	I/I	- Inversely associated with COVID-19-related mortality
***TMPRSS2* (33, 34)**	rs35074065	- Overexpression of TMPRSS2 protein - Reduced transcription of the MX1 gene - Increase the susceptibility to involvement and reduce cell antiviral defense
***DPP4* (40)**	rs3788979	- TT genotype is associated with decreased levels of DPP4 - Increased risk of COVID-19 infection
ABH (49, 52-54, 60, 61, 65)	O antigen	- Low concentration of Furin and mechanism of S-protein cleavage - prevent the virus from attaching, entering, and initially invading cells that express protein S
	An antigen	- Decreased level of Blautia - Increased the rate of inflammatory and autoimmune conditions - Elevated levels of VWF and factor VIII and risk of thrombosis - Significant increase in vascular adhesion molecules such as TCAM, P-selectin, and E-selectin which may increase leukocyte-endothelial interactions and intensify inflammatory state
	B antigen	- Increased the composition of Actinobacteria in the gut - Increased incidence of gastrointestinal inflammatory-based diseases such as Crohn's disease and ulcerative colitis, and may enhance the inflammatory response and involvement of patients - Elevated levels of VWF and factor VIII and risk of thrombosis
C3 (70, 72-74)	S allele (SS and SF genotype)	- Less weight loss, respiratory dysfunction, and less pathology in lung tissue - Increased attachment of leukocytes to the blood vessel wall - Basically, attachment to C3aR1, fire-up inflammatory state and cell injury
TNF-α (80)	rs1800629	- An allele is associated with increased cytokine storm
***MUC5B* (84, 85)**	rs35705950	T allele - Increase the secretion of MUC5B protein - Idiopathic pulmonary fibrosis
		G allele - Decrease the secretion of MUC5B protein - Increase risk of hospitalization and other comorbidities
***GST* (92)**	rs17856199 (GSTT1)	- Increase the rate of mortality and comorbidity
	rs366631 (GSTM1)	- Increase the rate of mortality and comorbidity
	rs1965 (GSTP1)	- Negative regulator in the tumor necrosis factor-alpha (TNF-α) – induced MAPK signaling
***MTHFR* (95, 96)**	rs1801133 (C677T)	- Hyperhomocysteinemia - Increased synthesis of ROS - Ease the SARS-CoV replication
***APOE* (104, 107)**	Apo E3	- Enhanced cytokine level
	Apo E4	- More enhanced cytokine level - Increase risk of comorbidities including dementia and delirium - Affects lipoprotein function, regulating the pre-inflammatory and anti-inflammatory role of macrophages
***DBP* (115, 116)**	rs7041	- GT genotype is associated with an increase the prevalence and mortality rate of infection - Induce more actin formation, inclination host's cells to viral invasion
***VKORC1* (120)**	rs9923231 (G1639A)	- Decrease in the rate of production and regain of vitamin K - Less agglutination disorder and thrombosis comorbidity

mozygote for the minor allele of rs744373 had the highest mortality rate (28.1%) compared to patients with SNP rs744373 heterozygous alleles (11.7%) and homozygous major alleles (17.2%). Also, the results revealed that the BIN1 allele might affect the replication of coronavirus. It seems that more studies are needed to investigate the anti-viral activity of BIN1, which might lead to the development of new therapies against COVID-19 (108).

Vitamin D Binding Protein (DBP) Polymorphism

Vitamin D binding protein (DBP) is a complex protein that belongs to the α-2–globulin family. This family regulates the amount of Vitamin D and its metabolites in blood circulation in different clinical conditions (109). Almost all DBPs are synthesized in the liver, and their concentration is influenced by several factors such as inflammatory cytokines (110). This circulating complex can act as a multifunctional protein that binds to actin proteins (109). In COVID-19, neutrophils and monocytes induce an inflammatory environment in the respiratory system. Also, COVID-19 is correlated with a state named disseminated intravascular coagulopathy (DIC) due to the polymerization of actin proteins mediated by the coagulation factor Va (111). DBP affinity to the actin compartment increases the accumulation

of DBP and mediates the formation of the actin complex, which may increase cell injury and a new opportunity for coronavirus invasion (112). Thus, low levels of active metabolites of vitamin D lead to an increased serum level of DBP, which might worsen the outcome of viral infection.

Additionally, DBP as a polymorphic protein has different variants in its alleles (110). The two prevalent variants named Gc1s (rs7041) and Gc2 (rs4588) are associated with infectious inflammatory conditions, such as hepatitis C and active tuberculosis (113, 114). Newly published studies reveal that the GT genotype in the rs7041 locus is substantially associated with the prevalence and mortality rate in patients with COVID-19. Patients with the TT genotype in the rs4588 locus lack a significant correlation (115, 116).

Vitamin K Epoxide Reductase Complex Subunit 1 (VKORC1) Gene Polymorphism

Interruption in lung parenchyma structure and coagulation state are common comorbidities reported in hospitalized patients with COVID-19 (16). Vitamin K is an important ingredient that can activate liver coagulation factor II and extra-hepatic endothelial anticoagulant named protein S (117). On the other hand, the protection of vascular and pulmonary elastic fibers is mediated by the production of matrix Gla protein (MGP), which is also dependent on the levels of vitamin K (118). Dofferhoff, et al. showed that MGP was highly increased in patients with COVID-19. They reported that extra-hepatic vitamin K deficiency leads to impaired endothelial protein S and MGP activation, which results in thrombosis and increased damage of elastic fibers in patients with severe COVID-19 (119). It was revealed that MGP production is increased in the lungs of individuals with COVID-19 pneumonia which can preserve inflammation-induced extracellular matrix degradation. As a result, the increased use of vitamin K in the lungs might decrease extra-hepatic stores of vitamin K and inhibit the activation of protein S in patients with COVID-19 (120). The reduction in vitamin K stores will be renewed through the vitamin K cycle, which rate is dependent on the polymorphism of the VKORC1 promoter gene (121). The surveys indicate that VKORC-1639A polymorphism has a close relationship with a decrease in the rate of vitamin K production, which favors minor agglutination disorder and thrombosis comorbidities in COVID-19 patients (120). However, more clinical trials are needed to investigate whether the prescription of vitamin K has considerable benefits to the patient or not.

Table 1 briefly classifies each gene polymorphism and a probable mechanism of its action that may predispose infected patients to severe outcomes.

Conclusion

New studies indicate the involvement of several genetic factors in the susceptibility of individuals to COVID-19 infection and the severity of their symptoms. A part of this difference is due to the presence of SNPs involved in the different stages of the virus life cycle and the host response against the virus. Previous studies in different countries and races have also confirmed the roles of genetic susceptibility in the clinical progression of COVID-19.

In particular, ACE2 polymorphism predisposes different races to susceptibility to getting infected. The variants such as N720D and K26R in European countries, besides variants such as R708Q and R708W in Eastern countries, can affect various susceptibility factors such as ACE2 gene expression to bind to the S protein as well as TMPSRR2 activity. Such a possibility could be promising for emerging treatments that affect the primary stage of the virus invasion through the body. Inhibition of the virus attack can effectively reduce mortality, hospitalizations, and complications from the infection. Another factor that has been extensively studied systematically reviewed, and meta-analyzed is the effect of blood group alleles on the tendency to infection. Disruption in the intestinal normal microbiota ratio and changes in thrombosis-causing factors such as VWF and factor VIII, along with increased production of vascular adhesion molecules, are examples of the mechanisms by which the two A and B alleles are most exposed to multiple complications of COVID-19. Such a complication will draw attention to the more excellent care and control of carriers of these alleles and full-scale therapies than those with blood type O carriers. It is noteworthy that, among other factors, the intake of vitamin D and vitamin K and variants related to their cycle in the body predispose people to different vulnerabilities to the virus. These findings confirm new and ongoing clinical trials that recommend using these vitamins in the daily diary. Collectively, host's genetic variations play critical roles in the various stages of the virus attack, from the virus entry to distribution in the body. In the future, affordable and rapid explorations using large-scale genomic studies will hopefully prepare more accurate perspectives on the role of the host's genetic background in susceptibility and vulnerability to COVID-19, which could establish personalized genomic approaches to the prevention and treatment of the patients.

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Conflict of interest

The authors declare no Conflict of interest.

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