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# Co-Evolution between New Coronavirus (SARS-CoV-2) and Genetic Diversity: Insights on Population Susceptibility and Potential Therapeutic Innovations

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## Abstract

The DNA sequences are different between the distinct individuals and these variations produce the species genetic diversity. SARS-CoV-2 virus is a zoonotic SARS-like coronavirus that spreads globally, causing the COVID-19 pandemic disease. The immune response genes are the most various and different in the human genome, correlating with infectious diseases. Genetic variants in the angiotensin-converting enzyme 2 (ACE2) receptor, TMPRSS2, HO-1, BCL11A, and CYP2D6 are predicted to either encourage or inhibit the interaction with the viral proteins and subsequently contribute to coronavirus genetic risk factors. The genetic susceptibility to SARS-CoV-2 was investigated by analyzing different genes' polymorphisms such as ACE2 and TMPRSS2, HO-1, and BCL11A. A specific genetic susceptibility to COVID-19 was found through different populations in TMPRSS2, ACE2, HO-1, and BCL11A genes. Particularly, ACE2 gene polymorphisms were shown to be correlated with pulmonary and cardiovascular conditions by modifying the angiotensinogen-ACE2 system, which recommends the possible explanations of COVID-19 susceptibility based on genetic diversity. Moreover, the COVID-19 treatment could be complicated by such genetic polymorphisms. In conclusion, a good characterization of functional polymorphisms and the host genetics can assist in identifying the pathophysiology of the disease pathway to stratify the risk evaluation and to personalize the treatment procedures.

**Keywords:** gene polymorphisms, infectious diseases, host genetics, SARS-CoV-2, TMPRSS2, HO-1, ACE-2, BCL11A, coronavirus, COVID-19

## 1. Introduction

Infectious diseases have been and continue to be a source of concern and intimidation for human and animal life, and due to the absence of effective strategies in disease control, epidemics appear and spread day after day and cause a significant increase in mortality. Over decades, genetic and genomic studies provided invulnerable evidence that the host showed a genetic variation in its response to infectious agents, that may otherwise affect epidemiological risks, morbidity, and

survival [1–4]. Determining the host genetic implications in the risk of the epidemic and its severity remains the biggest obstacle to the infectious disease research progression [5, 6]. Because of the large size of the samples required by quantitative genetic studies, the definition of disease resistance based on individual mortality must be changed because it is easy in any case to know if the subjects' mortality was happening due to the exposition to infectious diseases or not. But, this is not true in the case of survival because it is multisided, and it may depend not only on an individual's resistance to infectious agents but also on his ability to survive after getting a disease or infection [7, 8].

Obviously, interest has increased in the infectivity genetic regulation, which can be described as the capability of a pathogen to infect an individual upon contact. Comprehension of the genetic regulation of infectivity is especially relevant if there are contrary genomic associations between these traits and elements of tolerance or resistance [9–11]. Such unfavorable genetic associations could be arising if subjects with much genetic survival not only come over with infection but also have a tendency to shed more pathogens [12]. Endurance and resistance infectivity may be controlled by several gene sets with variable contributions, both in degree and direction for survival [7, 13]. Despite this, no study has investigated these three traits at the same time. It is worth noting that plenty of quantitative genetic studies revealed variation in genetic resistance [2, 14–16], however, only a few studies showed a genetic difference in disease survival [7, 8]. In the context of infectious diseases, genomic selection may definitely restrict the spread of the disease by implementing a mechanism for determining high-risk people of infection [1].

Almost two decades after the outset of the Severe Acute Respiratory Syndrome (SARS), produced by a beta coronavirus, recently called SARS-CoV-1, the world was surprised by the emergence of a more virulent and infectious new virus in late 2019. This virus soon spread to almost all parts of the world and quickly reached the epidemic disease state [17]. The new coronavirus 2019 (COVID-19) outbreak originated from the SARS-CoV-2 virus suddenly became a major public health threat. COVID-19 is characterized by different types of clinical characterizations: affected patients can be asymptomatic, symptomatic with mild respiratory symptoms, or manifest severe pneumonia [18–21]. It is noted that these estimations are variable and began to approach accuracy as more cases are described, examined, and analyzed. Curiously enough, there is a clear difference in these estimations among different countries, worthy to mention that, the differences in the severity of the virus were recorded between the sexes and different age categories [18, 20, 22]. The infected cases have increased drastically [23]. Transmission from one person to another has been confirmed [24]. The virus was discovered in Bronchoalveolar lavage (BAL) [22], saliva and nasopharyngeal swabs [25], sputum [26], and throat [27, 28]. Even though the number of patients with COVID-19 was asymptomatic or mildly symptomatic still indecisive until now, but some studies have suggested that the percentage is between 40 and 80% [29, 30].

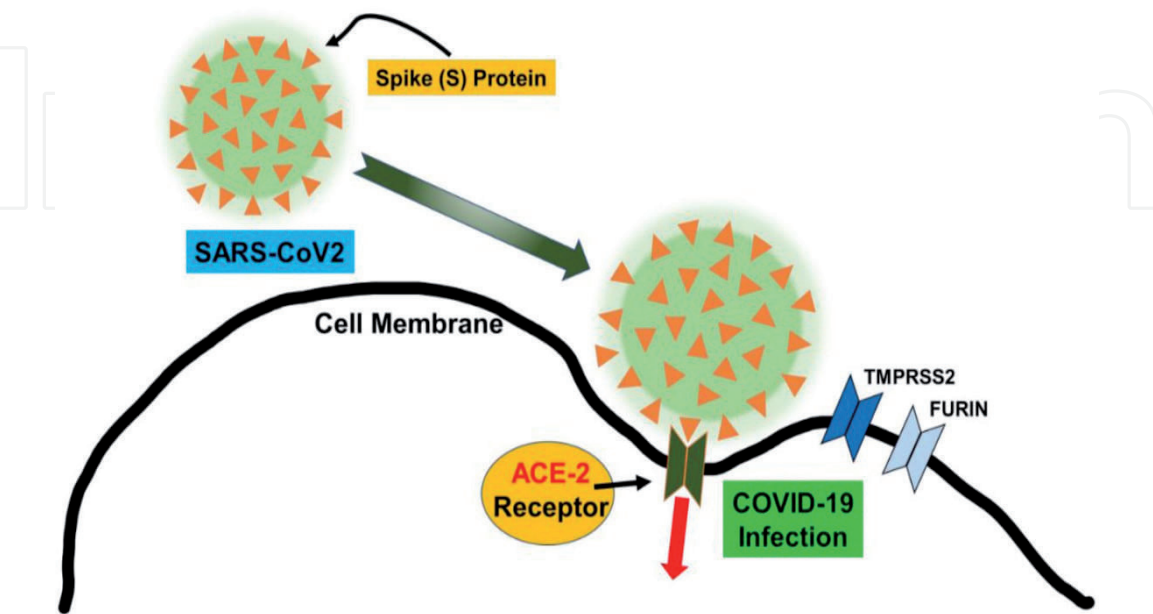
Among the most debatable characteristics in the clinical course and pathogenesis of COVID-19 is the heterogeneous hazard in the development to the acute form. Some significant clinical factors have been specified as severe disease predictors in different populations around the world, essentially include old age, male sex, obesity, and presence of multiple co-morbidities, such as diabetes mellitus, hypertension (HTN), cardiovascular disease, and impaired liver and renal function [20, 31–33]. In fact, some patients continue completely without symptoms until the final viral shedding, however, others experience a highly aggressive form of the disease [34–39]. These severe cases in the clinical picture of COVID-19 firmly propose that other co-factors may have a vital role in modifying disease development and progression. The suppressed immune response in the elders, co-morbidities,

or smoking condition, may explain the variances in the COVID-19 disease severity between individuals and populations [40], but severe disease has also been detected in young persons, apparently free from these risk factors. This shows that most risk factors clarifying COVID-19 disease severity are yet mysterious. Therefore, to recognize the mechanisms beyond COVID-19 disease severity is critical to provide suitable protective measures and sufficient triage approaches, drug innovation processes, and eventually the pandemic control. The genetic diversity between hosts can be explained the big difference in the incidence of SARS CoV-2 rates and the severity of COVID 19.

In this chapter, we will focus on some genetic variants and their implications for the severity of COVID-19. From these genes, we will take the consideration of the ACE2, TPRSS2, HO-1, and BCL11A genes, and the association between the DNA polymorphisms of these genes with the genetic susceptibility of the COVID-19, Whereas, systematic investigation of the functional polymorphism in these genes among diverse populations could tile the way for reliable medicine and personalized treatment approaches for COVID-19, this will call genetics to take the initiative in combating the virus pandemic.

## 2. Pathways of cellular infection by SARS-CoV-2

SARS-CoV-1 and SARS-CoV-2 connect to a similar receptor on the surface of human cells, known as angiotensin-converting enzyme 2 (ACE2) [41]. This complex particularly includes the receptor-binding domain (RBD) positioned within the virus spike protein (S protein). However, recent laboratory studies have revealed that unlike SARS-CoV-1, the SARS-CoV-2 RBD favors creating a greater binding capacity (i.e. 1204 versus 998 Å) [41, 42]. The SARS-CoV-2 infects and enters the infected cell by binding the viral spike protein with ACE2 of the host cell through the RBD. Even so, the splitting of spike protein needs to be done by human protease, where S protein subunits (S1 and S2) are broken apart from each other, with the last domain undergoes considerable structural modifications necessary to bind with the cell membrane of the host cell [43]. The transmembrane serine



**Figure 1.** Illustration of the COVID-19 virus spike protein. Across ACE-2 receptors, the spike invades the cell. Afterward, the spike is cleaved by the host cell proteases, membrane protease 2 (TMPRSS2), and furin, which results in COVID-19 infection activation [48].



protease 2 (TMPRSS2), together with lysosomal cathepsins, considers one of the most crucial proteases in this approach [44]. Moreover, a type 1 membrane-bound enzyme (furin), also splits the site between SARS-CoV-2 spike protein (both S1 and S2 subunits). Most significantly, furin can be expressed in numerous organs, involving the lungs. Furin stimulates the splitting of spike protein (S1/S2) after the binding of SARS-CoV-2 to ACE2 receptor, and this stimulation by itself is necessary to enter the virus into the cell [45]. This different pathway, which includes furin-mediate activation, would allow SARS-CoV-2 to be less dependent on co-expressions of TMPRSS2 on the cell surface of the infect cells. Hence, SARS-CoV-2 could be able to enter a wide range of low TMPRSS2 expressing cells. Lastly, disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) stimulate the release of ectodomains for a number of transmembrane proteins, such as ACE2 [46]. Therefore, increased ADAM17 activity is thought to be correlated with increased shedding of ACE2 and eventually decreases the possibility of cellular entry by SARS-CoV-2 [47] (**Figure 1**).

### 3. ACE2 expression in human tissues

The expression of ACE2 in the different human tissues was controversial because ACE2 was newly identified as a major binding site across which SARS-CoV-2 enters human host cells. Recently, many studies were performed to detect the cell types where ACE2 receptor is mainly expressed, which could describe the possible SARS-CoV-2 targets. One study was conducted to address the expression of ACE2 in various natural human tissues, and the analysis of the results regarding age and sex. Highest ACE2 expression levels were detected in the tissues of the small intestine, testicle, thyroid heart, adipose tissues, and kidneys. Esophagus, pancreas, lungs, liver, adrenal gland bladder, and colon were found to express the intermediate level while the lowest expression was found in the stomach nerves, blood vessels, uterus, muscle, spleen, bone marrow, and brain. Regarding lungs, the levels of ACE2 expression were upregulated and downregulated in relation to the immune pattern of men and women respectively [49]. ACE2 also was expressed in certain types of epithelial cells in the airway, such as type II alveolar epithelial cells and ciliated nasal epithelium. Moreover, it was found to be highly co-expressed with the TMPRSS2 in the nasal epithelium, which explains their higher infectivity by COVID-19 [50]. ACE2 is localizing also on the oral cavity mucosa. For now, these results revealed the underlying mechanism that the oral cavity poses a significant potential risk for 2019-nCoV susceptibility, and ACE2 was also expressed in lymphocytes inside the oral mucosa [51]. These findings have reminded us that COVID-19 attacks the lymphocytes and causes lymphopenia, mostly in severe forms of the disease [52].

More importantly, ACE2 also are expressed in endothelial cells [53]. That explains why COVID-19 disease affects multiorgan in the patients [54]. these results indicate that SARS-CoV-2 virus promotes the initiation of endotheliitis in many organs as a direct result of the viral intervention and the inflammatory response of the host. Additionally, the triggering of pyroptosis and apoptosis may have an important role in endothelial cell injury in COVID-19 patients and can account for the weakened systemic microcirculatory performance in various blood vessels and their clinical consequences in COVID-19 patients [55]. This supposition affords justifications for treatments to stabilize the endothelium during viral reproduction, especially by anti-inflammatory cytokines drugs, cholesterol-lowering drugs, and ACE inhibitors [56–59]. This approach can be especially appropriate for weak patients with an earlier endothelial disorder, such as hypertension, diabetes mellitus, obesity, cardiovascular disease co-morbidities patients [55].

#### **4. Implication of human polymorphism of ACE2 in disease susceptibility**

A lot of ACE2 variants have been recognized in different databases [60, 61]. Over the last decades, much focus has been assigned on some of ACE2 polymorphisms, due to their effects on the development of cardiovascular disease (CVD) and, more specifically, their association with hypertension (HT). ACE2 restricts the negative profibrotic and vasoconstrictor influences of AngII, as the breakdown of AngII to Ang (1-7) decreases the AngII oxidative stress of the cerebral arteries endothelium [62]. Ang (1-7) has been stated to have antifibrotic and vasodilation [63, 64]. Low cardiac expression of ACE2 levels has been notified in hypertension and diabetes heart failure [65, 66]. ACE2 gene polymorphisms were first detected in the Chinese people with different ACE2 variants (rs4830542, rs4240157, and rs4646155) linked to hypertension (HT) [67–70]. Also, ACE2 SNP rs21068809 (C > T) was found to be linked to the clinical features of HT [71]. In India, a study of 246 patients with HT and 274 normal subjects showed a connection of ACE2 rs21068809 SNP with HT [72]. In Brazilian cohorts, a study of genetic association of the combination of ACE2 G8790A and ACE I/D polymorphisms reveal susceptibility to HT [73]. ACE polymorphism has been described in African- Americans with HT [74].

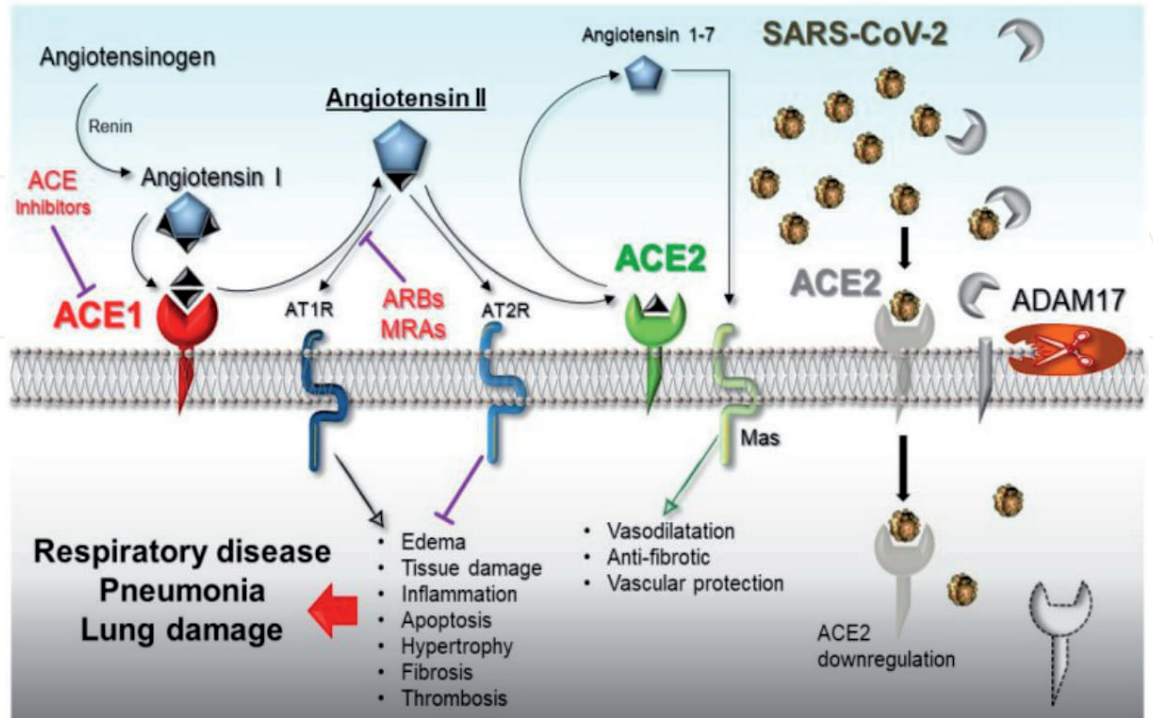
#### **5. Viral ACE2 receptor polymorphism and coronavirus infection**

ACE2 gene variants are still possible to affect SARS-CoV-2 infectivity. In SARS-CoV, the function of the S1 domain of the S protein is to mediate the binding of ACE2 receptors while the S2 domain is potentially undergoing post binding trans-conformational modulations which activate the fusion to the cell membrane [75]. The viral (RBD) found in S1 has been adjusted to amino acid number 270 to 510 [76]. The Leu584Ala point mutation of ACE2 significantly weakened the shedding activity of the enzyme and promoted the entrance of SARS-CoV into the host cells [77]. An ACE2 soluble form lacks the transmembrane and cytoplasmic domain was stated able to prevent SARS-CoV S protein binding to ACE2 [46]. Recombinant SARS-CoV-2 spike proteins were observed to downregulated ACE2 expression by releasing sACE2 and thus enhancing injury of the lung [78]. SARS-CoV and SARS-CoV-2 participate in the identity of 76% of the amino acid residues necessary for binding of ACE2 within the SARS-CoV-2 spike S1 domain. A lot of amino acid residues of the ten human ACE2 proteins were compared by multiple sequence alignment, a 100% identity among the ACE2 sequences was observed in four different ACE2 isoforms. The role of these ACE2 isoforms remains unpredictable in SARS-CoV-2 infection outcome. According to the work by Cao et al., [61] 32 polymorphisms of ACE2, including 7 hotspot variables (Ile486Val, Lys26Arg, Asn638Ser, Asn720Asp, Ser692Pro, Ala627Val, and Leu731Ile/Phe) were identified in different peoples, that make some individuals could be more or less susceptible to the virus than others.

In a preliminary study, the distribution of the allele frequency for 1700 polymorphisms in the ACE2 gene was conducted between various populations of the world. What is noteworthy is that 11 common and rare variants were detected linked to the high ACE2 expression. It was observed that their expression is irregularly distributed among different populations groups. This study found that the polymorphism of the ACE2 gene (variant 4,646,127) was closely related to the higher expression levels of the ACE2 gene in the East Asian population, and this paved the way to study this important issue more specifically [61]. These results were confirmed by a similar subsequent study by [79], which also evidenced that the allele frequency of these variants associated with overexpression of ACE2. Also, different ACE2 polymorphisms encoded a number of proteins for SARS-CoV-2 spike protein has

been studied, and it was found that each variant differs in compatibility with RBD sequence. Specifically, although the majority of genetic variants exhibited high physical similarity. Specifically, the two ACE2 gene alleles (rs143936283 and rs73635825) showed a quite low binding strength for the SARS-CoV-2 spike protein, which could mean a lower possibility of viral binding and possible to infection resistance [80]. It has been observed that the probability of some natural genetic variants of ACE2, particularly those assigned to attach with the SARS-CoV-2 spike protein, may be linked with flexible virus-host interaction, thus likely modifying severity and pathogenicity. A large analysis of the genome data-set was performed and showed that no less than nine human ACE2 variants (E23K, S19P, I21V, N64K, K26R, H378R, T27A, T92I, and Q102P) are prospective to increase predisposition to viral binding, while 17 other variants of ACE2 (that is, E37K, K31R, H34R, N33I, E35K, Y50F, D38V, G326E, N51S, M62V, D355N, K68E, F72V, Y83H, D509Y, G352V, and Q388L) were thought to be protected from viral entry, where they demonstrated a lower binding tendency to SARS-CoV-2 spike protein [81].

In another study, from five separate Italian centers, the authors found that three variants of ACE2 can be specified (p. Gly211Arg, lys26Arg, and p. Asn720Asp). It was noted that these three polymorphisms were recurrently identified in the Italian population rather than the East Asian population. These variants are closely located in the SARS-CoV-2 essential sequence of spike protein binding sites and therefore viral entry and division expected to be modified (for example, Asn720Asp is located on only 4 amino acids of TMPRSS2 cleavage site) [82]. This may tell a partial explanation for the high case mortality rate registered in Italy by comparison to China. Despite ACE2 practically serve as a receptor for coronavirus SARS entry into human host cells, another does not support the correlation between its common gene polymorphisms and receptivity or consequence of SARS [83]. It has also been observed that some ACE2 variants show differential efficacy in stimulating neutrophils, monocytes, natural killer cells (NK), macrophages, and T helper cells, thus



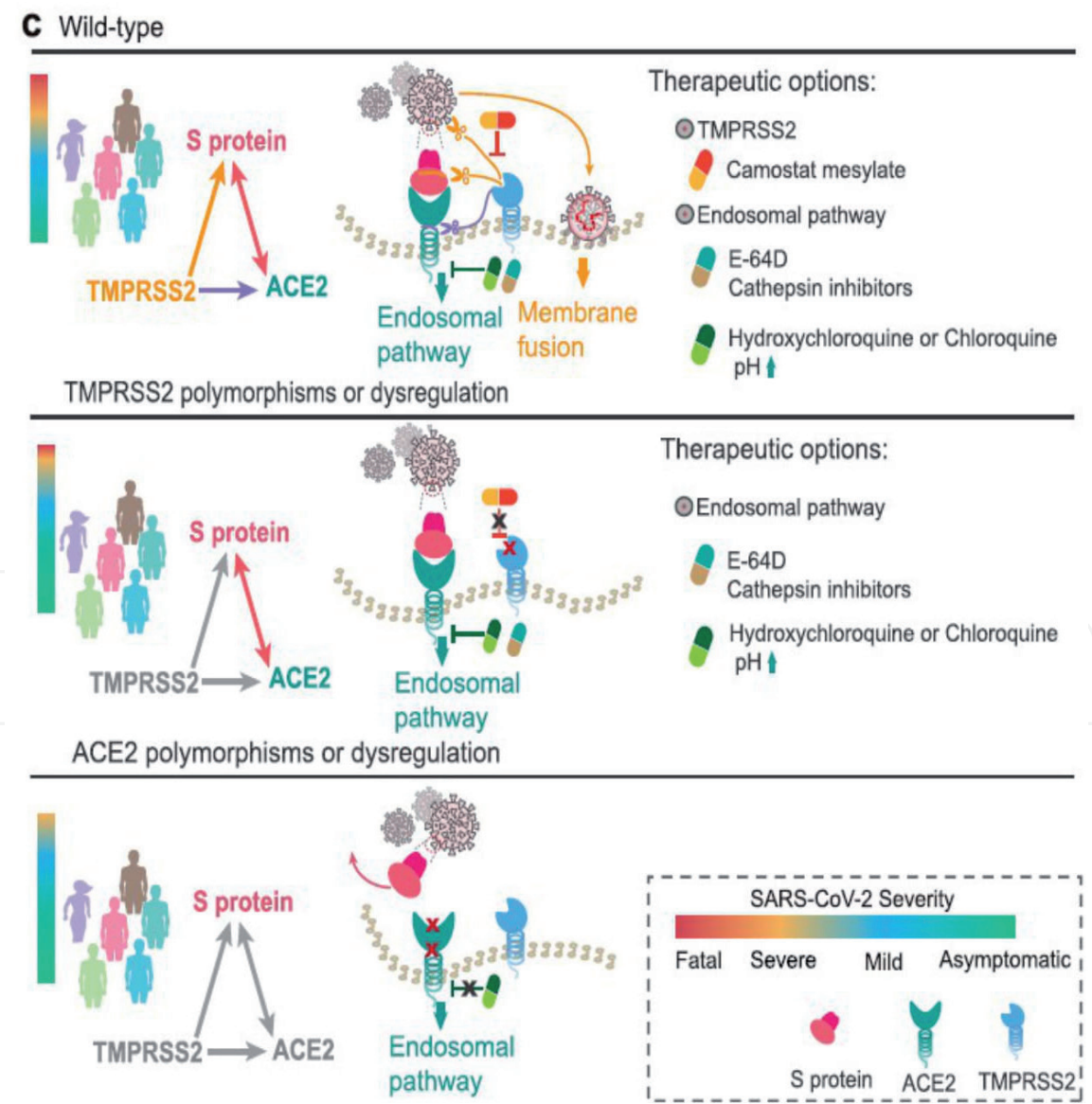
**Figure 2.** Diagrammatic representation for the renin-angiotensin system (RAS) pathway. As ACE2/Ang 1-7/ Mas-axis and ACE1/Ang-II/ AT1R-axis occur, SARS-CoV-2 inhibition by cleavage of ACE2 by ADAM17 appears. **ADAM17:** ADAM metalloproteinase domain 17; **ARBs:** angiotensin receptor blockers; **MRAs:** mineralocorticoid receptor antagonists [87].



may probably either enhance or reduce the inflammatory or “cytokine storm” [84], in addition to stimulating the processing of Ang II, thereby improving or exacerbating vasoconstriction and participating to the improvement or exacerbation of topical or systemic tissue infection [85, 86] (Figure 2).

6. TMPRSS2 polymorphism analysis with COVID-19 disease

TMPRSS2 and ACE2 have been associated with SARS-corona (CoV) disease, influenza, and SARS-CoV-2 in facilitating viral entrance into the infected host cell. TMPRSS2 considers as an androgen-reactive serine protease enzyme that cleaves SARS-CoV-2 Spike protein, mediating viral activation and entry [88]. Single-nucleotide polymorphisms of TMPRSS2 enzyme have been studied in several diseases such as in breast cancer, the rs2276205 (A > G) with low-frequency allele was correlated with increased patients’ endurance [89]. In prostate cancer, the rs12329760 (C > T) of TMPRSS2 has a higher frequency in men with prostate cancer in his family, while ERG gene fusion [90, 91] Rs383510 (T > C) and rs2070788



**Figure 3.** A polymorphism and dysregulation of ACE2, and TMPRSS2 in COVID-19 and a suggested model for active compound medicines (e.g., hydroxychloroquine, Camostat mesylate, and E-64D [a protease inhibitor] for COVID-19) [93].



(G > A) were correlated with aggressive H7N9, H1N1, and increased lung expression of TMPRSS2 [92]. A study by Hou et al., indicated that 4% of nonidentical variants of TMPRSS2 are stop-codon mutations, Meanwhile, 59% are harmful mutations in TMPRSS2 coding regions [93]. The harmful variants (p.Arg240Cys, p.Val160Met, p.Gly181Arg, p.Pro335Leu, p.Gly432Ala, and p.Gly259Ser) in the coding region of TMPRSS2, are the same with somatic alterations arising in various types of cancer. In the same contest, Hou et al. found that, the p. Asp435Tyr which is a key site for catalytic residue binding of TMPRSS2 has unique low-frequency allele, but pre-dominant SNPs in TMPRSS2 and offer possible descriptions for differential genetic infectivity to COVID-19 and for risk influences, such as those with tumor and male patients. By using the analysis of single-cell RNA-seq, Schuler et al. revealed that the expression of TMPRSS2 was upregulated in ciliated cells and alveolar epithelial type 1 cells and increased with humans aging [94]. This observation indicates that the developmental TMPRSS2 expression regulation may have a role in the relative protection of the children and infants from COVID-19 infection. Yet, it might be of great importance to investigate the link between TMPRSS2 polymorphisms and the age relationship with COVID-19 susceptibility (**Figure 3**).

## 7. Heme oxygenase-1 enzyme (HO-1) genetic polymorphisms and COVID-19 severity

Many studies demonstrated that the HO-1 gene polymorphisms, particularly the promoter region GT dinucleotide repeat mutation regulates the inducibility of HO-1 to ROS [95–101]. Subjects with more GT repeats have been believed to be more sensitive to cardiovascular endothelium diseases such as atherosclerosis coronary artery disease and aortic aneurysms [95, 98, 99]. The lower Expression level of HO-1 in those with more GT repeats make the patients to be more affected to decrease endothelial hemostasis and inflammation [95–101]. While, GT sequences short alleles are correlated with increased HO-1 inducibility, which in turn reduced inflammation and enhanced cytoprotection [101]. Patients with COVID-19 complications perhaps have longer GT sequences and decreased vessel hemostasis.

COVID-19 disease has poor effects in diabetic and obese individuals, maybe because those people are already having high interleukin 6 levels of (IL-6) and they are in a proinflammatory state due to leptin and insulin resistance [102, 103]. As a result, the negative clinical outcomes of COVID-19 infection in obese patients was recorded [103]. Peterson et al. have revealed that obesity raises high-density lipoprotein (HDL) oxidation [104]. Oxidized HDL (Ox-HDL) is thought to produce pro-inflammatory cytokines by the direct action on adipocyte stem cells [105]. Ox-HDL initiates an inflammatory cascading with inflammatory cytokines, tumor necrosis factor (TNF), interleukins (IL-6, IL-1), and increasing of Angiotensin II (ANG II), a biomarker for early cardiovascular system disorders [104]. This made the obese individuals are more sensitive to heart failure due to infection of COVID-19 [106]. Up-regulation of HO-1-derived bilirubin may enhance the COVID-19 bad effect, this risk was reduced by an increased HO-1 level [107, 108]. Hence, up-regulation of the level of HO-1 with pharmacological treatment [109] may have valuable action in acute inflammation conditions.

## 8. BCL11A polymorphisms

BCL11A Genetic polymorphisms were correlating to produce fetal hemoglobin in overall population, and these genetic variants were later found to be able to

modify the severity of  $\beta$ -thalassemia and sickle cell diseases. Although the elevation of fetal hemoglobin can ameliorate the severity of these disorders. In an attempt to best comprehend the genetic background of this heterogeneity, genome-wide surveys were performed with 362,129 joint SNPs on a large cohort population of  $\beta$ -thalassemia and sickle cell patients to explore the genetic linking and relationship with HbF levels, in addition to other traits related to red blood cells. Among the principal variants influencing HbF levels, BCL11A SNP rs11886868 in the was completely correlated with this trait. This BCL11A variant was correlated with raised fetal hemoglobin (HbF) production in beta-thalassemia patients. Also, the similar BCL11A variants were substantially correlated with sickle cell patients HbF levels. These findings show that modifying HbF levels by BCL11A variants, consider as an essential factor in improving the beta-thalassemia phenotype and may potentially help improve other hemoglobin disorders. These findings can help describe the molecular mechanisms for regulating fetal globin and may ultimately participate in the evolution of new therapeutic strategies for sickle cell anemia and beta-thalassemia [110–112]. Hence, these results can provide an explanation of why some individuals naturally exhibit diseases mild symptoms, while others have shown very acute clinical symptoms. Therefore, it is imperative to perceive the role of genetic polymorphisms of these genes in SARS-CoV-2 infection in human populations to interpret the observed heterogeneity in predisposition and COVID-19 infection severity [88, 113].

## **9. Genetic polymorphism and therapy effectiveness**

COVID-19 may be inactivated or partially treated by the following approaches: ACE2 receptor attaching site blocking either by antibody or specific ligand or using ACE2 soluble form that can neutralize the virus by binding the virus spike protein, and, yet, cover ACE2 binding site on the host cell surface and reducing the tissue injury. The genetic polymorphisms of cytochrome (CYP) 2D6 can affect drug metabolism using this approach, which contains 50% currently using drugs [114]. The metabolism of these genes can be increased by these polymorphisms and in turn, reduce their efficiency or significantly decline their metabolism causing drug toxicity [115]. Slow drug metabolizers permit toxic effects of the medications as chloroquine to become accumulated and resulting in cardiac problems with an increased hazard of cardiac arrest, specifically in diabetes and obesity patients. CYP2D6 Polymorphism is much high in Asians and African Americans [116–118], which extremely influenced by this disorder. One Korea study studying Lupus disease demonstrated considerable variation in the level of hydroxychloroquine due to polymorphisms of CYP2D6 [119]. This may explain the clinical outcomes differences when using this drug. Because of the metabolism abnormalities due to these genetic polymorphisms, resistant malaria strains will be arising [120–122]. Heart failure patients can be affected by the same CYP 2D6 gene polymorphisms since it is accountable for metoprolol metabolism [123, 124]. These gene variants affect several other medications such as barbiturates, Isoniazid (INH), serotonin reuptake inhibitor (omeprazole hydralazine sulfasalazine, etc.) [125]. Individuals with CYP2D6 polymorphisms and the HO-1 GT allele make therapy and disease outcomes challenging. Some of the patients who carry these polymorphisms will respond perfectly to drugs and have a low risk of COVID-19 patients to develop complications such as multiorgan failure and ARDS, while other patients will express drug toxicity levels and multiorgan problems [115]. This can describe why clinicians are unable to predict the multiorgan failure with COVID -19 disease and different outcomes from using 4-aminoquinolones.

## 10. Personalized medicine guided by host genetic of COVID-19

SARS-CoV-2 inhibition can be done by spike protein and ACE2 differential glycosylation [126]. Several polymorphisms, such as p.Pro389His, p.Met383Thr and p.Asp427Tyr slightly inhibited by hydroxychloroquine. This can be clarifying why hydroxychloroquine treatment was not significantly in a different hospital than others [127]. However, more pharmacogenomics experiments between the genetic data and drug response from COVID-19 patients are extremely needed. The viral entry to the host cell by binding to the cell membrane through S protein can be blocked by TMPRSS2 [88]. The SARS-CoV-2 pathogenesis and infection depend on the TMPRSS2 presence, in a high pH environment [128, 129]. The inhibitor of endosomal acidification such as hydroxychloroquine and CatB/L inhibitors might work only in absence of TMPRSS2- in SARS-CoV-2 infected and may not work or has no or less effective in patients with TMPRSS2 wild-type [128]. So far, the populations with missense polymorphisms and stop-gained of TMPRSS2 polymorphisms may be good sensitive to treatment with hydroxychloroquine. Furthermore, the patients who carry TMPRSS2 and ACE2 wildtype, a mix of hydroxychloroquine or chloroquine with camostat may have the best clinical advantage. The ACE2 can be cleaved by TMPRSS2 at Arginine 697 to 716 [130], which improves viral entry. Thus, patients with, p.Arg710Cys p.Arg708Trp, p.Arg716Cys and p.Arg710His polymorphisms in ACE2 might have fewer symptoms of COVID-19 disease as the cleavage site of ACE2 gene loses by these polymorphisms (**Figure 3**) [113].

## 11. Conclusion

The pandemic COVID-19 by SARS-CoV-2 coronavirus is multifactorial in which human inheritances might play a pivotal role together with the co-morbidity diseases and other risk factors. The disease clinical course has been depending on the link between genetic variants, such as the CYP2D6 enzyme system, HO-1 (anti-inflammatory gene), and ACE-2 enzyme. Beside ACE2 polymorphisms, there is TMPRSS2 gene variance that possibly changes the pathogenicity of the virus by changing the interaction between ACE2 and SARS-CoV-2 virus. A good characterization of functional polymorphisms and the host genetics can assist in identifying the pathophysiology of the disease pathway to stratify the risk evaluation and to personalize the treatment procedures.

## Conflict of interest

The authors declare no conflict of interest.



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