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Review

Host genetic diversity and genetic variations of SARS-CoV-2 in COVID-19 pathogenesis and the effectiveness of vaccination

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ABSTRACT

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), responsible for the outbreak of coronavirus disease 2019 (COVID-19), has shown a vast range of clinical manifestations from asymptomatic to life-threatening symptoms. To figure out the cause of this heterogeneity, studies demonstrated the trace of genetic diversities whether in the hosts or the virus itself. With this regard, this review provides a comprehensive overview of how host genetic such as those related to the entry of the virus, the immune-related genes, gender-related genes, disease-related genes, and also host epigenetic could influence the severity of COVID-19. Besides, the mutations in the genome of SARS-CoV-2 –leading to emerging of new variants– per se affect the affinity of the virus to the host cells and enhance the immune escape capacity. The current review discusses these variants and also the latest data about vaccination effectiveness facing the most important variants.

1. Introduction

In December 2019, an unknown cause of pneumonia was detected in Wuhan, China that was attributed to a seafood wholesale market. By sequencing samples of patients with pneumonia, a previously unrecognized β-coronaviruses (β-CoVs) was identified and named 2019-nCoV, also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. SARS-CoV-2 is the cause of coronavirus disease 2019 (COVID-19), an infection of the respiratory tract, which has a wide spectrum of clinical manifestations; while some cases will present mild symptoms, others will develop more serious complications entailing specialized management in the intensive care units (ICU) [2]. SARS-CoV-2 belongs to the B lineage of the β-CoVs. According to the whole-genome analysis, β-CoVs genomes encode 4 structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as numerous non-structural ones [3].

The receptor-binding domain (RBD) in the spike protein lets the virus interact with angiotensin-converting enzyme 2 (ACE2) of the host cells [4]. Accordingly, this virus mainly infects lung cells and respiratory tracts as ACE2 is mostly expressed on the surface of type II alveolar cells

Abbreviations: A, Alanine; ACE2, Angiotensin-converting enzyme 2; AF, Allele frequency; APOE, Apolipoprotein E; BMI, Body mass index; BSG, Basigin; CTLs, cytotoxic T cells; DBP, Vitamin D-binding protein; DPP-4, Dipeptidyl peptidase-4; E, Envelop; EEA, European economic area; EMT, Epithelial-mesenchymal transition; EU, European Union; GSTs, Glutathione S-transferases; HLA, Human leukocyte antigen; HPV, Human papilloma virus; HSV, Herpes simplex virus; ICU, Intensive care units; IFITM3, Interferon-induced transmembrane protein 3; IGS, IFNs-specific genes; IMV, Invasive mechanical ventilation; IRF7, interferon regulatory factor 7; ISG15, Interferon-stimulated gene 15; L, Leucine; LAG-3, lymphocyte-activation gene 3; M, Membrane; MBL, Mannose-binding lectin; MCP-1, Monocyte chemoattractant protein; MDS, Molecular dynamic simulations; N, Nucleocapsid; NET, Neutrophil extracellular trap; NSP1, Non-structural protein-1; NTD, *N*-terminal domain; OAS, oligoadenylate synthetase; PADIs, Peptidylarginine deiminases; PAMPs, Pathogen-associated molecular patterns; PF4, Platelet factor 4; PLPro, Papain-like protease; R, Arginine; RBD, Receptor-binding domain; RBM, Receptor-binding motif; RdRp, RNA-dependent RNA polymerase; ROS, Reactive oxygen species; RSV, Respiratory syncytial virus; S, Spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SGTF, S-gene target failure; SNPs, single nucleotide polymorphisms; SPEG, Striated muscle preferentially expressed protein kinase; TIM-3, T cell immunoglobulin and mucin-domain containing-3; TLRs, Toll-like receptors; TYK2, Tyrosine kinase 2; UK, United Kingdom; V, Valine; VOCs, Variants of concern; VOI, Variants of interest; VUM, Variants under monitoring; WES, whole-exome sequencing; β-CoVs, β-coronaviruses.

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of the lungs [5]. Since the expression of ACE2 is not equal in each individual and also, *ACE2* has shown recently-detected polymorphisms, the pathogenicity of SARS-CoV-2 differs occasionally [6]. In addition to ACE2, there are several host-related factors such as transmembrane protease, serine 2 (TMPRSS2), HLA, cytokines, sex hormones, and epigenetics which could influence the severity of COVID-19. Furthermore, SARS-CoV-2 genome mutations are an inevitable phenomenon responsible for altered encoded proteins, leading to different pathogenicity, harder detection, and possibly higher immune escape capacity. In addition to non-pharmaceutical measures, effective vaccines have been one of the most potent arsenals facing the COVID-19 pandemic [7]; nevertheless, there is always confrontation between newly-emerged SARS-CoV-2 variants and immune responses. In this review, we comprehensively discussed the interactions of SARS-CoV-2 and the host genetic and epigenetics, the virus mutations and emerging variants, and how vaccines could face SARS-CoV-2 variants.

2. Host genetic

2.1. SARS-CoV-2 entry mechanism-related genes

2.1.1. Ace2

Among different receptors that have been identified to be associated with COVID-19, ACE2 is one of the important ones which facilitates the spread of the virus to the vital organs [8]. The knowledge of ACE2 and its association with disease progression is less advanced, but there is an interesting consensus that genetic heterogeneity of ACE2 might be one of the reasons why some people may develop the severe form of COVID-19 and others only suffer from a mild symptom. Given this, the more we know about this receptor and its genetics, the better we could stratify patients, and subsequently, the better we can design treatments and measures.

The stream of studies has started and the results of each are interesting. The results of mining of whole-exome sequencing (WES) data of 6930 Italian control individuals took a veil off a number of *ACE2* variants that are responsible for protein stability. Among them, rare point mutations of (Leu351Val) and p.(Pro389His) seem to have an association with the spike protein of the SARS-CoV-2 virus [9]. Stawiski et al. have also noticed that rare *ACE2* variants may have an impact on the susceptibility of the individuals to SARS-CoV-2 [10]. The authors reported that while the presence of either human *ACE2* variants S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P, or H378R could make individuals more susceptible to develop COVID-19, K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, and D509Y might protect the individuals from the spread of the virus. Besides these variants, N90 and T92 are the most important ACE2 residues that prevent the entry of SARS-CoV-2 to the host's cells and are considered CoV host modifiers.

Apart from *ACE2*, the genetic background of other genes in the ACE2-related pathways could also alter the vulnerability of the host to the virus. In this vein, Lanjanian et al. have indicated that the extent to which ACE2-associated genes can play a role in virus susceptibility is actually greater than that of the receptor [11]. The results of their investigation showed that two mutations, K26R and S331F, might reduce the binding affinity of the receptor to the spike protein of the virus [11]; thus, there is controversial data about K26R mutation as it is not clear whether this mutation increases the susceptibility to the virus or reduces.

Although numerous studies declared that *ACE2* genetic variation might reshape SARS-CoV-2 pathogenicity and alter the susceptibility of the hosts to the virus, a considerable number of investigations have denied the presence of such correlation. The results of a cohort study in European, North-African, and Middle East countries failed to find any association between *ACE2* polymorphism and the mortality rate of COVID-19 [12]. Similarly, a study conducted in Spain on 120 patients also suggested the lack of correlation between *ACE2* polymorphism and the SARS-CoV-2 infection [13]. The results were interesting, as they reported that the extent of susceptibility to SARS-CoV-2 was not associated with *ACE2* genetic heterogeneity, but with the allele frequency (AF). The authors declared that the reason why East Asian populations have more susceptibility to the virus was due to the higher AFs in the eQTL variants, an event that leads to higher expression of ACE2 in the tissue [14].

2.1.2. Transmembrane protease, serine 2 (TMPRSS2)

TMPRSS2 is another identified receptor for SARS-CoV-2, which could spread the virus throughout the organs. The results of the previous studies were succeeded to find an association between the polymorphism of this receptor and the susceptibility to influenza [15]. Given this, a question has been raised that whether the genetic heterogeneity of *TMPRSS2* might have an influence on the progression of COVID-19. The results of an analysis on the expression levels of TMPRSS2 in the lungs led to the identification of seven blocks (I–VII) of variants that could increase the expression of the receptor in individuals [16]. Interestingly, it has been reported that European populations have the highest proportion of haplotypes than the Asian populations, leading to the increase of their susceptibility to the virus. Following the European populations, South Asia (46 %) and America (42 %) had the higher levels of haplotypes, while Africa (28 %) and East Asia (19 %) have reported to harbor the lowest frequency of the variants. The alleles associated with the increase in the expression of TMPRSS2 seem to have a frequency of lower than 1 % in the Eastern Asian population. By using WES, it became evident that rs75603675, rs61735792, and rs61735794, three variants of *TMPRSS2*, might increase the risk of SARS-CoV-2 in the individuals [17].

Notably, analyzing the sequence of *TMPRSS2* of 1177 COVID-19 patients revealed that p.V197M (rs12329760), which control the protease activity and the stability of the receptor, might be involved in the pathogenicity of the virus [18]. The frequency of missense variant rs12329760, also known as p.Val197Met, in TMPRSS2 was reported to be higher in mild COVID-19 cases as compared to the critically ill patients. Individuals harboring the higher frequency of the variant might have a milder form of the disease, without the requirement for hospitalization or oxygen therapy [18,19]. Wulandari et al. have also declared that there is a correlation between p.V197M and the viral load, suggesting that p.V197M could be used as a predictive factor to risk stratifying the patients.

As mentioned, p.V197M could destabilize TMPRSS2 protein and thereby attenuate the interaction between ACE2 and spike protein of the virus. Moreover, the substitution of valine (V) to methionine (M) in the catalytic site of TMPRSS2 protein reduces the ability of the receptor to facilitate SARS-CoV-2 spike-mediated entry into cells [20]. It could be assumed that due to the previous exposure to the virus, the East Asian population inherited more frequency of p.V197M due to natural selection and this is why they might be more resistant to the virus as compared to European ethnicity.

Given the importance of p.V197M in diminishing the risk of a severe form of COVID-19, a stream of studies has put their efforts to identify drugs that could target TMPRSS2. Camostat mesilate, a drug that received FDA approval for the treatment of chronic pancreatitis and postoperative reflux esophagitis, could target TMPRSS2 and be effective in the treatment of COVID-19 [20]. Apart from this, the development of some small-molecule inhibitors reducing the stability of TMPRSS2 protein might also be effective in either prevention or minimizing the severity of COVID-19. Interestingly, an important study showed that the Omicron variant could penetrate the cells by the endosomal route instead of the TMPRSS2-dependant way, implying the dangerous potential of this variant [21].

2.1.3. Furin (PCSK)

Furin is a type 1 membrane-bound protease that facilitates the entrance of the SARS-CoV-2 within the endothelial cells [22]. So far, 13

missense variants have been identified for the *FURIN* gene that could be associated with the susceptibility to the virus, and among them, 7 were reported to diminish the risk of SARS-CoV-2 progression in the individuals [23]. These protective variants have been mainly detected in Qatar and Kuwait. In contrast to the Middle East, it seems that *FURIN* variants could not exert protective effects against the viral spread. It has been reported that rs6226 and rs8039305 *FURIN* polymorphism in the African population is associated with the incidence of hypertension and disease mortality. Fuentes et al., on the other hand, failed to report any association between *FURIN* polymorphism and the incidence rate of COVID-19 [13].

2.1.4. Dpps (Dipeptidyl peptidases)

Dipeptidyl peptidase-4 (DPP-4) or CD26 which acts as a ligand for a variety of extracellular molecules could make interaction with several viral proteins, such as spike protein as well [24]. Thus far, the associations between different DPPs and viral proteins have been established in numerous studies. Interestingly, the genetic analysis conducted in China on 322 COVID-19 patients revealed that recurrent loss of function 1-bp insertion in gene *DPP7* was common among asymptomatic patients [25]. In another study, Śanchez et al. succeeded to find a correlation between the down-regulation of DPP-4 and the severity of COVID-19 [26]. Interestingly, in another study, it became evident that there is a relation between the expression level of DPP-4 and obesity. Given the established correlation between body mass index (BMI) and the need for IMV, the triangle between *DPP4* overexpression, obesity, and IMV in COVID-19 patients seems to be reasonable [27–31]. Accordingly, Latini et al. have introduced three missense and splice acceptor variants (c.95-2A > G, c.796G > A, c.1887 + 3G > A) in the *DPP4* gene which were associated with the severity of COVID-19, shedding more light on the contributory role of this receptor as a co-receptor for SARS-CoV-2 viral entry [32].

2.1.5. Apolipoprotein E (APOE)

The transferring of serum cholesterol to cells by means of cholesterol transport protein apolipoprotein E (APOE) could boost the trafficking of ACE2 to the endocytic entry site that facilitates the entry of SARS-CoV-2 to cells; this phenomenon subsequently elevates the risk of COVID-19 infection, proposing that probably there is a link between the expression of apolipoproteins and severity of the disease [33]. When secreted from the epithelial cells, cholesterol helps FURIN to cleave spike protein, and thereby, increase cell-to-cell transmission of SARS-CoV-2. The results of the previous study indicated that individuals with *APOE* ε3/ε4 might have increased risk of the virus entry as compared with ε3/ε3 subjects [34]; proposing that APOE4 can impact SARS-CoV-2 pathogenicity by altering intracellular levels of cholesterol. The ε4 variant of the *APOE* has also been reported to be found in more frequency in black Africans than Caucasians and Asians, suggesting why this population might be at higher risk of mortality due to SARS-CoV-2 infection [35]. In agreement, Kuo et al. indicated that the presence of the *APOE* ε4/ε4 allele elevates the severity of COVID-19 in the individuals and increases the mortality rate by four-times even in the absence of any pre-existing dementia, cardiovascular disease, or type-2 diabetes [36]. Since the ε4 variant of *APOE* could reduce lung respiratory capacity [37] and *APOE*-depleted mouse models have shown to be more prone to develop severe pulmonary hypertension [38] the association between this allele and the risk of death in COVID-19 patients seems to be reasonable.

2.1.6. Bsg (CD147)

Basigin (BSG) or CD147 is a member of the immunoglobulin superfamily, with the ability to facilitate the entrance of SARS-CoV-2 into the host cells [39]. By evaluating the gene expression profile of *BSG*, it became evident that the presence of one missense mutation (p.F275V) in the I-set domain of the protein could increase the affinity of the receptor to the spike protein of SARS-CoV-2 [40]. On the other hand, the existence of *BSG* antibodies could diminish the cytokine storm caused by the virus [41]. Moreover, Meplazumab, an anti-CD147 humanized antibody could prevent the spread of the virus into the hosts cells, and thereby, reduce the incidence rate of COVID-19 [42]. To provide a well-conceptualized overview, we represented the potential roles of SARS-CoV-2 entry mechanism-related genes in Fig. 1. Also, the details of entry mechanism-related genes were provided in Table 1.

2.2. Immune-related genes

2.2.1. Human leukocyte antigen (HLA)

To date, no genetic variation has been reported as much as HLAs to be associated with a wide range of human diseases [60]. In this regard, it comes as no surprise if different series of investigations have put an effort to identify a correlation between *HLA* variants and the susceptibility to the SARS-CoV-2 virus [61–63]. In the majority of cases, these investigations were successful. Allele typing of 37 COVID-19 patients in Taiwan revealed a significant relation between *HLA-B*4601*, *HLA-B*0703*, as well as *HLA-DRB1*0301* and the sensitivity to the SARS-CoV-2 virus [64]. Also, Vietzen et al. reported that among 361 COVID-19 patients with different types of the disease, those who had *HLA-E*0101* and were heterozygous for the *HLA-E*0101/0103* variant had an increased risk to be hospitalized or needing intensive care; it has been reported that probably the presence of *HLA-E*0101* and *HLA-E*0101/0103* variants might attenuate the $NKG2C^{+}$ NK cell responses, an event leading to the accelerated progression of COVID-19 [65,66].

In another study, Wang et al. evaluated *HLA* alleles in 69 critically ill patients and 215 COVID-19 patients with an asymptomatic, mild, or moderate type of the disease [25]. The authors demonstrated that among the class I HLA genes, *HLA-A*11:01*, *HLA-B*51:01*, and *HLA-C*14:02* alleles might be associated with poor prognosis in COVID-19 patients. *HLA-B*46:01* was another allele that could increase the severity of disease, while HLA-B*15:03 was associated with the protective effects. Moreover, they suggested that while *DRB1*14:04*, *DRB1*01:01*, and *DQA1*01:01* alleles could be classified as a risk factor for disease progression, harboring *DPB1*03:01* and *DRB1*12:01* alleles could exert ameliorating effects on the pace of disease development. Another study conducted on 28 COVID-19 patients with severe respiratory failure showed that the expression of HLA-DR was lower as compared to patients with a mild form of infection. Moreover, it seems that there is an association between *HLA-DR* expression and the number of CD4/CD19 lymphocytes and NK cells. Interestingly, it has also been suggested that *HLA* alleles might have a role in SARS-CoV-2-induced olfactory dysfunction in individuals, as the olfactory receptor gene appears to be MHC-linked.

The results of efforts accomplished by Campbell et al. also resulted in the identification of binding affinity between 9-mer and 15-mer peptides from the SARS-CoV-2 peptidome and 9,360 class I and 8,445 class II HLA alleles, respectively [67]. In MHC-binding assays, it became evident that there is a correlation between some epitopes of SARS-CoV-2 and *HLA-A*02:01*, *HLA-B*40:01*, *HLA-DRA*01:01*, *HLA-DRB1*07:01*, and *HLA-DRB1*04:01* alleles [68]. López et al. also have used a bioinformatic prediction tool to identify the top ten highly immunogenic epitopes on T cells that were associated with response to the SARS-CoV-2 virus [69]. They used the data provided from 14 countries and reported for the first time that only 7 HLA molecules, including *HLA-DPA1*01:03/DPB1*02:01*, *HLADPA1* 02:01/DPB1*01:01*, *HLA DPA1*03:01/DPB1*04:02*, *HLA-DQA1*05:01/DQB1*03:01*, *HLA-DRB1*01:01*, *HLADRB1* 07:01*, and *HLA-DRB1*09:01* had a high binding affinity for the SARS-CoV-2 virus. While cells express *HLA-A*02:03* and *A*31:01* are the best antigen presenters for the virus and could induce the highest immune responses, cells expressing *HLA-A*03:02* might fail to induce an acceptable immunity against the virus.

2.2.2. Cytokines

Among different cytokines that associate with COVID-19, perhaps type I IFNs are the most important ones. The results of the primary

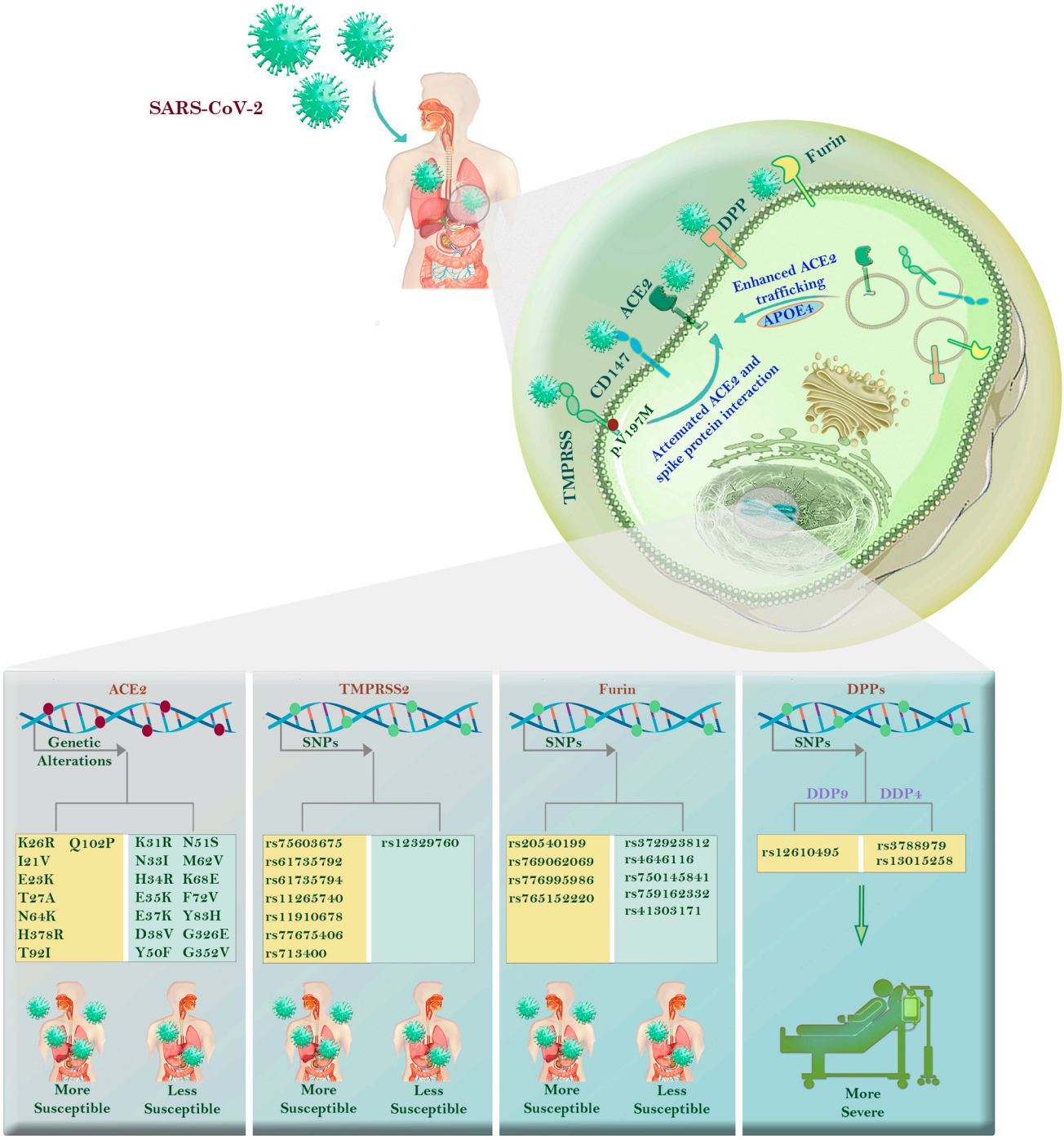


Fig. 1. The roles of SARS-CoV-2 entry mechanism-related genes in COVID-19. There are some entry mechanisms for SARS-CoV-2 in the host genome which their diversity could affect the severity of the COVID-19. Accordingly, ACE2 is the most known virus entry receptor which undergoes some alterations; some of which such as K31R, N33I, N51S, M26V, K68E, and F72V are associated with less susceptibility to the virus, while E23K, T27A, H378R, Q102P, and N64K reduce susceptibility. Similarly, some SNPs in TMPRSS2 include rs75603675, rs61735792, rs61735794, rs112657409, rs11910678, rs77675406, and rs713400 have an association with more severe disease; however, p.V197M (rs12329760) can destabilize TMPRSS2, and as a result, attenuate the interaction of ACE2 and spike protein. The presence of SNPs such as rs20540199, rs769062069 in the *FURIN* gene have roles in disease mortality. Patients carrying rs3788979 and rs13015258 in the *DPP4* genome, as well as those with rs12610495 in the *DPP9* genome, show higher inflammatory responses in lung tissue. Also, the higher risk of COVID-19 mortality could be associated with the ε4 variant of the *APOE* that enhances the trafficking of ACE2 toward the cell surface.

studies clearly suggested that the down-regulation in the expression of IFNs significantly facilitates the progression of the virus into the host's cells. Interestingly, demographic investigations have also succeeded to find a correlation between *IFN* genes and the susceptibility to the SARS-CoV-2; the authors declared that the presence of single nucleotide polymorphisms (SNPs) in the *IFN*-inducible genes *OAS1* and *MX1* can increase the risk of COVID-19 [70,71]. Castineira et al. also identified a rare loss-of-function mutation in *IFNAR2*, a receptor that prevents the entrance of the respiratory viruses such as Influenza and SARS-CoV-2 [72]. Of particular interest, they reported that individuals carrying this mutation might not even respond well to exogenous interferon treatment; suggesting that perhaps this genetic alteration occurs at the

Table 1
The details of entry mechanism-related genes, their mutations and outcomes.

Gene	Location	function	Mutation/ Polymorphism	Result	Drug/ Inhibitor	Ref
ACE2	Chr 17	A negative regulator of the renin-angiotensin system, and functions as the key SARS coronavirus receptor and stabilizer of neutral amino acid transporters	Leu351Val, p.(Pro389His), S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P, or H378R	Elevate the susceptibility to COVID-19	lividomycin, burixafor, quisinostat, fluprofylline, pemetrexed, spirofylline, edotecarin, diniprofylline	[9,11,23,43–45]
			K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, D509Y, N90, T92, rs73635825 (S19P), rs143936283 (E329G)	Protects individuals from the spread of the virus leading to an intrinsic resistance against SARS-CoV-2 virus		
TMPRSS2	Chr 21	An endothelial cell surface protein that is involved in the viral entry and spread of SARS-CoV-2. SARS-CoV-2.	rs75603675, rs61735792, rs61735794, rs112657409, rs11910678, rs77675406, rs713400, p.V197M	Increase the risk of SARS-CoV-2	camostat mesylate, nafamostat mesylate, Nafamostat, Gabexate, N-0385	[17,19,46–51]
			high V197M, low G8V (rs75603675) allele frequencies	Endowing resistance against SARS-CoV-2		
FURIN (PCSK)	Chr 15	A type 1 membrane-bound protease which its cleavage action is an essential activation step for the endothelial pathogenicity of SARS-CoV-2.	rs6226: P ¼ 1.3569e-09, OR ¼ 1.03; rs8039305: P ¼ 1.7643e-38, OR ¼ 1.05	Are associated with hypertension and disease mortality	Nicotine patches, Colchicine, Psoriasis Registry Austria (PsoRA), 3,5-dichlorophenyl) pyridine	[23,52,53]
DPPs	Chr 2	A multi-functional protein with the catalytic activity as well as functions as a binding protein and a ligand for a variety of extracellular molecules such as spike protein as well	rs3788979 TT, c.95-2A > G, c.796G > A, c.1887 + 3G > A, rs13015258, rs12610495	Increase the need for invasive mechanical ventilation in COVID-19	N/A	[24,54–56]
APOE	Chr 19	The transferring of serum cholesterol to cells by means of APOE could boost the trafficking of ACE2 to the endocytic entry site that facilitates the entry of SARS-CoV-2 to cells.	ε3/ε4 variant, ε4/ε4	Higher risk of mortality	N/A	[36,37,57]
BSG	Chr 19	a multifunctional transmembrane protein involved in inflammation and tumor invasion with the ability to facilitate the entrance of SARS-CoV-2 into the host cells.	p.F275V	Enhances the affinity of the receptor to the spike protein of SARS-CoV-2	Meplazumab, Azithromycin	[39,40,58,59]

ACE2: Angiotensin-converting enzyme 2**; Chr:** chromosome; **Leu:** Leucine; **Val:** Valine; **Pro:** Proline; **His:** Histidine; **S:** Serine; **I:** Isoleucine; **E:** Glutamic acid; **K:** Lysin; **R:** Arginine; **T:** Threonine; **A:** Alanin; **N:** Asparagine; **Q:** Glutamine; **D:** Aspartic acid; **Y:** Tyrosine; **F:** Phenylalanine; **M:** Methionine; **G:** Glycine; **TMPRSS2:** Transmembrane protease, serine 2; **PCSK:** Proprotein convertase subtilisin/kexin 9; **DPPs:**; Dipeptidyl peptidases; **APOE:** Apo lipoprotein E; **SARS-CoV-2:** Severe acute respiratory syndrome coronavirus 2; **BSG:** Basigin.

early stage of the disease when the viral load is high.

Inborn errors of the interferon regulatory factor 7 (IRF7) gene is the other genetic alterations that have been reported to be associated with COVID-19 pneumonia. Previously, the presence of a mutation in two loci of this gene, i.e., *IRF7* and *IRF9*, has been reported to increase the risk of life-threatening influenza in the individuals. Interestingly, when analyzed *in vitro*, it became evident that *IRF7*$^{-/-}$ and *IFNAR1*$^{-/-}$ fibroblasts were also more vulnerable to the SARS-CoV-2 virus [73].

Interferon-induced transmembrane protein 3 (IFITM3) is another cytokine-related protein that its genetic diversity was shown to be associated with COVID-19 severity. In the physiological condition, IFITM3 blocks the entrance of viral products into the host's cells by affecting the fluidity of the cell membrane [74]. In COVID-19 patients, the results of the gene sequencing of the rs12252 *IFITM3* variant revealed that 35 % of the patients with the severe form of the disease had the homozygous CC genotype [75]. When Wang et al. have deeply sequenced the genome of 332 COVID-19 patients with different forms of disease, they found that most genetic alterations associated with the severity of the disease were located in TMEM189–UBE2V1 and TMEM189–BE2V1 which are participating in the IL-1 signaling pathway [25]. For example, the presence of rs60220284 is an eQTL that increases the expression of IL-1 and is widely found in critically ill patients.

It is well-established that pro-inflammatory cytokines might recruit several tyrosine kinase receptors to propagate their signals into the nucleus, and as a result, change the expression of a wide range of genes. A non-receptor tyrosine kinase named tyrosine kinase 2 (TYK2), which belongs to the JAK family, has shown to be a member of IL-6R, type I interferon receptors, IL-12, IL-23, and IL-10 receptors-related signaling pathways [76]. Recently, a genetic variant rs74956615 on chromosome 19p13.2 near the gene encoding *TYK2* has been identified with the ability to elevate the expression of this non-receptor tyrosine kinase; notably, the overexpression of TYK2 could increase lung injuries and induce a life-threatening disease. Moreover, since TYK2 targets JAK inhibitors [77], *TYK2* variants can attenuate the therapeutic effects of JAK inhibitors in COVID-19 patients. It should be noted that JAK inhibitors were among the first drugs that their efficacy has been studied in COVID-19 patients [78]. Given this, identification of *TYK2* variants in the individuals might be beneficial for evaluating the therapeutic potential of JAK inhibitors.

Another variant of *TYK2* that has been identified in COVID-19 patients is rs10735079, which is located in the interferon-inducible oligoadenylate synthetase (OAS) gene cluster, a gene that is developed to produce RNase L [72].

2.2.3. Ccr/CXCR

The variation in the expression of chemokine receptors could also determine the susceptibility of host to the SARS-CoV-2. For example, the genome analysis conducted by Stikker et al. revealed that the presence of activating variants in regulatory regions of the chemokine receptor-encoding *CCR1* gene is associated with the severe type of COVID-19 [79]. Indeed, through enhancing the infiltration of monocytes and macrophages into the inflammatory site, the elevated CCR1 might

propagate inflammatory responses, and thereby, accelerate the progression of the disease. CCR2 is another chemokine receptor that in combination with monocyte chemoattractant protein (MCP-1) attracts monocytes and macrophages to the inflammatory site. The results of the genome-wide analysis revealed the presence of activating variants in gene encoding CCR2 in critically ill COVID-19 patients.

CCR5 32 bp deletion variant (Δ32), which its association with several viral infections has been previously established, could also increase the mortality rate of COVID-19 in the African population [80]. Gómez et al. conducted a study on 294 hospitalized COVID-19 patients and reported that the expression of *CCR5-Δ32* is lower in infected patients as compared to healthy counterparts. CXCR6 and its ligand CXCL16 are other molecules that their expression has been shown to have an association with the severity of COVID-19. The expression of CXCR6 on $CD8^+$ T cells mediates the homing of T cells to the lung in response to the CXCL16 gradient [72]. It has been reported that during COVID-19, several endogenous factors might exert their effects on the 3p21.31 locus to decrease the expression of CXCR6 on lung resident memory $CD8^+$ T cells, an event which is related to the accelerated progression of the disease and formation of the severe infection due to lower infiltration of $CD8^+$ T cells.

2.2.4. Toll-like receptors (TLRs)

The number of studies evaluating the importance of TLRs and their related signaling pathway in the pathogenicity of SARS-CoV-2 is growing day by day and the results suggest that the suppression of TLRs is associated with the progression of COVID-19 [81]. Like other related receptors, the allelic variation in *TLRs* seems to alter the risk of the individuals to the infection. For example, the deletion of *TICAM2*, a TLR adaptor protein, on chromosome 18 locus showed not only an increased risk of SARS-CoV-2 infection [82] but also an induction of pulmonary hemorrhage. Another investigation group also succeeded to find a correlation between the inborn errors of *TLR3* and the risk of life-threatening COVID-19 pneumonia [82]. Zhang et al. reported that individuals who have loss-of-function at the 13 candidate loci were more susceptible to develop COVID-19 pneumonia as compared to the patients with asymptomatic or benign infection. Fallerini et al. have also reported the presence of loss-of-function variants in *TLR7* in two families with COVID-19; they reported this genetic variant in 2.1 % of male patients with a severe type of the disease [83]. Interestingly, the loss-of-function variants of *TLR7* seem to be related to the requirement with intensive care and mechanical ventilation. It has been suggested that *TLR7* deficiency might impair type I and II IFN responses and this is why this rare genetic alteration may be accompanied by the severe type of the disease.

2.2.5. Complement system

The significant role of the complement system in the pathogenesis of the SARS-CoV-2 infection is undeniable, and thus far, several medications have been developed to target the complement components to treat COVID-19 [84]. Mannose-binding lectin (MBL) is a pattern recognition molecule that its deficiency has been shown to increase the risk of several bacterial infections in children; in COVID-19, it has also been declared that there is a correlation between low MBL levels and the susceptibility to the SARS-CoV-2 virus [85]. On the other hand, C3 deficiency could act in favor of hosts and protect the individuals from respiratory symptoms of SARS-CoV-2. The rs11385949 G > GA (chromosome 3 cluster rs11385942 variant) is another genetic variant that could increase the severity of COVID-19 through complement hyperactivation [86]. It has been reported that the upper airways viral load and sC5b-9 were higher in the carries of rs11385949; further highlighting the contributory role of the complement system in the pathogenesis of SARS-CoV-2.

2.2.6. NK cell-related genes

Through expressing NKG2A, NK cells could induce cytotoxicity in virally infected cells independent of MHC molecules. Given this, the immunotype of NK cells could also be a risk factor for host susceptibility to the virus [87]. In this vein, the high expression of perforin, NKG2C, and Ksp37 was observed in NK cells isolated from the severe COVID-19 patients [88]. Or, the expression of NKG2A has been reported to be elevated in NK cells and cytotoxic T cells (CTLs) harvested from COVID-19 patients to induce exhausted phenotype in the lymphocytes. The up-regulation of *NKG2A* has been reported to be temporary, as once the patients are recovered, the expression of this receptor is reduced on the lymphocytes. Apart from NKG2A, lymphocyte-activation gene 3 (LAG-3) and T cell immunoglobulin and mucin-domain containing-3 (TIM-3) are other inhibitory receptors that their expression was shown to have an upward trend in NK cells of COVID-19 patients [89]. Taken together, these findings all together declare that the immunotype of NK cells could determine the outcome of the patients in response to COVID-19 infection.

2.2.7. Vitamin D-binding protein (DBP)

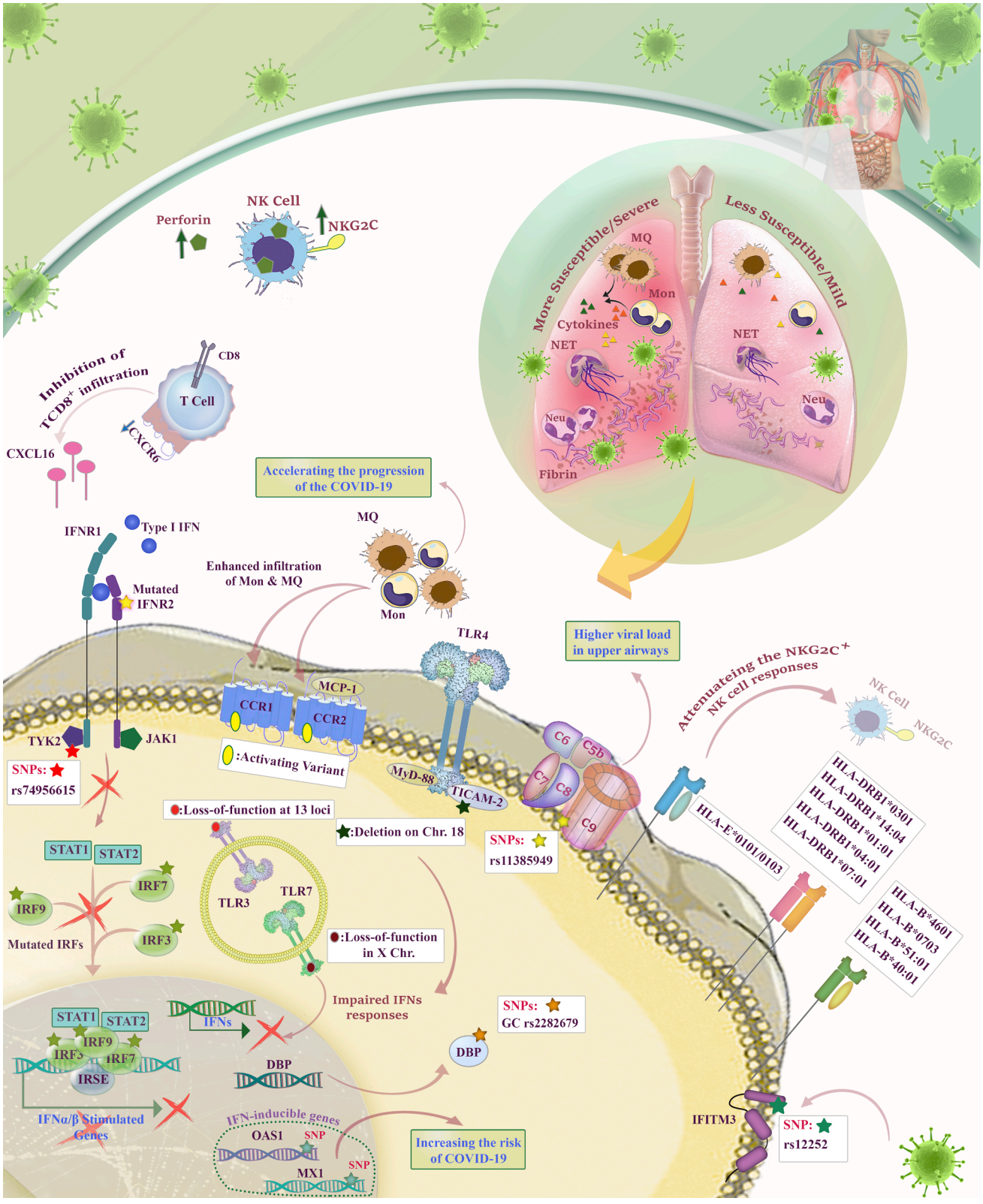
Vitamin D-binding protein (DBP) is a polymorphic protein encoded by a gene located at chromosome 4q11–q13 that binds to vitamin D and regulates total and free vitamin D metabolite levels [90]. It has been reported that some allele variations such as rs7041 locus and rs4588 locus can increase the affinity of the protein for vitamin D. In COVID-19, surprisingly, rs7041 variant of *DPB* has been shown to have an association with prevalence and mortality of the patients. GT genotype could also confer the SARS-CoV-2 virus susceptibility in the populations of Germany, Mexico, Italy, Czech, and Turkey [91]. Another variant of *DBP* with the ability to increase the severity of COVID-19 is encoded by the GC gene. It has been reported that those patients who carried GC rs2282679 polymorphism might suffer from the more severe type of the disease [92]. Fig. 2 has been designed to provide an overview of the roles of immune-related genes in the pathogenicity of COVID-19.

2.3. Gender-related genes

2.3.1. Sex hormones

From the first description of COVID-19, when it became evident that men are more susceptible to severe types of the disease as compared to women, the attention has been attracted to sex hormones as strong modulators [93,94]. The production of sex hormones is derived from a complex pathway consists of several enzymes [95]. The regulatory region of *CYP19A1,* which is a gene responsible for encoding a member of the cytochrome P450 superfamily of enzymes, could influence the local biosynthesis of estrogen [96]. With this regard, the activity of *CYP19A1* to encode aromatase −which catalyzes the last step of estradiol (E2, or 17β-estradiol) synthesis [97]− is higher in ovarian granulosa cell, the placenta, the testicular Leydig cell, and other sites such as brain and skin fibroblasts [98]; notably, the highest level of aromatase is found in ovarian granulosa cell which implies higher levels of estrogen in women [99]. In a murine model of COVID-19, it became evident that blockage of estrogen could result in the elevation in the number of inflammatory cells in the lung, tissue damage, and disease progression. In the clinical settings, it has also been observed that the duration of hospital stay was significantly lower in non-menopausal women [100]. Acheampong et al. have claimed that as compared to the male patients, even menopausal women cope better with the severe type of COVID-19 and recover faster, as women produce higher levels of estrogen in this period than men [101]. Estrogen levels (above 70 pg/ml) was shown to have a negative correlation with the expression levels of several pro-inflammatory cytokines, such as IL-6, IL-8, IL-2R, and TNF-α in COVID-19 patients and this clearly explains why this hormone could halt the over-reaction of immune cells against SARS-CoV-2 [102].

The results of a study conducted in Italy revealed that prostate cancer patients who were received androgen deprivation therapy (ADT) were less likely to develop severe COVID-19 compared to the non-ADT group. Montopoli et al. also indicated that androgen could increase the



(caption on next page)

Fig. 2. The roles of immune-related genes in COVID-19. As illustrated, some *HLA* variants are associated with susceptibility to SARS-CoV-2 such as *HLA-DRB1*0301*, *DRB1*14:04*, *DRB1*01:01*, *DRB1*04:01*, *DRB1*07:01*, *HLA-B*4601*, *B*0703*, *B*51:01*, and *B*40:01*. Also, heterozygote *HLA-E*0101/0103* can attenuate the NKG2C^{+} NK cell responses. The infection of a cell with SARS-CoV-2 could result in the secretion of type I IFNs which consequently interact with adjacent IFNR1/2-expressing cells to initiate the signaling pathway ending in anti-viral responses; however, the presence of rs74956615 in *TYK2* –endocing a tyrosine kinase-related to IFNR1 signaling– induces TYK2 overexpression, and consequently, hurts the lung cells. Moreover, rs10735079 in *TYK2* is associated with reduced *OAS* expression and attenuated anti-viral responses. Notably, some SNPs in *OAS* and *MX1* could elevate the risk of COVID-19, as well. Similarly, mutations in *IRF7* and *IRF9* –components of IFN signaling pathway– boost SARS-CoV-2 susceptibility. rs12252 in *IFITM3* also attenuates the ability of IFITM3 to block the entrance of viral products into the cells. CCR1 and CCR2-MCP-1 could enhance the infiltartion of monocytes and macrophages and induce inflammation; with this regard, the pressence of activating variants in CCR1 and CCR2 has been observed in critically ill COVID-19 patients. Besides, the lower expression of CXCR6 could reduce the infiltration of CD8^{+} T cells in the lung, leading to more severe disease. The mutations in TLRs such as the deletion in *TICAM2*, which is related to TLR-4 initial signaling, could influence the risk of COVID-19. Similarly, loss-of-function of TLR-3 and TLR-7 impairs the IFNs responses. The overexpression of complement system components is another agent magnifying the severity of the disease. In patients carrying rs11385949, the levels of upper airway viral load and sC5b-9 were greater than others. Regarding the roles of DBP in the regulation of vitamin D levels, patients harboring GC rs2282679 could experience the severe type of the disease. Furthermore, The NK cells isolated from severe cases of COVID-19 have shown higher expression of NKG2C and secretion of perforin. Moreover, it was shown that Cit-H3 has significant roles in NET formation and consequently higher inflammation and cardiovascular complications.

virulence of the SARS-CoV-2 virus and increase the sensitivity of males to the disease [103]. The cross-talk between androgens and TMPRSS2 may be, at least partly, a reason why elevated levels of androgens could enhance the severity of the disease [101,104]. In contrast to these, some studies have declared that the opposite may be true and the low levels of testosterone might have devastating effects on COVID-19 progression [105]. A study focused on hospitalized men revealed that the decrease in the circulating testosterone levels might increase the severity of the disease and mortality rate [102]. Indeed, reduction in testosterone levels has been introduced as a risk factor for men; however, these findings have not yet been confirmed, and currently, the application of ADT and estrogen in the management of COVID-19 is expected to be beneficial for severe types of the disease [106].

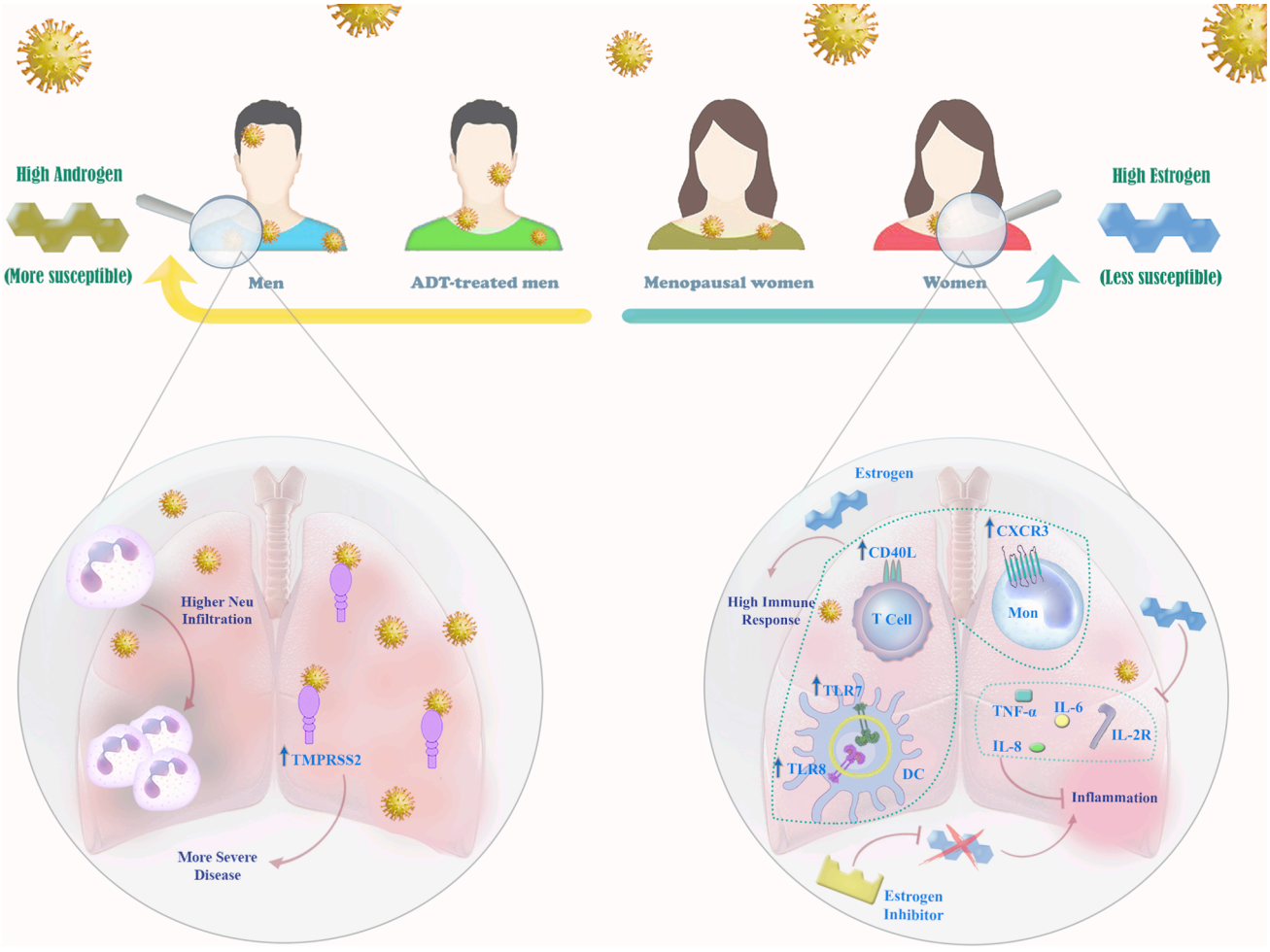


Fig. 3. The roles of sex hormones in COVID-19. The differences in COVID-19 severity between genders have directed studies toward the roles of sex hormones in this context. Based on sex hormones, the susceptibility to SARS-CoV-2 has a range from "higher androgen" to "higher estrogen"; with this regard, men are more susceptible to experience the severe types of COVID-19 and women seem to show much milder disease. This difference is interestingly observed in ADT-treated men and menopausal women who have different levels of androgen and estrogen compared with non-treated men and non-menopausal women. Higher androgen results in neutrophil infiltration and higher expression of TMPRSS2 which are related to the severity of the disease. Higher estrogen, on the other hand, induces upregulation of TLR-7, TLR-8, CD40L, CXCR3, and IFNs that consequently promotes immune responses. Estrogen can also hamper inflammation via downregulation of IL-6, IL-8, IL-2R, and TNF-a.

2.3.2. Immunological factors in males and females

Apart from the sex hormones, the differences in the immune system of males and females may be another factor that might explain why men are more prone to develop the severe type of COVID-19 as compared to women [107]. Generally, the female immune system is stronger, as a wide range of essential immune-related genes is located on the X chromosome [108]. The biallelic expression of such genes in women, including *TLR7*, *TLR8*, *CD40L*, *CXCR3*, and interferons leads to higher immune responses and reduces the susceptibility to viral infections [109]. In a murine model of COVID-19, while the inflammatory cytokines and chemokines in SARS-CoV-2-infected male and female mice showed equal levels at the early stage of the disease, these levels robustly elevated in the male mice after 3 days of infection [110]. The number of neutrophils infiltrated into the lungs of male mice was shown to be 5-fold higher as compared to female mice at day 4; suggesting that the susceptibility of male mice to SARS-CoV-2 infection correlates with increased inflammatory cell recruitment. The roles of sex hormones in the severity of the COVID-19 were illustrated in the Fig. 3.

2.4. Disease-related genes

2.4.1. Genes related to cilia dysfunction; DNAH7 and CLUAP1

One of the mechanisms through which SARS-CoV-2 could induce lung damage is mediated through the impairment of respiratory cilia. The expression of DNAH7, which is responsible for the maintenance of silica function, has been shown to be downregulated during infection of human bronchial epithelial cells by the SARS-CoV-2 virus [111]. Apart from SARS-CoV-2, some genetic variants of this gene could also reduce its expression levels, and thereby, increase the risk of mortality in COVID-19 patients. The variants of *SLC39A10* including super-variant chr2_197, SNPs rs200008298 (3 prime UTR), rs4578880 (intron), and rs113892140 (upstream) are other genetic abnormalities that have been reported to be associated with cilia dysfunction in COVID-19 patients [112]. It has been also suggested that the upper variant consists of a SNP rs2301762, which is located in 5 prime UTR of gene *CLUAP1*, could induce cilia dysfunction and thereby increase the severity of COVID-19 [113,114].

2.4.2. Genes related to cardiovascular diseases; DES and SPEG

Striated muscle preferentially expressed protein kinase (SPEG) is from the myosin light chain kinase protein family and is encoded by the *SPEG* gene. SPEG has an important role in the maintenance and activity of cardiac and skeletal muscles [115]. Additionally, *DES* is the gene that is translated into Desmin, a muscle-specific type III intermediate filament, which could regulate the architecture of the sarcomere [116]. The mutation in *DES* and *SPEG* has been previously shown to be associated with cardiomyopathy [116,117]. Recently, it became evident that SNP rs71040457 located downstream of *DES* and the upstream of *SPEG* is associated with the incidence of cardiomyopathy in COVID-19 patients [118,119].

2.4.3. Genes related to thromboembolic diseases

STXBP5/STXBP5-AS1 are one of the most important genes that their association with the thromboembolic disease have been previously established [120]. It has been indicated that the lack of *STXBP5* in mice could increase von Willebrand factor levels in plasma, induce artery thrombosis, and impair platelet secretion and activation. Given these, *STXBP5* is considered to be a strong risk factor for venous thromboembolic disease. Thus far, 101 SNPs have been identified in the gene encoding *STXBP5;* of which 89 are located in the intron of *STXBP5* and 6 are located in the intron of gene *STXBP5-AS1*. Hu et al. reported that the variations within *STXBP5/STXBP5-AS1* could increase the mortality risk in COVID-19 patients [121]. Abu-Farha et al. also introduced three genetic risk variants, including rs13109457-A, rs12029080-G, and rs6687813-A in COVID-19 patients that increased the levels of D-dimer and subsequently enhance the risk of thrombosis [122].

2.4.4. Genes related to mitochondrial dysfunction; TOMM7

During infection, the SARS-CoV-2 virus recruits the mitochondria of the infected cells to produce reactive oxygen species (ROS), an event that leads to excessive production of inflammatory cytokines and eventually cytokine storm [123,124]. On the other hand, to avoid the progression of the disease, the immune system targets the mitochondria of the damaged cells to suppress SARS-CoV-2-induced production of ROS; an event which in turn leads to mitochondria dysfunction and induction of apoptosis in the infected cells [123]. The results of previous studies revealed that mitochondrial DNA are released from the damaged organs and the assessment of circulating cell-free MT-DNA in the plasma of COVID-19 patients could be a poor prognostic factor [125]. Given these, it has been suggested that early detection of MT-DNA in COVID-19 patients could be beneficial to provide a promising overview about the survival state of the patients, the risk of ICU hospitalization, or organ failure.

Recently, the genome analysis revealed the presence of 5 intergenic variant SNPs on chromosome 7, which are associated with mitochondria function [126]. For example, SNP rs55986907 seems to alter the expression of *TOMM7*, which encodes a subunit of the translocase of the outer mitochondrial membrane. The down-regulation of *TOMM7* in COVID-19 patients could result in intensified mitochondria dysfunction.

2.5. Other genes

2.5.1. ABO blood group

It was reported that individuals with the gene encoding blood group A antigens have a higher risk for COVID-19 development as compared to other blood groups; on the other hand, those who harbor neither A nor B genes (blood group O) might have protective effects against the SARS-CoV-2 virus [66]. Even in deceased patients, this distribution pattern is observable. Apart from blood group A, Zietz et al. have indicated that cases who possess RHD gene might also have a higher rate of COVID-19 infection [127]. According to the study conducted by Barnkob et al., although ABO and RhD blood group could be a risk factor for the SARS-CoV-2 virus infection, these markers could not determine the chance of hospitalization or mortality in the patients [128]. In agreement, Latz et al. declared that having blood group A might not necessarily predict the chance of hospitalization in COVID-19 patients [129].

2.5.2. GSTT1-M1 genes

Glutathione S-transferases (GSTs) are from the family of enzymes that regulate cellular detoxification. The results of in-depth analysis revealed that polymorphism in genes encoding this family of enzymes could increase the risk of respiratory disease; proposing perhaps there is an association between *GSTT1* and *GSTM1* gene polymorphisms and the incidence of COVID-19 [130]. In this regard, Saadat et al. have reported the correlation between *GSTT1* polymorphisms and the prevalence as well as mortality of COVID-19 in the East-Asian population [131]. Abbas et al. also conducted another study to evaluate the effect of *GSTT1* and *GSTM1* genes polymorphism on COVID-19 severity [132]. Their results indicated that individuals who carried $GSTT1^{-/-}$ had a higher mortality rate as compared with $GSTT1^{+/+}$ carriers. The dual polymorphism in *GSTT1* and *GSTM1* genes ($GSTT1^{-/-}$ and $GSTM1^{-/-}$ genotype) may also increase the risk of pulmonary fibrosis in COVID-19 patients.

2.5.3. LZTFL1 genes

The 3p21.31 region has been shown to be involved in some kinds of respiratory failures previously. Leucine zipper transcription factor like 1 (LZTFL1) which its gene is located in 3p21.31 could regulate the trafficking of proteins to the ciliary membrane [133]. This protein has a regulatory role in the epithelial-mesenchymal transition (EMT) process which is a viral response pathway [134,135]. According to multiomics and machine learning methods, a gain-of-function risk A allele of an SNP, rs17713054G > A was detected as the probable causative variant to enhance the expression of LZTFL1. Regarding the role of LZTFL1 in

EMT process and the gain-of-function of 3p21.31, LZTFL1 could be a novel target in COVID-19 therapy [136].

3. Host epigenetic

3.1. Epigenetic regulation of ACE2

Comparison between the DNA methylation profiles across five genomic loci of the *ACE2* promoter in COVID-19 patients revealed that there is a difference in methylation pattern according to sex [137]. In cancer patients, the hypomethylation of *ACE2* promoter leading to *ACE2* up-regulation has been reported, which makes these patients more vulnerable to COVID-19 [138]. Accordingly, Yang et al. used UALCAN database to ascertain the correlation between cancer and *ACE2* hypomethylation [139]. The results were interesting, as it became evident that with the advance of age, carcinoma stage, and the severity of cancer, the methylation levels of the *ACE2* promoter were significantly decreased [139]. Patients with oxidative stress disease such as lupus are another susceptible group to SARS-CoV-2 infection [140]. The results of the in-depth analysis succeeded to find the footprint of epigenetic regulation in this event. It has been suggested that in response to oxidative stress, hypomethylation might occur in the promoter of *ACE2*, an event that facilitates the viral entry to the host cells.

Apart from DNA methylation, post-translational modifications at the *N*-terminal tails of histones is another epigenetic-related mechanism that could regulate the expression of ACE2 [141]. In a mouse germ cell line, it became evident that the absence of *EZH2* and subsequently down-regulation of *H3K27me3* could increase the expression of *ACE2* [142]. Additionally, alteration in the expression of *HAT1*, *HDAC2*, and *KDM5B* are other parameters that determines the sensitivity of an individual to the SARS-CoV-2 infection [143]. It should be noted that the impact of epigenetics on the susceptibility of the individuals to the SARS-CoV-2 virus is still a new field and numerous investigations should be yet conducted to ascertain the importance of post-translational modification of *ACE2* on the outcome of the patients. But, if it becomes evident that epigenetic regulators of *ACE2* might have a role in the prevalence rate of COVID-19, it could be suggested that epigenetics-based therapies might be a promising option, especially for high-risk groups.

3.2. X chromosome inactivation

Besides DNA methylation which could alter the expression of *ACE2*, X-chromosome inactivation is another epigenetic-related mechanism that could promote or attenuate *ACE2* expression [144]. *ACE2* gene is located on the area of the X-chromosome (Xp22.2) that can escape X-inactivation, which in turn, result in higher expression levels of *ACE2* in females as compared to males [9,145,146]. It is well-established that the prevalence rate of COVID-19 is higher in females as compared to males; but, how the overexpression of ACE2 in females is not associated with the more aggressive type of the disease? The answer is found in the way that the SARS-CoV-2 virus binds to ACE2. The results of the in-depth analysis revealed that 16 residues of the receptor-binding motif (RBM) of SARS-CoV-2 binds to 20 residues on ACE2 in males [147]. In females, however, the same SARS-CoV-2 RBM can bind to ACE2 on either of the two X chromosomes. This unique event in females reduces the probability of pulmonary edema during COVID-19 [148].

TLR7 is another gene located on the X chromosome, which its role in the protection against the SARS-CoV-2 is well-established. In similarity to *ACE2*, *TLR7* escapes from X-chromosome inactivation, but its expression is not dependent on the sex hormones [149]. Given this, it seems that the serum levels of TLR7 and in turn interferons are higher in females as compared to males. The results of a study revealed that loss-of-function variants of X-chromosomal *TLR7* in males resulted in impaired type I and II IFN responses, and all in all, these findings confirm why the prevalence of severe types of COVID-19 is higher in males as compared to females [109,150,151].

3.3. Induction of epigenetic modifications by BCG vaccination

It has been claimed that some microbial products or selected live attenuated vaccines, such as BCG can train the immune cells to induce more vigorous immune responses through integrating with epigenetic modifications [152]. For example, in the models of yellow fever, Rob J W Arts et al. have reported that BCG vaccination could prime monocytes to release more IL-1β through epigenetic reprogramming, and thereby, reduce the viremia in the patients [153]. BCG vaccination has also shown to be associated with the increase in the expression of some epigenetic mediators, including H3K4me1, H3K4me3, and H3K27ac that could increase the secretion of pro-inflammatory cytokines such as IL-6, IL-1b, and TNF-α from monocytes [154]. The non-specific protective property of BCG vaccination against other viral infection, including influenza A (H1N1), herpes simplex virus (HSV), respiratory syncytial virus (RSV), and the human papilloma virus (HPV) has previously been reported [155]. Given the viral protection offered by BCG, it is proposed that perhaps BCG vaccination could induce a prophylaxis impact against the SARS-CoV-2 virus; and this is the reason proposed by many researchers that why children with intense vaccination program are more resistance against COVID-19 [142].

Numerous studies have also compared the COVID-19 crises in countries with mandated BCG policies and those which do not have universal vaccination program [156]. The results were interesting; it became evident that the number of infected cases and deaths were dramatically lower in the countries with BCG vaccination. Additionally, it seems that BCG vaccination not only could remarkably reduce the requirement to hospital admission in COVID-19 patients but also could ameliorate the effects of the virus on the hosts, leading to less severe type of the disease [157].

3.4. Regulation of inflammatory pathway genes by histone modifications

Once TLRs recognize the viral pathogen-associated molecular patterns (PAMPs) of the SARS-CoV-2 virus, they propagate the signaling that activates histone modification, which in turn, leads to the expression of IFNs and TNF [158]. It has been claimed that H3K4me3 and H3K9me2 are the main regulators of histone modification that could increase the expression of IFNs due to COVID-19 infection [159–161]. Another cytokine that its expression during COVID-19 could be regulated by the histone modification and cis/*trans*-factors interaction is IL-6. It has been reported that those individuals who were infected by SARS-CoV-2 possess higher positive histone modification markers in the promoter of genes encoding ACE2 and IL-6 [162,163]. Through enhancing the activity of leukocytes, and reinforcing the expression of cytokines, cytokine receptors, IFN-stimulated genes, and signal transduction genes, histone modification could recruit the host defense responses in favor of COVID-19 progression.

3.5. Histone citrullination

Another epigenetic modification that has been identified in COVID-19 patients is citrullination of arginine residues on histones (Cit-H3), which facilitates the binding of transcription factors to the chromatin [144,164]. In response to the elevated calcium levels and pro-inflammatory cytokines, such as TNF-α, peptidylarginine deiminases (PADIs) such as PAD1, PAD2, PAD3, PAD4, and PAD6 induce citrullination of histone H3 and H4, and increase the accessibility of transcription factors to the chromatin [165–167]. It should be noted that Cit-H3 plays a fundamental role in neutrophil extracellular traps (NETs) [168]. The cell-free DNA analysis from COVID-19 patients indicated that SARS-CoV-2 increases Cit-H3, and thereby, enforces neutrophils to release NETs, which subsequently induce apoptotic cell death in lung epithelial cells or induce cardiovascular complications.

Moreover, there is a positive association between the levels of Cit-H3 and platelet counts, suggesting that abnormal platelet count could also induce NETs in COVID-19 patients [169]. The analysis of RNA sequencing of lung samples harvested from COVID-19 patients showed that the expression of platelet factor 4 (PF4) was increased by 5.5-fold, shedding light on the importance of platelets in the induction of NETosis [170]. Notably, Cit-H3 could also sustain the pluripotent cell count during early embryogenesis [171]. Given the high prevalence of Cit-H3 in COVID-19 patients and based on the role of this epigenetic modification and stem cell pluripotency, several clinical trials are investigating the impact of cell therapy against COVID-19 [172].

3.6. Interaction between human epigenetics factors and SARS-CoV-2 proteins

Analyzing the interactions between virus and host proteins revealed that there are 132 proteins in humans that the SARS-CoV-2 virus could bind to them. Among these proteins, 8 are epigenetic modifiers. HDAC2, BRD2-BRD4, and CUL2 complex binds to viral NSP5, viral E protein, and viral ORF10, respectively [173]. Concerning HDAC2, it became evident that when NSP5 binds to this epigenetic modifier, it prevents the nuclear localization of HDAC2, and thereby, suppresses the regulatory impact of this molecule on inflammation and interferon responses. As mentioned before, HDAC2 enhances the expression of IFNs-specific genes (IGS) through deacetylation of H4K16 at ISG promoters [174]. ORF10 is another SARS-CoV-2 virus protein that through interaction with Cullin-RING E3 ubiquitin ligase complex consists of CUL2, ELOB, ELOC, RBX1, and ZYG11B enhance viral proliferation in the host's cells [175,176].

3.7. Epigenetic modulation of SARS-CoV-2 infection and age-related epigenetic

From the first description of COVID-19, one question remained unanswered that why the disease prevalence, as well as severity, are intensified by the advance of age? The answer to this question might be found, at least partly, in the lifetime accumulation of epigenetic modification during the aging process [14]. The alteration in the methylation of *ACE2*, expression of HDACs, and SIRTs in different ages all together suggest that epigenetic modulation could control the susceptibility of individuals to viral infections according to their age group [14,115,177]. Thus far, some models have been developed to estimate variation in methylation levels in selected DNA CpGs according to age, called biological age molecularly or DNAmAge [116]. Mongelli et al. have also reported that after COVID-19 infection, especially in those who were younger than 60 years, there is an increase in so-called DeltaAge; indeed, a positive DeltaAge is determined as an acceleration of the biological blood clock [178]. Telomere is another age-related driver that might be involved in COVID-19 [179]. The results of an interesting study revealed the negative correlation between telomerase length and the severity of COVID-19; the shorter is the telomeres length, the more aggressive is the type of the disease [180,181]. Despite this finding, still, little is known about the predictive value of telomere length in COVID-19 severity.

4. Virus genome mutations

The study of mutations in SARS-CoV-2 has been investigated in numerous studies [182–185]. In the following, the presence of alterations in SARS-CoV-2 variants is discussed.

4.1. Structural proteins

4.1.1. Spike protein

Regarding the continuous evolution of SARS-CoV-2, the following data is according to the time of article writing, 7 February 2022, as stated by WHO [186]. Indeed, the categorization of variants is performed based on variants of concern (VOCs), variants of interest (VOI), variants under monitoring (VUM), and formerly monitored variants.

4.1.1.1. Currently designated variants of concern (VOCs). For these variants, clear evidence is available indicating a significant impact on transmissibility, severity, and/or immunity that is likely to have an impact on the epidemiological situation in the European Union (EU)/European economic area (EEA). The combined genomic, epidemiological, and *in vitro* evidence for these properties invokes at least moderate confidence [187].

4.1.1.1.1. WHO label: Alpha (VOC 20212/01, 20I/501Y.V1, or B.1.1.7). The United Kingdom (UK) variant of the SARS-CoV-2 virus, also known as VOC 202012/01, 20I/501Y.V1, or B.1.1.7, was primarily detected in November 2020 and has shown to have a dramatic mortality rate as compared with previous variants. Notably, as compared to the parental strain of D614G, B.1.1.7 variant is more transmissible [188]. Given the high contagious rate, this variant of the virus turned to be the dominant form of the virus in England and other countries [189]. Seventeen mutations have formed this variant, among them 8 occurred in the S protein (6 substitutes and 2 deletions), 4 located in ORF1ab protein, 3 target ORF8 protein, and 2 on N protein [190]. It should be noted that the deletion at positions 69 and 70 (del69–70) causes S-gene target failure (SGTF) −which served as a proxy in the United Kingdom for identifying B.1.1.7 cases− in at least one RT-PCR–based diagnostic assay [191,192]. Substitution in amino acids N501Y, A570D, P681H, T716I, S982A, and D1118H are other spike mutations that have been recognized in this variant of the virus [193]. Interestingly, it has been claimed that the majority of mutations in the B.1.1.7 variant are adoptive and have arisen due to positive selection. It is also suggested that these mutations probably have been formed in an immunocompromised individual and in response to convalescent plasma treatment [194].

Another mutation that has been identified in B.1.1.7 variant is Q27stop that truncates the ORF8 and results in immune escape of the virus [195]. In another study, Mohandas et al. have evaluated the pathogenicity B.1.1.7 variant and compared it with a variant with D614G mutation in hamsters [196]. Their results revealed that the disease produced by B.1.1.7 variant was coupled with bodyweight loss, but mild lung pathology. Although the impact of B.1.1.7 variant on the mortality rate of the host has not yet been established, it is evident that B.1.1.7 variant is more transmissible rather than lethal.

4.1.1.1.2. WHO label: Beta (B.1.351, 501Y.V2). B.1.351 variant which was firstly found in South Africa in December 2020 is one of the most transmissible variants of the SARS-CoV-2; but in similarity to B.1.1.7 variant, the effect of this variant on the mortality rate of the disease has not yet been established [193,197]. This variant was more prevalent and invasive in young individuals with no underlying health conditions. Using a mathematical model, it became evident that this variant is 50-fold more transmissible than previously circulating variants found in South Africa [198]. So far, 9 mutations have been identified in the S protein of the virus, including L18F, D80A, D215G, Δ242–244, R246I, K417N, E484K, N501Y, and A701V [199]. It should be noted that N501Y mutation, which is in common with B.1.1.7 variant, can reinforce the affinity of the virus to ACE2, and may reduce the efficacy of three classes of therapeutically relevant monoclonal antibodies (mAbs) and neutralizing antibodies especially against B.1.351 variant [200]. One of the major concerns about B.1.351 variant in South Africa was the interaction of the virus with HIV; although it seems that HIV infection could not affect SARS-CoV-2 replication, further evaluation is still required in this field [197,201].

4.1.1.1.3. WHO label: Gamma (P.1, B.1.1.28.1). The lineage P.1 (Gamma variant), which has been found in Brazil in January 2021, acquired 21 mutations including 1 insertion, 1 deletion, 4 synonymous mutations, and 15 non-synonymous mutations [202]. Notably, three of these mutations (K417T, E484K, and N501Y) could enhance the affinity

of the virus to ACE2. It should be noted that as compared with B.1.1.7 and B.1.351, this variant has the most changes in the spike protein. It has been suggested that the P.1 variant is 2.2-fold more transmissible than previous non-*P*1 variants, especially in adults [203]. It has also been reported that P.1 variant might be more lethal than previous variants [202,204]. Martins et al. have suggested that there is a correlation between SARS-CoV-2P.1 variant and the hospitalization [205].

4.1.1.1.4. WHO label: Delta (G/452.V3, B.1.617). Delta variants of the SARS-CoV-2 virus (B.1.617.2) were first detected in India in March 2021, but very soon, they have found their way to other countries [206]. The outbreak of this variant was coupled with the sharp increase in the number of SARS-CoV-2 cases and deaths. It has been reported that Delta variants are about 50-times more transmissible than Alpha variants as it displaced Alpha variant as the dominant strain in England [207]. The viral load is also higher in Delta variant as compared with other variants. Accordingly, a study in Scotland showed that the hospital admission rate for patients with the Delta variant was as twice higher as the Alpha variant [208]. Thus far, three distinct lineages have been identified within this variant, each of them has different mutation profiles. For example, B.1.617.1, also known as VOI, was defined by the spike protein amino acid alterations, including L452R, E484Q, D614G, P681R, and Q1071H. B.1.617.2, which is the most contagious virus in this category and labeled as VOC-21APR-02, was defined by the spike mutations such as T19R, Δ157-158, L452R, T478K, D614G, P681R, and D950N; but it lacks mutation at E484Q. While according to WHO, B.1.617.2 is classified as a VOI as a result of its high transmissibility, the UK classifies this virus as VOC [200,209].

4.1.1.1.5. WHO label: Omicron (B.1.1.529). On 26 November, WHO determined the B.1.1.529 lineage as a new VOC which is designated as omicron [210]. According to data from South Africa, the daily numbers of cases diagnosed with COVID-19 showed a considerable rise from 273 on 16 November to more than 1200 by 25 November. Most newly diagnosed individuals were from the province of Gauteng where the first Omicron SARS-CoV-2 was identified [211]. Notably, the infection percentage of Delta variant was 80 % which is determined as about 90 % for the Omicron, implying the higher transmissibility of Omicron over Delta. Also, the early doubling time of Omicron was lower than Delta and Beta as well (1.2 vs 1.5 and 1.7, respectively) [212]. Of note, the Omicron variant showed a higher half-life than others and analysis of virus survival time showed this variant tends to be more persistent on plastic and skin surfaces compared with other variants [213]. Inline, according to a recent retrospective study conducted in South Africa, the rate of reinfection due to Omicron was higher than the previous variants [214]. Also, investigating the neutralizing activity of sera against a range of VOCs showed that the Omicron variant has resistance to neutralization of patient sera who affected other variants, while the Alpha variant could induce a wide range of immunity [215].

The concern about this particular variant was initiated from the presence of notably large number of mutations (more than 60 mutations including substitutions, deletions, and insertions) [216], several of which are in the spike of the virus [211]. Mutations in the spike include 30 substitutions including A67V, T95I, Y145D, L212I, S371L, G339D, S373P, S375F, N440K, K417N, G446S, S477N, T478K, Q493R, E484A, G496S, Y505H, Q498R, N501Y, T547K, D614G, H655Y, P681H, N679K, N764K, D796Y, Q954H, N856K, N969K, and L981F; one insertion (three amino acids, [EPE]) at position 214, and also three deletions out of H69/V70, G142/V143/Y144, and N211. Notably, D614G in the spike seems a vital mutation available in all VOCs [217], which was shown to be associated with higher upper respiratory tract infection and lower age of patients [218]. Six substitutions (L2084I, K856R, A2710T, P3395H, T3255I, and I3758V) and two deletions in four amino acids (amino acid 2083, 3674, 3675, and 3676) were also detected within *ORF1a* of Omicron variant. Besides, ORF9b harbors P10S substitution and three deletions at positions 27–29. There are some other mutations in the envelope, membrane, and nucleocapsid; however, the main mutations are located in the spike gene. Based on the mutations, the Omicron variant has recently categorized into two lineages, BA.1 and BA.2 [219]. According to whole-genome mutational mapping and phylogenetic analysis, both BA.1 and BA.2 carry 51 mutations in the genome which 32 are shared with both lineages and each of them harbors 19 signature mutations; among those 19 mutations, BA.1 shows 13 and BA.2 has 7 in the S region [220].

In addition, according to the NextStrain, recent evidence of monitoring SARS-CoV-2 genome showed new massive mutations in a 56 years old man infected with the Delta variant include 34 mutations in the spike [221]. The proximity of those mutations in the Delta variant and the typical mutations of the Omicron variant might strengthen the hypothesis of co-circulation of Delta and Omicron and the emergence of the so-called DelMicron which is not a new variant, but a combination of two existing strains: Delta and Omicron.

4.1.1.2. Currently designated variants of interest (VOIs). Variant of interest (VOI) is the variant that has specific genetic markers and is related to alteration of receptor binding, reduction of neutralization strength by antibodies of previous infection or vaccination, and diminished effectiveness of therapies that might need one or more public health actions [187]. Although the genomic, epidemiologic, and *in vitro* evidence are available for these variants, the findings are relatively in their infancy and more details should be obtained.

4.1.1.2.1. WHO label: Lambda (C.37). C.37 was another lineage of the SARS-CoV-2 virus found in South America in August 2020 [206]. It possesses a deletion in the ORF1a gene (Δ3675-3677) which is in common with Alpha, Beta, and Gamma variants, and also carries several nonsynonymous mutations in the spike gene, including Δ246-252, G75V, T76I, L452Q, F490S, and T859N [206]. Notably, while T76I and L452Q mutations at the spike protein could increase the infectious ability of the variant as compared to other types of the virus, deletion Δ246-252 occurs at the *N*-terminal domain of the spike protein is responsible for immune evasion of the virus [207]. It should be noted that although this variant is still a VOI, the resistance against developed vaccines might be a concern, as it could cause another breakthrough infection [222].

4.1.1.2.2. WHO label: Mu (B.1.621). The Mu variant was initially isolated on January 2021, from Colombia. During the dominance of the Gamma variant, the Mu variant outnumbered the other ones and turned into the dominant epidemic form in Colombia; with this regard, until August 30, 2021, this variant was recognized in 39 countries. Spike domains of the Mu variant harbor several mutations such as T95I and YY144-145TSN in the *N*-terminal domain (NTD), the E484K, R346K, and N501Y in RBD, and the P681H, D614G, and D950N in other regions [209]. Notably, the E484K −which is also shared with the Beta and Gamma variants− could markedly decrease the sensitivity of the virus to antibodies produced after vaccination and/or natural SARS-CoV-2 infection [223,224].

4.1.1.3. Currently designated variants under monitoring (VUM). These additional variants of SARS-CoV-2 have the same infectious properties as VOC; however, data of phenotypic or epidemiological features are vague which needs boosted monitoring [187].

4.1.1.3.1. Az.5. AZ.5, formerly known as B.1.1.318, carries D614G, E484K, D796H, T95I, P681H, and ΔY144 mutations. A study from Gabonese population demonstrated that AZ.5 variant had an elevated (31 %) circulation between February and May 2021 which might be due to D614G, E484K, and ΔY144 mutations that may account for higher transmission and attenuated vaccine efficacy [225].

4.1.1.4. Formerly monitored variants. Formerly monitored variants are former VOCs, VOIs, and VUMs that were recategorized due to at least one of the following criteria: 1) the variant is no longer detected globally, 2) the variant has been circulating for a long time, but with no influence on the general epidemiological circumstances, or 3) the

variant has no concerning properties according to scientific data [186].

4.1.1.4.1. WHO label: Zeta (P.2). The Zeta variant or lineage P.2 of the SARS-CoV-2 virus is indeed a sub-lineage of B.1.1.28, which was first detected in Brazil in April 2020 [226]. Unlike B.1.1.28, it does not have N501Y and K417T mutations; however, it possesses the E484K, D614G, and V1176 mutations. Some of the Zeta variants, but not all, might have F565L mutation, as well. The prevalence of the Zeta variant is relatively lower than B.1.1.28 and<0.5 % of the viral samples detected worldwide show this strain [227]. As compared to the original B.1 variant, the Zeta variant might bring more severe type of disease. Also, it needs the higher titer of antibodies to be neutralized as compared to the original B.1 variant. Indeed, this variant contains many mutations presented in the Alpha, Beta, Delta, and Gamma variants that make the virus easier to penetrate the target cells and induce resistance to vaccines.

4.1.1.4.2. WHO label: Iota (B.1.526). The Iota variant, also known as B.1.526 detected in November 2020, was first considered to be a VOC. D614G, E484K, and T951 were three mutations that have been detected in the spike protein of this variant [228]. The former was reported to increase the affinity of the virus to ACE2 and E484K was suggested to be associated with immune escape from monoclonal as well as neutralizing antibodies [229]. Notably, it was indicated that T951 mutation might not have any effect on the antigenicity of the virus [230]. Higher affinity toward ACE2 and elevated spike stability, viral infectivity, viral fusogenicity, and viral replication were observed in this variant [231].

4.1.1.4.3. WHO label: Eta (B.1.525). The variant B.1.525, known as the Eta variant, was first identified from the nasopharyngeal swabs of two asymptomatic COVID-19 cases in Nigeria in December 2020 [232]. This variant is now circulating in twenty-six countries. Unlike the Alpha, Beta, and Gamma variants, Eta variant does not carry N501Y mutation. It possesses, E484K, N439K, Y453F mutations, and ΔH69/ΔV70 deletion. Indeed, the co-existence of E484K mutation and a new F888L mutation makes Eta variant distinct from other variants of the SARS-CoV-2 virus [233]. These mutations have increased its transmissibility, facilitated the viral escape from antibodies, and enhanced the risk of re-infection in patients [232].

4.1.1.4.4. WHO label: Kappa (B.1.617.1). Kappa variant of the SARS-CoV-2 virus is one of the three sub-lineages of B.1.617, which is also known as B.1.617.1 [234]. This variant was first identified in India in December 2020 and was characterized by three amino acid alterations, including L452R, E484Q, and P681R in the spike protein. Among them, L452R could increase the affinity of the spike protein for ACE2 and induce immune escape. E484Q also enhances the binding of the protein to ACE2. Overall, this variant is a double mutant strain of the virus that appeared worrying. The E484Q mutation, which is identical to the E484K mutation, and the L452R mutation, enable the evasion of the virus from the immunity [235–237].

4.1.1.4.5. WHO label: Epsilon (B.1.427, B.1.429). As a sub-lineage of B.1.427 and B.1.429, epsilon variant (CAL.20C) which was firstly detected in July 2020 possesses five mutations in the spike protein that among them I4205V and D1183Y occur in the ORF1ab-gene and S13I, W152C, and L452R occur in the spike protein's S-gene [236,238]. It has been demonstrated that the higher titers of antibody form vaccinated individuals with a Wuhan-1 isolate–based messenger RNA vaccine or convalescent individuals are required to neutralize Epsilon variant; indeed, the L452R mutation is the reason that reduces the efficacy of antibodies [239]. Moreover, the S13I and W152C mutations could result in a total loss of neutralization for all NTD-specific mAbs. Carroll et al. revealed that the Epsilon variant has higher virulence and more rapid replication in the upper respiratory tract as compared to ancestral B.1 (614G) or B.1.427 [240]. The authors also reported that Epsilon variant has faster dissemination from airways to parenchyma, and thereby, it could induce more severe lung damage at early and late stages of the disease.

4.1.1.4.6. WHO label: Theta (P.3). The results of the genome sequencing of COVID-19 samples from the Philippines resulted in the identification of two new mutations, E484K and N501Y, in the Spike protein of the SARS-CoV-2 virus [241]. Very soon, it became evident that these mutations could emerge a new variant of the virus known as lineage P.3 or theta variant, primarily identified in February 2021. P.3 variant contains similar VOC mutations in the Spike protein, such as E484K, N501Y, and P681H, which affect the transmissibility and immune escape of the virus [242]. Other mutations, including D614G, H1101Y, E1092K, and V1176F are also detectable in more than 95 % of P.3 variants. In addition to these, synonymous spike protein mutations (593G and 875S), three amino acid deletion (LGV141_143del), as well as Q1180H, have been reported to exist in most, but not all P.3 variants [243–245].

4.1.1.5. An overview of notable missense mutations in SARS-CoV-2 spike

4.1.1.5.1. D614G mutation. It was reported that an amino acid change in the spike of the virus, D614G, was presented early during the pandemic, and viruses containing G614 are now prevalent in many places around the world [246]. Ozono et al. have reported that among numerous identified mutations in the spike protein, the D614G mutation was associated with the highest viral entry, suggesting that variants possessing this mutation might be more transmissible [247]. Plante et al. have also suggested that SARS-CoV-2 with D614G mutation could produce higher infectious titers in nasal washes and the trachea, but not in the lungs; suggesting that this variant may mainly infect the upper respiratory tract [248]. It should be noted that the D614G mutation might assemble a more functional S protein into the virion, and thereby, produce stronger pathogenicity.

By using GISAID (Global Initiative on Sharing All Influenza Data) and bioinformatics models, Korber et al. have proposed that G614 mutation is mostly accompanied by three other mutations, including C241T, C3037T, and C14408T (C and T imply cysteine and threonine, respectively) that could change the amino acid sequence of RNA-dependent RNA polymerase (RdRp) [249]. Volz et al. have indicated that infection with the G614 variant was associated with higher viral load and younger age of patients [250]. Moreover, Flores et al. proposed that the higher pathogenicity of the G614 variant might have an impact on the vaccination program [251]. To obviate this challenge, Weissman et al. have tested the efficacy of the antibodies against G614 and stated that the G614 pseudovirus was moderately susceptible to neutralization either by mAbs against the RBD or convalescent sera [227].

4.1.1.5.2. N440K mutation. The reports suggest that the existence of N440K mutation in SARS-CoV-2 increases the lethality of the virus at least 15-times as compared to earlier variants [252]. Moreover, the N440K variant could induce higher infectious viral titers as compared to the Alpha variants. It should be noted that despite the concerns about this variant, recent reports suggested that N440K variant is slowly being replaced by other variants such as B.1.617 and B.1.1.7.

4.1.1.5.3. L452R mutation. L452R, a common mutation found in the Delta and Kappa variants, replaces leucine (L) with arginine (R) at position 452 in the RBM of RBD [253]. This mutation not only enhances the affinity of the virus to ACE2 but also reduces the vaccine-stimulated antibodies and confers escape from HLA-A24-restricted cellular immunity; HLA-A24 is a prominent HLA-class I alleles in the East/Southeast Asian populations [254]. L452R mutation could also increase the stability of the S protein, enhance viral replication, and thereby, increase viral infectivity [255].

4.1.1.5.4. S477G/N mutation. The S477 mutation (S477G and S477N) is the most frequently exchanged amino acid residue in the RBDs of SARS-CoV-2 mutants, which reinforces the interaction between the spike protein and human ACE2 [232]. Notably, since serine (S) 477 is located in a solvent-exposed random coil loop, it does not have any interaction with ACE2; but, the substitution of this amino acid with asparagine could establish a hydrogen bond and stabilized spike protein-ACE2 interaction [233].

4.1.1.5.5. E484Q/K mutation. The E484Q mutation observed in the Kappa variant could reinforce the affinity of the virus to ACE2 receptor

and diminish the ability of vaccine-stimulated antibodies to target this altered spike protein [256]. E484K is another mutation that was found frequently in Gamma [257], Zeta [226], and the Beta variants [203]; this mutation is known as an escape mutation, as it can shield the virus from the host's immune responses or mAbs against the SARS-CoV-2 virus [258].

4.1.1.5.6. N501Y mutation. N501Y mutation (also known as Nelly) enhances the affinity of the spike protein to ACE2 [259]. This mutation is found in Alpha, Beta, and COH.20G/501Y variants [238]. In a study conducted by Tian et al., the authors combined kinetics assay, single-molecule technique, and computational method to study the interaction between RBD of spike protein and ACE2 [260]. Their results indicated that RBD with the N501Y mutation showed a stronger interaction with ACE2. Interestingly, Liu et al. have reported that among different spike protein substitutions, only N501Y was able to replicate in the upper airway in the hamster model and primary human airway epithelial cells [241].

4.1.1.5.7. P681H mutation. The non-synonymous P681H mutation found in Alpha variant and lineage B.1.1.207 results in the replacement of proline (P) by histidine (H) at position 681. The results of the epidemiological analysis revealed that this mutation does have any association with neither higher infection rate nor higher prevalence [242,261]. The variants of the virus possessing this mutation could be effectively neutralized by the sera from fully vaccinated individuals [262]. The results of Lubinski et al. also indicated that spikes containing P681H could be more easily cleaved by FURIN-like proteases [263].

4.1.1.5.8. P681R mutation. The results of the in-depth analysis revealed that SARS-CoV-2 variants harboring P681R mutation have higher pathogenicity, as compared to the parental virus, probably due to enhanced viral fusogenicity; however, the results of *in vitro* assays indicated that P681R variant did not necessarily show higher growth kinetics [264]. Liu et al. also indicated that the presence of P681R mutation in Delta, but not Alpha variant, is associated with enhanced replication via increased S1/S2 cleavage [265].

4.1.1.5.9. A701V mutation. At the end of 2020, the Malaysian Ministry of Health succeeded to identify a new mutation within the spike protein in 60 samples at which alanine (A) was replaced by valine (V) at position 701 [98]. Apart from Malaysia, this mutation has been reported in South Africa, Australia, the Netherlands, and England [99]. The prevalence rate of A701V is about 0.18 % of cases, and it was shown that the presence of this mutation could accelerate the transmission rate of the virus [266]. Indeed, A701V mutation which was detected in the Beta variant could be one of the reasons behind the higher transmissibility of the Beta variant [267].

To provide an accurate overview, we summarized all the relevant data concerning SARS-CoV-2 variants and mutations in Table 2. Also, the structure of SARS-CoV-2 genome and the distribution of its variants were represented in Fig. 4.

4.1.2. Envelope

The envelope protein (E protein) –the smallest structural component of SARS-CoVs that controls ion channel activity, virion assembly, and replication– is responsible for severe acute respiratory syndrome[268]. The results of a study conducted by Chai et al. also indicated that the DLLV motif which is located at the C-terminal of E protein makes an interaction with the PDZ and SH3 domains of PALS1 (protein associated with Lin-7) located on the epithelial of lung cells [269]. NCBI database succeeded to identify about 259 non-synonymous mutations over the C-terminal domains (CTD), NTD, and transmembrane of E protein from different samples collected from all over the world [270].

Generally, mutations in E protein might have an influence on the replication and propagation of the SARS-CoV-2 virus [252]. In this vein, 16 mutations have been identified at CTD of E protein that target the DFLV amino acid motif and affect the interaction of the E protein with PALS. Mutations such as Ser68Phe, Pro71Ser, and Leu73Phe are other CTD-related mutations in E protein that affect protein stability [270].

4.1.3. Membrane

Mutations in the membrane (M) gene of the SARS-CoV-2 virus is rare [254]. The mutations in the M gene (M:I82T mutation) results in the emergence of a new sub-B.1 clade, B.1.I82T; the frequency of this mutation was increased in the USA and Europe. It has been reported that M mutations could increase the pathogenicity of the virus for younger individuals. D178H is another identified mutation in the M protein; the sub-lineage B.1.1.7-M:V70L-S:D178H is found exclusively in 31 states of the USA. The V70L mutation is another genetic abnormality that has been identified in the TM2 transmembrane helix [254].

4.1.4. Nucleocapsid

Nucleocapsid (N) protein of the SARS-CoV-2 virus possesses three dynamic disordered regions that contains putative transiently-helical binding motifs [271]. In a study conducted in Saudi Arabia, two consecutive mutations, including R203K and G204R were found in the N protein of SARS-CoV-2; notably, these mutations have been found mostly in B.1.1.7 and P.1 lineages [272]. Interestingly, it seems that the frequency of R203K and G204R mutations is growing globally, as their global incidence frequency (IF) increased from 0 % in August 2020 to 76 % in November 2020. These mutations in N protein have shown to be associated with enhanced viral RNA binding to host proteins. Moreover, the aforementioned alterations could impair interferon responses in the host. It has also been reported that R203K and G204R mutations could increase the infectivity of the virus for the host's cells, and thereby, produce the more severe type of the disease.

4.2. Non-structural proteins

4.2.1. ORF1ab (open reading frame1ab)

ORF1ab (ORF1a/b) refers to ORF1a and ORF1b that are conserved in the genomes of SARS-CoV-2. The genes encode large polyproteins that are catalyzed into several non-structural proteins by proteolysis [257]. Six ORFs exist in the SARS-CoV-2 genome that is participated in the regulation of viral replication and cellular signaling [273]. It has been indicated that V121D substitution could destabilize the ORF1ab non-structural protein-1 (NSP1), which is involved in the activation of the type-1 interferons, and attenuate the efficacy of vaccination [259]. The three-dimensional structure analysis of SARS-CoV-2 also revealed that a serine was replaced by glycine at position 723 in the ORF1ab NSP2 and a proline was replaced by isoleucine at position 1010 in the ORF1ab NSP3. Indeed, the mutation in NSP2 could increase the transmissibility of the virus, however, the mutations in NSP3 could differentiate SARS-CoV-2 from other SARS viruses [274].

Other mutations that were identified in NSP3 are V843F, A889V, and G1691C. While G1691C reduces the flexibility of the protein, V843F and A889V alter the biding pattern of SARS-CoV-2 and reduce the sensitivity of the virus to papain-like protease (PLPro) inhibitor GRL0617 [259]. The V843F mutation could also attenuate the ability of the virus to stimulate interferon-stimulated gene 15 protein (ISG15), and thereby, enhance viral spread. Notably, simultaneous mutation of V843F and A889V might have the same binding affinity as wild-type PLPro; this could be due to the fact that, unlike V843F which could damage the protease structure, A889V could neutralize this damage.

ORF1ab is another non-structural 6796 amino acids protein that in complex with several proteins could regulate viral genomic replication and synthesis. So far, 8 mutations have been identified in the gene encoding ORF1ab [275]. T609I mutation has been identified from the SARS-CoV-2 virus in California/United States, whereas G818S and F4321L were found from the samples collected from Sweden and India. In addition, M902I and T6891M have been found in Korea and F3071Y, S3120L, L3606X, and L3606F were detected from samples of Spain, China, Italy, and Japan, respectively [275].

4.2.2. Other ORFs

Freundt et al. have indicated that mutation in ORF3a protein, which

Table 2
The details of SARS-CoV-2 variants, their mutations and characteristics.

PANGO Linage	WHO label	Location	Identified	Key Spike mutations	Characteristics
Currently designated variants of concern (VOCs)					
B.1.1.7	Alpha	United Kingdom	September 2020	N501Y, D614G, P681H	This variant resulted in a highe hospitalization rate, need for ICU, and evasion from the immune system; however, was sensitive to vaccines.
B.1.351	Beta	South Africa	October 2020	K417N, E484K, N501Y, D614G, A701V	Elevated hospitalization and need for ICU were associated with the Beta variant that accompanied with resistance to mAbs, convalescent plasma, and vaccine sera as well.
P.1	Gamma	Brazil	January 2021	K417T, E484K, N501Y, D614G, H655Y	Gamma variant resulted in an elevated hospitalization and mortality rate that was resistant to mAbs, convalescent plasma, and vaccine sera.
B.1.617.2	Delta	India	February 2021	L452R, T478K, D614G, P681R	Delta variant has been a serious variant with much higher transmissibility, hospitalization rate and mortality. This variant was less susceptible to mAbs than the Wuhan strain.
B.1.1.529	Omicron	South Africa and Botswana	November 2021	A67V, D614G, T95I, H655Y, N679K, …	Omicron variant has the highest transmissibility, while has shown lower hospitalization rate and deaths. It has higher resistance to mAbs, but is weaker against cellular immunity.
Currently designated variants of interest (VOIs)					
C.37	**Lambda**	Peru	December 2020	L452Q, F490S, D614G	This variant showed an elevated immune resistance.
B.1.621	Mu	Colombia	January 2021	R346K, E484K, N501Y, D614G, P681H	It could evade immune defenses in a similar way to the Beta variant and had lower sensitivity to Abs.
Currently designated variants under monitoring (VUM)					
C.36 + L452R	**N/A**	Egypt	December 2020	L452R, D614G, Q677H	This variant could escape from the cellular immunity restricted to HLA-A24.
AZ.5 (B.1.1.318)	N/A	India	January 2021	E484K, D614G, P681H	Due to several mutations, it could escape from immune responses.
P.1 + P681H	N/A	Italy	February 2021	D614G, E484K, H655Y, K417T, N501Y, P681H	N/A
B.1.617.2 + E484X (d)	N/A	India	April 2021	L452R, T478K, D614G, P681R, E484X (d)	This variant is a part of B.1.617.2 (Delta).
B.1.617.2 + Q613H	N/A	India	April 2021	L452R, T478K, D614G, P681R, Q613H	N/A
B.1.617.2 + Q677H	N/A	India	April 2021	L452R, T478K, D614G, P681R, Q677H	It had resistance to mAbs.
B.1.617.2 + K417N	Delta plus	UK	June 2021	L452R, T478K, D614G, P681R, K417N	This variant has been associated with high mortality rates, evasion from immunity and lower mAbs effects.
C.1.2	N/A	South Africa	June 2021	D614G, E484K, H655Y, N501Y, N679K, Y449H	It could evade mAbs effectively.
AY.4.2	N/A	UK	June 2021	L452R, T478K, D614G, P681R, A222V, Y145H	N/A
Formerly monitored variants					
B.1.1.523	N/A	Russia	May 2020	E484K, S494P	Some mutations in it were similar to the Delta variant which facilitate its escape ability from the immune responses.
B.1.427/ B.1.429	Epsilon	USA	September 2020	L452R, D614G	The higher mortality rates and lower neutralization titers were two characteristics of the Epsilon variant.
C.16	N/A	N/A	October 2020	L452R, D614G	N/A
B.1.526.1	N/A	USA	October 2020	L452R, D614G	N/A
B.1.1.519	N/A	Mexico	November 2020	T478K, D614G	This variant was associated with increased hospitalization and mortality rates and reproduction number.
B.1.1.7 + E484K	N/A	UK	December 2020	E484K, N501Y, D614G, P681H	N/A
B.1.525	Eta	Nigeria	December 2020	E484K, D614G, Q677H	It had a lower neutralization rate.
B.1.617.1	Kappa	India	December 2020	L452R, E484Q, D614G, P681R	Kappa variant showed a higher transmissibility* and greater ability to escape from vaccination.
B.1.214.2	N/A	Belgian	December 2020	Q414K, N450K, ins214TDR, D614G	The severity and the ability to evade the immune responses were higher in this variant.
A.23.1 + E484K	N/A	UK	December 2020	V367F, E484K, Q613H	It showed 1.3 % mortality rate.
A.28	N/A	N/A	December 2020	E484K, N501T, H655Y	N/A
B.1.351 + P384L	N/A	South Africa	December 2020	P384L, K417N, E484K, N501Y, D614G, A701V	N/A
B.1.526	Iota	USA	December 2020	E484K, D614G, A701V	This variant had higher mortality among older adults and an enhanced ability to evade the immunity.
B.1.526.2	N/A	USA	December 2020	S477N, D614G	N/A
P.2	Zeta	Brazil	January 2021	E484K, D614G	It resulted in notable reduction in the neutralization ability of vaccine and mAbs.

(*continued on next page*)

Table 2 (*continued*)

PANGO Linage	WHO label	Location	Identified	Key Spike mutations	Characteristics
P.3	Theta	The Philippines	January 2021	E484K, N501Y, D614G, P681H	N/A
A.27	N/A	France	January 2021	L452R, N501Y, A653V, H655Y	This variant could evade the immune responses.
B.1.351 + E516Q	N/A	N/A	January 2021	K417N, E484K, N501Y, E516Q, D614G, A701V	N/A
B.1.1.7 + L452R	N/A	UK	January 2021	L452R, N501Y, D614G, P681H	It induced higher resistance to mAbs and evaded HLA-restricted immunity.
B.1.1.7 + S494P	N/A	UK	January 2021	S494P, N501Y, D614G, P681H	This variant induced resistance to Abs, particularly in combination with N501Y.
AT.1	N/A	Russia	January 2021	E484K, D614G, N679K, ins679GIAL	N/A
R.1	N/A	Japan	January 2021	W152L, E484K, G769V	This variant continued to appear in Japan and was associated with immune escape.
B.1.616(c)	N/A	France	February 2021	V483A, D614G, H655Y, G669S	N/A
B.1.620	N/A	Lithuania	February 2021	S477N, E484K, D614G, P681H	It had higher severity with an enhanced ability to evade the immunity and mAbs neutralization.
B.1.617.3	N/A	India	February 2021	L452R, E484Q, D614G, P681R	N/A
AV.1	N/A	UK	March 2021	N439K, E484K, D614G, P681H	N/A

WHO: World health organization; PANGO: Phylogenetic assignment of named global outbreak; PHE: Public health engineering; VOC: Variant of concern; **ICU:** Intensive care units; **mAbs:** Monoclonal antibody; **VOI:** Variant of interest; **HLA:** Human leukocyte antigen; **N/A:** Not available.
*; Cause community transmission in several countries, but have not yet been confirmed to be more infectious or transmissible.

is necessary for vesicle formation and Golgi fragmentation, could attenuate the ability of SARS-CoV-2 to induce cell death in the host's cells [276]. Also, Hsing et al. have identified 4 mutations in the gene encoding ORF3a of the SARS-CoV-2; G251V mutation obtained from Italian, Korean, and Swedish COVID-19 patients, K136X and G196V were found in variants from Spain, and M128L was detected from the variants found in Korea [275].

In another study conducted on 2 Italian COVID-19 patients who were infected by B1.1 lineage, a nucleotide mutation was found in ORF6, which eliminated 6 amino acids from the C-terminal of the protein. This mutation was unique: although it affects neither viral replication nor neutralizing activities of the patients' antibodies, it impairs antiviral IFN-based host response [277].

Hsing et al. also recognized 1 mutation (L84S) in the gene encoding ORF8 from the SASR-CoV-2 variants in Spain, India, and China [275]. Accordingly, Pereira et al. have detected several nonsense mutations and 3 deletions in the ORF8 gene [195]. Even though the exact function of ORF8 is still unknown, this protein seems to have the most variable structure and it appears that the changes in OFR8 could affect the spread of the virus.

5. An overview of the effects of mutations on the efficacy of vaccines

Although one side of the battle is the virus itself, researchers put much efforts to develop effective therapeutic approaches such as anti-viral agents in order to overcome it which have been discussed in several studies [278–281]. As the COVID-19 pandemic began, strives to develop effective vaccines were started wishing to win this battle. The first administration of anti-SARS-CoV-2 vaccine goes back to December 2020. Until 23 December 2021 (the latest guidance document of WHO), more than 20 vaccines have been confirmed to be evaluated according to WHO conditions and 14 have finalized the status of assessment [282]. Currently, 9 vaccines have been approved and utilized worldwide, including BBIBP-CorV (Sinopharm), CoronaVac (Sinovac Biotech), Covaxin (Bharat Biotech), AZD1222 (University of Oxford and Astra-Zeneca), Ad26.COV2.S (Janssen and Johnson & Johnson), Sputnik V (Gamaleya), mRNA-1273 (Moderna and NIAD), BNT162b2 (Pfizer and BioNTech), and NVX-CoV-2373 (Novavax and CEPI). Of note, BBIBP-CorV, CoronaVac, and Covaxin are from inactivated virus vaccines category, AZD1222, Ad26.COV2.S, and Sputnik V are from the adeno-viral vector-based vaccines category, NVX-CoV-2373 is a protein subunit vaccine, and mRNA-1273 and BNT162b2 are from the mRNA-based vaccines category [7]. On 23 August 2021, FDA approved the first COVID-19 vaccine known as Pfizer-BioNTech COVID-19 Vaccine for administration in individuals 16 years of age and older [283]. Also, on 31 January 2022, FDA approved the second COVID-19 vaccine i.e., Moderna COVID-19 Vaccine in individuals 18 years of age and older [284]. The comparison of vaccines, their characteristics, effectiveness, and shortcomings have been reviewed in several noteworthy studies [285–288]; however, we will briefly go over it in the following.

As discussed above, the presence of mutations could strengthen SARS-CoV-2 to be more transmissible and fatal [289,290]. Besides, mutations cause SARS-CoV-2 to escape the immune system [291,292]. It has been reported that some spike mutations such as D614G, C14408T, N440K, S477G/N, N501Y, P681H, etc. could elevate the affinity of the SARS-CoV-2 spike to the host cells; however, others like E484Q/K empower the capacity of the virus to escape from immune responses. Regarding the fact that the initial development of all vaccines has been performed based on the S protein found in the conventional Wuhan-hu-1 strain [7], it could be inferred that the alteration of SARS-CoV-2 in the spike region might be responsible for virus evasion from the immunity adopted either by natural infection or vaccine. The following sections will discuss the effectiveness of different SARS-CoV-2 vaccines against different VOCs. Nonetheless, as the global vaccination program did not initiate since the first variant emerged, the interaction of vaccines and various VOCs generated some discrepancy data. As the proportion of vaccinated people around the world rises up, more accurate data from the role of variants and mutations could be obtained such as situations that have been seen in the domination of Delta and Omicron variants. Accordingly, we categorized the following sections into two parts: before and after global vaccination.

5.1. Before global vaccination

The evaluation of Alpha variant susceptibility to BBIBP-CorV exhibited that this vaccine could neutralize the viruses effectively; however, BBIBP-CorV lose its potential capacity against Beta variant as the neutralization rates of most sera samples were reduced [293,294]. Moreover, CoronaVac could induce satisfying neutralizing Abs in the

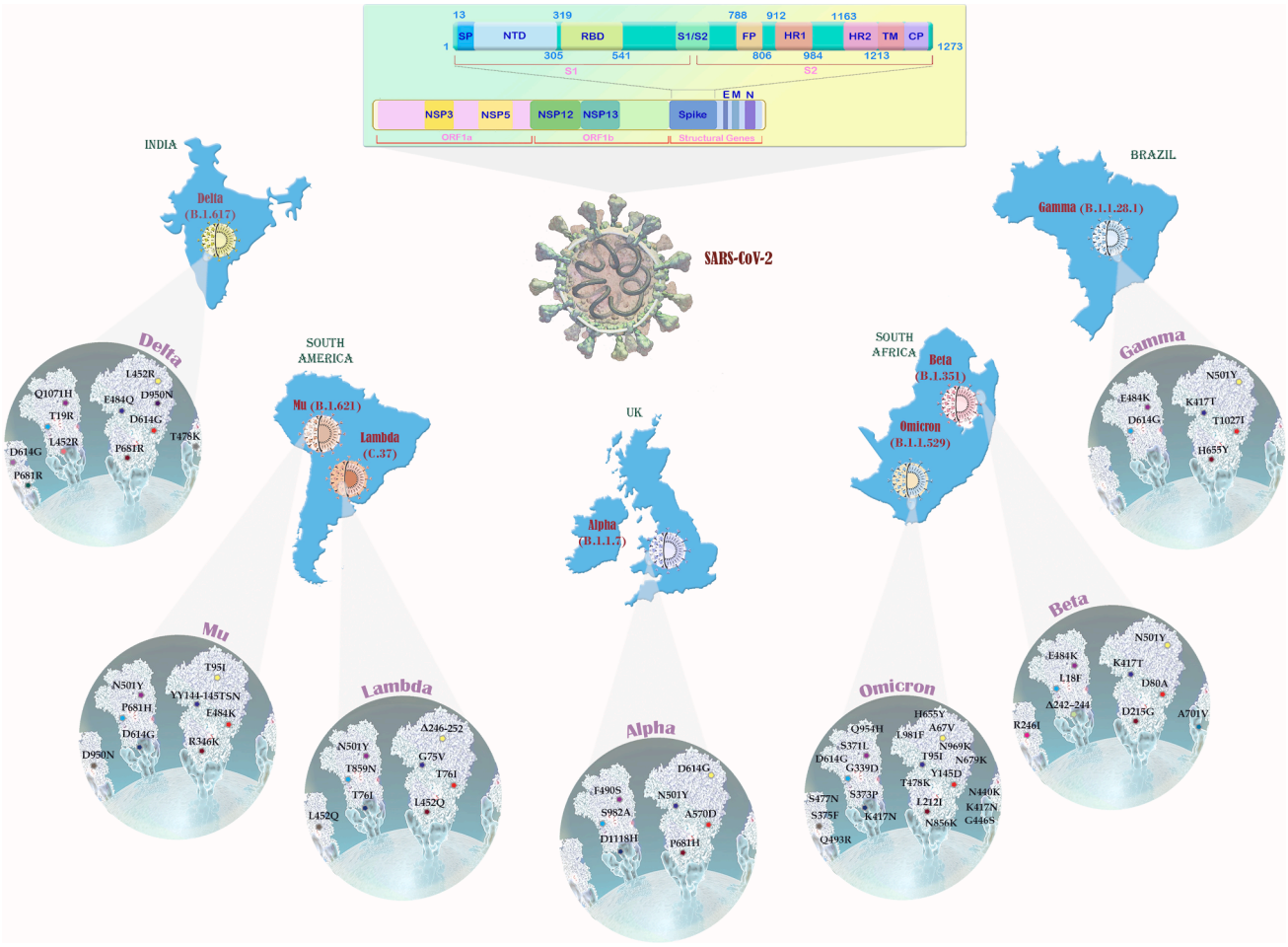


Fig. 4. The structure of SARS-CoV-2 genome and its variants. The genome of SARS-CoV-2 consists of ORF1a, ORF1b, and structural genes. While NSP3 and NSP5 of ORF1a encode papain-like protease and 3CL protease respectively, NSP12 and NSP13 of ORF1b encode RNA polymerase and helicase, respectively. The structural genes are responsible for the spike (S), envelope (E), membrane (M), and nucleocapsid (N) encoding. The spike-encoding region consists of two general regions S1 and S2 where the majority of mutations are related to this part. As illustrated, SARS-CoV-2 is categorized into different lineages based on the presence of mutations. Each bunch of mutations could give the SARS-CoV-2 various pathogenicity capacities letting variants have different transmissibility and severity.

contexts of the Alpha and Epsilon variants, but not in the Beta [295], Gamma, and Zeta [296]. Similarly, Covaxin showed proper neutralizing capacity facing the Alpha variant which was not observed against the Beta and Delta variants [297]. The evaluation of AZD1222 against Alpha and Beta variants showed the advantages of this vaccine facing the Alpha with 70.4 % efficacy [298] compared with the Beta with 10.4 % efficacy [299]. A study showed that the effectiveness of Ad26.COV2.S was 64.0 % in moderate to severe COVID-19 cases and 81.7 % in severe critical COVID-19 cases [300] and its ability to induce T cell-mediated anti-virus responses was satisfying in almost all VOCs [301]. The neutralizing activity of Sputnik V in the participant's sera was satisfying against the Alpha variant; however, the titer of Abs was reduced in variants harboring E484K mutation like Beta [302]. Inline, NVX-CoV-2373 showed 85.6 % efficacy against the Alpha variant, while it had 51 % effectiveness against the Beta variant [303,304]. By contrast, the effectiveness of mRNA-1273 was remarkably higher than other vaccines against the Alpha variant and particularly the Beta variant with 100 % and 96.4 % efficacy, respectively [305]. Similarly, BNT162b2 showed remarkable effectiveness against Alpha (93 %) and Beta (75 %) variants [306]. Nonetheless, the protection of BNT162b2 against the Beta variant was significantly decreased compared with the Alpha variant [307]; further highlighting the fact that spike mutations such as A701V, K417N, and E484A affect the efficacy of all vaccines facing the Beta variant. Taken together, it could be inferred that all the aforementioned vaccines could generate proper immune reactions ranging from neutralization to the T cell responses against all VOCs; however, almost all of them have an attenuated capacity facing the Beta variant that shows its evasion ability from the immune system. With this regard, a systematic review and *meta*-analysis study which searched a total of 4844 records from three databases evaluated the effectiveness of vaccines in various SARS-CoV-2 variants, and reported that the BNT162b2 vaccine had the most satisfying effectiveness against each VOC compared with other available vaccines [308].

5.2. *After global vaccination; Delta and Omicron variants*

The Delta variant contains mutations which facilitate the immune evasion capacity. The evaluation of mutations roles affecting the immunity showed that L452R mutation in the Delta variant gives similar infectious properties as N501Y gave to the Alpha and Beta variants. Moreover, T478K presented in the Delta variant could influence the neutralization capacity of antibodies [309]. The neutralization ability of CoronaVac vaccine against Delta variant was reduced by 2.47 times that was greater than the decline for the Alpha variant (1.62 times) [310]. Also, the serum neutralizing antibody titers of Covaxin were reduced by 2.7 times facing the Delta variant [311]. Covishield, a similar vaccine produced by AstraZeneca, showed a reduction in the serum neutralization levels against the Delta variant, as well [312]. According to several studies, the serum neutralization antibody titers after the administration of BNT162b2 were also reduced 1.41–11.30 times against this variant

[313–318]; inferring that the immune neutralizing antibody that adopted from various vaccines are less effective against the Delta variant.

A test-negative case–control study (SARS-CoV-2 test-positive cases and test-negative controls) evaluated the efficacy of inactivated vaccines such as BBIBP-CorV and CoronaVac vaccines against the Delta variant. Accordingly, single dose was not sufficient to induce proper protectivity; however, two doses of inactivated vaccines showed an average effectiveness determined as 72.5 % [319]. Furthermore, some studies from the United Kingdom and Scotland which evaluated the effectiveness of BNT162b2 and AZD1222 demonstrated similar results showing the efficacy of BNT162b2 and AZD1222 against the Delta variant about 87.9 % and about 60 %, respectively [208,320]. Notably, the effectiveness of mRNA-1273 was determined as 86.7 % against the Delta variant; however, as time passes after the second dose, the efficacy of mRNA-1273 reduced [321]. Overall, it could be concluded that −despite the lower neutralization capacity of vaccines− all are effective against the Delta variant; however, the amount of efficacy varies as it is at the highest level for the mRNA-based vaccines (about 85 % for the mRNA-based vaccines and 65–70 % for others).

The Omicron variant has high numbers of mutations which let this variant to escape from the immune responses more effortlessly. Generally, all available vaccines prepare immunity against S protein of SARS-CoV-2 [322]; this region of the Omicron variant carries more than 30 mutations that might dramatically affect the immune responses-induced by vaccines. It was shown that K417N mutation in the RBD region −which interestingly was carried by the Beta variant− is probably the most considerable cause of antibody disruption in the Omicron variant. Notably, E484A is another mutation which accompanies K417N to empower the antibody disruption [323]. Omicron variant could resist 7 out of 8 approved mAbs and several other mAbs targeting epitopes of RBD and NTD [324]. The primary source of RBD-specific memory B cells could be triggered by booster doses; interestingly, after boosting vaccination, the population of B cells detecting the full-length Omicron variant expanded and pre-existing resting memory B cells differentiated into effector B cells with the ability to recognize the Omicron variant [325].

A study exhibited that only 20–24 % of patients with the Omicron variant had neutralizing antibody after primary BNT162b2 vaccination and no one showed neutralization after primary CoronaVac vaccine [326]. Similarly, two doses of BBIBP-CorV could not neutralize the Omicron variant effectively; however, a booster dose whether as a homologous or heterologous dose could significantly elevate the neutralization titers facing the Omicron variant [324]. The evaluation of Ad26.COV2.S, mRNA-1273, and BNT162b2 also showed that the Omicron variant could notably escape from immunity-induced by those stated vaccines (primary administration); nevertheless, receiving the third dose of mRNA-1273 and BNT162b2 considerably promoted the cross-neutralization possibly through the cross-activation of pre-existing innate and adaptive immune mechanisms [327]. In harmony, two doses of CoronaVac and/or BNT162b2 were able to provide 50 % neutralization against the Omicron after one month; nonetheless, the administration of booster dose of BNT162b2 to previously-two doses vaccinated individuals (CoronaVac and/or BNT162b2) notably enhanced the neutralizing ability-one month post booster dose. Interestingly, three doses of BNT162b2 was more potent to produce neutralization compared with other vaccines [328], implying the noteworthy capacity of BNT162b2 facing the Omicron variant. Moreover, the mix of BBIBP-CorV and BNT162b2 showed satisfying outcomes by increasing the immunity against Omicron [329]. With this regard, it was shown that booster dose with mRNA-based vaccines could restore the neutralization capacity of the immune system [330]. An interesting study evaluated the real-world effectiveness of BNT162b2 vaccination in 5 to 11 years old children. Among 94,728 individuals matched with unvaccinated controls, the estimated effectiveness was 51 % after second dose. Besides, the effectiveness of BNT162b2 was higher in youngest age group (5 and 6 years old) compared with older ones [331].

Overall, SARS-CoV-2 could evolve continuously and as time passes, we may encounter much more mutations that might alter the effectiveness of vaccines. It could be inferred that all typically approved vaccines have shown effectiveness against this virus; however, the quality and quantity of responses were more satisfying against the Alpha variant. Accordingly, Beta, Delta, and Omicron seem to have a higher ability to escape from the immunity. Indeed, all vaccines could protect patients from being severely ill and this is the key effect of vaccination that has helped nations pass this striking wave of COVID-19; however, seems that BNT162b2 and to wider category, mRNA-based vaccines would be a better strategy to overcome the domination of the virus and probably the best choice in order to augment the immunity against the Omicron variant regardless of the type of previously-administered vaccines. As the high proportions of people worldwide have received two doses of vaccines and the Omicron circulates rapidly, the booster dose is of importance, particularly as a heterologous booster strategy. Table 3 provided details of vaccines administered in the COVID-19 conditions.

6. Conclusion and future perspective

The SARS-CoV-2, responsible for COVID-19, was turned into a new concern to public health due to its high transmissibility capacity and mortality which causes asymptomatic to severe illness. There could be reasons account for this wide spectrum of clinical manifestations, among which the mechanisms associated with the entry of the SARS-CoV-2 have attracted great attention. ACE2 is the most important receptor of SARS-CoV-2 spike protein distributing mainly on the respiratory cells. The presence of *ACE2* variants such as E23K and K26R is associated with higher ACE2-spike affinity, while S19P and E329G could reduce the affinity. Similarly, there is genetic heterogeneity in other host-related factors such as *TMPRSS2*, *FURIN*, *DPP4*, *APOE*, and *CD147* which could either facilitate the entry of virus to the host cells and lead to more severe disease or impede the interaction of virus with the cells. Moreover, diversity in the immune-related genes is another agent affecting the severity of COVID-19. Some *HLA* variants such as *HLA-A*11:01* and *HLA-B*51:01* are associated with poor prognosis; however, *HLA-B*15:03* showed a protective effect. Likewise, genetic heterogeneity in cytokines, CCR/CXCR, TLRs, components of the complement system, NK cell-related genes, and vitamin D-binding protein strikingly affects the responses against SARS-CoV-2. In addition to genetic factors, host epigenetics may also influence COVID-19 severity. Accordingly, *EZH2* absence and *H3K27me3* downregulation could increase the expression of *ACE2*, while some histone modification regulators such as H3K4me3 and H3K9me2 can induce the expression of inflammatory pathways like IFNs.

Regarding the mutations concerning SARS-CoV-2, the genome of virus is per se a unique agent affecting the severity of COVID-19. According to the WHO classification, SARS-CoV-2 is categorized into VOC, VOI, VUM, and formerly monitored variants. The most famous mutation is D614G which is associated with higher viral entry and load due to higher interaction of spike and ACE2. In addition, N440K, L452R, S477G, and S477N enhance the affinity of spike-ACE2 leading to higher viral infectivity. Besides, D614G and E484Q/K are responsible for higher SARS-CoV-2 immune escape. Based on the global knowledge about COVID-19 and new education about how to manage the clinical manifestations, we inferred that the Delta variant has been the most severe wave of COVID-19 as this variant showed notable mortality worldwide. Nevertheless, data from the Omicron wave is not yet enough to analyze the strength of this variant.

One of the most imperative works facing COVID-19 has been the development of an efficient vaccine. Till now, more than 20 vaccines have been confirmed. The data concerning the efficacies of these vaccines differ from study to study, however, the average efficacy of mRNA-vaccines, particularly the Pfizer-BioNTech product, seems to be higher compared with others. All available vaccines are remarkably effective

Table 3
An overview of SARS-CoV-2 vaccines and their efficacy and safety profile against several variants.

Name	Developer	Country of origin	Date of validity	Schedule and rout of administration	Age group	Effectiveness/ Advantages (average)	Adverse events/ Challenge	Identifier
Inactivated vaccines								
BBIBP-CorV	Sinopharm	China	WHO approved on May 2021 for use in COVAX.	Two doses, 3–4 weeks apart, IM	18 Yrs and older	88 % for Alpha N/A for Beta 73 % for Gamma 72.5 % for Delta <50 % for Omicron (2 doses) N/A for Omicron (3 doses)	The most commonly reported AEs were fever, pain at the site of injection, headaches, and fatigue	NCT04984408
CoronaVac	Sinovac Biotech	China	Validated for emergency use (WHO) on June 2021	Two doses, 4 weeks apart, IM	18 Yrs and older	N/A for Alpha N/A for Beta N/A for Gamma 72.5 % for Delta 50 % for Omicron (2 doses) N/A for Omicron (3 doses)	The most common AE was pain at the site of injection. Other side effects included fatigue, diarrhea, and muscle pain. Most of these side effects were mild and lasted only for 2 days.	NCT04456595
Covaxin	Bharat Biotech	India	Validated for emergency use (WHO) on November 2021	Two doses, 28 days apart, ID	18 Yrs and older	N/A for Alpha N/A for Beta N/A for Gamma 65 % for Delta <50 % for Omicron (2 doses) N/A for Omicron (3 doses)	The most commonly reported AEs were fever, headaches, irritability, pain and swelling at the site of injection.	N/A
CoviVac	Chumakov Centre	Russia	Approved for use in Russia on February 2021	Two doses, 14 days apart	18 Yrs and older	Phase 1/2 trial is ongoing.	No serious AEs were reported.	NCT04619628
Viral vector vaccines								
AZD1222 (Covishield)	Oxford–AstraZeneca	UK, Sweden	EMA approved on April 2021	Two doses, 4–12 weeks apart, IM	18 Yrs and older	70.4 % for Alpha 10.4 % for Beta 78 % for Gamma 60 % for Delta <50 % for Omicron (2 doses) N/A for Omicron (3 doses)	The most commonly reported AEs were vomiting, diarrhea, fever, swelling, redness at the injection site and low levels of blood platelets. Enlarged lymph nodes, decreased appetite, dizziness, sleepiness, sweating, abdominal pain, itching and rash. Importantly, high risk of thrombocytopenia syndrome was reported mainly in younger female.	NCT04516746
Sputnik V	Gamaleya Research Institute of Epidemiology and Microbiology	Russia	Approved in Russia and then on 59 other countries (as of April 2021).	Two doses, 21 days apart, IM	18 Yrs and older	94 % for Alpha N/A for Beta N/A for Gamma 81 % for Delta <50 % for Omicron (2 doses) N/A for Omicron (3 doses)	AEs are mainly mild with no signs of vaccine-induced immune thrombotic thrombocytopenia.	NCT04530396
JNJ-78436735; Ad26. COV2.S	Janssen vaccines (Johnsons & Johnsons)	Netherland, USA	Validated for emergency use (FDA) on February 2021	Single dose, IM	18 Yrs and older	74 % for Alpha 64 % for Beta N/A for Gamma 71 % for Delta N/A for Omicron	The most common AEs were pain at the site of injection, headache, tiredness, muscle pain, and nausea which were usually mild or moderate. The incidence of hypersensitivity and the itchy rash was 1 in 1000 people.	NCT04505722
Convidicea (Ad5-nCoV)	CanSino Biologics	China	Approved in China on February 2021	Single dose, IM	18 Yrs and older	65.7 % efficacy in preventing moderate symptoms and 91 % efficacy in preventing severe disease	Common AEs were headache, myalgia, fatigue, shivers, fever, and arthralgia.	NCT04552366

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Table 3 (*continued*)

Name	Developer	Country of origin	Date of validity	Schedule and rout of administration	Age group	Effectiveness/ Advantages (average)	Adverse events/ Challenge	Identifier
RNA vaccines								
BNT162b2	Pfizer-BioNTech	Multinational	FDA approved on August 2021	Two doses, 21 days apart, IM	16 Yrs and older	93 % for Alpha 75 % for Beta 88 % for Gamma 87.9 % for Delta <50 % for Omicron (2 doses) 76 % for Omicron (3 doses)	The common AEs affecting more than 1 in 10 people are pain at the site of injection, tiredness, headache, muscle aches, chills, joint pain, and fever, respectively.	NCT04848584
mRNA-1273	Moderna, BARDA, NIAID	USA	FDA approved on December 2020	Two doses, 28 days apart, IM	12 Yrs and older	100 % for Alpha 96.4 % for Beta 78 % for Gamma 86.7 % for Delta <50 % for Omicron (2 doses) N/A for Omicron (3 doses)	The most common AEs were pain at the site of injection, fatigue, headache, myalgia, and arthralgia. Anaphylaxis was reported in 2.5 cases per million administered doses.	NCT04470427
Protein subunit vaccines								
NVX-CoV2373	Novavax and the Coalition for Epidemic Preparedness Innovations	USA	Validated for emergency use (WHO) on December 2021	Two doses, 21 days apart, IM	18–84	86 % for Alpha 51 % for Beta N/A for Gamma N/A for Delta N/A for Omicron	Pain at the site of injection and tenderness, as well as fatigue, headache and muscle pain were the most commonly reported AEs.	NCT04611802
EpiVacCorona	VECTOR center of Virology	Russia	The third phase of a clinical trial was launched in November 2020.	Two doses, 21–28 days apart, IM	18 Yrs and older	Preliminary data of the Phase III study showed 79 % efficacy	It was reported that no adverse reactions caused were recognized.	NCT04780035
DNA vaccines								
Zycov D	Cadila Healthcare	India	Approved by Drugs Controller General of India on August 2021	Three doses, 28 and 56 days apart for second and third doses, respectively, ID	12 Yrs and older	66.6 % efficacy against symptomatic and 100 % against moderate or severe disease	No serious AEs were observed. Even fever or fatigue is uncommon post-vaccination.	N/A
Recombinant vaccines								
ZF2001/ ZIFIVAX (ZF-UZ-VAC-2001)	Anhui Zhifei Longcom and Chinese Academy of Sciences	Uzbekistan	Approved in China on March 2021 for emergency use	Three doses over a period of 2 months	18 Yrs and older	93 % for Alpha N/A for Beta N/A for Gamma 78 % for Delta N/A for Omicron	The most common AEs were mild or moderate including pain at the site of injection, redness, and swelling.	NCT04646590

ID: Intradermal; **IM:** Intramuscular; **AE:** Adverse event; **EMA:** European Medicines Agency; **N/A:** Not available.

against severe cases of COVID-19 until the Omicron has emerged; nonetheless, studies reported that the third dose of any vaccine could considerably empower the capability of the immune system facing the Omicron variant. Therefore, an urgent need for completing the vaccination program is required to attain a healthy community. Moreover, the necessity of achieving a proper drug to fight SARS-CoV-2 seems to be neglected. Although big companies are investigating this context, there is a great area of study for future research to focus on the development of a potent drug to impede the pathogenic features of the virus and also to treat the life-threatening manifestations such as acute respiratory distress syndrome. Finally, it is worth mentioning that a novel important area of future research is to develop a universal vaccine, known as pan-vaccines or super vaccines; indeed, they can fight not only against SARS-CoV-2 variants but also against other coronaviruses that could potentially be a new pandemic condition in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Data** availability **statement

Data sharing not applicable to this article as no datasets were

generated or analyzed during the current study.

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