Annals of Research in Oncology
Vol. 6(2), 82-98, 2026

REVIEW

GENETIC AND EPIGENETIC CONTRIBUTORS TO COVID-19 OUTCOMES: A COMPREHENSIVE REVIEW

Asadoor **Amirkhani Namagerdi** [1, 2, *], Massimiliano **Quinitiliani** [3], Shendi **Shani** [3], Marcella **Barbarino** [4], Francesca **Ciani** [1, *]

[1] Department of Veterinary Medicine and Animal Production, University of Naples Federico II, Italy.
[2] Division of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester (MN), U.S.A.
[3] Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia, Pennsylvania, USA.
[4] Department of Medical Biotechnologies, University of Siena, Italy.
*Correspondence to: AmirkhaniNamagerdi.Asadoor@mayo.edu;
https://orcid.org/0000-0002-0803-4948;
ciani@unina.it;
https://orcid.org/0000-0002-9188-6761

ABSTRACT: SARS-CoV-2 infection results in a broad spectrum of COVID-19 disease, from mild or no symptoms to hospitalization and death. The degree of the adaptive immune response to SARS-CoV-2 and some pre-existing diseases has been linked to the severity of COVID-19 disease, and a recent genome-wide association study (GWAS) of the risk of critical illness found a strong genetic component. Many assume that the diversity of HLA increases the likelihood that a species can survive pandemics. The requirement for a species to have a diversified immune system to survive a pandemic is believed to be the cause of the HLA system's widespread polymorphism. Two genomic regions are associated with severe COVID-19: one region on chromosome 3, which contains six genes, and one region on chromosome 9 that determines ABO blood groups. Numerous ACE2 and TMPRSS2 polymorphisms that affect the expression of COVID-19-related receptors have been linked to risk factors and disease susceptibility. Differential cytokine production in COVID-19 patients may be linked to genetic variations in the regulatory regions of cytokine genes. The plasma miRNA expression profile at an early stage of COVID-19 is profoundly disrupted by SARS-CoV-2 infection, which makes miRNAs extremely useful as early indicators of severity and mortality. An inflammatory outburst and lymphopenia are associated with severe COVID-19, which may worsen the prognosis for cancer. Through mechanisms including cytokine storm, tissue hypoxia, poor T-cell responses, autophagy, neutrophil activation, and oxidative stress, SARS-CoV-2 infection may increase cancer susceptibility and speed cancer progression.

Doi: 10.48286/aro.2026.126

Impact statement: This review clarifies how genetic and epigenetic factors shaper COVID-19 susceptibility, severity, and outcomes, offering a framework to improve risk stratification, personalized care, and oncology-oriented research in future clinical studies.

Key words: *COVID-19; HLA; ACE2; ABO blood group; microRNAs; cancer.*

Received: Jan 25, 2026/**Accepted:** June 08, 2026

Published: June 30, 2026

INTRODUCTION

SARS-CoV-2 is a member of the same coronavirus family (Betacoronavirus) as the SARS and MERS viruses, which were responsible for two of the most devastating epidemics in recent years (1). SARS-CoV-2 infects alveolar epithelial cells through receptor-mediated endocytosis. The SARS-CoV-2 spike protein (S) binds to the ACE2 receptor, which is expressed in several organs, including the lung, heart, kid-

ney, and intestine. For the detection of viruses, the innate immune system utilizes a variety of pattern recognition receptors (PRRs). Plasmacytoid dendritic cells detect the incoming viral genomic RNA in the endosome through Toll-like receptor 7 (TLR7). Other cell types express endosomal TLR3 (variety of cells) and TLR8 (myeloid cells) that can also recognize endocytosed double-stranded RNA (dsRNA) or single-stranded RNA (ssRNA), respectively (2). Alveolar and interstitial macrophages contribute to the immune response against SARS-CoV-2 and can adopt either pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes depending on the local microenvironment (3). Macrophage Activation Syndrome may further explain the high serum levels of CRP, which are normally lacking in viral infections (4). Certain proteases, such as Transmembrane Serine Protease 2 (TMPRSS2) and Cathepsin L (CTSL), cleave to S domains to mediate membrane fusion and virus infectivity after the receptor binds, allowing the virus to enter the host cell cytosol through acid-dependent proteolytic cleavage of the S protein (3). Pro-inflammatory cytokines, Interleukin (IL)-1b and IL-18, are released by macrophages, epithelial cells, and endothelial cells when their inflammasomes are activated. These cytokines cause neutrophilia and leukopenia, which add to the pathogenic inflammation that causes the severity of COVID-19 symptoms (5). Higher blood plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), IP-10, MCP-1, macrophage inflammatory protein 1α (MIP1α), and tumor necrosis factor (TNF) were seen in patients with severe COVID-19 who needed intensive care in hospitals (6). The infected cells display viral peptides inside major histocompatibility complex (MHC) class I antigens during the course of the viral infection cycle. Viral peptides shown in class I will activate CD8+ T lymphocytes, which can lyse tissue cells infected with viruses. Professional antigen presenting cells, such as dendritic cells, macrophages, and B-lymphocytes, use MHC class II molecules to deliver viral peptides to CD4+ T cells in the early stages of infection (7). Adaptive immune responses are particularly important because SARS-CoV-2 suppresses antigen presentation by downregulating MHC class I and II molecules, which in turn suppresses T cell mediated immune responses (8). Like antibodies, SARS-CoV-2 T cells are detected within a week from the onset of symptoms (9). CD4+ and CD8+ T cells elicited by SARS-CoV-2 infection are directed against a range of antigens, including structural and non-structural proteins, and are significantly associated with milder disease (2). Chronic viral infections can result if CD8+ or CD4+ T cells have difficulty identifying the HLA class I or II antigens on the cell surface or lower expression levels of the HLA molecules (10). Environmental, demographic, and geographic factors have also been proposed as contributors to differences in COVID-19 outcomes across populations (11). Despite major advances in understanding COVID-19 pathogenesis, substantial variability remains in disease susceptibility, severity, and mortality among individuals and populations. While environmental, demographic, and clinical factors contribute to this heterogeneity, increasing evidence suggests that host genetic and epigenetic determinants also play a critical role in shaping immune responses and clinical outcomes. The following sections review the current evidence regarding the genetic and epigenetic factors associated with COVID-19 susceptibility, severity, and prognosis.

COVID-19 AND THE HLA SYSTEM

HLA biology and antigen presentation

Many assume that the diversity of HLA increases the likelihood that a species can survive pandemics. The extensive polymorphism of the HLA system is thought to result from the need for a species to be immunologically diverse to survive a pandemic. For example, HLA-B27 confers some protection against HIV and hepatitis C (12). The expression of HLA genes is known to be influenced by age, sex, and obesity, all identified as key factors in the severity of COVID-19 (13). It is generally known that several chronic illnesses and viral infections, including HIV, HBV, H1N1, and HCV, are linked to specific HLA alleles (14). After being vaccinated, people who exhibit HLA class I and/or class II molecules with low affinity for SARS-CoV-2 peptides are likely to be more susceptible to serious infections and experience weak or non-sterilizing immunity (15). The MHC, located on the short arm of chromosome 6, is the most complex genetic system in the human genome and includes the human leukocyte antigen (HLA) genes. The primary function of the HLA transmembrane proteins expressed by the classical (A, B, C, DR, DQ, and DP) HLA genes is to present tiny pathogen-derived peptides to T cells as antigens, which sets off an immune response (13) (**Figure 1A** (16)).

The peptide-binding site is formed by the α1 and α2 domains of HLA class I (A, B, and C) molecules. Cyto-

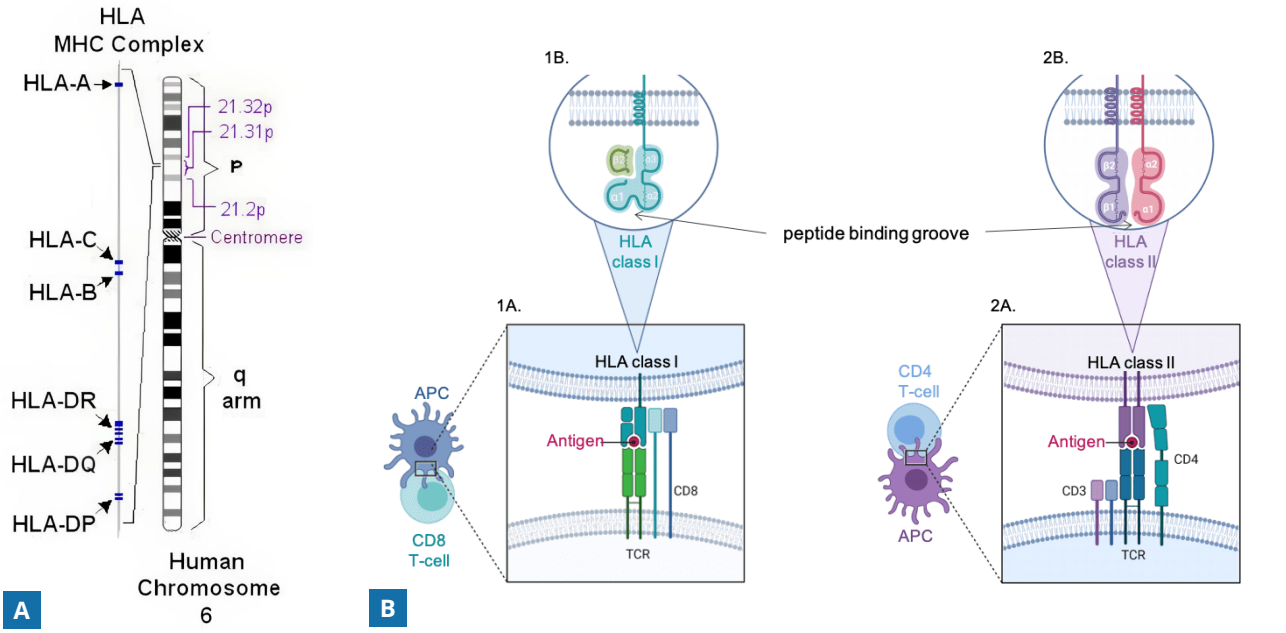

Figure 1. *HLA locus organization and main MHC functions.*

toxic CD8+ lymphocytes are presented with short peptides of 8-10 amino acids that are generated from viral proteins produced by an infected cell. Helper CD4+ cells are presented with 13-25 amino acid peptides from endocytosed antigens by the α1 and β1 domains of HLA class II (DR, DQ, DP) molecules (17). There may be four sets of digits in each HLA allele name, separated by colons. An HLA prefix is followed by a particular HLA locus, such as HLA DQ-A1. A star (HLA-DQA1*) separates the HLA locus from the first two digits. The allele group (HLA-DQA1-01) is designated by the first two digits. A specific HLA allele is indicated by the third and fourth digits (HLA-DQA1*01 02). The mutations in the allele are described by the second four digits (10). Cytotoxic CD8+ T lymphocytes identify immunogenic peptide-MHC class I complexes that are shown on nucleated cells. Antigen-presenting cells, such as dendritic cells (DCs), macrophages, or B cells, can activate CD4+ T lymphocytes by presenting immunogenic peptide–MHC class II complexes. This results in the coordination and control of effector cells (18) (**Figure 1B** (19)).

Overall, HLA class I and class II molecules play a central role in shaping antiviral immunity by regulating antigen presentation and T-cell activation, thereby potentially influencing susceptibility to and severity of SARS-CoV-2 infection.

HLA-Cw15:02, DR*03,01, and HLA-B*46:01, B*07:03, DRB1*12:02 were linked to resistance and severity of SARS-CoV, respectively, according to Wang *et al*. (20). Numerous studies have investigated whether specific HLA alleles influence susceptibility to SARS-CoV-2 infection or the clinical severity of COVID-19. However, findings have often varied across populations, reflecting differences in ethnic background, study design, and sample size. Langton *et al*., (13) using next generation sequencing (NGS), analyzed and compared the class I and class II classical HLA genes of 49 patients admitted to the hospital with severe respiratory disease following COVID-19 infection with those obtained from a group of 69 asymptomatic hospital workers who had evidence of COVID-19 exposure based on blood antibody testing. They discovered that the severe patient's allele frequency of HLA-DRB1*04:01 differed significantly from that of the staff group that did not exhibit any symptoms. There was a significantly lower frequency of the haplotype DQA1*01:01-DQB1*05:01-DRB1*01:01 in the asymptomatic group compared to the background population. The population of North-Western Europe has higher frequency of these alleles. The various statistical analyses presented in the current article indicate that while DRB1*04:01 may be protective, other DRB1*04 alleles, such as DRB1*04:02 and DRB1*04:05, may be associated with an increase in disease severity. In the current study, the alleles most strongly related to COVID-19 severity (DRB1*01:01 and DRB1*04:01) were the only alleles to show significant, positive correlations to latitude and inverse correlations to longitude (13).

These findings suggest that some HLA alleles that are more prevalent in certain European populations may be associated with a reduced risk of severe COVID-19. However, such associations should be interpreted cautiously because HLA effects are strongly influenced by population structure, environmental factors, and viral evolution (13).

Weiner *et al.* (21) examined the relationship between COVID-19 severity and HLAs in 435 participants who registered between March 2020 and August 2020 and came from Germany (n = 135), Spain (n = 133), Switzerland (n = 20), and the United States (n = 147). They tested their results by meta-analyzing data from prior genome-wide association studies (GWAS). They described a potential association of HLA-C*04:01 with a severe clinical course of COVID-19. Carriers of HLA-C*04:01 had twice the risk of intubation when infected with SARS-CoV-2. These findings are biologically plausible, as HLA-C*04:01 has fewer predicted binding sites for relevant SARS-CoV-2 peptides compared to other HLA alleles. Also, their findings suggest that HLA class I alleles have a relevant role in immune defense against SARS-CoV-2. An ecological study strongly suggests a permissive role of HLA-C*01 and B*44 towards SARS-CoV-2 infection across Italy (22). Wang *et al*. (23) reported the first host genetic study in the Chinese population by deeply sequencing and analyzing 332 COVID-19 patients categorized by varying levels of severity from the Shenzhen Third People's Hospital. They found that the patients' worst outcomes are considerably predisposed by the HLA-A*11:01, B*51:01, and C*14:02 alleles.

Collectively, these findings suggest that several HLA class I and class II alleles may contribute to increased susceptibility or disease severity. However, many associations have been reported in specific populations and require validation in larger multiethnic cohorts.

Protective and Risk HLA Variants

Several HLA alleles have been proposed as protective or risk factors for COVID-19, largely depending on their ability to efficiently present SARS-CoV-2-derived peptides and promote effective T-cell responses.

Nguyen *et al*. (24) performed a comprehensive *in silico* analysis of viral peptide MHC class I binding affinity across 145 HLA-A, -B, and -C genotypes for all SARS-CoV-2 peptides. A variety of HLA alleles were used to successfully sample and represent the SARS-CoV-2 proteome. They discovered that the allele with the fewest predicted binding peptides for SARS-CoV-2 was HLA B*46:01, indicating that people with this allele would be more susceptible to COVID-19. Conversely, they found that HLA-B*15:03 showed the greatest capacity to present highly conserved SARS-CoV-2 peptides that are shared among common human coronaviruses, suggesting that it could enable cross-protective T-cell-based immunity. Poulton *et al*. (25) analyzed data from 80 patients who tested positive for SARS-CoV-2 RNA who had previously been HLA typed to support transplantation. They reported a significant HLA association with HLA DQB1*06 and infection. In Italy, only the HLA-C*01 and HLA-B*44 alleles, which are present with a higher frequency in the northern regions of Italy, remained positively associated with COVID-19 (10). Correale *et al*. (22) suggested that healthy individuals carrying HLA-B*44 and/or C*01, and to a lesser extent, HLA-A*25, HLA-B*08 alleles may be more susceptible to SARS-CoV-2 infection. Correale *et al*. (26) revealed later that the direct correlation of HLA-C*01, and HLA-B*44 gene expression and COVID-19 risk was completely lost just after the first pandemic wave in Italy. On the contrary, the expression of the HLA-B*49 allele in specific populations emerged as inversely correlated to the risk of COVID-19 and could be considered as a protective factor.

The frequency of the two most prevalent HLA haplotypes in the Italian population varies significantly between the northern, central, and southern regions, according to a study conducted in Italy using a geographic epidemiological analysis, with HLA-A*01:01 g-B*08:01 g-C*07:01 g DRB1*03:01 g (the most frequent haplotype nationwide) showing a decreasing frequency gradient, and HLA-A* 02:01 g-B*18:01 g-C*07:01 g-DRB1*11:04 g (the second most frequent haplotype) an increasing frequency gradient from North to South (10). A study conducted with 82 Chinese patients found that the HLA-C07:29 and HLA-B15:27 alleles were more frequently detected in the COVID-19 group than in the control population (27). Novelli *et al*. (28) analyzed the HLA allele frequency distribution in a group of 99 Italian patients affected by a severe or extremely severe form of COVID-19. After the application of Bonferroni's correction for multiple tests, a significant association was found for HLA-DRB1*15:01, -DQB1*06:02, and -B*27:07, after comparing the results to a reference group of 1017 Italian individuals, previously typed in their laboratory. Yung *et al*. (29) investigated the HLA-B genotypes in 190 unrelated Chinese patients with confirmed COVID-19, identified a significant positive association between the B22 serotype and SARS-CoV-2

infection. According to the study by Barquera *et al*. (30), the HLA class II alleles DRB1*01:01, DRB1*10:01, DRB1*11:02, and DRB1*13:01 present more SARS-CoV-2 peptides, while the HLA-DRB1*03:02, DRB1*03:03, and DQA1*01:02/DQB1*06 were found to be the worst presenters of SARS-CoV-2-derived peptides. HLA-A*:01:01-g-B*08:01 g C*07:01g-DRB1*03:01g and HLA-A*02.01g-B*18.01g-C*07.01g-DRB1*11.04g, the two most prevalent HLA haplotypes in the Italian population, had a regional distribution that overlapped that of COVID-19 and demonstrated a significant positive (suggestive of susceptibility) and negative (suggestive of protection) correlation with both COVID-19 incidence and mortality, according to Pisanti *et al*. (31). Littera *et al*. (32) showed that the extended haplotype HLA-*02:05, B*58:01, C*07:01, DRB1*03:01 has a protective effect against SARS-CoV-2 infection in the Sardinian population. Genetic factors that resulted in having a negative influence on the disease course were presence of the HLA-DRB1*08:01 allele and G6PDH deficiency, but not the beta thalassemic trait. Shkurnikov *et al*. (33) identified HLA-A, HLA-B, and HLA-C genotypes of n = 111 deceased patients with COVID-19 (Moscow, Russia) and n = 428 volunteers with NGS. Three HLA-A alleles were highly overrepresented in these groups: HLA A*02:01 and HLAA* 03:01 were tightly associated with low risk while HLAA* 01:01 contributed to the high-risk group. Yu *et al*. (34) verified that HLAB*15:27 and HLA-DRB1*04:06 were linked to COVID-19 susceptibility in China by comparing against many subpopulation groupings as a control. Weak binding affinities toward viral proteins were expected for both alleles. Wang *et al*. (35) used NGS to genotype 82 COVID-19 patients for the HLA -A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1 loci. They demonstrated that, when the revised P-value was taken into account, only HLA-C*07:29 and B*15:27 were significant. According to Romero Lopez *et al*. (36), there is a positive association with HLA A*03:02 and a negative correlation with the cumulative incidence per million people for both A*31:01 and HLA-A*02:03 frequencies. The authors concluded that, with this result, HLA A*02:03 and A*31:01 were associated with better immunity against the infection and that HLA A*03:02 can be considered as a risk factor. HLA-A*02:02, HLA-B*15:03, HLA-C*12:03, HLAA*02:03, and HLA-A*31:01 were identified as protective alleles in a number of studies, while HLA-A*25:01, HLA-B*46:01, HLA-C*01:02, HLA-A*24:02, HLADPA1*02:02, HLA DPB1*05:01, HLA-DQB1*03:01, and HLA-DRB4*01:01 were identified as risk alleles (37).

Furthermore, population-specific studies continued to identify additional alleles associated with either susceptibility or protection. Farahani *et al*. (38) reported significant associations between severe COVID-19 and HLA-B38, HLA-A68, HLA-A24, and HLA-DRB101 in an Iranian cohort. Augusto *et al*. (46) found that HLA-B15:01 was significantly associated with asymptomatic SARS-CoV-2 infection, while Letovsky *et al*. (39) identified several alleles associated with either increased (HLA-A68:01, HLA-C01:02, HLA-DQB103:02, HLA-DRB108:02 and HLA-DRB114:06) or decreased (HLA-DRB108:03, HLA-C05:01 and HLA-B*38:01) likelihood of SARS-CoV-2 infection. The list of potentially relevant HLA variants continues to expand as additional studies are performed.

HLA and immune dysregulation

Beyond genetic susceptibility, HLA-related mechanisms may also contribute to immune dysregulation and hyperinflammatory responses during COVID-19. The CDC issued a notice on May 14, 2020, alerting medical professionals to the multisystem inflammatory syndrome (MIS-C) linked to COVID-19. MIS-C presents clinical features resembling Kawasaki disease (KD). The HLA region, particularly HLA-B and HLA-C variants, has been proposed among the genetic factors potentially involved in susceptibility to KD-like manifestations.

Other studies explored the relationship between HLA polymorphisms and markers of disease severity. Elevated serum ferritin levels, which are associated with hyperinflammation and poor clinical outcomes in COVID-19, were reported more frequently in patients carrying specific HLA variants such as HLA-C*03.

Spinetti *et al*. (40) compared ICU patients with severe COVID-19 to noncritically ill hospitalized COVID-19 patients and showed reduced mHLA-DR expression on circulating CD14+ monocytes at ICU admission, indicating a dysfunctional immune response and impaired antigen-presenting capacity during severe disease.

The immune cell, cytokine, and HLA-G (including receptor) levels of a COVID-19 patient during his hospital stay were documented in a case study by Zhang *et al*.(41). In general, HLA-G levels rose following viral clearance and decreased during the active replication phase, suggesting a possible relationship with cytokine-mediated immune regulation.

A recent study documented evidence of SARS-CoV-2 antigens circulating in the blood up to 14 months after infection and reported an association between

Table 1. *Summary of selected studies investigating the association between HLA polymorphisms and COVID-19 susceptibility, severity, immune response, and clinical outcomes.*

CATEGORY	REPRESENTATIVE HLA ALLELE(S)	REPORTED ASSOCIATION	KEY REFERENCE(S)
Protective alleles	HLA-B*15:03	Enhanced presentation of conserved SARS-CoV-2 peptides; potential cross-reactive immunity	Nguyen *et al*. (24)
Protective alleles	HLA-B*15:01	Associated with asymptomatic SARS-CoV-2 infection	Augusto *et al*. (46)
Protective alleles	HLA-DRB1*04:01	Increased frequency among asymptomatic individuals	Langton *et al*. (13)
Risk alleles	HLA-C*04:01	Severe disease and increased risk of intubation	Weiner *et al*. (21)
Risk alleles	HLA-B*46:01	Low predicted peptide-binding capacity; increased susceptibility	Nguyen *et al*. (24)
Risk alleles	HLA-A*11:01, HLA-B*51:01, HLA-C*14:02	Associated with worse clinical outcomes	Wang *et al*. (23)
Risk alleles	HLA-B*15:27, HLA-DRB1*04:06	Associated with susceptibility in Chinese populations	Yu *et al*. (34)
Population-specific associations	HLA-B*38, HLA-A*68, HLA-A*24, HLA-DRB1*01	Associated with severe COVID-19 in Iranian patients	Farahani *et al*. (38)
Antigen presentation efficiency	DRB1*01:01, DRB1*10:01, DRB1*11:02, DRB1*13:01	Efficient presentation of SARS-CoV-2 peptides	Barquera *et al*. (30)
Antigen presentation efficiency	DRB1*03:02, DRB1*03:03, DQA1*01:02/DQB1*06	Poor presentation of SARS-CoV-2 peptides	Barquera *et al*. (30)
Immune dysregulation	HLA-C*03; reduced mHLA-DR expression	Hyperinflammation and impaired antigen presentation	Spinetti *et al*. (40)
Vaccine-related outcomes	HLA-A*03:01	Increased reactogenicity following Pfizer-BioNTech vaccination	Bolze *et al*. (43)

antigen positivity and post-acute sequelae of COVID-19 (PASC) involving several symptom domains (42) (**Table 1**).

COVID-19, CYTOKINES, ABO, ACE2 AND TMPRSS2 GENES

Genetic susceptibility loci identified by GWAS

SARS-CoV-2 infection results in a broad spectrum of COVID-19 disease, from mild or no symptoms to hospitalization and death. A recent genome-wide association study (GWAS) of the risk of critical illness revealed a significant genetic component (44). Genetic loci from COVID-19 GWAS in peer-reviewed publications to date represent a mixture of risk variants for SARS-CoV-2 infection (blue upward arrows) and severe COVID-19 with complications (red downward arrows). More loci are anticipated to appear as sample sizes increase. N/A indicates that the MHC on chromosome 6 was omitted from the reporting in this article due to high heterogeneity of putative associations from the individual studies in the meta-analysis (**Figure 2**) (45).

The genes identified through physical association with accessible COVID-19 variants have known roles in viral replication, interferon response, and inflammation (46). Host genetic predisposition to COVID-19 is now increasingly recognized, and whole-genome and candidate gene association studies regarding COVID-19 susceptibility have been performed. Several common and rare variants in genes related to inflammation or immune responses have been identified (47). A previous study identified two genomic regions that are associated with severe COVID-19: one region on chromosome 3, which contains six genes, and one region on chromosome 9 that determines ABO blood groups. The sole region on chromosome 3 that is strongly linked to severe COVID-19 at the genome-wide level, according to a dataset recently made public by the COVID-19 Host Genetics Initiative (48). The genes ACE2, IL6, TMPRSS2, and TNF are often highlighted. FURIN, CXCL10, OAS1, OAS2,

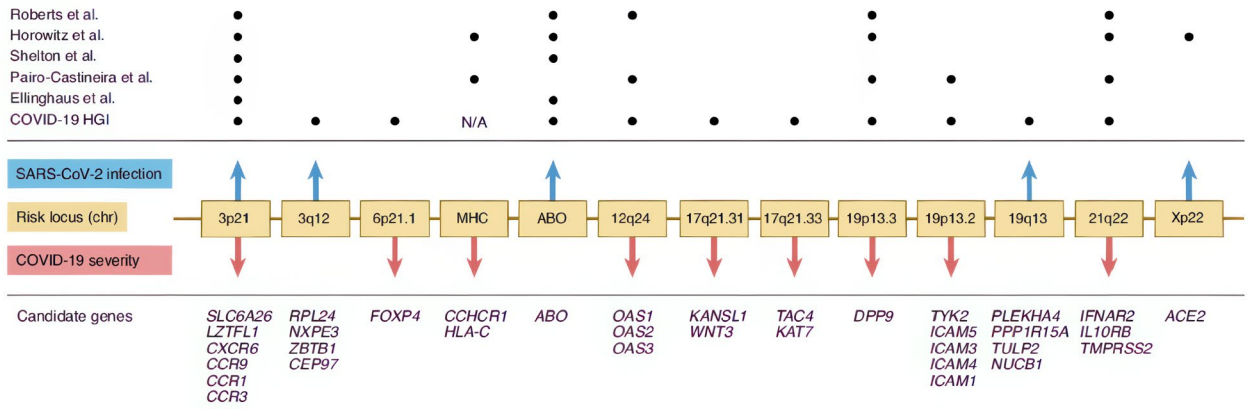

Figure 2. *Genetic loci from COVID-19 GWAS in peer-reviewed publications to date.*

OAS3, and ISG15 are emerging genes for COVID-19 (49). Using the Infinium Methylation EPIC array13, Corley *et al*. (50) examined genome-wide DNAm profiles in peripheral blood mononuclear cells from nine patients with severe COVID-19. Droplet digital PCR revealed detectable plasma SARS-CoV-2 RNA in patients with severe COVID-19. The idea that SARS-CoV-2 suppresses host IFN responses was supported by their finding of notable hypermethylation in the regulatory areas of genes implicated in the type I IFN response linked to severe COVID-19, including first-line antiviral defense genes like IFITM1 and ISG20. The SARS-CoV-2 viral host receptor ACE2 gene was also linked to abnormal levels of DNA linked to severe COVID-19, which supports research that suggests ACE2 is up-regulated during SARS-CoV-2 infection. On the other hand, they found that the cytokine genes linked to severe COVID-19 and the regulatory regions of genes related to immunological inflammation, such as the antiviral MX1 genes and the NLRP3 inflammasome, had substantial hypomethylation. Wei *et al*. (51) extracted biological concepts from the titles and abstracts of the gathered research publications using PubTator, a deep learning-based entity extraction tool created by the National Library of Medicine (NLM). They linked COVID-19 disease to the top ten genes, which include ACE2, TMPRSS2, IL6, CRP, TNF, CD4, ACE, CD8A, IFNG, and FURIN. Immune cells from patients with severe *versus* moderate COVID-19 disease showed differential expression of several of these genes (PAXBP1, IFNAR2, OAS1, OAS3, TNFAIP8L1, GART). The scientists found that the gene locus in TMEM189 (PEDS1, HGNC:16735)-UBE2V1 (HGNC:12494), which is implicated in the IL-1 signaling pathway, was associated with the severity of COVID-19. An investigation found inborn errors of Toll-like receptor 3 (TLR3, HGNC:11849) – and interferon regulatory factor 7 (IRF7, HGNC:6122) – dependent type I IFN immunity related to life-threatening COVID-19 pneumonia (52).

Compared to COVID-19 patients with powerful interferon responses, many SARS-CoV-2-infected people have blunted and/or delayed interferon responses and suffer from more severe illness (46). SARS-CoV-2 dsRNA genomes are sensed by the RIG-I/MDA5 and RNAseL pathways (53). One of the earliest known IFN-stimulated gene (ISG) antiviral pathways was the OAS/RNaseL pathway. Three catalytically active OAS genes (OAS1-3) and one inactive gene (OASL) have been identified in humans (54). The chr12q24.13 locus encoding OAS1-OAS3 antiviral proteins has been associated with COVID-19 susceptibility and severity (55). Banday *et al*. (55) analyzed patients of European (n = 2,249) and African (n = 835) ancestries with hospitalized *versus* non-hospitalized COVID-19; the risk of hospitalized disease was associated with a common OAS1 haplotype. They concluded that decreased OAS1 expression due to a common haplotype contributes to COVID-19 severity.

Cytokine genes and inflammatory responses

Genetic variation in cytokine-related genes has been proposed as an important determinant of the inflammatory response to SARS-CoV-2 infection and may contribute to disease severity.

Differential cytokine production in COVID-19 patients may be linked to genetic variations in the regulatory regions of cytokine genes. Cytokines and chemokines SNPs are associated with the severity of COVID-19 (53).

Single-nucleotide polymorphisms (SNPs) of interferons, TNF, IL1, IL4, IL6, IL7, IL10, and IL17 are among the gene variants that predispose patients to the severe form of COVID-19, also known as SARS-COV-2 (53). The COVID-19 virus causes cytokine storms, which are excessive inflammatory reactions linked to the release of proinflammatory cytokines like interleukin-6 (IL-6), IL-1β, IL-10, IL-18, IL-4, IL-33, interferon (IFN)-γ, and tumor necrosis factor alpha (TNFα) (54). In severe COVID-19 patients, an increase in IL-6 levels has been observed and is related to the disease's poor prognosis. Several gene variants in IL6 (HGNC:6018) with differential cytokine expression and with different disorders have been reported (5). The cis-regulatory landscapes of human immune cell types with established roles in disease severity were linked to putatively functional COVID-19 risk variants by Pahl *et al*. (44), who used high-resolution chromatin conformation capture to map these disease associated elements to their effector genes to obtain insight into how human genetic variation attenuates or exacerbates disease after SARS-CoV-2 infection. 16 genes related to inflammation, the interferon response, and viral replication were implicated by this functional genomic approach.

Various cytokines and VEGF have higher serum levels in COVID-19 patients compared to healthy subjects, suggesting that cytokines and their receptors play a role in disease development.

Collectively, these findings support a central role for cytokine-related genetic variation in modulating the inflammatory response and clinical severity of COVID-19.

ABO blood group and COVID-19 susceptibility

Several genome-wide association studies have identified the ABO blood group locus as a potential genetic factor influencing susceptibility to SARS-CoV-2 infection and COVID-19 severity. Ellinghaus *et al*. (56) conducted a GWAS involving 1980 patients with COVID-19 and severe disease (defined as respiratory failure) at seven hospitals in the Italian and Spanish epicenters of the SARS-CoV-2 pandemic in Europe. They found cross-replicating relationships between rs657152 at locus 9q34.2 and rs11385942 at locus 3p21.31. The association signal included the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1 at locus 3p21.31.

Shelton *et al*. (57) identified several non-genetic conditions as risk factors for hospitalization, and the genetic variants LZTFL1 rs13078854 and ABO rs9411378 were associated with COVID-19 outcome severity and diagnosis, respectively. Adjacent genes in the 3p21.31 locus, such as SLC6A20, CCR9, FYCO1, CXCR6, and XCR1, may be responsible for the association. The ABO blood group locus and the association signal at locus 9q34.2 were in co-occurrence. Pereira *et al*. (58) identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system. While blood type A is commonly referred to as a risk factor, blood type O is primarily linked to decreased rates of SARS-CoV-2 infection. Blood type A is most closely linked to the severity and mortality of COVID-19, although findings on the likelihood of severe consequences are more mixed. In contrast, most studies characterize blood type O as protective against disease progression. Blood antigens have been proposed as contributing to intracellular absorption, signal transduction, or adhesion, and blood groups may act as receptors and/or co-receptors for bacteria, viruses, and parasites (59).

Overall, available evidence suggests a role for the ABO blood group system in susceptibility to SARS-CoV-2 infection and clinical outcomes, although the biological mechanisms underlying these associations remain incompletely understood.

ACE2 and TMPRSS2 variants

Most African populations could be protected to some degree because they lack some genetic susceptibility risk factors or have low level expression of allelic variants, such as ACE2 and TMPRSS2, that are thought to be involved in increased infection risk or disease severity (60). Numerous ACE2 and TMPRSS2 aberrations that impact the expression of COVID-19-related receptors have been linked to risk factors and disease susceptibility. Besides its role in SARS-CoV-2 infection, ACE2 acts as a negative regulator of the renin-angiotensin system and a facilitator of amino acid transport (5). The ACE2 system is a critical protective pathway against heart failure with reduced and preserved ejection fraction, including myocardial infarction and hypertension, lung disease, and diabetes mellitus (61). Unfortunately, the function of ACE2 is lost following the binding of SARS-CoV-2. According to a recent study, South Asian and East Asian groups have genetic markers of the highest ACE2 expression, whereas Africans have the lowest levels of ACE2 expression (62). Africans showed a genetic tendency for the lowest levels of TMPRSS2 (HGNC:11876) expression, while East Asians showed the greatest levels (5). While two mutations (p. Leu-

351Val and p. Pro389His) were expected to interfere with SARS-CoV-2 spike protein binding, three common missense alterations in ACE2 (p. Asn720Asp, p. Lys26Arg, and p. Gly211Arg) have been predicted to interfere with protein structure and stabilization (60). These studies provide information on the genetic overlap between immunological factors and COVID-19, indicating possible avenues for further investigation and clinical testing (63).

COVID-19 AND MICRORNAS

Biological role of miRNAs in SARS-CoV-2 infection

COVID-19 and MicroRNAs Noncoding RNAs (ncRNAs) do not encode a protein but rather modulate chromatin regulation and gene expression. These comprise piwi-interacting RNAs (piRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), small interfering RNAs (siRNAs), ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), and long noncoding RNAs (lncRNAs) (64). Human miRNAs can interact with other single-stranded RNAs, including viral genomes, in addition to post-transcriptionally regulating mRNAs (65). SARS-CoV-2 infection deeply disturbs the plasma miRNA expression profile from an early stage of COVID-19, making miRNAs highly valuable as early predictors of severity and mortality (66). miRNAs are proposed as promising biomarkers, new targets, and tools in therapeutic approaches, but also as prognostic factors in SARS-CoV-2 infection (**Figure 3**) (62).

Given their ability to regulate both viral and host gene expression, miRNAs have emerged as important modulators of SARS-CoV-2 infection and disease progression.

Several studies have investigated the role of miRNAs in regulating key host factors involved in SARS-CoV-2 entry and antiviral immune responses, including ACE2, TMPRSS2, and interferon-related pathways. In their respective 3'-UTRs, Pierce *et al*. (67) found 43 miRNAs targeting ACE2, 107 for TMPRSS2, 20 for IFN-α, 29 for IFN-β, and 47 for IFN-γ using five miRNA computational methods (miRWalk, MicroT4, miRMap, RNAhybrid, and TargetScan). There were 7 predicted lung-enriched miRNAs (the top 5 miRNAs were miR-141-3p, miR-4270, miR-331-3p, miR-200a 3p, and miR-218-5p) that targeted the ACE2 mRNA 30-UTR and 25 predicted lung-enriched miRNAs (the top 5 miRNAs were miR-4763-3p, let-7d-5p, miR-

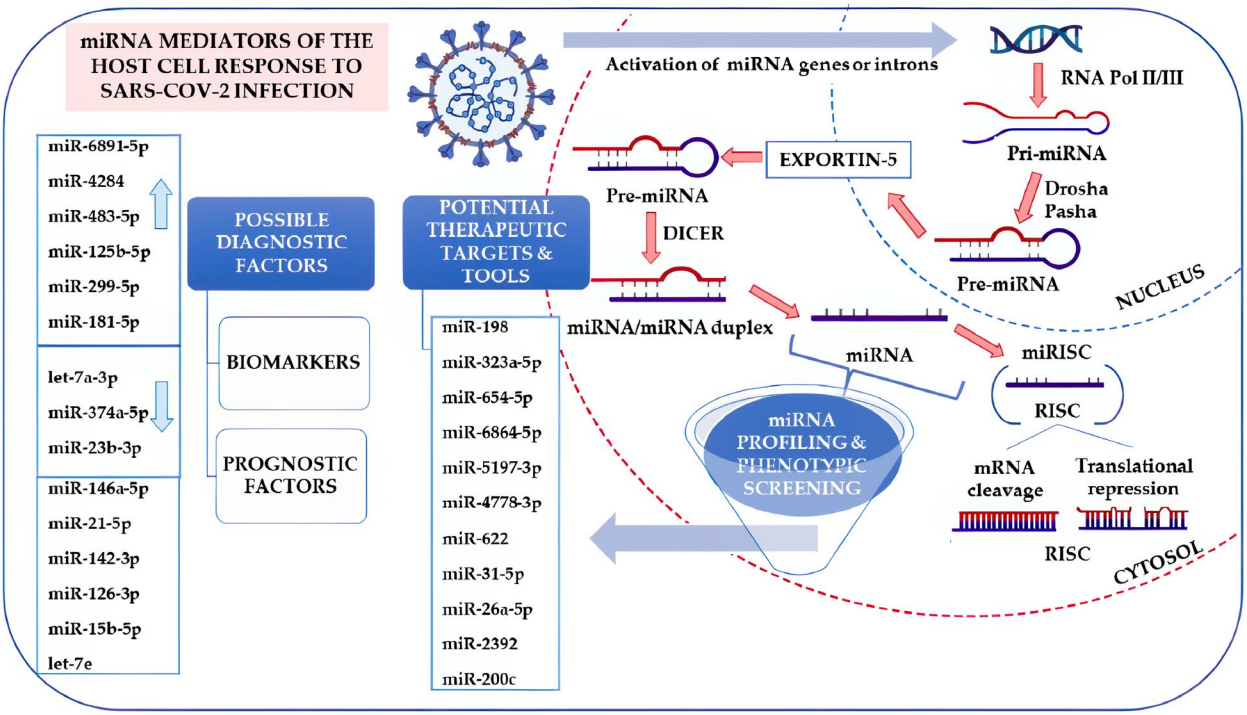

Figure 3. *Proposed roles of microRNAs in SARS-CoV-2 infection and COVID-19 pathogenesis. Host and viral miRNAs may regulate key pathways involved in viral entry (ACE2 and TMPRSS2), interferon signaling, cytokine production, immune-cell activation, and inflammatory responses. Altered miRNA expression profiles have also been associated with disease severity, prognosis, and potential therapeutic targets, highlighting their relevance as biomarkers and modulators of host-virus interactions. miRNAs Regulating Viral Entry and Host Responses.*

4530, let-7e-5p, and miR-181a 5p) that targeted the TMPRSS2 mRNA 30-UTR. The 30-UTRs of IFN-α and IFN-β mRNAs contained two (miR-203a-3p and miR-361-5p) and one (miR-145-5p) predicted binding sites, respectively, for lung-enriched miRNAs, whereas IFN-γ harbored nine (miR-128-3p, miR-143-3p, miR-181b-5p, miR-181d-5p, miR-24-3p, miR-26a-5p, miR-26b-5p, miR-340-5p, and miR-664b 3p). Interestingly, in human lung tissue, the only miRNAs that share both target mRNAs (TMPRSS2 and IFN-γ) are miR-181b-5p, miR-181d-5p, and miR-664b-3p. Using single-cell RNA-sequencing-based data, two miRNAs, hsa-miR-302c-5p and hsa-miR-16-5p, were identified to be potential virus-targeting miRNAs across multiple cell types from bronchoalveolar lavage fluid samples. The results showed that these miRNA/target pairs are involved in the ACE2 receptor network, regulating pro-inflammatory cytokines and immune cell maturation and differentiation (65).

miRNAs and immune dysregulation

Beyond viral entry mechanisms, miRNAs may contribute to immune dysregulation and inflammatory responses that characterize severe COVID-19. Increases in plasma cytokine storms, including TNF-α, IL-1β, IL-6, miR-146a, miR-146b, and IL-8, are associated with miR-125b, miR-138, miR-199a, and miR-21 in acute respiratory distress syndrome and COPD (68). Recent studies include the role of ID02510.3p miRNA, ID00448.3pmiRNA, miRNA 3154, miRNA 7114-5p, miRNA 5197-3p, ID02750.3p miRNA and ID01851.5p-miRNA, miR-5197-3p, miR-17-5p and miR-20b-5p in control COVID-19 pathogenesis by binding to the genome of SARS-CoV-2 (69). These findings suggest that miRNA-mediated regulation may influence both cytokine production and host antiviral responses during SARS-CoV-2 infection.

miRNAs as diagnostic and prognostic biomarkers

Nersisyan *et al*. (70) introduced six miRNAs, including miR-21-3p, miR-195-5p, miR-16-5p, miR-3065-5p, miR-424 5p, and miR-421, that potentially regulated all human coronaviruses through direct binding to the viral genome. The high predictive accuracy reported in these studies highlights the potential utility of miRNA signatures for disease detection and risk stratification. The miR-21-3p binds to the human coronavirus genome the best. Supervised machine learning analysis revealed that a three-miRNA signature (miR-423-5p, miR-23a-3p, and miR-195-5p) independently classified COVID-19 cases with an accuracy of 99.9% (71). The three miRNA signature identified SARS-CoV-2 infection in a ferret COVID-19 model with 99.7% accuracy and differentiated SARS-CoV-2 infection from influenza A (H1N1) infection and healthy controls with 95% accuracy (71). The inflammatory miR-31-5p was the most significantly increased of the 55 miRNAs that were changed in COVID-19 patients in the early stages of the illness (71). In addition to their diagnostic value, miRNAs may represent novel therapeutic targets because of their ability to modulate both viral replication and host immune pathways. Pawlica *et al*. (72) discovered a viral miRNA-like small RNA, named CoV2-miR-O7a (for SARS-CoV-2 miRNA-like ORF7a-derived small RNA). Its abundance ranges from low to moderate compared to host miRNAs, and it is associated with Argonaute proteins, core components of the RNA interference pathway. They discovered potential targets for CoV2-miR 7a, such as the interferon signaling-related Basic Leucine Zipper ATF-Like Transcription Factor 2 (BATF2). According to Li *et al*. (73), when comparing human COVID-19 patients to healthy controls, 35 miRNAs were elevated and 38 miRNAs were downregulated. The following is a list of the top 10 genes: hsa-miR-16-2-3P, hsa-miR-5695, hsa-miR-10399-3P, hsa-miR-6501-5P, hsa miR-361-3P, hsa-miR-361-3p, hsa-miR-4659a-3p, hsa-miR-142-5p, hsa-miR-4685-3p, hsa-miR 454-5p, and hsa-miR-30c-5p. Hsa-miR-183-5p, Hsa-miR-627-5p, Hsa-miR-941, Hsa-miR-21-5p, Hsa-miR-20a-5p, Hsa-miR-146b-5p, Hsa-miR-454-3p, Hsa-miR-18a-5p, Hsa-miR-340-5p, and Hsa-miR-17-5p were the ten genes that had the biggest decrease. Notably, miR-627-5p was the most downregulated miRNA, changing by 2.3 times in comparison to the controls, whereas miR 16-2-3p was the most upregulated miRNA, changing by 1.6 times. Four miRNAs (miR-127-3p, miR-21-5p, miR-285p, and miR-34a-5p) were found by Salem *et al*. (74) to regulate the TGF-beta signaling system, interleukin-4 and 13 signaling, IL-17 signaling pathway, and B cell receptors (BCRs) signaling pathway. They have been suggested as possible biomarkers for a variety of COVID-19 disease characteristics, including susceptibility, severity, course of complications, prognosis, and potential treatments (75). Therefore, a profile of the circulating miRNA at various phases of COVID-19 disease may offer valuable clinical information and point the way for future treatments (76).

Therapeutic potential and future perspectives

In addition to their diagnostic value, miRNAs may represent novel therapeutic targets because of

Table 2. *Representative microRNAs associated with SARS-CoV-2 infection, their major targets, level of evidence, and potential clinical relevance.*

miRNA	MAIN TARGET(S)	EVIDENCE TYPE	PROPOSED CLINICAL RELEVANCE
miR-141-3p	ACE2	Computational	Potential regulation of viral entry
miR-181b-5p	TMPRSS2, IFN-γ	Computational	Modulation of antiviral responses
miR-181d-5p	TMPRSS2, IFN-γ	Computational	Immune regulation
hsa-miR-302c-5p	ACE2 network	Computational/Transcriptomic	Potential antiviral activity
hsa-miR-16-5p	ACE2 network	Computational/Transcriptomic	Regulation of immune-cell maturation
miR-21-3p	Coronavirus genomes	Computational	Potential broad antiviral activity
miR-423-5p, miR-23a-3p, miR-195-5p	Biomarker signature	Experimental + Machine Learning	Diagnostic/prognostic biomarker
CoV-2-miR-O7a	BATF2 pathway	Experimental	Viral immune-evasion mechanism

their ability to modulate both viral replication and host immune pathways. Pawlica *et al*. (72) discovered a viral miRNA-like small RNA, named CoV2-miR-O7a (for SARS-CoV-2 miRNA-like ORF7a-derived small RNA), which associates with Argonaute proteins and may regulate interferon-related pathways through targets such as BATF2. Furthermore, several host miRNAs have been implicated in regulating inflammatory responses, cytokine production, and viral-host interactions, suggesting potential applications in both therapeutic intervention and disease monitoring.

Overall, current evidence supports a multifaceted role of miRNAs in COVID-19, ranging from the regulation of viral entry and immune responses to their potential use as biomarkers and therapeutic targets. However, many findings remain based on computational predictions or small cohorts and require validation in larger and more diverse populations. A summary of representative miRNAs, their principal targets, level of evidence, and potential clinical relevance is presented in **Table 2**.

COVID-19 AND CANCER

Impact of the COVID-19 pandemic on cancer care

Regular health service delivery was seriously hampered during the COVID-19 pandemic. The potential of COVID-19 infection for patients necessitated careful assessment, and resources were reallocated to COVID-19 services. There was a halt to cancer screening programs, fewer medical professionals were available, and some patients had trouble getting the best care in a timely way (77).

These disruptions raised concerns regarding delayed diagnosis, treatment interruptions, and potentially worse outcomes among patients with cancer.

Shared biological mechanisms between COVID-19 and cancer

Beyond healthcare-related consequences, several biological pathways appear to be shared between COVID-19 and cancer progression.

An inflammatory outburst and lymphopenia are associated with severe COVID-19, which may worsen the prognosis for cancer (78). Zong *et al*. (79) described the four main signaling pathways at the junction of COVID-19 and cancer: cytokine, type I interferon (IFN-I), androgen receptor (AR), and immunological checkpoint signaling. They also emphasized the clinical and molecular parallels between COVID-19 and cancer. Depletion of B cells, natural killer cells, and CD8+ and CD4+ T cells is linked to COVID-19 progression. COVID-19 susceptibility is increased by the expression of receptors such as transmembrane protease serine 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) (80). Through mechanisms including cytokine storm, tissue hypoxia, poor T-cell responses, autophagy, neutrophil activation, and oxidative stress, SARS-CoV-2 infection may increase cancer susceptibility and speed cancer progression (81).

SARS-CoV-2 infection and cancer-related molecular pathways

According to Serwaa *et al*. (82), SARS-CoV-2 infection affects different cancer cellular phenotypes as well as the expression of molecular cancer markers and proinflammatory cytokines. They demonstrated how SARS-CoV-2 infection affects some crucial cellular processes related to prostate and colorectal cancer cell proliferation, death, and migration. The primary receptor of the SARS-CoV-2 virus, angiotensin-converting enzyme 2 (ACE2), is extensively expressed on the cell surface of pancreatic cells, including exocrine glands and pancreatic islets, making these cells a prime target for the virus (1). Moreover, CREB1, PTEN, SMAD3, and CASP3 have been reported to be differentially expressed in pancreatic adenocarcinoma according to TCGA database analyses. Although current evidence does not support a direct causal relationship between SARS-CoV-2 infection and pancreatic carcinogenesis, these observations suggest potential overlap between molecular pathways involved in cancer biology and those affected during SARS-CoV-2 infection (83).

Vaccination, immunotherapy, and clinical outcomes

Grippin *et al*. (84) demonstrated that mRNA vaccines targeting SARS-CoV-2 also make tumors more susceptible to immune checkpoint inhibitors (ICIs). For many cancer patients, ICIs prolong survival. In several large retrospective populations, receiving SARS-CoV-2 mRNA vaccinations within 100 days of starting ICI is linked to considerably enhanced median and three-year overall survival.

These findings highlight the potential interaction between vaccination-induced immune activation and the efficacy of cancer immunotherapies, warranting further investigation in prospective studies.

SARS-CoV-2 infection and cancer-related molecular pathways

Recent evidence has also highlighted the potential involvement of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway at the intersection between COVID-19 and cancer biology. Activation of cGAS-STING signaling during the early stages of SARS-CoV-2 infection may promote antiviral immunity through induction of type I interferon responses. Conversely, persistent activation of this pathway may contribute to excessive inflammation and tissue damage. Interestingly, cGAS-STING signaling has also emerged as a promising therapeutic target in oncology because of its ability to enhance antitumor immune responses and improve the efficacy of immunotherapies (85). These observations suggest that molecular pathways involved in host antiviral defense may also influence cancer progression and therapeutic responsiveness, highlighting potential areas for future translational research.

CONCLUSIONS

Every disease has a genetic component, to varying degrees. Variations in our DNA and differences in how that DNA functions, alongside the environment, contribute to disease processes (86). By identifying the causal processes that explain why some people are more seriously affected by the disease after contracting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, human genetics can help understand the biology and epidemiology of coronavirus disease 2019 (COVID-19) (78).

Although advanced age, male sex, and several comorbidities are recognized risk factors for severe COVID-19, these variables alone do not fully explain the marked heterogeneity observed in clinical outcomes. A growing body of evidence indicates that host genetic factors contribute to individual susceptibility, disease severity, immune responses, and clinical prognosis (45).

The studies reviewed here highlight the potential role of multiple genetic determinants, including HLA polymorphisms, cytokine-related genes, ABO blood groups, ACE2 and TMPRSS2 variants, and microRNA-mediated regulatory pathways. These genetic factors may influence viral entry, antigen presentation, inflammatory responses, immune regulation, and vaccine-related outcomes. In addition, emerging evidence suggests complex interactions between COVID-19 and cancer-related biological pathways.

Despite considerable progress, many reported genetic associations remain population-specific and have not been consistently replicated across independent cohorts. Differences in ethnicity, study design, sample size, viral variants, and environmental factors may partly explain these discrepancies. Therefore, larger multiethnic studies, functional investigations, and integrative genomic approaches are needed to clarify the biological significance of these findings and their potential clinical applications. A better understanding of host genetic variability may contribute to improved risk stratification, personalized preventive strategies, and the development of targeted therapeutic approaches for current and future viral outbreaks.

COMPLIANCE WITH ETHICAL STANDARDS

Funding

The University of Naples Federico II financed the Agreement between Temple University and University of Naples Federico II, with Resolution no. 90/2023.

Conflicts of interest

The authors declare no competing interests.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Authors' contributions

AAN, MB, FC: conceptualization. AAN, MQ, SS, MB, FC: investigation, data curation, writing – original draft. AAN, FC: writing – review & editing.

Publications ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

The writing and contents of the article are entirely original and were developed entirely by the authors.

REFERENCES

1. Namagerdi AA, Ciani F, d'Angelo D, Napolitano F, Avallone L. COVID-19, Environment, Clinicopathologic Features, Laboratory Findings and Diagnosis, Treatment, Vaccines, Animals, and Cancer. Ann Res Oncol. 2022;02(1):34. doi: 10.48286/aro.2022.40.
2. Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. Science 2022;375(6585):1122-1127. doi: 10.1126/science.abm8108.
3. Abassi Z, Knaney Y, Karram T, Heyman SN. The Lung Macrophage in SARS-CoV-2 Infection: A Friend or a Foe? Front Immunol. 2020;11:1312. doi: 10.3389/fimmu.2020.01312.
4. Paces J, Strizova Z, Smrz D, Cerny J. COVID-19 and the immune system. Physiol Res. 2020;69(3):379-388. doi: 10.33549/physiolres.934492.
5. Fricke-Galindo I, Falfán-Valencia R. Genetics Insight for COVID-19 Susceptibility and Severity: A Review. Front Immunol. 2021;12:622176. doi: 10.3389/fimmu.2021.622176.
6. Tay MZ, Poh CM, Rénia L, Macary PA, Ng LFP. The trinity of COVID-19: immunity, inflammation, and intervention. Nat Rev Immunol. 2020;20:363-74. doi: 10.1038/s41577-020-0311-8.
7. Rijkers GT, Weterings N, Obregon-henao A, Lepolder M, Dutt TS, Overveld FJ Van, et al. Antigen Presentation of mRNA-Based and Virus-Vectored SARS-CoV-2 Vaccines. Vaccines (Basel). 2021;9(8):848. doi: 10.3390/vaccines9080848.
8. Gu W, Gan H, Ma Y, Xu L, Cheng ZJ, Li B, et al. The molecular mechanism of SARS-CoV-2 evading host antiviral innate immunity. Virol J. 2022;19(1):49. doi: 10.1186/s12985-022-01783-5.
9. Bertoletti A, Tan AT, Le Bert N. The T-cell response to SARS-CoV-2: kinetic and quantitative aspects and the case for their protective role. Oxf Open Immunol. 2021;2(1):iqab006. doi: 10.1093/oxfimm/iqab006.
10. Migliorini F, Torsiello E, Spiezia F, Oliva F, Tingart M, Maffulli N. Association between HLA genotypes and COVID-19 susceptibility, severity and progression: a comprehensive review of the literature. Eur J Med Res. 2021;26(1):84. doi: 10.1186/s40001-021-00563-1.
11. De Larochelambert Q, Marc A, Antero J, Le Bourg E, Toussaint JF. Covid-19 Mortality: A Matter of Vulnerability Among Nations Facing Limited Margins of Adaptation. Front Public Health. 2020;8:604339. doi: 10.3389/fpubh.2020.604339.
12. Neumann-Haefelin C. HLA-B27-mediated protection in HIV and hepatitis C virus infection and pathogenesis in spondyloarthritis. Curr Opin Rheumatol. 2013;25(4):426-433. doi: 10.1097/BOR.0b013e328362018f.
13. Langton DJ, Bourke SC, Lie BA, Reiff G, Natu S, Darlay R, et al. The influence of HLA genotype on the severity of COVID-19 infection. HLA. 2021;98(1):14-22. doi: 10.1111/tan.14284.
14. Mobini Kesheh M, Shavandi S, Hosseini P, Kakavand-Ghalehnoei R, Keyvani H. Bioinformatic HLA Studies in the Context of SARS-CoV-2 Pandemic and Review on Association of HLA Alleles with Preexisting Medical Conditions. Biomed Res Int. 2021;2021:6693909. doi: 10.1155/2021/6693909.
15. Jordan SC. Innate and adaptive immune responses to SARS-CoV-2 in humans: relevance to acquired immunity and vaccine responses. Clin Exp Immunol. 2021;204(3):310-320. doi: 10.1111/cei.13582.

16. Conversation T, Nguyen BA, Nellore A, Thompson R. Your genes could determine whether coronavirus puts you in the hospital – and we're starting to unravel which ones matter. 2020. p. 1-6.
17. Sanchez-Mazas A. A review of HLA allele and SNP associations with highly prevalent infectious diseases in human populations. Swiss Med Wkly. 2020;150:w20214. doi: 10.4414/smw.2020.20214.
18. Wieczorek M, Abualrous ET, Sticht J, Álvaro-Benito M, Stolzenberg S, Noé F, et al. Major Histocompatibility Complex (MHC) Class I and MHC Class II Proteins: Conformational Plasticity in Antigen Presentation. Front Immunol. 2017;8:292. doi: 10.3389/fimmu.2017.00292.
19. Douillard V, Nasir J, Pearson N, Rosenfeld J, Limou S. Exploring the puzzle of HLA immunogenetics in COVID-19 patients. 2021. Available from: https://www.covid19hg.org/blog/2021-12-15-exploring-the-puzzle-of-hla-immunogenetics-in-covid-19-patients/.
20. Wang SF, Chen KH, Chen M, Li WY, Chen YJ, Tsao CH, et al. Human-leukocyte antigen class I Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. Viral Immunol. 2011;24(5):421-6. doi: 10.1089/vim.2011.0024.
21. Weiner J, Suwalski P, Holtgrewe M, Rakitko A, Thibeault C, Müller M, et al. Increased risk of severe clinical course of COVID-19 in carriers of HLA-C*04:01. EClinicalMedicine. 2021;40:101099. doi: 10.1016/j.eclinm.2021.101099.
22. Correale P, Mutti L, Pentimalli F, Baglio G, Saladino RE, Sileri P, et al. HLA-B*44 and c*01 Prevalence Correlates with Covid19 Spreading across Italy. Int J Mol Sci. 2020;21(15):5205. doi: 10.3390/ijms21155205.
23. Wang F, Huang S, Gao R, Zhou Y, Lai C, Li Z, et al. Initial whole-genome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility. Cell Discov. 2020;6(1):83. doi: 10.1038/s41421-020-00231-4.
24. Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, et al. Human leukocyte antigen susceptibility map for SARS-CoV-2. J Virol. 2020;94(13):e00510-20. doi: 10.1128/JVI.00510-2.
25. Poulton K, Wright P, Hughes P, Savic S, Welberry Smith M, Guiver M, et al. A role for human leucocyte antigens in the susceptibility to SARS-Cov-2 infection observed in transplant patients. Int J Immunogenet. 2020;47(4):324-328. doi: 10.1111/iji.12505.
26. Correale P, Baglio G, Parrella R, Saladino RE, Cuomo N, Scarano F, et al. A rapid ecologic analysis, confirmed by a case–control study, identifies class I HLA alleles correlated to the risk of COVID-19. J Transl Med. 2025;23(1):303. doi: 10.1186/s12967-025-06285-w.
27. Gutiérrez-Bautista JF, Rodriguez-Nicolas A, Rosales-Castillo A, López-Ruz MÁ, Martín-Casares AM, Fernández-Rubiales A, et al. Study of HLA-A, -B, -C, -DRB1 and -DQB1 polymorphisms in COVID-19 patients. J Microbiol Immunol Infect. 2022;55(3):421-427. doi: 10.1016/j.jmii.2021.08.009.
28. Novelli A, Andreani M, Biancolella M, Liberatoscioli L, Passarelli C, Luigi V, et al. HLA allele frequencies and susceptibility to COVID-19 in a group of 99 Italian patients. HLA. 2020;96(5):610-614. doi: 10.1111/tan.14047.
29. Yung Y, Lau K, Chan CCH, Xia JT, Wong RSM, Wu AKL, et al. Association of HLA-B22 serotype with SARS-CoV-2 susceptibility in Hong Kong Chinese patients. HLA. 2021;97(2):127-132. doi: 10.1111/tan.14135.
30. Barquera R, Collen E, Di D, Buhler S, Sanchez-mazas A. Binding affinities of 438 HLA proteins to complete proteomes of seven pandemic viruses and distributions of strongest and weakest. HLA. 2020;96(3):277-298. doi: 10.1111/tan.13956.
31. Pisanti S, Deelen J, Gallina AM, Caputo M, Citro M, Abate M, et al. Correlation of the two most frequent HLA haplotypes in the Italian population to the differential regional incidence of Covid-19. J Transl Med. 2020;18(1):352. doi: 10.1186/s12967-020-02515-5.
32. Littera R, Campagna M, Deidda S, Angioni G, Cipri S, Melis M, et al. Human Leukocyte Antigen Complex and Other Immunogenetic and Clinical Factors Influence Susceptibility or Protection to SARS-CoV-2 Infection and Severity of the Disease Course. The Sardinian Experience. Front Immunol. 2020;11:605688. doi: 10.3389/fimmu.2020.605688.
33. Shkurnikov M, Nersisyan S, Jankevic T, Galatenko A, Gordeev I, Vechorko V, et al. Association of HLA Class I Genotypes With Severity of Coronavirus Disease-19. Front Immunol. 2021;12:641900. doi: 10.3389/fimmu.2021.641900.
34. Yu X, Ho K, Shen Z, Fu X, Huang H, Wu D, et al. The Association of Human Leukocyte Antigen and COVID-19 in Southern China. Open Forum Infect Dis. 2021;8(9):ofab410. doi: 10.1093/ofid/ofab410.

35. Wang W, Zhang W, Zhang J, He J, Zhu F. Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19). HLA. 2020;96(2):194-196. doi: 10.1111/tan.13941.
36. Romero-López JP, Carnalla-Cortés M, Pacheco-Olvera DL, Ocampo-Godínez JM, Oliva-Ramírez J, Moreno-Manjón J, et al. A bioinformatic prediction of antigen presentation from SARS-CoV-2 spike protein revealed a theoretical correlation of HLA-DRB1*01 with COVID-19 fatality in Mexican population: An ecological approach. J Med Virol. 2021;93(4):2029-2038. doi: 10.1002/jmv.26561.
37. Yoonha PJ, Rakosi-Schmidt R, Liu J. The Role of MHC System in COVID-19 Susceptibility: A Qualitative Review of Current Literature. North Am J Med Sci. 13(1). Retrieved from https://www.najms.com/index.php/najms/article/view/541.
38. Farahani RH, Esmaeilzadeh E, Asl AN, Heidari MF, Hazrati E. Frequency of HLA Alleles in a Group of Severe COVID-19 Iranian Patients. Iran J Public Health. 2021;50(9):1882-1886. doi: 10.18502/ijph.v50i9.7061.
39. Letovsky SI, Cao X, Hollenbach JA, Mack SJ, Maiers M. Association between HLA genetics and SARS-CoV-2 infection in a large real-world cohort. Genes Immun. 2025;26(3):213-221. doi: 10.1038/s41435-025-00328-4.
40. Spinetti T, Hirzel C, Fux M, Walti LN, Schober P, Stueber F, et al. Reduced Monocytic Human Leukocyte Antigen-DR Expression Indicates Immunosuppression in Critically Ill COVID-19 Patients. Anesth Analg. 2020;131(4):993-999. doi: 10.1213/ANE.0000000000000504.
41. Zhang S, Gan J, Chen BG, Zheng D, Zhang JG, Lin RH, et al. Dynamics of peripheral immune cells and their HLA-G and receptor expressions in a patient suffering from critical COVID-19 pneumonia to convalescence. Clin Transl Immunology. 2020;9(5):e1128. doi: 10.1002/cti2.1128.
42. Georgopoulos AP, James LM, Peterson PK. Human Leukocyte Antigen (HLA) at the Root of Persistent Antigens and Long COVID. J Immunol Sci. 2025;9(1):1-3. doi: 10.29245/2578-3009/2025/1.1257.
43. Bolze A, Neveux I, Schiabor Barrett KM, White S, Isaksson M, Dabe S, Lee W, Grzymski JJ, Washington NL, Cirulli ET. HLA-A*03:01 is associated with increased risk of fever, chills, and stronger side effects from Pfizer-BioNTech COVID-19 vaccination. HGG Adv. 2022;3(2):100084. doi: 10.1016/j.xhgg.2021.100084.
44. Pahl MC, Coz C Le, Su C, Sharma P, Thomas RM, Pippin JA, et al. Implicating effector genes at COVID-19 GWAS loci using promoter-focused Capture-C in disease-relevant immune cell types. Genome Biol. 2022;23(1):125. doi: 10.1186/s13059-022-02691-1.
45. Karlsen TH. Understanding COVID-19 through genome-wide association studies. Nat Genet. 2022;54(4):368-369. doi: 10.1038/s41588-021-00985-x.
46. Augusto DG, Murdolo LD, Chatzileontiadou DSM, Sabatino JJ, Yusufali T, Peyser ND, et al. A common allele of HLA is associated with asymptomatic SARS-CoV-2 infection. Nature. 2023;620(7972):128-136. doi: 10.1038/s41586-023-06331-x.
47. Velavan TP, Pallerla SR, Rüter J, Augustin Y, Kremsner PG, Krishna S, et al. Host genetic factors determining COVID-19 susceptibility and severity. EBioMedicine. 2021;72:103629. doi: 10.1016/j.ebiom.2021.103629.
48. Zeberg H, Pääbo S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. Nature. 2020;587(7835):610-612. doi: 10.1038/s41586-020-2818-3.
49. Wu M, Zhang Y, Grosser M, Tipper S, Venter D, Lin H, et al. Profiling COVID-19 Genetic Research: A Data-Driven Study Utilizing Intelligent Bibliometrics. Front Res Metr Anal. 2021;6:683212. doi: 10.3389/frma.2021.683212.
50. Corley MJ, Patterson BK, Peluso MJ, Yeung ST, Sacha JB, Pang APS, et al. Genome-wide DNA methylation profiling of peripheral blood reveals an epigenetic signature associated with severe COVID-19. J Leukoc Biol. 2021;110(1):21-26. doi: 10.1002/JLB.5HI0720-466R.
51. Wei CH, Kao HY, Lu Z. PubTator: a web-based text mining tool for assisting biocuration. Nucleic Acids Res. 2013;41(Web Server issue):W518-22. doi: 10.1093/nar/gkt441.
52. Zhang Q, Bastard P, Liu Z, Le Pen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020;370(6515):eabd4570. doi: 10.1126/science.abd4570.
53. Kazem M, Yaser V, Ghaidaa M, Lateef R, Awsi A, Hosseinipour A, et al. Individual genetic variability, mainly of Proinflammatory cytokines, cytokine receptors, and toll-like receptors, dictates the pathophysiology of COVID-19 disease. J Med Virol. 2022;94(9):4088-4096. doi: 10.1002/jmv.27849.

54. Choi UY, Kang JS, Hwang YS, Kim YJ. Oligoadenylate synthase-like (OASL) proteins: dual functions and associations with diseases. Exp Mol Med. 2015;47(3):e144. doi: 10.1038/emm.2014.110.
55. Banday AR, Stanifer ML, Florez-vargas O, Onabajo OO, Papenberg BW, Zahoor MA, et al. Genetic regulation of OAS1 nonsense-mediated decay underlies association with COVID-19 hospitalization in patients of European and African ancestries. Nat Genet. 2022;54(8):1103-1116. doi: 10.1038/s41588-022-01113-z.
56. Ellinghaus, Degenhardt, Valenti, Franke, Karlsen, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med. 2020;383(16):1522-1534. doi: 10.1056/NEJMoa2020283.
57. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Sonmez T, Coker D, et al. Trans-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity. Nat Genet. 2021;53(6):801-808. doi: 10.1038/s41588-021-00854-7.
58. Pereira E, Felipe S, de Freitas R, Araújo V, Soares P, Ribeiro J, et al. ABO blood group and link to COVID-19: A comprehensive review of the reported associations and their possible underlying mechanisms. Microb Pathog. 2022;169:105658. doi: 10.1016/j.micpath.2022.105658.
59. Cooling L. Blood Groups in Infection and Host Susceptibility. Clin Microbiol Rev. 2015;28(3):801-70. doi: 10.1128/CMR.00109-14.
60. Mariam SH. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Pandemic: Are Africa's Prevalence and Mortality Rates Relatively Low? Adv Virol. 2022;2022:3387784. doi: 10.1155/2022/3387784.
61. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 2020;126(10):1456-1474. doi: 10.1161/CIRCRESAHA.120.317015.
62. Xiao F, Han M, Zhu X, Tang Y, Huang E, Zou H, et al. The immune dysregulations in COVID-19: Implications for the management of rheumatic diseases. Mod Rheumatol. 2021;31(5):927-32. doi: 10.1080/14397595.2020.1868673.
63. Meng Z, Zhang C, Liu S, Li W, Wang Y, Zhang Q, et al. Exploring genetic loci linked to COVID-19 severity and immune response through multi-trait GWAS analyses. Front Genet. 2025;16:1502839. doi: 10.3389/fgene.2025.1502839.
64. Amirkhani Namagerdi A, d'Angelo D, Ciani F, Iannuzzi CA, Napolitano F, Avallone L, et al. Triple-Negative Breast Cancer Comparison With Canine Mammary Tumors From Light Microscopy to Molecular Pathology. Front Oncol. 2020;10:563779. doi: 10.3389/fonc.2020.563779.
65. Li C, Wang R, Wu A, Yuan T, Song K, Bai Y, et al. SARS-COV-2 as a potential microRNA sponge in COVID-19 patients. BMC Med Genomics. 2022;15(Suppl 2):94. doi: 10.1186/s12920-022-01243-7.
66. Fernández-pato A, Virseda-berdices A, Resino S, Ryan P, Martínez-gonzález O, Pérez-garcía F, et al. Plasma miRNA profile at COVID-19 onset predicts severity status and mortality. Emerg Microbes Infect. 2022;11(1):676-688. doi: 10.1080/22221751.2022.2038021.
67. Pierce JB, Simion V, Icli B, Pérez-Cremades D, Cheng HS, Feinberg MW. Computational Analysis of Targeting SARS-CoV-2, Viral Entry Proteins ACE2 and TMPRSS2, and Interferon Genes by Host MicroRNAs. Genes (Basel). 2020;11(11):1354. doi: 10.3390/genes11111354.
68. Fani M, Zandi M, Ebrahimi S, Soltani S, Abbasi S. The role of miRNAs in COVID-19 disease. Future Virol. 2021:10.2217/fvl-2020-0389. doi: 10.2217/fvl-2020-0389.
69. Srivastava SP, Srivastava R, Chand S, Goodwin JE. Coronavirus Disease (COVID)-19 and Diabetic Kidney Disease. Pharmaceuticals (Basel). 2021;14(8):751. doi: 10.3390/ph14080751.
70. Nersisyan S, Engibaryan N, Gorbonos A, Kirdey K, Makhonin A, Tonevitsky A. Potential role of cellular miRNAs in coronavirus-host interplay. PeerJ. 2020;8:e9994. doi: 10.7717/peerj.9994.
71. Farr RJ, Rootes CL, Rowntree LC, Nguyen THO, Hensen L, Kedzierski L, et al. Altered microRNA expression in COVID-19 patients enables identification of SARS-CoV-2 infection. PLoS Pathog. 2021;17(7):e1009759. doi: 10.1371/journal.ppat.1009759.
72. Pawlica P, Yario TA, White S, Wang J, Moss WN, Hui P, et al. SARS-CoV-2 expresses a microRNA-like small RNA able to selectively repress host genes. Proc Natl Acad Sci U S A. 2021;118(52):e2116668118. doi: 10.1073/pnas.2116668118.
73. Li C, Hu X, Li L, Li JH. Differential microRNA expression in the peripheral blood from human patients with COVID-19. J Clin Lab Anal. 2020;34(10):e23590. doi: 10.1002/jcla.23590.

74. Salem S, Lotfy R, Eltaweel N, Elbadry M. Association of plasma microRNAs with COVID-19 severity and outcome. J Genet Eng Biotechnol. 2024;22(4):100433. doi: 10.1016/j.jgeb.2024.100433.
75. Jankovic M, Nikolic D, Novakovic I, Petrovic B, Lackovic M, Santric-Milicevic M. miRNAs as a Potential Biomarker in the COVID-19 Infection and Complications Course, Severity, and Outcome. Diagnostics (Basel). 2023;13(6):1091. doi: 10.3390/diagnostics13061091.
76. Belete MA, Anley DT, Tsega SS, Moges N, Anteneh RM, Zemene MA, et al. The potential of circulating microRNAs as novel diagnostic biomarkers of COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2024;24(1):1011. doi: 10.1186/s12879-024-09915-8.
77. Stannard R, Lambert PC, Lyratzopoulos G, Andersson TML, Khan S, Rutherford MJ. The long-lasting impacts of the COVID-19 pandemic on population-based cancer survival: what are the implications for data analysis? Epidemiology. Br J Cancer. 2025;132(8):673-8. doi: 10.1038/s41416-024-02931-0.
78. Derosa L, Melenotte C, Griscelli F, Gachot B, Marabelle A, Kroemer G, et al. The immuno-oncological challenge of COVID-19. Nat Cancer. 2020;1(10):946-64. doi: 10.1038/s43018-020-00122-3.
79. Zong Z, Wei Y, Ren J, Zhang L, Zhou F. The intersection of COVID-19 and cancer: signaling pathways and treatment implications. Mol Cancer. 2021;20(1):76. doi: 10.1186/s12943-021-01363-1.
80. Chen VHE, Tay JK, Gurung R, Nair S, Tay DJW, Tan KS, et al. ACE2 and TMPRSS2 gene expression is reduced acutely in SARS-CoV-2 patients but returns to normal with recovery. Sci Rep. 2025;15(1):12828. doi: 10.1038/s41598-025-96279-x.
81. Tyagi S, Tyagi N, Singh A, Gautam A, Singh A, Jindal S, Singh RP, Chaturvedi R, Kushwaha HR. Linking COVID-19 and cancer: Underlying mechanism. Biochim Biophys Acta Mol Basis Dis. 2025;1871(1):167563. doi: 10.1016/j.bbadis.2024.167563.
82. Serwaa A, Oyawoye F, Owusu IA, Dosoo D, Manu AA, Sobo AK, et al. In vitro analysis suggests that SARS-CoV-2 infection differentially modulates cancer-like phenotypes and cytokine expression in colorectal and prostate cancer cells. Sci Rep. 2024;14(1):24625. doi: 10.1038/s41598-024-75718-1.
83. Zamorano Cuervo N, Grandvaux N. ACE2: Evidence of role as entry receptor for SARS-CoV-2 and implications in comorbidities. Elife. 2020;9:e61390. doi: 10.7554/eLife.61390.
84. Grippin AJ, Marconi C, Copling S, Li N, Braun C, Woody C, et al. SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade. Nature. 2025;647(8089):488-497. doi: 10.1038/s41586-025-09655-y.
85. Augusto DG, Hollenbach JA. SARS-CoV-2 infection. Curr Opin Immunol. 2022;76:102178. doi: 10.1016/j.coi.2022.102178.
86. Jackson M, Marks L, May GHW, Wilson JB. The genetic basis of disease. Essays Biochem. 2018;62(5):643-723. doi: 10.1042/EBC20170053.