Precis Med Clin OMICS. 2021 December; 1(1):e122770. doi: 10.5812/pmco.122770.

Published online 2022 March 13. **Review Article**

COVID-19 Risk Factors for Disease Severity and Mortality: A Matter of Precision Medicine?

Seyed Mohamad Hossein Ghaderian [1], Bahar Naghavi Gargari [2, 3, *] and Parham Pooladgar [4]

[1] Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Basic Sciences, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Department of Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: bnaghavi@sbmu.ac.ir

Received 2022 January 19; **Accepted** 2022 February 02.

Abstract

Context: As a contagious acute respiratory disease, COVID-19 was announced by the World Health Organization (WHO) as a pandemic on 11 March 2020. The clinical manifestation of COVID-19 includes fever, cough, taste/smell loss, and acute respiratory distress syndrome (ARDS) due to viral pneumonia. The severity of symptoms varies among patients ranging from asymptomatic to acute pneumonia. Predicting patients at risk and disease severity in the different patients is controversial. The prevention of rapid progression of the disease, better prognosis, and decline of mortality are possible by knowing the risk factors of the disease. There is an essential question about different patients experiencing the infection from asymptomatic to acute disease.

Methods: For this study, we searched the databases including ISI Web of Science, Scopus, and PubMed with a combination of keywords COVID-19, COVID-19 risk factors, COVID-19 causes, and personalized medicine in COVID-19. All studies related to our study were searched for data collection.

Results: The clinical variability of COVID-19 infection is associated with various risk factors like age, sex, comorbidity, lifestyle, virus mutation, host immune response, and genetic background.

Conclusions: The studies reported the significant heterogeneity in risk and outcome of COVID-19 infection among patients. Individualized therapy can occur by unraveling various phenotypes and underlying pathobiology of COVID-19 infection.

Keywords: COVID-19, Coronavirus, SARS-CoV-2, Personalized Medicine, Precision Medicine, Host Genetics, Viral Genome, Risk Factors

1. Context

The World Health Organization (WHO) announced the coronavirus disease 2019 (COVID-19) pandemic on 11 March 2020 (1). The sudden onset of the disease resulted in millions of infected patients and hundreds of thousands of deaths worldwide (2). The clinical manifestation of COVID-19 includes fever, cough, taste/smell loss, and acute respiratory distress syndrome (ARDS) due to viral pneumonia. Symptoms vary among patients ranging from asymptomatic to mild and acute pneumonia (1).

Identification of risk factors for severe outcomes of disease potentially helps to make more accurate predictions and treatment approach. Some important risk factors such as age and male gender for COVID-19 severity and mortality were indicated in previous research (2). Underlying medical comorbidities, including diabetes mellitus, chronic respiratory disease, cardiovascular disease, cancer, and hypertension are reported as potential predictive factors for severe COVID-19 and increased rate of mortality (2). In current study we aimed to discuss about most important risk factor for severe COVID-19 cases.

2. Methods

For this study, we searched the databases including ISI Web of Science, Scopus, and PubMed with a combination of keywords COVID-19, COVID-19 risk factors, COVID-19 causes, and personalized medicine in COVID-19. All studies related to our study were screened for data collection.

3. Results

3.1. Risk Factors

Recent studies indicated that conditions such as long COVID-19 could lead different patients with COVID-19 infection to experience acute to mild disease (3). For instance,

a number of COVID-19 patients experience long COVID-19 which refers to symptoms that endure long after recovery from initial coronavirus infection. Long COVID-19 can influence various organs in respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems. Symptoms like cardiac abnormalities, dyspnea, cognitive impairment, fatigue, stress disorder, muscle pain, concentration problems, and headache are common in long COVID-19 patients (3).

Furthermore, risk factors such as neutrophil count, white blood cell count, lymphocyte count, D-dimer, albumin, high body temperature, dyspnea symptoms, respiratory rate, and procalcitonin were indicated to be associated with the risk of ICU admission in COVID-19 patients (4).

The declines of lymphocytes and D-dimer and the increases of CK, PT, and creatinine are among other risk factors that are reported to be associated with the progression of the disease (4). Myocardial injury, renal injury, early cellular immunodeficiency, and abnormal coagulation are also demonstrated to be involved in the progression of COVID-19 (4).

Identification of these risk factors can be helpful in prevention of rapid progression of the disease, timely intervention of patients at high risk, and decreasing the mortality rate (4). Studies have showed that revealing the interactions between SARS-CoV-2 and host is essential in understanding the mechanisms of the infectious process, transmission and resistance, as well as difference in disease outcomes (5). Currently, different factors including gender, age, viral load, blood groups, comorbidity conditions, and genetic variants are reported to be influential on COVID-19 sensibility and outcomes (6).

Along with host and viral factors, environmental factors such as air pollution may indirectly affect susceptibility to SARS-CoV-2 (5) via weakening of immune responses.

3.1.1. Genetic Factors

Recognizing host's genetic and genomics susceptibility to infection potentially helps in the precise treatment of COVID-19 (5). Using genome-wide association studies (GWAS) several susceptibility alleles in numerous genes have been recognized to have associations with severe and/or life-threatening COVID-19 phenotypes (5). Some indicators were known as predictive genomic markers; while, some genes with high penetrance alleles might be proper for patient classification and pharmacological treatment and may be considered as prognostic markers.

Understanding the intricate link between genotypes and phenotypes along with pathway analysis are the main approaches for studying the risk factor genes. For example, innate and humoral immune responses to COVID-19 involve various genetic and epigenetic factors (7-9). Thus, not surprisingly the immune system deficits can lead to different outcomes in patients with COVID-19 and heterogeneity of clinical phenotypes. Identifying the pathogenic mechanisms of different variants of virus and their functions in COVID-19 development are helpful for development of treatment and predictive test in personalized medicine (5).

For instance, available studies have revealed that mutations in genes involved in the regulation of type I beta interferon response and the presence of anti-interferon antibodies in the serum is associated with the risk of ICU admission and severity of COVID-19 outcomes (5). Therefore, studying the genomic aspects of COVID-19 patients in sera can lead to identification of valuable risk factors and improve the diagnostic as well as treatment approaches (10).

Several available studies have indicated that the pathogenesis of COVID-19 is associated with a 'cytokine storm' characterized by dysregulated production of pro-inflammatory cytokines and chemokines such as CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1A, and CCL4/MIP1B (10). Thus, revealing the genetic basis of variation in immune mechanisms that lead to cytokine storm provides a precision medicine approach that is likely to yield benefits for subpopulations or even individual patients at the risk of sever COVID-19 (10).

High-throughput RNA sequencing (RNAseq) technologies, transcriptomic analyses of patients with COVID-19, and studies about the diagnostic and therapeutic values of miRNAs and lncRNAs have demonstrated the differentially expressed genes (DEGs) in the host immune system and related signaling pathways (10).

In their study Li et al. indicated 25,482 DE mRNA, 23 DE miRNA, and 410 DE lncRNAs in peripheral blood samples of patients with infection compared to controls. AKT1, TNFRSF1B, FCGR2A, CXCL8, STAT3, and TLR2 are among the several genes that positively regulate the cytokine production. Besides, numerous miRNAs and lncRNAs involved in regulation of the immune effector process and NIK/NF-kappaB signaling have been identified in their work (10).

In a cohort study at university of Ankara, Turkey, killer immunoglobulin-like receptor (KIR) and ligands were genotyped from asymptomatic to severe COVID-19 patients (11). The results showed that clinical parameters such as age, CRP, comorbidities number, D-dimer, telomeric centromeric KIR genotypes (t AA, t AB1, and c AB1) and ligands were different between cohorts (11). According to this study, two prediction models were designed, composed of age, blood group, and the number of comorbidities in the first model and the same parameters in addition to KIR genotypes and their cognate ligands in the second one. This risk model may help predict the disease severity in COVID-19 infection before disease appearance (11).

Other studies performed in Spain and Italy on a gene cluster at chromosome 3 identified a risk locus for immune genes including CCR9, CXCR6, XCR1, CCR1, and CCR2 (12). Furthermore, the GenOMICC study reported other genetic variants in IFNAR2 and OAS2. The patients with TLR3, IRF7, and IFNAR1 variants had innate immune response dysfunction. Further, Beksac and colleagues, found the rare loss of function variants of TLR7 on X-chromosomal affects interferon responses. So, a potential relationship between the severity of the disease and inherited variants is found (11, 13).

Using system biology and genetic technologies was promising for determining the genetic factors of the virus and host involved in predisposition to infection and increasing the severity of disease (14). Coronavirus pathogenesis was surveyed using the SARS-CoV model, disease phenotypes, and different dynamic transcriptional pathways in various genetic backgrounds (14).

In a study by Asgari and Pousaz (15) 13 loci in the human genome were identified among which four loci influence the susceptibility to COVID-19 and nine loci influence disease severity. Also, more than 40 candidate genes were effective in immune and lung function that might affect COVID-19 outcome. Variants of *TYK2* gene was among the genes associated with infection susceptibility and increased risk of being hospitalized. Variants in DPP9 were also associated with serious SARS-CoV-2 outcomes (15).

3.1.2. Immune Response Risk Factors

Several studies have revealed that host immunity variation is related to susceptibility to infectious diseases. The relationship between the development of SARS and HLA-B*4601, HLA-B*0703, and HLA-DRB1*0301 was found in an available case-control study (16).

Adaptive immune response against COVID-19 is a vital defense mechanism via antibodies production, which is however a time-consuming process (20 days on average) (17).

In previous study on severe acute respiratory syndrome coronavirus (SARS-CoV) infection Zhang et al. (17) evaluated the effect of mutations in *Mannose-binding Lectin* (*MBL*), a gene involved in the innate immune response on susceptibility to SARS-CoV. They showed one mutation in codon 54 and three polymorphisms in *MBL* gene were related to susceptibility to COVID-19 (17).

The COVID-19 virus enters host cells through an endocytic pathway. The main viral protein known as SARS-CoV-2 spike protein causes the fusion of the virus particles to the host cell using Angiotensin-converting Enzyme 2 (ACE2). ACE2 has an essential function in renal, vascular and myocardial physiology. A number of studies have demonstrated the effect of several ACE2 variants on protein stability and communication between spike protein and ACE2. Also, the variations of proteolytic cleavage site are indicated to affect virus infection, declining or increasing affinity between ligand-receptors can occur by other variants as well. ACE2 polymorphisms in regulatory and non-coding regions such as promoters can be involved in various expression levels of ACE2 among different individuals (18).

3.2. Genome-Wide Association Studies in COVID-19

Today, it is essential to understand the risk factors of COVID-19 infection and find proper treatment and vaccines (19). The proteins involved in the viral life cycle and host defense as genetic factors have a vital function in infection and disease severity. GWAS has been used to determine the genetic risk factors in the infection, such as mapping HLA peptide binding cleft amino acid variants. While, GWAS generally fails to identify rare variation that may influence disease susceptibility, it can provide significant information for a substantial proportion of the common genetic variation underlying a range of traits. For instance, GWAS based pharmacogenomics approaches have indicated that rare variants on specific drug targets have significant impact on receptor-drug interactions (20, 21).

As mentioned, ACE2 have major role in SARS-CoV-2 pathogenesis. The studies showed that ACE2 truncation variants are essential for viruses' entry into human cells, but CCR5 and FUT2 deletion/truncation variants are protective against pathogens. Men are hemizygous for ACE2 variants because ACE2 is on the X chromosome. The extracellular Peptidase Domain (PD) and cytoplasmic domain of ACE2 are separated via a single transmembrane helix of ACE2 (22). An essential receptor for coronaviruses is PD, which interacts with the Receptor-binding Protein (RBD) that is the C-terminal of the S protein (22). Mapping of RBD-PD interface with Genome Aggregation Database (gnomAD) showed that missense variants of ACE2 including Ser19Pro, Ile20Val, Thr27Ala Glu37Lys, Gly326Glu, and Glu329Gly (23). A number of studies have indicated that various missenses with medium-range depletion or enrichment could cause weak or enhanced PD-RBD (24). However, non-missense variants of PD truncation and structural perturbations have adverse effects on PD–RBD communication and viral entry in carrier individuals (19). Chen and Brest's studies demonstrated that ACE2, TMPRSS2, and ADAM17 variants are involved in disease severity (25, 26). On the other hand, studies showed that a high level of IFN-III production in the upper airways of patients causes a mild pathology of infection in the patients and leads efficiently to the transcription of genes that prevent SARS-CoV-2. However, the overexpression of IFNs was exhibited in the lower airways of patients with severe COVID-19 that demonstrate gene pathways related to higher apoptosis

and lower proliferation (27).

3.3. OMICS Technologies in COVID-19

Genomics, transcriptomics, proteomics, and metabolomics as Omics technology can be used to find the pathogenic mechanisms, diagnosis, and target therapy of COVID-19 (28).

The studies in males and females with COVID-19 showed that metabolites regulate part of immune responses. Furthermore, the metabolic reprogramming of cells is performed via immune-stimulating, leading to disease outcomes through altering metabolic plenty. A positive correlation has been indicated among kynurenic acid (KA) and a high KA to kynurenine (K) ratio and age, inflammatory cytokines, and chemokines, but the negative relationship was observed between KA and a high KA to K ratio with T cell responses, indicating that immune responses in males are related to KA production. Male patients with acute infection had a higher KA to K ratio than patients with the stabilized conditions. There was no relationship between age, disease severity, and the KA: K ratio in females, but this ratio had a positive correlation with T cell responses. Moreover, there was lower serum glutamate in patients with severe COVID-19 than in patients with the stabilized condition because KA inhibits glutamate release. Also, the relationship of cytokine levels and aryl hydrocarbon receptor activation with Kynurenine aminotransferase expression was found in older males (28). Some studies found that metabolites such as palmitoleic and arachidonic acid positively correlate with inflammatory function, and some of them have neurologic roles like glutamate and cysteine-S-sulfate. However, metabolites that have a negative effect on COVID-19 are related to the urea cycle and nitric oxide (NO) synthesis pathway, such as proline, citrulline, and glutamine (28).

The studies demonstrated an increased risk of secondary bacterial infections in acute patients with COVID-19. The diagnosis of secondary infection in patients with COVID-19 is challenging and increases mortality (29). Lactate, C-reactive protein (CRP), and procalcitonin are biomarkers for acute sepsis, but no specific biomarker was found for a secondary infection. Therefore, the determination and compliment of disease-specific biomarkers may help diagnose secondary bacterial infections in COVID-19. So, metabolomics may aid in using personalized antimicrobial therapy in patients. The patient metabolic profile was determined via metabolomics analysis that shows the patient's metabolic condition (29).

Mutations and new variants of SARS-CoV-2 have been found via genomic analysis. Transcriptome sequences determine gene expression changes of SARS-CoV-2 in various biological samples. Proteomics and metabolomics approaches are used to determine the pathogenic mechanisms, potential target drugs, and vaccines (30). Two critical applications of proteomics in COVID-19 infection are (1) virus identification, pathogen diagnosis, mutation determination, and identification of posttranslational modification and (2) investigation of the effect of the virus on host cells at the protein level such as finding drug targets, diagnosis of pathologic pathway, immunogenicity, and biomarkers identification (30). Proteomics studies in SARS-CoV-2-infected ACE2-expressing A549 cells showed abnormalities in many antiviral pathways. Polymerase (RNA) II polypeptide B, the production of ephrin-B1, thymidylate synthase, and dihydrofolate reductases were declined via ubiquitination. Studying the correlation between ubiquitination and viral pathogenesis can help to discover potential drug targets. Moreover, the analysis of translatome and proteome indicated that SARS-CoV-2 infection may intervene with various pathways such as translation, proteostasis, glycolysis, splicing, and nucleotide synthesis pathways (30).

Metabolomics studies have showed that glucose metabolism, lipid metabolism, and amino acid metabolism have vital roles in COVID-19 infection (30). Moreover, gut metabolites regulate immune and neuroendocrine systems that connect the gut-liver, lung, and gut-brain axes. Furthermore, changes in the fecal metabolome indicate gastrointestinal metabolism and absorption, which has a crucial role in identifying pathogenesis, diagnostic and prognostic markers, and therapeutic targets (31).

3.4. Prcision Medicine in COVID-19

The studies report significant heterogeneity in risk and outcome of COVID-19 infection. Individualized therapy can be developed by unraveling the various phenotypes and underlying pathobiology of virus. Today, there is no proper antiviral drug, specific and effective vaccine, or antibody against COVID-19. However, hundreds of treatments have experimented with different drugs and pharmacological agents with various mechanisms to prevent virus function in the host (32). Predictive approaches lead to determining target phenotypes and precision therapies proportional to patients' requirements (33). For instance, personalized treatment has been indicated to lower mortality rates in COVID-19 hospitalized patients (32).

4. Conclusions

Clinical variability of COVID-19 infection has been reported to be associated with various risk factors like age, sex, comorbidity, lifestyle, virus mutation, host immune response, and genetic background variation. Determining

biomarkers and drug targets that help to early diagnosis and timely treatment of critical patients are of crucial importance. Determining the various-host phenotypes, precise mechanism of pathogenesis and taking advantages of omics approaches will help to develop individualized therapy.

Footnotes

Authors' Contribution: Study concept and design: Bahar Naghavi Gargari; Analysis and interpretation of data: Seyed Mohamad Hossein Ghaderian, Bahar Naghavi Gargari, and Parham Pooladgar; Drafting of the manuscript: Seyed Mohamad Hossein Ghaderian, Bahar Naghavi Gargari, and Parham Pooladgar; Critical revision of the manuscript for important intellectual content: Seyed Mohamad Hossein Ghaderian and Bahar Naghavi Gargari.

Conflict of Interests: The authors declare no conflict of interest.

Funding/Support: The authors declare no founding was involved in the study.

References

1. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. *J Chin Med Assoc*. 2020;**83**(3):217–20. doi: 10.1097/JCMA.0000000000000270. [PubMed: 32134861]. [PubMed Central: PMC7153464].
2. Khan A, Althunayyan S, Alsofayan Y, Alotaibi R, Mubarak A, Arafat M, et al. Risk factors associated with worse outcomes in COVID-19: a retrospective study in Saudi Arabia. *East Mediterr Health J*. 2020;**26**(11):1371–80. doi: 10.26719/emhj.20.130. [PubMed: 33226105].
3. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ*. 2021;**374**:n1648. doi: 10.1136/bmj.n1648. [PubMed: 34312178].
4. Xing Y, Wang H, Yao XH, Li Y, Huang JT, Tang J, et al. Analysis of factors for disease progression in 61 patients with COVID-19 in Xiaogan, Hubei, China. *Eur Rev Med Pharmacol Sci*. 2020;**24**(23):12490–9.
5. Colona VL, Vasiliou V, Watt J, Novelli G, Reichardt JKV. Update on human genetic susceptibility to COVID-19: susceptibility to virus and response. *Hum Genomics*. 2021;**15**(1):57. doi: 10.1186/s40246-021-00356-x. [PubMed: 34429158]. [PubMed Central: PMC8384585].
6. Vetter P, Vu DL, L'Huillier AG, Schibler M, Kaiser L, Jacquerioz F. Clinical features of covid-19. *BMJ*. 2020;**369**:m1470. doi: 10.1136/bmj.m1470. [PubMed: 32303495].
7. Zhang Q, Bastard P, Bolze A, Jouanguy E, Zhang SY, Covid Human Genetic Effort, et al. Life-Threatening COVID-19: Defective Interferons Unleash Excessive Inflammation. *Med (N Y)*. 2020;**1**(1):14–20. doi: 10.1016/j.medj.2020.12.001. [PubMed: 33363283]. [PubMed Central: PMC7748410].
8. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*. 2020;**370**(6515):eabd4570.
9. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann H, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;**370**(6515):eabd4585.
10. Li CX, Chen J, Lv SK, Li JH, Li LL, Hu X. Whole-Transcriptome RNA Sequencing Reveals Significant Differentially Expressed mRNAs, miRNAs, and lncRNAs and Related Regulating Biological Pathways in the Peripheral Blood of COVID-19 Patients. *Mediators Inflamm*. 2021;**2021**:6635925. doi: 10.1155/2021/6635925. [PubMed: 33833618]. [PubMed Central: PMC8018221].
11. Beksac M, Akin HY, Gencer-Oncul EB, Yousefzadeh M, Cengiz Seval G, Gulten E, et al. A model integrating Killer Immunoglobulin-like Receptor (KIR) haplotypes for risk prediction of COVID-19 clinical disease severity. *Immunogenetics*. 2021;**73**(6):449–58. doi: 10.1007/s00251-021-01227-4. [PubMed: 34536086]. [PubMed Central: PMC8449213].
12. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med*. 2020;**383**(16):1522–34. doi: 10.1056/NEJMoa2020283. [PubMed: 32558485]. [PubMed Central: PMC7315890].
13. van der Made CI, Simons A, Schuurs-Hoeijmakers J, van den Heuvel G, Mantere T, Kersten S, et al. Presence of Genetic Variants Among Young Men With Severe COVID-19. *JAMA*. 2020;**324**(7):663–73. doi: 10.1001/jama.2020.13719. [PubMed: 32706371]. [PubMed Central: PMC7382021].
14. Schafer A, Baric RS, Ferris MT. Systems approaches to Coronavirus pathogenesis. *Curr Opin Virol*. 2014;**6**:61–9. doi: 10.1016/j.coviro.2014.04.007. [PubMed: 24842079]. [PubMed Central: PMC4076299].
15. Asgari S, Pousaz LA. Human genetic variants identified that affect COVID susceptibility and severity. *Nature*. 2021;**600**(7889):390–1. doi: 10.1038/d41586-021-01773-7. [PubMed: 34239107].
16. Lin M, Tseng HK, Trejaut JA, Lee HL, Loo JH, Chu CC, et al. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. *BMC Med Genet*. 2003;**4**:9. doi: 10.1186/1471-2350-4-9. [PubMed: 12969506]. [PubMed Central: PMC212558].
17. Zhang H, Zhou G, Zhi L, Yang H, Zhai Y, Dong X, et al. Association between mannose-binding lectin gene polymorphisms and susceptibility to severe acute respiratory syndrome coronavirus infection. *J Infect Dis*. 2005;**192**(8):1355–61. doi: 10.1086/491479. [PubMed: 16170752]. [PubMed Central: PMC7202438].
18. Bakhshandeh B, Sorboni SG, Javanmard AR, Mottaghi SS, Mehrabi MR, Sorouri F, et al. Variants in ACE2; potential influences on virus infection and COVID-19 severity. *Infect Genet Evol*. 2021;**90**:104773. doi: 10.1016/j.meegid.2021.104773. [PubMed: 33607284]. [PubMed Central: PMC7886638].
19. Chakravarty S. COVID-19: The Effect of Host Genetic Variations on Host-Virus Interactions. *J Proteome Res*. 2021;**20**(1):139–53. doi: 10.1021/acs.jproteome.0c00637. [PubMed: 33301685]. [PubMed Central: PMC7737537].
20. Hauser AS, Chavali S, Masuho I, Jahn LJ, Martemyanov KA, Gloriam DE, et al. Pharmacogenomics of GPCR Drug Targets. *Cell*. 2018;**172**(1-2):41–54 e19. doi: 10.1016/j.cell.2017.11.033. [PubMed: 29249361]. [PubMed Central: PMC5766829].
21. Wang B, Yan C, Lou S, Emani P, Li B, Xu M, et al. Building a Hybrid Physical-Statistical Classifier for Predicting the Effect of Variants Related to Protein-Drug Interactions. *Structure*. 2019;**27**(9):1469–1481 e3. doi: 10.1016/j.str.2019.06.001. [PubMed: 31279629].
22. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*. 2020;**367**(6485):1444–8. doi: 10.1126/science.abb2762. [PubMed: 32132184]. [PubMed Central: PMC7164635].
23. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. *Nat Methods*. 2010;**7**(4):248–9. doi: 10.1038/nmeth0410-248. [PubMed: 20354512]. [PubMed Central: PMC2855889].
24. Hadi-Alijanvand H, Rouhani M. Studying the Effects of ACE2 Mutations on the Stability, Dynamics, and Dissociation Process of SARS-CoV-2 S1/hACE2 Complexes. *J Proteome Res*. 2020;**19**(11):4609–23. doi: 10.1021/acs.jproteome.0c00348. [PubMed: 32786692]. [PubMed Central: PMC7640954].

25. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. *Aging cell*. 2020;**19**(7). e13168.
26. Brest P, Refae S, Mograbi B, Hofman P, Milano G. Host Polymorphisms May Impact SARS-CoV-2 Infectivity. *Trends Genet*. 2020;**36**(11):813–5. doi: 10.1016/j.tig.2020.08.003. [PubMed: 32828550]. [PubMed Central: PMC7416730].
27. Sposito B, Broggi A, Pandolfi L, Crotta S, Clementi N, Ferrarese R, et al. The interferon landscape along the respiratory tract impacts the severity of COVID-19. *Cell*. 2021;**184**(19):4953–4968 e16. doi: 10.1016/j.cell.2021.08.016. [PubMed: 34492226]. [PubMed Central: PMC8373821].
28. Cai Y, Kim DJ, Takahashi T, Broadhurst DI, Yan H, Ma S, et al. Kynurenic acid may underlie sex-specific immune responses to COVID-19. *Sci Signal*. 2021;**14**(690). doi: 10.1126/scisignal.abf8483. [PubMed: 34230210]. [PubMed Central: PMC8432948].
29. McCreath G, Whitfield PD, Roe AJ, Watson MJ, Sim MAB. A Metabolomics approach for the diagnosis Of SecondAry InfeCtions in COVID-19 (MOSAIC): a study protocol. *BMC Infect Dis*. 2021;**21**(1):1204. doi: 10.1186/s12879-021-06832-y. [PubMed: 34856937]. [PubMed Central: PMC8637512].
30. Yang J, Yan Y, Zhong W. Application of omics technology to combat the COVID-19 pandemic. *MedComm (2020)*. 2021;**2**(3):381–401. doi: 10.1002/mco2.90. [PubMed: 34766152]. [PubMed Central: PMC8554664].
31. Lv L, Jiang H, Chen Y, Gu S, Xia J, Zhang H, et al. The faecal metabolome in COVID-19 patients is altered and associated with clinical features and gut microbes. *Anal Chim Acta*. 2021;**1152**:338267. doi: 10.1016/j.aca.2021.338267. [PubMed: 33648648]. [PubMed Central: PMC7847702].
32. Shrestha GS, Paneru HR, Vincent JL. Precision medicine for COVID-19: a call for better clinical trials. *Crit Care*. 2020;**24**(1):282. doi: 10.1186/s13054-020-03002-5. [PubMed: 32487260]. [PubMed Central: PMC7266425].
33. Fang FC, Schooley RT. Treatment of Coronavirus Disease 2019-Evidence-based or Personalized Medicine? *Clin Infect Dis*. 2022;**74**(1):149–51. doi: 10.1093/cid/ciaa996. [PubMed: 32667978]. [PubMed Central: PMC7454443].