

Variants of Coronavirus and Cardiovascular Diseases

Mahintaj Dara^{1*} | Mahsa Saffar² | Mehdi Dianatpour^{1,2} | Nader Tanideh¹ | Negar Azarpira³ | Mahdieh Talebzadeh⁴

*Correspondence: Mahintaj Dara

Address: ¹Stem Cells Technology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; ²Department of Medical Genetics, Shiraz University of Medical Sciences, Shiraz, Iran; ³Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; ⁴Department of Molecular Medicine, school of Advanced Medical Science and Technology, Shiraz University of Medical Sciences, Shiraz, Iran

e-mail ✉: dara.nahintaj@gmail.com

Received: 26 September 2022; Accepted: 21 October 2022

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ABSTRACT

Context: Coronavirus disease 2019 (COVID-19) is a viral infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that spread around the world rapidly and has become a pandemic and a major global concern. SARS-CoV-2 is an enveloped virus with a positive-strand RNA genome that encodes structural and nonstructural viral proteins. Among the structural proteins, spike surface glycoprotein or S protein is necessary for the infection of host cells. Mutations in the S protein can cause dangerous variants of coronaviruses with higher transmission rates that are not easily detectable by routine diagnostic tests and are treatment resistant, leading to a more severe illness and a higher mortality rate. This review aimed to present a comprehensive evaluation of the latest studies on S protein mutations, coronavirus variants, and their relationship with the type, rate, and severity of the cardiovascular disease.

Evidence Acquisition: Researchers search GISAID, PubMed/Medline, Google Scholar, Web of Science, Wiley Online Library, and Research Gate for the internationally valid investigation that includes original, reviews, letters or commentaries, or any other published data.

Results: Since the outbreak of the COVID-19 pandemic disease, more than 30 mutations in the S protein. The mutations in the S protein increase the affinity and strength of its binding to the host cell receptor. Although the main host of the virus is the respiratory system, Cardiovascular damage, especially myocardial injury, has a significant share in patients with covid-19, which is of great importance due to the increase in the mortality rate.

Conclusion: The mutations in the S protein increase the affinity and strength of its binding to the ACE2 receptor. Therefore, the signaling pathways associated with cardiovascular damage and inflammation are activated quickly, causing cardiovascular manifestation, severe forms of the disease, and death as a result of infection with concerning variants of SARS-CoV-2.

Keywords: COVID-19, S Protein, SARS-Cov-2 Variants, Cardiovascular Diseases

Introduction

At present, Coronavirus Disease 2019 (COVID-19) has become a global concern and challenge (Islam *et al.*, 2021). So far, hundreds of millions of people have been infected with COVID-19, and killed millions of people (Spychalski *et al.*, 2020). The severity of the disease varies from person to person, that can be asymptomatic or lead to severe respiratory symptoms and even death in others (Lotfi *et al.*, 2020). The most important risk factors for the severe type of the disease include cardiovascular diseases, chronic respiratory diseases, diabetes, age, immune system disorders, and cancer (Jordan *et al.*, 2020, Rashedi *et al.*, 2020; Razeghian-Jahromi *et al.*, 2022; Kaviani *et al.*, 2022). Since the beginning of the COVID-19, different variants of the virus have emerged with strong transmission and pathogenicity. Coronavirus (SARS-CoV-2) belongs to the Coronaviridae family (Gomes, 2020). Seven strains of the coronavirus family can infect humans, which can cause different signs ranging from cold with major symptoms such as fever and sore throat to upper and lower respiratory tract infections resulting in pneumonia, severe respiratory tract infection, and even death (Gomes, 2020). These seven strains include HCoV-229E, HCoV-OC43, SARS-CoV, human coronavirus NL63, human coronavirus HKU1, MERS-CoV, and SARS-CoV-2 (Huang *et al.*, 2020b; Gorbalenya *et al.*, 2020).

SARS-CoV-2 is a positive strand RNA virus with a 29.9kb length and 11 open reading frames in the genome that are responsible for coding structural (ORF3a,6,7a,7b,8 and 10) and nonstructural (ORF 1a,1b) proteins located in the 3' and 5' ends of the genome, respectively (Abdelzaher *et al.*, 2020; COVID-19 Host Genetics Initiative, 2021; Wang *et al.*, 2020). Structural proteins include spike surface glycoprotein (S), envelope protein (E), matrix protein (M), and nucleocapsid (N). S protein is essential for the infection of host cells (Wang *et al.*, 2020). Viruses attach to host cell receptors by the S protein, and fusion of the virus to the cell membrane leads to the entrance of the virus into the cells (Wang *et al.*, 2020). S protein is a 180-kDa trimeric protein with 1273 amino acids and is responsible for the crown like shape of the virus as well as for the determination of host tropism and pathogenesis (Mousavizadeh and Ghasemi, 2021). In SARS-CoV-2, the S protein binds to the Angiotensin-Converting Enzyme 2 (ACE2) receptors. It is an enzyme that acts as a cellular doorway to entry and infection of cells. S protein consists of two subunits, S1 and S2. The S1 that is located at the N-terminal region of the protein forms the globular head and binds the virus to the ACE2 receptor by the Receptor Binding Domain (RBD) (Herrera *et al.*, 2020). Subunit S2 is positioned at the C-terminal region of the protein and forms the virus stalk. It also consists of the Fusion Peptide (FP), Hepta-peptide Repetitive sequence 1 and 2 (HR1 & HR2), Transmembrane (TM) domain, and cytoplasm domain that is involved in the fusion of the virus into the host cell membrane (Xiong *et al.*, 2020).

Mutations in the S protein increase the affinity of the protein to the receptor or the strength of the receptor binding so have resulted in dangerous variants of SARS-CoV-2. These mutant viruses have a higher transmission rate, more severe illness and mortality (Almubaid and Al-Mubaid, 2021). In addition, it is more difficult to diagnose and treat these variants (Almubaid and Al-Mubaid, 2021). since outbreak of the COVID-19 pandemic disease, Nearly, 96.5% amino acid residues in the human SARS-CoV-2 spike protein have undergone mutations (Laha *et al.*, 2020).

Although the main host of the virus is the respiratory system, this receptor is present both in solution and on the surface of the membrane of different organs and cells, including cardio myocytes (Huang *et al.*, 2020a). Cardiovascular damage, especially myocardial injury, has a significant share in patients with covid-19, which is of great importance due to the increase in the mortality rate (Bansal, 2020). In the present study, a comprehensive evaluation of the latest studies on S protein mutations, coronavirus variants and their relationship with the type, rate and severity of cardiovascular disease was performed.

Evidence Acquisition

The data were collected from valid papers published in Pubmed/Medline, Google Scholar, GISAID, Wiley Online Library, Web of Science, and Research Gate databases. Different types of articles including original studies, narrative or systematic studies, letters to editors, commentaries, and case reports were reviewed. The used keywords included “S protein mutation”, “concerning variants of SARS-CoV-2”, “signaling pathways”, “cardiovascular manifestations”, and their combination with “COVID-19”.

Table 1: S protein mutations in COVID-19 concerning variants (53).

B.1.1.7	B.1.351	P.1	B.1.617.2	B.1.1.529		
United Kingdom Variant (Alpha)	South Africa variant (Beta)	Brazilian Variant (Gamma)	Indian Variants (Delta)	South Africa Variants (Omicron)		
H69-	D80A	L18F	T19R	T19I	S373P	Q498R
V70-	D215G	T20N	G142D	L24-	S375F	N501Y
Y144-	L241-	P26S	E156-	P25-	T376A	Y505H
N501Y	L242-	D138Y	F157-	P26-	D405N	D614G
A570D	A243-	R190S	R158G	A27S	R408S	H655Y
D614G	K417N	K417T	L452R	H69-	K417N	N679K
P681H	E484K	E484K	T478K	V70-	N440K	P681H
T716I	N501Y	N501Y	D614G	G142D	L452R	N764K
S982A	D614G	D614G	P681R	V213G	S477N	D796Y
D1118H	A701V	H655Y	D950N	G339D	T478K	Q954H
E484K		T1027I		S371F	E484A	N969K
		V1176F			F486V	

*Circled items indicate common mutations between the variants.

Results

UK Variant (Alfa)

The United Kingdom variant was first detected in England in December 2020 and is also known as the Alpha variant, British variant, or English variant. The transmission rate of this variant is 50% higher in comparison to the primary COVID-19 (Gravagnuolo *et al.*, 2021). Nearly 23 mutations have been detected in this variant. The most important mutation is N510Y in the receptor binding domain of the S protein (Tian *et al.*, 2021). This S protein alteration improves the attachment of the virus to the ACE2 receptors, helps the virus escape from antibodies, and consequently causes rapid virus transmission and infection across the globe (Davies *et al.*, 2020).

South African Variant (Beta)

The South African variant was first detected in Eastern Cape Province of South Africa in October 2020 (Makoni, 2021). This variant is known as the Beta-variant or lineage B.1.351, and ten mutations have been detected in the S protein (Makoni, 2021). Mutation E484K, which was the first detected South African variant, changes glutamic acid to lysine in the RBD domain of the S protein, subsequently decreasing the viral susceptibility to monoclonal antibodies and vaccine effectiveness (Weisblum *et al.*, 2020). This variant has been reported in South Africa, America, Canada, Australia, New Zealand, and East Asia (Tegally *et al.*, 2020).

Brazilian Variant (Gamma)

On 6 January 2021, the National Institute of Infectious Disease detected the Brazilian variant in four people who had traveled to Brazil (Naveca *et al.*, 2021). This variant was named the Gamma-variant or P1 lineage (Naveca *et al.*, 2021). There are 10 mutations in the S protein of the Brazilian variant, which significantly reduce the susceptibility of the virus to monoclonal antibodies (Garcia-Beltran *et al.*, 2021).

Indian Variant (Delta)

The Indian variant refers to the B.1.617.2 lineage that is also known as the Delta variant. It was detected in India in December 2020 and February 2021 and was quickly spread around the world (Mahase, 2021). There are seven mutations in the S protein of this variants, with four distressing ones including D614G, E484G, L452R, and P681R (Patil *et al.*, 2021). These mutations enhance the virus transmission rate, increase the virus's ability to bind to cell surface receptors, and cause it to escape from the host's immune system (Chanda, 2020). The Delta variant is 50-60% more transmissible than the

Alpha variant, which is 50-60% more transmissible than the original strain of COVID-19 (Chanda, 2020). As a consequence, this variant is currently the most quickly spreading dangerous mutation in the world and can possibly become the globally dominant variant.

South Africa Variant (Omicron)

Omicron variant first appears in November 2021, possibly in South Africa and also detected in Botswana and Hong Kong (He *et al.*, 2021). Currently, 6 sub variants of Omicron have been identified that including: 21K or BA.1, 21L or BA.2, 22A or BA.4, 22B or BA.5, 22C or BA.2.12.1, and 22D or BA.2.75 (He *et al.*, 2021). This variants are one of the more concerning variants due to the large number of mutations (more than 30 mutations) in receptor binding domain and N-terminal domain of S protein gene that increase in transmission and immune evasion of this variant family that play key roles in ACE2 binding and antibody recognition (Zhao *et al.*, 2022; Kandeel *et al.*, 2022).

Concerning Variants and Cardiovascular Disease

Since the beginning of covid-19, it has been known that cardiovascular diseases like arrhythmia, thrombotic complications, acute myocardial infarction, and myocarditis, have a significant share in patients with covid-19 (Dhakal *et al.*, 2020). On the other hand, previous cardiovascular diseases are one of the important risk factors in severe forms of covid-19 and death in patients (Dhakal *et al.*, 2020). The 6 important mutations in the S protein that enhance the virus transmission rate, increase the virus's ability to bind to cell surface receptors, and cause it to escape from the host's immune system include D614G, E484G, L452R, P681R E484K, and N501Y (Souza *et al.*, 2022) (Table 2).

Table 2: COVID-19 mutations in concerning variants and their subsequent effects.

Concerning mutations	Amino acid replacement	Effects
D614G	Aspartic acid (D) to Glycine (G)	Increased transmission rate, increased binding of the RBD to the ACE2 receptor, and increased infectivity (Di Giacomo <i>et al.</i> , 2021, Zhang <i>et al.</i> , 2020).
N501Y	Asparagine (N) to Tyrosine (Y)	Increased binding affinity to hACE2 (Mathavan and Kumar, 2020).
E484Q	Glutamic acid (E) to Glutamine (Q)	Enhanced ACE2 receptor binding ability and reduced vaccine-stimulated antibodies (Verghese <i>et al.</i> , 2021).
E484K	Glutamic acid (E) to Lysine (K)	Changes in antigenicity and improved ability of the virus to evade the host's immune system (Janra <i>et al.</i> , 2021).
L452R	Leucine (L) to Arginine (R)	Enhanced ACE2 receptor binding ability and reduced vaccine-stimulated antibody (Deng <i>et al.</i> , 2021).
P681R	Proline (P) to Arginine (R)	Enhanced ACE2 receptor binding ability and reduced vaccine-stimulated antibody (Saito <i>et al.</i> , 2021).

So far, more than 30 mutations in the S protein have been reported, all of which increase the invasive properties of SARS-CoV-2 and cardiovascular damage (Souza *et al.*, 2022).

The mutations in the S protein increase the affinity and strength of its binding to the ACE2 receptor (Sriram *et al.*, 2020). SARS-CoV-2 binding to the ACE2 receptor, entrance, and proliferation into the myocardium possibly deteriorates the normal function of cardio myocytes and myocardial injury (Weckbach *et al.*, 2021). In the patient with previous heart disease, COVID-19 caused electrolyte imbalance that led to arrhythmias (Weckbach *et al.*, 2021).

On the one hand, the need for oxygen increases due to infection, and on the other hand, hypoxia occurs due to improper functioning of the respiratory system. In this condition, the metabolic balance of cardiovascular cells is disturbed which can lead to Acute Myocardial Infarction (Nartikoeva and Takoeva, 2021).

ACE2 is an enzyme that acts as a cellular doorway to entry and infection of cells (Rouaud *et al.*, 2022). Although the main host of the virus is the respiratory system, this receptor is present in the vascular endothelium. ACE2 is a member of the renin-angiotensin system (RAS) pathway which have a protective role, especially in cardiovascular health (Rouaud *et al.*, 2022). Normally in this pathway, renin which is released from the kidney, cleavages Angiotensinogen to angiotensin I (ANGI). Then in this cascade, angiotensin II (ANGII) from ANGI is catalyzed by ACE. ANGI is also converted to ANG (1-9) and ANGI to ANG (1-7) by ACE2. ANG (1-7) binds to MAS and angiotensin 2 (AT2R) receptors and caused vasodilation and has anti-apoptotic, anti-fibrosis, and anti-inflammatory effects (Rouaud *et al.*, 2022). Therefore, hypertension, cardiac fibrosis, and thrombosis are reduced.

When SARS-CoV-2 expose to the host cells, the S protein on the surface of the virus is cleaved at the S1/S2 site by the enzyme called Furin and then the Receptor binding domain (RBD) in the S1 subunit binds the ACE2. The S2 subunit is cleaved by a cellular protease, TMPRSS2 (transmembrane serine protease 2), and fused to the host cell membrane (Rouaud *et al.*, 2022).

By binding the virus to the ACE2, it prevents the conversion of ANGI and ANGI to ANG (1-7) and its binding to the MAS and AT2R receptors (Rouaud *et al.*, 2022). therefore, the fate of the RAS signaling pathway is changed. ANGI is attached to angiotensin 1(AT1R) receptors and causes vasoconstriction, inflammation, proliferation, and fibrosis so increasing hypertension, cardiac fibrosis, and thrombosis (Fig. 1) (Pitek *et al.*, 2016).

Activation of these signaling pathways triggers a cytokine storm and increases inflammation in the body. The interaction of pro-inflammatory cytokines, immune cells, and complement components causes platelets to activate and clots formation (Pitek *et al.*, 2016).

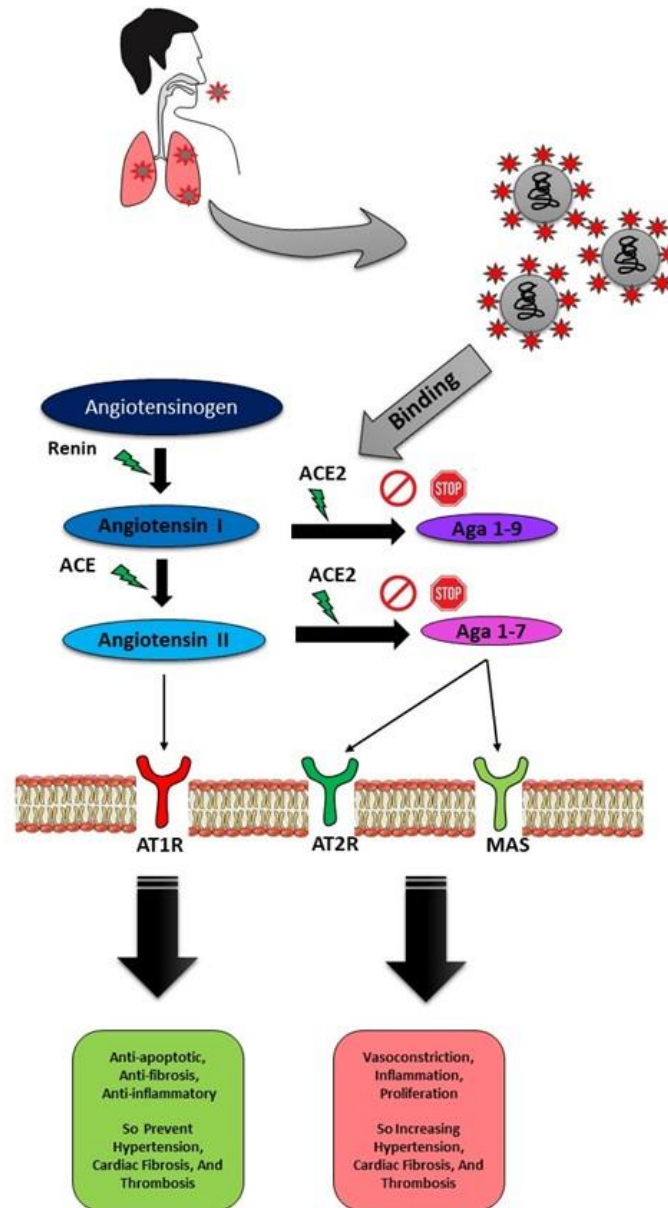


Figure1: SARS-CoV-2 infection signaling pathway in cardiovascular diseases.

Some COVID-19 patients develop thrombocytopenia, a severe pro-inflammatory state that can be difficult to manage. Studies show that myocardial injury and mortality risk are increased among COVID - 19 patients with thrombocytopenia. Systemic inflammation significantly contributes to myocardial injury (Borrelli *et al.*, 2021).

The mutations in the S protein increase the affinity and strength of its binding to the ACE2 receptor. Therefore, these signaling pathways associated with heart damage and inflammation are activated quickly, causing severe forms of the disease as a result of infection with concerning variants of SARS-CoV-2.

According to the study conducted on May 20, 2022, patients infected with B.1.617.2 (delta variant) had a higher rate of severe disease, intubation, coronary artery disease (CAD), hypertension, acute coronary syndrome, and mortality (Varga *et al.*, 2020).

The Delta variant is more contagious and causes more severe symptoms than the other variants. This is due to the mutation in S protein of Delta variant that increased the affinity of virus to the ACE-2 receptors on endothelial cells, which play an important role in the regulation of fibrinolysis and platelet aggregation (Varga *et al.*, 2020). Delta variant infection resulted in systemic thrombo-embolization, and cardiovascular damage. Recently, studies show the Omicron variant and its impact on heart attacks (Özköse *et al.*, 2022).

Conclusion

Mutations in the S protein have caused dangerous SARS-CoV-2 variants. So far, more than 30 mutations in the S protein have been reported, that increase the invasive properties of SARS-CoV-2 and cardiovascular damage. The mutations in the S protein increase the affinity and strength of its binding to the ACE2 receptor. Therefore, the signaling pathways associated with heart damage and inflammation are activated quickly, which deteriorates the normal function of cardio myocytes and myocardial injury and causes severe forms of the disease as a result of infection with concerning variants of SARS-CoV-2.

Acknowledgement: The authors would like to thank Ms. Firoozeh. Dara for improving the use of English in the manuscript.

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