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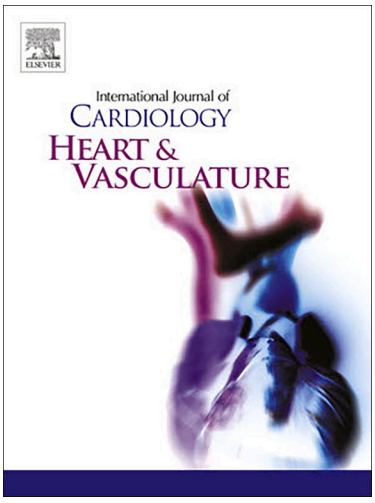

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Kamna Srivastava

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Association between COVID-19 and cardiovascular disease

Kamna Srivastava*

Molecular Cardiology Lab,
Dr. B R Ambedkar Centre for Biomedical Research,
University of Delhi, Delhi-110007
Tel: 0091-11-27666272
E mail: kamna_srivastava@hotmail.com; Kamna605@gmail.com
***Corresponding Author:**

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) has reached a pandemic level. SARS-CoV-2 infects host cells through ACE2 receptors, leading to COVID-19-related pneumonia. The rapid increase in confirmed cases makes the prevention and control of COVID-19 extremely serious. Real-time reverse transcription-PCR (RT-PCR) assays remain the molecular test of choice for the etiologic diagnosis of SARS-CoV-2 infection while radiographic findings (chest computed tomography [CT]) and antibody-based techniques are being introduced as supplemental tools. Novel virus also cause chronic damage to the cardiovascular system, and attention should be given to cardiovascular protection during treatment for COVID-19.

Acute cardiac injury determined by elevated high-sensitivity troponin levels is commonly observed in severe cases and is strongly associated with mortality. This review suggests that cardiovascular comorbidities are common in patients with COVID-19 and such patients are at higher risk of morbidity and mortality. The continuation of clinically indicated ACE inhibitor and ARB medications is recommended in COVID-19. We review the basics of coronaviruses, novel molecular targets for the coronaviruses with a focus on COVID-19, along with their effects on the cardiovascular system.

KEY-WORDS Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Antagonists, Comorbidity, Coronavirus, COVID-19, Heart Failure, Heart Transplantation, SARS Virus

INTRODUCTION In December 2019, a novel coronavirus (SARS-CoV-2) was identified in COVID-19 patients in Wuhan, Hubei Province, China and since then rapidly spreading across the world. On 11 March, the World Health Organization (WHO) declared COVID-19 a pandemic. The causative agent for this pneumonia has been officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the WHO. SARS-Cov2 virus is the pathogen responsible for COVID-19 **[1- 3]**. Active COVID-19 patients are those who have been diagnosed with the disease and are currently undergoing treatment in hospitals or are lodged in quarantine facilities. As the India gears up for the third lockdown from May 4, the total number of coronavirus patients in India has gone up to 33,050 while the death toll has reached 1,074, showed latest figures from the Health Ministry. The total number of active coronavirus patients in India stood at 23,651 while 8,324 have been have been cured of coronavirus. The health minister also said that the mortality rate in COVID-19 patients in India is 3% as compared to 7% globally and around 86% of the fatalities have been reported among those with co-morbidities like diabetes, hypertension, chronic kidney and heart related issues.

Novel virus strain, SARS-CoV-2, an enveloped, positive-sense, single-stranded RNA betacoronavirus of the family Coronaviridae. Coronaviruses infecting humans included several mild common cold viruses e.g. hCoV-OC43, HKU, 229E5. However, over the past two decades, highly pathogenic human coronaviruses have emerged, including SARS-CoV in 2002 and 2003 with 8,000 cases worldwide and a death rate of approximately 10%, and MERS-CoV in 2012, which caused 2,500 confirmed cases and a fatality rate of 36% **[4-6]**. The betacoronavirus genome encodes several structural proteins, including the glycosylated spike (S) protein that functions as a major inducer of host immune responses. This Spike protein mediates host cell invasion by both SARS-CoV and SARS-CoV-2 via binding to a receptor protein called angiotensin-converting enzyme 2 (ACE2) located on the surface membrane of host cells [**7-9]** .This invasion process requires S protein priming which is facilitated by the host cell produced serine protease TMPRSS2 [**8]**. The interaction between viral Spike protein and ACE2 on the host cell surface is of significant interest since it initiates the infection process. It is reported that binding affinity of SARS-CoV-2 S protein to ACE2 is about 10−20 times higher than that of SARS-CoV S protein **[4, 7].** Hence, it is speculated that this may contribute to the reported higher transmissibility and contagiousness of SARS-CoV-2 as compared to SARS-CoV [**10].** The rapid increase in confirmed cases makes the prevention and control of COVID-19 extremely serious **[2, 3]**.

The SARS-Cov2 virus achieves cell entry through an S (spike) high-affinity protein binding to the catalytic domain of the ACE2 receptor; pneumocytes are particularly vulnerable **[4]**. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells **[11-13]**. Moreover, it is known that not all pneumocytes are equally threatened by SARS-CoV-2 infection, but Type II pneumocytes are in greater danger, that really matters for short and long term prognosis in terms of acute lung injury and pulmonary fibrosis. There are a number of promising treatments and vaccines under investigation, but none with proven clinical efficacy at this time.

METHODS

The investigator reviewed and summarized the rapidly evolving data regarding evidence linking COVID-19 with increased morbidity and mortality from cardiovascular disease. Search methods and strategies for identification of studies Literature search was performed in WHO reports, PubMed, Scopus, Science Direct and also in American Heart Association journals, Nature, JAMA, BMJ and THE LANCET journals using following terms:ACE2, coronavirus, COVID-19 and 2019-nCoV, COVID-19 and CVD, Cardiovascular Risk and Diseases to find articles published from January 05 to May 20, 2020. Old data that had inappropriate topics and were not pertinent to the focused purpose of the study were excluded from the studies. Some of the information pertaining to India is taken from the Ministry of Health, Government of India as the data on infection, mortality and survival from COVID-19 are rapidly changing.

SARS-CoV-2 and Infection

SARS-CoV-2 is spread predominantly via respiratory droplets. Transmission may occur from both symptomatic and asymptomatic patients, with secondary infection rates ranging 0.5-5% **[13, 14]**. SARS-CoV-2 has been demonstrated to remain stable **[15]** and the median incubation time is 4-5 days and 97.5% will experience symptoms within 11.5 days of exposure **[16, 17]**. The most common symptoms are fever and dry cough, which are shared with many other viral syndromes. Conspicuously, rhinorrhea and diarrhea were also reported with COVID-19 in some cases [14] Reports from China **[18]** demonstrate that a significant majority of patients (81%) had mild symptoms (no pneumonia or mild pneumonia) from COVID-19. Among those with more significant symptoms, people experienced severe symptoms (dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen

ratio <300, and/or lung infiltrates >50% within 24 to 48 hours) and 5% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Predominantly, the clinical manifestations of COVID-19 are respiratory symptoms, some patients develop cardiovascular disorders **[3].** According to Coronavirus disease 2019 (COVID-19) Situation Report – 51 from World Health Organization, people of all ages can be infected by the new coronavirus. Research from early cases in China **[3]** suggests that some individuals are more vulnerable to the worst outcomes of the virus. The virus poses a particular risk to people over the age of 60 and those we have underlying medical conditions, including: Cardiovascular disease, Hypertension, Diabetes, Chronic respiratory disease, Cancer.

Diagnosis of COVID-19

Pathogen of COVID-19 has been detected in upper and lower respiratory tracts in initial assessments. It is also detected in fecal and blood samples. Real-time reverse transcription-PCR (RT-PCR) assays remain the molecular test of choice for the etiologic diagnosis of SARS-CoV-2 infection while radiographic findings (chest computed tomography [CT] and antibody-based techniques are being introduced as supplemental tools. RT-PCR is an expensive test and no access to diagnostic facility during COVID-19 pandemic advocates conducting new researches on other diagnostic approaches such as Chest- CT **[19]**. However, there are few limitations indicated with the use of RT-PCR test such as, long amplification time, complex processing, need for quality controlled laboratories, expensive and requirement of trained specialists.

The COVID-19 Treatment

With the exposure of ACE2 as a target for SARS-CoV-2 invasion, blocking the combination of virus and ACE2 has become one of the therapeutic directions. No approved drug regimen has been reported to treat infected cases so far. However, recently another proposed treatment Chloroquine, an old drug for treatment of malaria, has been suggested with apparent effectiveness and acceptable safety against COVID-19 associated pneumonia **[20, 21]**. While several drug trials are ongoing, there is currently no proof that hydroxychloroquine or any other drug can cure or prevent COVID-19. The misuse of hydroxychloroquine can cause serious side effects and illness and even lead to death. WHO is coordinating efforts to develop and evaluate medicines to treat COVID-19. Using monoclonal antibodies has not been proven in viral respiratory diseases and influenza, as yet **[22]**.

Steroids and methylprednisolone seem to be widely used in the recent pandemic. The effectiveness of other medicines and regimens such as Chloroquine, Vitamin C, and Chinese medicine, as well as Lopinavir/Ritonavir combination therapy and Remedesevir are being evaluated in China. To devise therapeutic strategies to counteract SARS-CoV-2 infection, it is crucial to develop a comprehensive understanding of how this coronavirus hijacks the host during the course of infection, and to apply this knowledge towards developing both new drugs and repurposing existing ones. Clinical trials are ongoing for treatment of COVID-19 with the nucleotide analog RNA-dependent RNA **[23-25].**

At present, the prevention and treatment of coronavirus is the most urgent research hotspot in the scientific and medical field. In addition to ACE2, are there any other targets for SARS-CoV-2 invasions. APN plays an important role in the survival of viruses - we can control the virus by inhibiting the expression of APN **[26]**. Studies have shown that the direct and specific binding of MERS-CoV S1 with human DPP4 leads to the occurrence of Middle East respiratory syndrome (MERS) **[27]**. AGO4 can combine with virus-derived siRNA (vsiRNA) to mediate the methylation of virus DNA and TGS, thus inhibiting the transcription and replication of virus **[28]**. The researchers further demonstrated that both SARS-CoV replication and invasion (mediated by the spike protein) were limited by the IFITM protein. IFITM limits the ability of various envelope viruses to enter the host and also regulates cell tropism independently of the expression of viral receptors. The sequence homology between SARS-CoV-2 and SARS-CoV viruses leads the prediction that IFITM can be a target for studies aiming to protect against new coronavirus invasion [29]. The following targets related to coronavirus research are APN, DPP4, AGO4, IFITM3, HSPA1B, ITGB6, TMPRSS2 and Cathepsin **[27-35]** are summarized in Table-1.

Angiotensin Converting Enzyme 2 and COVID-19

The RAAS is well characterized in hypertension, heart failure, and beyond. ACE2 is involved in heart function and the development of hypertension and diabetes mellitus. ACE converts angiotensin I (Ang I) to Ang II, predominantly in the lungs. The effects of Ang II are dependent on receptor binding: AT1 receptor binding stimulates the classical effects of Ang II, ranging from increased oxidative stress, through to vasoconstriction. ACE2 is an enzyme attached to cell membranes in the lungs, endothelium, and heart, as well as the kidneys. Its main pharmacological

effect is to lower blood pressure by catalysing the cleavage of Ang I to Ang 1-9 and of Ang II to Ang 1-7 (vasodilatory, anti-inflammatory activity). ACE2 has additional affinity for other vasoactive substrates, including apelin-13 and bradykinin. ACE2 has a strong affinity for type 1 and type 2 receptors of Ang II and regulates blood pressure, humoral balance, inflammation, cell proliferation, hypertrophy, and fibrosis. Moreover, the tissue specific expression of ACE2 suggests that it may play a role in regulating cardiovascular and renal functions and fertility. Several studies have indicated that both SARS-CoV-2 and SARS-CoV enter human cells through the ACE2 receptor on the surface of human cells. So comparing with tissues without ACE2, tissues expressing ACE2 are accessible to invade by the SARS-CoV-2 **[36, 37]**. This also lays a theoretical foundation for the main transmission and prevention methods of COVID-19.

There are reports that sex difference exists, with men having higher ACE2 levels. Higher circulating levels were reported in heart failure, atrial fibrillation, and renal disease **[38]**. SARS-CoV-2 shares both high sequence similarity and the use of the same cell entry receptor, angiotensin-converting enzyme 2 (ACE2), with severe acute respiratory syndrome coronavirus (SARS-CoV).

COVID-19 and Cardiovascular disorders

COVID-19 patients with pre-existing heart disease may suffer a heart attack or develop congestive heart failure. This due to a combination of the severe viral illness and its increased demands on the heart, increased heart rate compounded by low oxygen levels due to respiratory symptoms, myocarditis and increased propensity for blood clot formation. In addition to the increase in these heart problems, a more unusual condition called myocarditis has also been observed in COVID-19 patients. In addition, some patients with underlying cardiovascular diseases (CVDs) might have an increased risk of death **[3]**. COVID-19 also poses a challenge for heart transplantation, impacting donor selection, immunosuppression, and post-transplant management **[39-41]**. How does cardiovascular disease increase the risk of severe illness and death from COVID-19 and understanding the underlying mechanisms is of the greatest importance, so that treatment of these patients can be timely and effective and mortality reduced.

Clinical controversy with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with COVID-19

There has been a clinical controversy whether the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) might be detrimental or beneficial in COVID-19. These two classes of drugs are widely prescribed in patients with hypertension and cardiovascular disorders. We have reported **[42]** our work on ACE gene expression in patients with essential hypertension and normal healthy population. In another study **[43]**, we have reported the role of Angiotensin type I receptor in patients with essential hypertension and normal healthy controls as pathological and physiological differential expression at mRNA and protein levels. Individuals have proposed stopping such drugs due to concern over up-regulation of the ACE2 receptor acting as the SARS-CoV-2 entry point; others paradoxically suggest prescribing this class of drugs to counteract a dysregulated angiotensin–aldosterone system. Symptoms are more severe in patients with CVD, which might be associated with increased levels of ACE2 in these patients compared with healthy individuals. There is a links between the renin–angiotensin–aldosterone system (RAAS) and the ACE2 receptor specifically; expanding on the observation that hypertension is prevalent among those diagnosed with COVID-19 **[44-46]**. Whether patients with COVID-19 and hypertension who are taking an ACE inhibitor or angiotensin-receptor blocker should switch to alternative antihypertensive therapy remains controversial, and further investigation is required.

Antiviral drugs and CVD in patients with COVID-19

Antiviral treatments are used to alleviate the disease symptoms. Studies on Remedesevir, as an antiviral agent, revealed its in vitro activity against the COVID-19 virus and its safety was proven in Ebola trials. The drug is currently not approved for any indication globally [The US Food and Drug Administration (FDA) reviewed the investigational new drug (IND) application filed by the company for remdesivir to treat COVID-19 and granted investigational new drug authorisation to study the drug in February 2020]. Evaluating the efficacy of anti-influenza drugs such as Umifenovir and Oseltamivir against COVID-19 virus is interesting but lacks any biological plausibility. Many antiviral drugs can cause cardiac insufficiency, arrhythmia or other cardiovascular disorders. Antiviral drug induced heart damage during COVID-19 treatment is a

major concern and the monitoring of the risk of cardiac toxicity with the use of antiviral drugs is important. In a study of 138 patients with COVID-19, 89.9% were given antiviral drug **[1, 47]**.

Acute cardiac injury in patients with COVID-19

In a report by Huang et al **[3]** myocardial injury associated with the SARS-CoV-2 was found in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan. These patients had elevated cardiac troponin I (hs-cTnI) levels (>28 pg/ml) levels. In this report, four of five patients with myocardial injury were admitted to the intensive-care unit (ICU) and the systolic blood pressure levels were significantly higher in patients treated in the ICU than in those not treated in the ICU. Wang et al have **[48]** reported that out of 138 patients with COVID-19 in Wuhan, 36 patients with severe symptoms were treated in the ICU1. The levels of biomarkers of myocardial injury were significantly higher in patients treated in the ICU than in those not treated in the ICU (median creatine kinase (CK)-MB level 18 U/l versus 14 U/l, $P < 0.001$; hs-cTnI level 11.0 pg/ml versus 5.1 pg/ml, $P = 0.004$), suggesting that patients were having complications involving acute myocardial injury. · Among the confirmed cases of SARS-CoV-2 infection reported by the National Health Commission of China (NHC), some of the patients presented with heart palpitations and chest tightness rather than with respiratory symptoms and fever were later diagnosed with COVID-19. Therefore, in patients with COVID-19, the incidence of cardiovascular symptoms is high, owing to the systemic inflammatory response and immune system disorders during disease progression. The exact mechanism of cardiac involvement in COVID-19 remains unclear. One potential mechanism is direct myocardial involvement mediated via ACE2. ACE2 is widely expressed not only in the lungs but also in the cardiovascular system and, therefore, ACE2-related signalling pathways might have a role in heart injury. Other proposed mechanisms of myocardial injury include a cytokine involvement **[3-6]**, and respiratory dysfunction caused by COVID-19, is detrimental to myocardial cells. Some COVID-19 patients who appear to be having a heart attack are instead suffering from marked inflammation of the heart muscle, called myocarditis. It is not clear whether myocarditis is due to a direct effect of the virus on the heart muscle, or whether it is due to an overactive immune response to the virus, so doctors do not yet know how best to treat these patients. Coronavirus disease 2019 is associated with a high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias.

Patients with pre-existing CVD

Wu et al **[49]** reported in a 12-year follow-up survey of 25 patients who recovered from SARS-CoV infection that 68% had hyperlipidaemia, 44% had cardiovascular system abnormalities and 60% had glucose metabolism disorders. In these patients, the serum concentrations of free fatty acids, lysophosphatidylcholine, lysophosphatidylethanolamine and phosphatidylglycerol were significantly increased as compared to individuals without a history of SARS-CoV infection [49]. The most significant metabolic disruptions were the comprehensive increase of phosphatidylinositol and lysophospha tidylinositol levels in recovered SARS patients, which coincided with the effect of methylprednisolone administration investigated further in the steroid treated non-SARS patients with severe pneumonia. Authors further suggested that the high-dose pulses of methylprednisolone might cause long-term systemic damage associated with serum metabolic alterations. However, the mechanisms by which SARS-CoV infection leads to disorders of lipid and glucose metabolism are still uncertain. [According to the Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Version 6), elderly people with comorbidities such as hypertension, coronary heart disease or diabetes are more likely to be infected with SARS-CoV-2. Therefore, in patients with SARS-CoV-2 infection, underlying CVD can aggravate the pneumonia and increase the severity of symptoms. When infected with SARS-CoV-2, cardiac insufficiency is more likely to occur, in these patients. For patients with cardiac insufficiency who have underlying heart disease, SARS-CoV-2 infection might act as a precipitating factor to worsen the condition and lead to death. However, it has not been shown any causative role of such co-morbidities to SARS-CoV-2 infection. In fact, ACE2 expression had been shown to lower with age **[50]**.

Klok et al **[51]** evaluated the incidence of the outcome of venous thromboembolism (VTE) and arterial thrombotic complications in all COVID-19 patients admitted to the ICU of 2 Dutch university hospitals and 1 Dutch teaching hospital and they suggested that the composite outcome consisted of acute pulmonary embolism (PE), deep-vein thrombosis (DVT), ischemic stroke, myocardial infarction or systemic arterial embolism.

How has the India, lesser mortality by **the COVID-19 pandemic?**

According to Ministry of Health, Government of India, India's COVID-19 death rate of about 3.1% is much lower than 12.72% of Italy, 12% of UK, 9.73% of Spain, 3.4% of the US and 5.98% global

death rate. The fatality rate in India rises by approximately 30% if a person has cardiovascular disease, diabetes, chronic respiratory disease, or hypertension. There could be three possibilities:

1. India's 40-days lockdown may and Physical distancing is one of the best ways to slow the infection with COVID-19.
2. Researchers have proposed that the widespread BCG vaccination for tuberculosis, or resistance to malaria have helped India from the Covid-19 pandemic.
3. Medical experts belief that relatively young population, may be the reasons for the low mortality rate in India

These data might have different explanations: 1) the number of tests carried out, 2) What is the structure of the population and geographical conditions, 3) the percentage of smokers, however there is no significant association found between smoking and severity of disease, 4) the possible existence of a different virus strain, 5) Male female ratio in a locality as well as in population. Here, we cannot ignore the role of ethnicity as there could also be some peculiar genetic characteristics of the population that may have an impact on the susceptibility to viral infection, the disease severity.

CONCLUSIONS

COVID-19, caused by SARS-CoV-2, is a global pandemic. SARS-CoV-2 is thought to infect host cells through ACE2 to cause COVID-19, while also causing damage to the myocardium. However, the specific mechanisms are uncertain. Patients with underlying CVD and SARS-CoV-2 infection have an adverse prognosis. Cardiovascular comorbidities are common in patients with COVID-19 and such patients are at higher risk of morbidity and mortality. However, it is not known if the presence of cardiovascular comorbid conditions pose independent risk or whether this is mediated by other factors such as age, Gender, smoking status etc. Therefore, particular attention should be given to cardiovascular protection during treatment for COVID-19.

The continuation of clinically indicated ACE inhibitor and ARB medications is recommended based on the available evidence at this time. There are a number of promising treatments under investigation, but none with proven clinical efficacy to date. Extensive efforts are underway to find specific vaccines and antivirals against SARS-CoV-2. Meanwhile, cardiovascular risk factors and conditions should be judiciously controlled per evidence-based guidelines. Ethnicity might be

playing some role as there could be some peculiar genetic characteristics of the population that may have an impact on the susceptibility to viral infection, the disease severity. In addition to ACE2, are there any other targets for SARS-CoV-2 invasions such as APN, DPP4, AGO4, IFITM3, HSPA1B, ITGB6, TMPRSS2 and Cathepsin. These novel targets might provide some useful leads to guide scientific researchers to explore the molecular targets. Present review could help determine the researchers to define the molecular targets and clinical presentation of the virus, identify risk factors for infection to develop effective treatments and preventive interventions in COVID-19.

Table 1. Novel molecular targets related to COVID-19 research

Novel Targets	Common Name	Family	Explaination/s
DPP4	Dipeptidyl peptidase	proline-specific serine proteases	Specific binding of MERS-CoV S1 with human DPP4 leads to the occurrence of Middle East respiratory syndrome (MERS) **[27]**.
APN	aminopeptidase N	astrocyte antigen CD13	APN plays an important role in the survival of viruses which can be controlled by inhibiting the expression of APN **[26]**.
AGO4	Argonaute 4	endonuclease	AGO4 can combine with virus-derived siRNA (vsiRNA) to mediate the methylation of virus DNA thus inhibiting the transcription and replication of virus **[28].**
IFITM3	interferon induced membrane protein	interferon induced membrane protein	IFITM limits the ability of various envelope viruses to enter the host and regulates cell tropism independently of the expression of viral receptors **[29]**.
EGFR	epidermal growth factor receptor	transmembrane glycoprotein	Inhibition of EGFR signaling could prevent SARS and other respiratory viral infections from resulting in Pulmonary dysfunction **[30]**.
HSPA1B	heat shock 70 kDa protein 1B	heat shock proteins	Pulmonary endothelial injury is related to the expression of HSP-70 protein **[31-32]**.
ITGB6	Integrin	Transmembrane receptors	ITGB6 is expressed in pulmonary epithelial cells, and control over the occurrence of specialized pulmonary fibrosis **[33].**
TMPRSS2	transmembrane protease serine 2	protease serine 2	SARS-CoV-2 infection is caused by binding of the viral surface spike protein to the human ACE2 receptor following activation of the spike protein by transmembrane protease serine **[34].**
Cathepsin	endosomal protease	Protease	SARS-CoV infection was blocked by specific inhibitors of the pH-sensitive endosomal protease cathepsin **[35]**.

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CONFLICT OF INTEREST

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