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ACE2 enhance viral infection or viral infection aggravate the underlying diseases

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ABSTRACT

ACE2 plays a critical role in SARS-CoV-2 infection to cause COVID-19 and SARS-CoV-2 spike protein binds to ACE2 and probably functionally inhibits ACE2 to aggravate the underlying diseases of COVID-19. The important factors that affect the severity and fatality of COVID-19 include patients' underlying diseases and ages. Therefore, particular care to the patients with underlying diseases is needed during the treatment of COVID-19 patients.

Contents

1. Overview

The order *Nidovirales* includes four families: *Coronaviridae*, *Arteriviridae*, *Roniviridae*, and *Mesoniviridae* with positive-sense, single-stranded RNA genomes that may infect animals and humans [1–3]. The family *Corornaviridae* is divide into four main subgroups (or genera): α, β, γ, and δ. Alpha and β genus coronaviruses infect mammals while γ and δ viruses infect primarily birds. So far, only seven coronavirus members from the α and β subfamilies are found to infect humans. They are the α-coronaviruses HCoV-229E and HCoV-OC43, and the β-coronaviruses SARS-CoV

Abbreviations: COVID-19, Coronavirus Infectious Disease-19; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus −2 SARS-CoV-2, Middle East Respiratory Syndrome 2: MERS-2; ACE2, Angiotensin converting enzyme 2; ACEI, ACE inhibitor; SNP, Single Nucleotide Polymorphism; S, Spike: TMPRSS2, Transmembrane protease, serine 2; R0, Reproductive number; RAS, Renin-angiotensin system; RBD, Receptor binding domain; CVD, cardiovascular disease; PAH, pulmonary artery hypertension.

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(SARS-CoV-1), HCoV-NL63, CoV-HKU1, MERS-CoV, and SARS-CoV-2. HCoV-229E, HCoV-OC43, HCoV-NL63, and CoV-HKU1 produce the generally mild symptoms of the common cold [3,4]. SARS-CoV (SARS-CoV-1), MERS-CoV, and SARS-CoV-2 cause symptoms that are potentially severe. They use different receptors to enter their permissive cells for a successful infection and the receptors are summarized in Table 1. After entry to the permissive cells, the virus will reproduce viral particles and the replicated viral particles can be transmitted to other people to cause infectious diseases.

Alpha-coronaviruses and some β-coronaviruses often infect human but only cause mild diseases such as common cold [4–6]. However, some other beta-coronaviruses (CoV) have been imposing tremendous health problem to humans by causing severe acute respiratory syndrome (SARS) [7–9]. In the last two decades, three major outbreaks of beta-coronavirus infection have occurred, resulting in disastrous consequences to humans. The first pandemic originated from Guangdong province, China in November of 2002. It lasted for almost a year in the south of China and Vietnam, involved more than 30 countries, and ended up with 8096 cases and 774 deaths (https://www.who.int/csr/sars/country/table2004_04_21/en/). The patients appeared to have severe acute respiratory syndrome (SARS). This was also called SARS-1 and the virus was named SARS-CoV-1. The second beta-coronavirus pandemic occurred in Middle Eastern countries in 2012 and was hence named Middle East respiratory syndrome coronavirus (MERS-CoV) [10]. The infection was transmitted to 25 countries and resulted in 1360 cases and 527 deaths (http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-january-2020.html). The current (third) pandemic of beta-coronavirus (SARS-CoV-2) has affected almost all countries, resulting in the disease named COVID-19. Here, we attempt to analyze the available data from publications or from official WHO and USA CDC resources and underscore the associations between COVID-19 and its comorbidities.

2. SARS-CoV-2, origination of the COVID-19, and spreading.

Like other coronaviruses, SARS-CoV-2 is a single strand positive RNA virus with 29,811 nucleotides that encodes 12 putative open reading frames responsible for more than 26 proteins through ribosomal frameshifting and host proteasomal processing [11,12]. The first step of viral infection is attachment, which depends on the interaction of the viral surface with cellular receptors. The SARS-CoV-2 spike protein (S) is cleaved by the human furin enzyme to generate two subunits, S1 and S2, that are arranged to extrude outward from the viral particle. Both S1 and S2 play crucial roles for viral entry [3]. The S1 subunit binds to the host receptor angiotensin converting enzyme 2 (ACE2) (Table 1). While its binding to the membrane-bound ACE2 promotes viral attachment to infected cells, the soluble ACE2 might prevent viral infection by binding to S1 [13]. The S2 subunit, after S1′s interaction with ACE2, promotes viral fusion with the host cell membrane via interaction with transmembrane protease, serine 2 (TMPRSS2) and enables viral entry [3]. Interestingly, TMPRSS2 has the proteolysis effect on ACE2, which augments the entry of SARS-CoV-1 and probably CoV-2 [14–16]. After entry, viral particle is endocytosed to the endosome and uncoated in a pH-related manner. Viral RNA is released to the host endoplasmic reticulum (ER). Not only do viral protein translation and RNA transcription happen in the ER, but also viral polyprotein processing: viral subgenomic RNAs and stem looped RNAs are formed in the ER. Newly generated viral particles are assembled in the Golgi body for exit out of cells. The viral membrane protein (M), important for maintaining viral structure and the viral envelop protein (E) together play roles in viral assembly and release. Although the basis of viral replication is outlined as above, many aspects are still not understood, especially for the polyprotein processing, ribosomal frameshifting and formation of subgenomic RNAs. We will specifically discuss the interaction of SARS-CoV-2 with ACE2 in this minireview.

Viral origin has been a standing hot topic of SARS-CoV-2 for a variety of reasons. Here we trace the early published information that are more reliable than those from the mass media. The first two confirmed COVID-19 cases occurred in Wuhan, China on December 8th and 10th of 2019. The patients never went to the Huanan seafood market that was disputed to be a potential origin of SARS-CoV-2. In the next 10 days (December 13 to 23), more cases were found. Among the total 25 cases found during these 10 days, 15 patients went to the seafood market; therefore, the seafood market was argued to be the origin of SARS-CoV-2. An epidemiological analysis of the first 425 cases in Wuhan found that most subsequently obtained infections were not originated from the Huanan seafood market [17]. It is now more or less denied by epidemiologists that the Huanan seafood market could have any link with the virus [18,19]. However, the seafood market origin of SARS-CoV-2 became mythologized. The outbreak in Wuhan caused the viral spreading to other provinces in China by late January while it was later transmitted to other countries: first to Thailand, then USA, France, Germany and Italy. Sothern Korea and Italy are among the first countries with outbreaks in February [17,20]. It quickly became a pandemic and affects more than 200 countries now with more than 3 million cases and over 200,000 deaths globally.

A previously isolated bat coronavirus (BatCoV RaTG13) has been identified that shares more than 96% homology in nucleotide sequences and more than 97% homology in amino acid sequences with SARS-CoV-2 [21]. This study implied that the SARS-CoV-2 might have originated from bats. However, bats are not a common resident animal in the city of Wuhan. Therefore, an intermediate host for SARS-CoV-2 is believed to exist assuming it is a zoonotic virus. One study found that a coronavirus isolated from the pangolin is 91.02% and 90.55% identical in nucleotide sequences to SARS-CoV-2 and BatCoV RaTG13, respectively [22]. Another study showed that SARS-CoV-2 is possibly associated with coronaviruses derived from some wild animals, including *Paguma larvata*, *Paradoxurus hermaphroditus*, in the same branch of the phylogenetic tree [23]. However, they all are unlikely the intermediate host because the genome and ORF1a homology show that the virus is not even close to SARS-CoV-2. Given SARS-CoV-2 is originated from bat RaTG13, the virus from the intermediate host should be closer to SARS-CoV-2 than to the RaTG13. Although it is difficult to find it, the intermediate host is still the interest of virologists [24,25]. Surprisingly, a research group screened the susceptibilities of different companion animals to SARS-CoV-2 infection and found that cats and ferrets are very susceptible to SARS-CoV-2. On the contrary,

Table 1
The Receptors for the Human Pathogenic Coronaviruses.

Subfamily	Name	Receptor
alpha-coronavirus	HCoV-229E	aminopeptidase N (APN) [3,82]
alpha-coronavirus	HCoV-OC43	N-Acetylneuraminic acid (Neu5Ac or NANA) [10,83]
beta-coronavirus	SARS-CoV-1)	angiotensin converting enzyme 2 (ACE2) [10,62,84]
beta-coronavirus	HCoV-NL63	angiotensin converting enzyme 2 (ACE2) [10,64]
beta-coronavirus	CoV-HKU1	dipeptidyl peptidase 4 (DPP4) [10,85]
beta-coronavirus	MERS-CoV	dipeptidyl peptidase 4 (DPP4) [10,86]
beta-coronavirus	SARS-CoV-2	angiotensin converting enzyme 2 (ACE2) [21,68]

SARS-CoV-2 poorly infects and replicates in dogs, pigs, chickens, and ducks [26].

3. Underlying diseases of COVID-19 and the Renin-angiotensin system (RAS).

The first recorded COVID-19 case in the USA was in Seattle, Washington on January 19th, 2020 in a patient who traveled back from Wuhan, China. Two days later, cases were reported in Chicago on January 21st, 2020. Another two days later, COVID-19 cases were confirmed in California and Arizona. These early cases all occurred in patients who traveled from China. Due to its highly contagious nature, SARS-CoV-2 has proven catastrophic in both prevalence and fatality in the United States. The most important difference between SARS-CoV-2, SARS-CoV-1 (2002) and MERS-CoV (2009) is that SARS-CoV-2 is highly contagious with a much higher reproductive number (R0) of 5.7 [27] or 3.57 [28] is rapidly spreading to other countries and territories to cause COVID-19. More importantly, epidemic data suggests that the COVID-19 might become a seasonal pandemic at a similar or even a larger scale [29]. Although the final fatality rate is the most accurate and can only be obtained when the pandemic is over, the current data shows that it could be very high in some countries. Interestingly, the fatality by COVID-19 clearly correlates with whether the patients have one or more underlying diseases. The CDC webpage have listed 10 high-risk underlying diseases; the top comorbidities include hypertension and cardiovascular diseases (CVDs) [30–33] and occur at significantly higher rates in the African American and non-white Hispanic groups in the USA [34].

The abovementioned comorbidities of COVID-19, hypertension, DM and CVDs, are closely associated with RAS signaling. Angiotensin I is generated from angiotensinogen by renin after being stimulated by several conditions such as low blood pressure, bleeding and dehydration [35–38]. Angiotensin I is then converted to angiotensin II by angiotensin converting enzyme (ACE) [39,40]. Angiotensin II constricts vasculature to elevate the blood pressure. Therefore, abnormally high levels of angiotensin II cause hypertension and also aggravate DM sequelae and induce CVDs as shown in Fig. 1. Several ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been clinically used to treat the relevant diseases. Angiotensin II can be subsequently hydrolyzed by ACE2 to generate angiotensin peptides, mainly Angiotensin-[1–7], also called Ang-(1–7) [41]. Ang-(1–7) is a vascular dilator and hence reduces blood pressure (See Fig. 1). ACE II also hydrolyzes the angiotensin I to other peptide angiotensin such as Angiotensin-[1–9] that is another vascular dilator [42–44]. Therefore, the RAS signaling is a balanced system that must be maintained for the healthy cardiovascular system with normal blood pressure and normal cardiovascular function.

A theory for explaining how the aforementioned comorbidities significantly increase the fatality of COVID-19 was based on the fact that these patients have a history of taking drugs such as ACEIs, ARBs and ibuprofen [45,46]. These drugs not only inhibit ACE but increase the level of ACE2 as well. The increase of ACE2 might elevate the chances of infection of SARS-CoV-2, which directly relates to the viral infection and fatality. This theory is shown in the left side of Fig. 1 as "ACE2 enhancing viral infection" [45,46]. However, this theory does not explain why the onset of COVID-19 in these patients is so rapid that an emergent rescue is needed and many of them still die. Furthermore, it contradicts the recently published reports that using ARBs and ACEIs improved COVID-19 [47–49]. Some critical reviews analyzed the available evidence and found that it does not support a deleterious effect of RAS blockers in COVID-19 [50–52]. Therefore, it is suggested that there is currently no reason to discontinue RAS blocking ACEIs in stable patients who suffer from the COVID-19 [50].

ACE2 is a cell membrane protein in lungs, arteries, heart, kidney and intestines [53–55]. ACE2 converts angiotensin II to peptide Ang-(1–7) or angiotensin I to peptide Ang-(1–9); both peptides are vasodilators [35,41,56–58]. Therefore, ACE2 physiologically reduces blood pressure and is anti-hypertensive when the angiotensin II is elevated. SARS-CoV-2 spike protein (S) is cleaved by the human furin enzyme to generate S1, which binds to the host receptor, ACE-2. It is possible that the released free spike or the cleaved S1 protein in the blood might bind to cellular membrane ACE2 of heart, artery and alveolar lung cells to block the conversion of Angiotensin II to Ang-(1–7) and/or Angiotensin I to Ang-(1–9), which is consistent with a previous experimental result on SARS-CoV-1 [59]. The interaction with SARS-CoV-2 S protein might exhaust ACE-2 or damage ACE-2 function. Therefore, our hypothesis, as shown in the right side of Fig. 1 as "Viral aggravating existing diseases", is that comorbidities in COVID-19 patients are aggravated by the infection of SARS-CoV-2 to causes higher fatalities because the viral S protein interacts with ACE2 to inhibit ACE2 function. This hypothesis is also supported by a clinical finding that an imbalance of the AngII-ACE2-Ang- (1–7) axis occurs in human pulmonary artery hypertension (PAH), with reduced ACE2 levels implicated in the pathogenesis of severe PAH [60]. However, an animal study demonstrated that ACE2 level in lung is low and that Prolyloligopeptidase (POP) is the main enzyme responsible for Ang II conversion to Ang-(1–7) in the lungs [61]. Therefore, an alternative mechanism might exist when ACE2 is exhausted in COVID-19 patients.

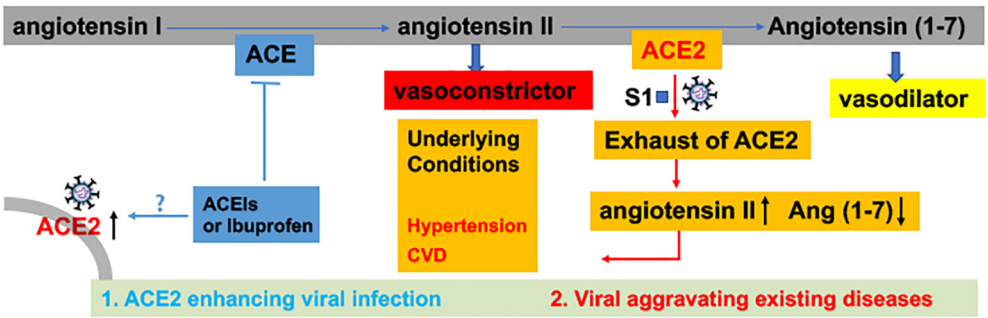

Fig. 1. Two theories to explain the severity of COVID-19: 1. ACE2 enhancing viral infection, and 2. Viral aggravating existing diseases. ACE catalyzes the conversion of angiotensin I to angiotensin II, a vasoconstrictor. Angiotensin II is converted by ACE2 to Angiotensin-(1–7), a vasodilator. Theory 1 suggests that using ACEI/ARB increases ACE2, which further enhances viral infection. Theory 2 suggests that ACE2 can be either exhausted or functionally inhibited by S1 so that more angiotensin II and less Angiotensin-(1–7) are produced, which would aggravate underlying diseases.

4. ACE2 and spike protein

ACE2 is the receptor of spike proteins of beta-coronaviruses including SARS-CoV-1, HCoV-NL63 and SARS-CoV-2. Li et al. (2003) isolated ACE2 from SARS-CoV Vero E6 cells [62]. They found a high-affinity binding between ACE2 and the S1 domain of SARS-CoV-1 spike protein and showed that anti-ACE2 antibody could inhibit viral replication in Vero E6 cells. They reported the crystal structure of SARS-CoV-1 envelope-anchored spike protein with ACE2 [63]. The receptor-binding domain (RBD) of SARS-CoV-1 spike protein includes a core and a receptor-binding motif (RBM) that specifically recognizes ACE2. The interactions between RBD and ACE2 are critical for the host range and cross-species infections of SARS-CoV-1. A study of receptor analysis showed that human coronavirus NL63 (HCoV-NL63) spike protein uses ACE2 as the receptor for infection of SARS-CoV [64]. Unlike SARS-CoV-1 and SARS-CoV-2, HCoV-NL63 infects mainly children and causes only mild respiratory disease [65]. Both SARS-CoV-1 and SARS-CoV-2 can cause severe acute respiratory syndrome. The amino acid sequence similarities of SARS-CoV-1 and SARS-CoV-2 in the spike protein, RBD, and RBM are 76%, 73% and 50%, respectively [66]. A novel furin cleavage site was identified at the boundary between the S1/S2 subunits of SARS-CoV-2 but not in SARS-CoV-1 and other closely SARS-related CoVs [67]. Recent studies revealed that SARS-CoV-2 uses ACE2 as a receptor for cellular entry [67,68]. SARS-CoV-2 first binds to ACE2 via RBD of its spike protein and then fuses viral and host membranes [67]. The study also showed that SARS-CoV-1 spike polyclonal antibodies block SARS-CoV-2 mediated entry into host cells and cross-neutralizing antibodies may provide protection against SARS-CoV-2 [67].

Structure analyses of SARS-CoV-2 spike protein with ACE2 complex have elucidated that the efficiency of ACE2 usage is the key determinant of SARS-CoV-2 transmissibility [67,69,70]. In the presence of the amino acid transporter B0AT1, the human ACE2 structure can form a dimer of heterodimers via its collectrin-like domain [70]. The peptidase domain of ACE2 can interact with the RBD of SARS-CoV-2 spike protein through polar interactions, and the mode of binding interface is similar to that between SARS-CoV-1 and ACE2 [70]. Walls et al. determined cryo-EM structures of the SARS-CoV-2 spike ectodomain trimer in open and closed conformations [67]. In the closed conformation, the ACE2 binding motifs are buried at the interface between protomers. SARS-CoV-2 spike protein can recognize ACE2 in the open conformation and initiate membrane fusion and viral entry. They also showed that the binding affinity of SARS-CoV-2 and ACE2 is comparable to or higher than those for SARS-CoV-1. Wang et al. reported the crystal structure of SARS-CoV-2 spike RBD with human ACE2 [69]. They identified more contacted residues and larger buried surface areas in SARS-CoV-2/ACE2 than in SARS-CoV-1/ACE2 complex. As shown in Fig. 2, SARS-CoV-2 binds to ACE2 via the RBM of its spike RBD. Key residues in ACE2 can strengthen the binding affinity of SARS-CoV-2/ACE2 complex (Table 2). For example, ACE2 residue S19 can form a strong polar contact with SARS-CoV-2 residue A475, where some monoclonal antibodies could not effectively neutralize the viral mutation A475V in this site [71]. D355 in ACE2 can form hydrogen-bonds with T500 and G502 in SARS-CoV-2. Molecular dynamics study suggested that D355 is involved in a critical hydrogen-bonding network of RBD-ACE2 interaction [72]. ACE2 residue M82 and SARS-CoV-2 residue F486 are involved in hydrophobic interactions at the interface. F486 has been identified as a binding site for neutralizing antibodies [73]. These results explain the efficient transmission of SARS-CoV-2 in humans.

The sequence variants in ACE2 have been found to be related to human complex disorders. Several case-control association studies identified the ACE2 genetic single nucleotide polymorphisms associated with hypertension [74,75]. The coding mutations in key residues of ACE2 may alter the binding affinity of SARS-CoV-2/ACE2 complex and change pathogenicity of ACE2. High-throughput

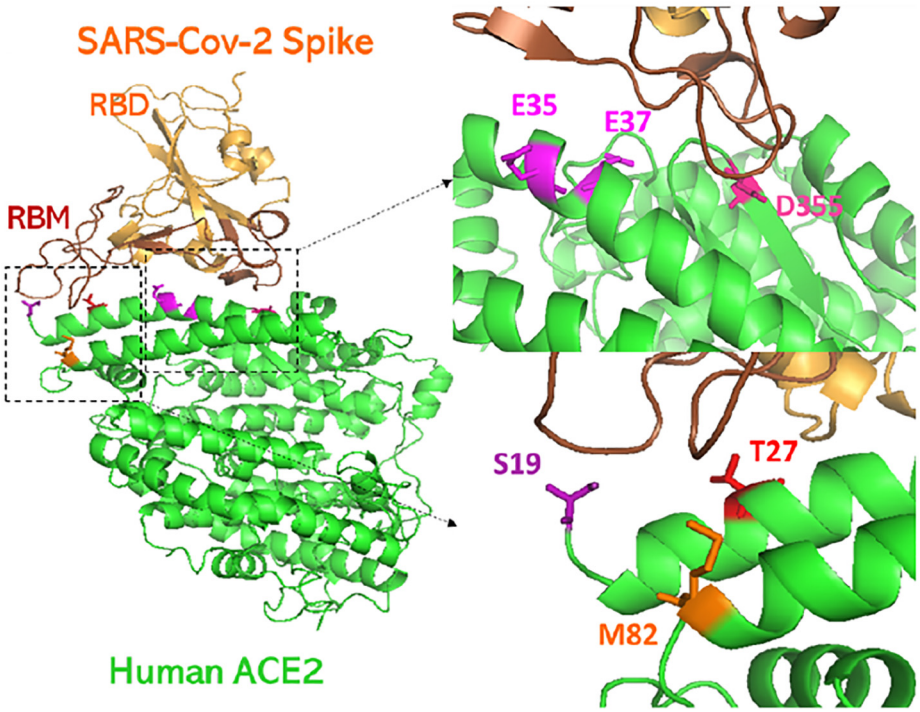

Fig. 2. The structure of human ACE2 with SARS-Cov-2 Spike RBD: Human receptor ACE2 (green), SARS-CoV-2 spike receptor-binding domain (RBD, yellow orange) and receptor-binding motif (RBM: brown) were shown as cartoons. ACE2 contacted residues, including S19 (purple), T27 (red), E35 and E27 (magenta), M82 (orange) and D355 (hot pink), were displayed as sticks. The image was generated using PyMOL (http://www.pymol.org/) based on PDB ID: 6LZG. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Effects of human single nucleotide variants located in contact residues at the SARS-CoV-2 RBD/ACE2 interface.

dbSNP	Mutation	Binding Affinity Prediction			Mutation Pathogenicity Prediction				Allele Count in Different Populations				
		Distance-to-interface	Change	Affinity	SIFT	Polyphen2	REVEL	CADD	African	Latino	East Asian	European (Finnish)	European (non-Finnish)
rs73635825	S19P	2.83	0.086	Increasing	Tolerated	Probably Damaging	0.166	1.862	63	0	0	0	0
rs781255386	T27A	3.498	1.004	Increasing	Tolerated	Benign	0.021	0.787	0	2	0	0	0
rs1348114695	E35K	2.693	−0.668	Decreasing	Tolerated	Benign	0.022	0.303	0	0	2	0	1
rs146676783	E37K	3.314	−1.226	Decreasing	Tolerated	Probably Damaging	0.163	2.669	2	0	0	6	0
rs766996587	M82I	3.382	−0.521	Decreasing	Tolerated	Benign	0.016	−0.646	5	0	0	0	0
rs961360700	D355N	3.547	−0.901	Decreasing	Deleterious	Probably Damaging	0.430	3.005	0	0	0	0	2

The effects of variants on binding affinity were predicted using mcsm-ppi2 (http://biosig.unimelb.edu.au/mcsm_ppi2/). Mutation pathogenicity predictions were extracted from dbNSFP (https://sites.google.com/site/jpopgen/dbNSFP). Allele counts in different populations were downloaded from gnomAD (https://gnomad.broadinstitute.org/).

sequencing technologies have been used to identify the rare single nucleotide variants (SNVs) in different populations. We collected 227 missense variants from the Genome Aggregation Database (gnomAD: https://gnomad.broadinstitute.org/). Of 227 missense SNVs, 6 rare mutations can be mapped onto the contact residues at the SARS-CoV-2 RBD/ACE2 interface (Table 2 and Fig. 2). S19P (rs73635825) and T27A (rs781255386) have positive binding energy changes, indicating that these two SNVs can increase the ACE2-RBD binding affinity. S19P has 63 alleles (0.3% allele frequency) in the African population. S19 is interacting partner of SARS-CoV-2 residue A475 [69]. It's observed the SARS-CoV-2 mutation A475V can reduce the sensitivity to some monoclonal antibodies [71]. The increased binding affinity may result the SARS-CoV-2 mutant became resistant to neutralizing antibodies. In addition, S19P in African population is predicted as a possibly damaging variant. In contrast, T27A present in Latino population are predicted to be a benign variant. The other four mutations (E35K, E37K, M82I and D355N) have negative binding energy changes and can weaken the binding affinity of SARS-CoV-2/ACE2 complex. One possible explanation is that these mutations can disrupt the interaction network of protein complex. For example, D355 forms a hydrogen bond with SARS-CoV-2 residues T500 [72], D355N (rs961360700) in European population (non-Finnish) can break this hydrogen-bonding network and reduce the protein–protein interaction between SARS-CoV-2 spike RBD and ACE2. These findings indicate that the sequence variants in different populations can have different effects on protein function of ACE2 and the protein–protein interaction between ACE2 and SARS-CoV-2 spike protein, which may result in the different health disparities of COVID-19.

5. COVID-19 and health disparities.

Different disparities have been reported in populations with COVID-19 whose deaths are related to older age, male sex, and concomitant diseases [34]. First, it was noted that the deaths caused by COVID-19 clearly associate with age of the patients. This was first reported for the COVID-19 populations in Wuhan, China [76] where the median age of patients who died was 75 (range 48 to 89). Another study estimated the death rate in China was 0.66% and was increasing by age to 6.4% for age 60 and older, and to 13.8% for age of 80 or older [77,78]. A similar situation was confirmed in UK with 80% of COVID-19-related deaths in those aged 65 years and over and in the USA with those in the 65–84 years age group accounting for 25% of cases, 46% of intensive care unit admissions and 46% of deaths [79,80]. The link between death rate and age has been observed in many countries [81].

Many factors could connect age to COVID-19-caused fatalities. One of the important facts is that the aforementioned comorbidities of hypertension, DM and CVDs are less common in younger people than that in older people. The underlying diseases links to both the case fatality of COVID-19 and the economically disadvantaged groups and/or socially isolated communities. For example, as Dr. Yancy summarized [34], 1) more than 50% of COVID-19 cases and nearly 70% of COVID-19 deaths involve African American individuals, although they make up only 30% of the population in Chicago; 2) 70.5% of deaths have occurred among African American persons, who represent 32.2% of the state's population in Louisiana; 3) 33% of COVID-19 cases and 40% of deaths have occurred among African American individuals, who represent 14% of the population in Michigan; and 4) New York City is the epicenter of COVID-19 in the USA, African Americans and Hispanics have accounted for 28% and 34% of deaths, respectively (population representation: 22% and 29%, respectively). Dr. Yancy also noted that it is likely that some, if not most, of these differences in disease rates and outcomes will be explained by concomitant comorbidities. However, it is possible that the majority of the disparity has to do with access to healthcare, education about the virus and its symptoms, or other well-documented socioeconomic disparities in US healthcare.

The claims that COVID-19 disproportionately affects the individuals of minority groups and aged people are not only supported by reported data but also by our hypothesis that SARS-CoV-2 infection generates spike protein that interacts with ACE2 to either exhaust ACE2 or inhibit ACE2 function or both so that the comorbidities are aggravated (Fig. 1). The top comorbidities in COVID-19 patients are hypertension, and cardiovascular disease, all of which are directly related to ACE2. Therefore, we suggest that ACE2-SARS-CoV-2 spike interaction is a specific target not only for treatment of the severe diseases but also for prophylactic control of the infection of SARS-CoV-2. The strategies of using the target might be better against the spike protein of SARS-CoV-2 than ACE2 because targeting ACE2 per se might impose a detrimental effect on the patient who has the underlying diseases.

6. Final remarks

Here we reviewed recently published information with regard to COVID-19, especially the biological role of ACE2 in the pathogenesis of COVID-19 and certain comorbid diseases. We hypothesized that ACE2 plays a key role in the severity and fatality of COVID-19 and viral infection exhausts ACE2 or functionally inhibits ACE2 to aggravate the comorbidities of COVID-19 patients. Our hypothesis emphasizes the relationship between COVID-19 and the comorbid diseases which not only interpret high fatalities of COVID-19 in aged people but may also contribute to socioeconomic disparities of COVID-19. The medical intervention strategies

of using the target might be better against the spike protein of SARS-CoV-2 than ACE2 because targeting ACE2 per se might impose a detrimental effect on the patient who has the underlying diseases.

Declaration of Competing Interest

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

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