# ACE-2 in the highlight of COVID-19
# A proposed pathology and potential correlations

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## Abstract:

Pneumonia caused by the novel corona virus has derived the whole world into an emergency situation, bringing to mind similar epidemics including H1N5, dengue, SARS-CoV and MERS. Although SARS-CoV-2 didn't result in such a huge number of deaths when compared to, for example, Spanish influenza, it is categorized as having high infectivity rate. The trials to control the spread of the virus are often challenged by the lack of knowledge which means more time is needed to build a view regarding the pathological actions of the virus in order to properly target it. Recent reports declared that SARS-CoV-2 uses ACE-2 as a means to infect cells. This paper aims at addressing briefly the protective roles of ACE-2 in the lungs and the brain based on previous literature review and studies on other viruses that also use ACE-2 as a target for cellular entry. We hypothesized that COVID-19 pathology may be a consequence of viral Mediated down-regulation of ACE-2. In addition, we provided insights on the potential correlation between COVID-19 severity and male gender or smoking.

## Key Words:

ACE-2, SARS-CoV-2, COVID-19, Smoking, Gender

## Introduction:

COVID-19 has become an immense concern to the world since the outbreak of the novel coronavirus (recently named the SARS-CoV-2) in Hubei, China. Local Chinese news agencies traced back the first confirmed COVID-19 case to Wuhan on 17th of November 2019. This outbreak has later been declared a global pandemic by the WHO since its unexpected spread to several countries including Japan, Iran, South Korea and Italy, leading to respiratory failure, and subsequent death to thousands of victims around the world.[1] Zhou et al., pointed to Angiotensin-converting enzyme-2 (ACE-2) as the potential functional receptor for SARS- CoV-2 which has been confirmed after by the analysis of the receptor binding motif.[2–5] ACE-2 was shown to be found in various tissues including the lungs, the brain, the intestines, the liver and the heart, where it is supposed to play beneficial effects to these tissues.[6] In context, ACE-2 has been reported to be up-regulated in certain disorders such as hepatic or cardiac injury possibly as a compensatory mechanism to ameliorate or inhibit pathological alterations.[7,8] Moreover, ACE-2 has been recognized to be homologous to ACE with counteracting functions. Where ACE is known to catalyze the conversion of Ang-I to the vasopressor agent Ang-II through the removal of two amino acids from the C-terminus of the peptide chain, ACE-2 cleaves another amino acid from Ang-II to produce Ang-(1-7) with vasodilating properties.[8] Recently, lungs have been identified as the primary site that exhibits manifestations secondary to SARS-CoV-2 infection. However, few reports suspected viral dissemination into the brain, and we aimed to provide a summary of Clinical trials that concluded the protective roles of ACE-2 in the lungs and brain.

## ACE-2 & SARS-CoV-2 and lungs:

ACE-2 is believed to display protective functions in lungs. A study showed that ACE-2 knock out mice was severely affected by ARDS triggered by acid aspiration and sepsis in respect to wild type mice.[9] These results were consistent with another study concluded that H5N1 infection in ACE-2 KO mice caused them to survive for a short period and to exhibit more pronounced complications as compared to wild type mice while the administration of a recombinant human ACE-2 prolonged the overall survival of infected mice, and resulted in an apparent decline in the H5N1-induced lung histopathology.[10] The same study reported an increased serum Angiotensin-2 levels combined with down-regulation of ACE-2 expression in the lungs secondary to H5N1 infection. The symptoms reported in this study included, pulmonary edema, increased inflammatory cell infiltration and alveolar wall thickness, formation of hyaline membranes and proteinaceous debris which are similar to those experienced due to SARS-CoV-2 infection as shown in the study by Tian and colleagues describing clinical manifestations in two patients presenting with COVID-19.[10,11] Interestingly, it was found that SARS-CoV which has been shown to be a homolog of SARS-CoV-2 down-regulates ACE-2 through its spike protein after cell entry which could also be linked to the current SARS-CoV-2 induced pathology.[12]

## ACE-2 & SARS-CoV-2 and the brain:

Few studies attributed the fatal effects of COVID-19 to a neurological origin. For instance, Li et al demonstrated the presence of SARS-CoV infection in the brains of both patients and animal models in which the brainstem was severely affected, and highlighted the development of neurological symptoms in patients with COVID-19 which included headache, nausea and vomiting.[13] Although the presence of SARS- CoV-2 in the brain has not yet established, the presence of its closely related SARS-CoV, together with H5N1 that both rely on ACE-2 receptors to enter the cells in the cerebrospinal fluid obtained from infected people suggests, it could also happen with COVID-19.[13,14] This is supported by the findings reported by Mao and colleagues showing that about 88%

of patients presented with COVID-19 experienced neurological symptoms including cerebrovascular manifestations and altered consciousness.[15] These findings suggest that the potential SARS-CoV-2 mediated down regulation of ACE-2 expression in the brain combined with the substantial increase in angiotensin-2 activity might be a cause. Consistently, a study showed that ACE-2 KO mice exhibited a significant decline in cognitive function accompanied by an increase in oxidative stress and decreased SOD-3 levels.[16]

Impairment of the cardiorespiratory center in the brainstem secondary to infection is another proposed pathology that is suggested by Li et al since the nucleus of the solitary tract and nucleus ambiguous are located right there.[13] The nucleus of the solitary tract receives sensory afferent neurons from the mechanoreceptors and chemoreceptors present in the lungs, while both provide innervation to the smooth muscles and blood vessels of the airways.[17,18] One more study showed that SARS-CoV could disseminate into the brain following clearance from the lungs.[19] However, it appears that SARS-CoV-2 might follow a complicated cascade that encompasses all previously proposed pathologies which will of course need further investigation such as obtaining a differential expression of ACE-2 during early and late stages of the disease to specify the best action that must be taken in order to reverse it.

## SARS-CoV-2 and gender:

Clinical epidemiological studies showed that males had a higher fatality rate (64 % vs 36%) and are more prone to experience severe complications secondary to COVID-19 infection than females (67% vs 33%) proposing a potential correlation between disease severity and gender.[20,21] A recent study that is not peer reviewed , stated that ACE-2 is highly expressed in Asian men which might be a predisposing factor for this specific population other than women or patients of other ethnicities, providing that ACE-2 is the entry point for SARS-CoV-2 into the cells.[22] This is consistent with another study showed that renal ACE-2 expression and activity are relatively high in male mice than females (1.6 and 1.5 fold respectively) while the treatment with 17 β-estradiol resulted in a diminished ACE-2 activity.[23] However, these findings seem contradictory to another recent study concluded that a negative correlation does exist between ACE-2 expression and COVID-19 fatality.[24] On the contrary, the same study reported that ACE-2 expression is significantly higher in Asian females compared to males and other ethnicities where it is induced by either androgen or estrogen, and decreases by old age in both genders.[24]

Taking everything into account, it appears that ACE-2 over- expression is not a risk factor for contracting the infection as evidenced by the incidence rate being (51% for males and 49% for females), but it might be contributing to disease severity in terms of heavy viral load that would then result in severe down- regulation of ACE-2 causing the host to experience more suffering.[25] In context, it has been reported that ACE-2 expression is slightly increased at low SARS-CoV titer, but significantly decreased at higher viral titer or with time after infection without missing that inflammatory mediators also play a role in this repression.[24] Moreover, the high fatality rate among males may be also explained by being the population that carries the highest risk for cardiovascular diseases which have been reported to be a co-morbidity with COVID-19.[20] In addition, it was reported that the serine protease TMPRSS2 which has been identified as a possible target for SARS-CoV-2 is expressed in spermatogonia besides the presence of ACE-2 in spermatogonia, Leydig and Sertoli cells of human testicles which would mean high tendency of viral dissemination into various organs than females and consequently more pronounced symptoms.[2,25]

## SARS-CoV-2 and smoking:

Furthermore, Cai issued a potential correlation between smoking and the severity of COVID-19.[26] Although he stated that this suspected predisposition is insignificant based on the study conducted by Zhang and colleagues, the changes that smoking induce into the lung epithelium which would vary according to the years of smoking and the number of cigarettes smoked per day could be a cause.[26,27] Studies showed that smoking destroys ciliated epithelium and disrupts its function which protects the lungs through the production of mucus and rapid clearance of pathogens leaving smokers at high risk of experiencing more complications due to respiratory infections than non-smokers.[28] Interestingly, a study revealed that ACE-2 which has been shown to be a lung-protective, is predominantly found in cilia implicating the potential role of smoking in disease severity.[29] Moreover, smoking has been reported to down-regulate CXCL-10, a chemokine that is important for the recruitment of macrophages, neutrophils and natural killer cells, minimizing the capacity of the innate immune system to suppress viral replication.[30] This is evidenced by another study showed that CXCL-10 and its receptor CXCR-3 are highly expressed in the lungs of mice infected with SARS- CoV in an attempt to clear the virus which strongly suggests a link between smoking and the severity of COVID-19.[19]

## Conclusion:

In brief, it seems that SARS-CoV-2 is capable of inducing pathology to most of the tissues that express ACE-2 which would result in varying disease outcomes depending on the patient immune status or the existence of other health complications. We also provided new insights on the possible underlying causes that contributed to increased disease severity in patients who are males or smokers, and hypothesized that COVID-19 pathology may arise from viral Mediated down-regulation of ACE-2. In context, we recommend obtaining a differential expression of ACE-2 during early and late stages of the disease to be able to confirm our hypothesis. This could be carried out either in humans or mice models, however the latter is preferred, because they could be sacrificed to observe the different effects of the disease on all tissues expressing ACE-2 such as the brain, the lungs, the heart, the liver, the kidneys, the intestines and the testicles providing us a detailed overview of the pathological cascades mediated by the virus which would accordingly reflect on the actions that must be employed to eliminate patient suffering. In case of a confirmed link between disease severity and down-regulation of ACE-2, clinical trials using recombinant human ACE-2 should be immediately initiated.

## Disclosure:

The authors declare no conflicts of interest.


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## Author contributions:

The hypothesis was primarily suggested by K. Sorour, other authors did a literature review and wrote the paper along with help from K. Sorour


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