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Role of ACE-2 Receptors in Multi-Systemic Manifestations of COVID-19

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1. Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which was first discovered in late 2019, is currently wreaking havoc around the world. The most common symptom of this illness is a type of extreme acute respiratory distress syndrome. Aside from the pulmonary manifestations, the virus is known to affect several other organs.

Angiotensin-Converting Enzyme-2 (ACE-2) is a receptor that is found abundantly in the body and is present in varying amounts in most cells. These receptors are the key site for SARS-CoV-2 recognition and entry. They are also known to aid in virus replication. The ACE2/angiotensin axis operates by counteracting the deleterious effects of the renin-angiotensin system (RAS), which is responsible for maintaining the body's physiological and pathophysiological equilibrium. Apart from the direct viral effects and the damage caused by inflammatory mediators, the interaction between RAS and ACE2/angiotensin after infection may also result in serious organ damage. Furthermore, diseases including diabetes and hypertension are known to increase the number of ACE2 receptors in the body, making individuals more susceptible to extreme SARS-COV-2 infection.

The widespread existence of ACE-2 receptors is thought to play a vital role in the wide array of presentations of Corona virus disease (COVID-19). Through this study, we aim to review the various organ-specific pathologic manifestations of COVID-19.

2. Introduction

Coronavirus disease (COVID-19) is an infectious disease primarily causing respiratory illness. The world health organization (WHO) describes it as an infectious virus transmitting via droplets when in close contact with an infected person. It has been noted that COVID-19 affects many organ systems evoking a widespread inflammatory response. All immune- hematological manifestations of COVID-19 occur within the general population. Many COVID-19 patients suffer from gastrointestinal problems with decreasing frequency of symptoms which might even cause myopathy by Cytokine-mediated sensitive receptors on the muscular fibers [1]. Current data indicates that the glycoprotein coat of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus phylogenetically is very similar to bat coronavirus, which adheres to angiotensin converting enzyme-2 (ACE2) receptor protein of both bat and human origin [2]. ACE2 is a membrane-bound enzyme. Since it is a mono-carboxypeptidase, ACE2 participates in the breakdown of several substrates which include angiotensin I and II [3]. SARS-CoV-2 virus is identified by a spike protein which allows attachment to the angiotensin-converting enzyme ACE2, playing a role of viral receptor and is thus expressed on

the surface of many pulmonary cells along with extra pulmonary cell types including renal, cardiac, endothelial, and intestinal cells [4]. It is mainly expressed in the kidney and heart cells and produces angiotensin-1-7 from its source angiotensin II. ACE2 acts in a counter-regulatory way to ACE [5]. Using metallic carboxyl peptidase angiotensin receptor ACE2, SARS-CoV-2 invades the human cells. Several proteases are activated which helps in the interaction of ACE2 receptor and viral spike proteins (S1). This causes the breakdown of the ACE2 receptors of the host [6]. ACE2 is a dominant-negative regulator of the renin-angiotensin system, which will have an opposing effect on ACE-receptors in multiple organ systems ranging from respiratory to the renal system [7].

3. ACE2 Receptors

An important and crucial component of the renin-angiotensin system (RAS) is ACE2 [8]. Angiotensin-converting enzyme 2 (ACE2) was identified as a negative regulator of the RAS by converting Angiotensin (Ang) 2 to Angiotensin 1-7. Thus, ACE2 counteracts the role of the angiotensin-converting enzyme (ACE) which generates Ang 2 from Ang 1 [9]. After the cloning of ACE2 in 2000, three major ACE2 functions have been described so far. First, ACE2 has appeared as a potent negative regulator of the RAS counterbalancing ACE multiple functions. ACE2 provides a protective role in the cardiovascular system via targeting angiotensin II. Second, ACE2 was found to be an important receptor for the SARS COV-2 that can lead to acute lung failure. ACE2 down regulation can strongly contribute to preventing severe lung failure and infection in other organs by the SARS COV-2. Third, ACE2 can also be associated with amino acid transporters and can play a vital role in the absorption of amino acids from the gut and the kidney [10]. Importantly, ACE2 has been identified as a key SARS-coronavirus receptor and plays a protective role in SARS pathogenesis [11]. SARS-CoV-2 was reported to enter cells via binding to ACE2, followed by its priming by Trans membrane protease serine 2 (TMPRSS2) [12]. The attachment of ACE2 receptors with SARS COV-2 depends on multiple factors. And multiple mechanisms can control ACE2 expression.

3.2. Relationship between ACE2 and SARS COV-2

SARS-CoV-2 has a strong affinity to bind with the ACE2 receptor in humans, establishing a major link between Covid-19 and RAS [13]. The S protein of SARS-COV-2 has a 3-D structure responsible for maintaining van der Waal forces [14]. The receptor- Receptor binding domain (RBD) of the SARS-COV-2 consists of a receptor-binding-determining region (RBDR) that can recognize ACE2 [15]. The RBD of SARS-COV-2 has 394-glutamine residues which can be recognized by critical lysine 31 residue present on human ACE2 receptors [16].

It has been noted in various studies that SARS-COV infection can lead to elevation of ACE2 soluble levels in the blood, urine, and bodily fluids in the pathological stages, inducing ACE2 down regulation. RAS and ACE2/angiotensin-(1–7)/MAS receptor axis imbalance is also noticed leading to multiple organ injury [17, 18]. Some studies also suggest the role of the Ang II and angiotensin II type 1 receptor (AT1R) axis in promoting COVID-19 progression which can lead to inflammation, vasoconstriction, fibrosis, and other organ injuries [19]. The ACE2 expression hike in the endothelial cells may also lead to other immune responses like endothelial damage, neutrophilia, etc., [20, 21]. The frequency of immune responses in Covid-19 is higher than other viral infections [22-24].

3.3. TMPRSS2 and SARS-COV-2

TMPRSS2 is a membrane-bound serine protease. The evidence says that TMPRSS2 is autoclaved to produce a secreted protease [25]. Priming of viral S proteins of coronavirus by proteases of the host cell is essential for the virus to enter into cells and involves the cleavage of S protein [26].

Some studies show the spread of SARS-CoV-2 also depends on the activity of TMPRSS2. Entry depends on the binding of the surface unit S1 of the S protein to a cell receptor that facilitates viral binding to the surface of target cells. Therefore, coronavirus uses the ACE2 receptor for entry and the serine protease TMPRSS2 for protein S priming [27]. There is strong evidence that TMPRSS2 expressing cells are way more vulnerable to SARS CoV-2 infection. TMPRSS2 is highly expressed in respiratory tissue making coronavirus more susceptible to cause respiratory infection [28, 29]. A study noted lack of TMPRSS2 within the airways reduces respiratory pathology by the virus.

4. COVID Infection Oral Manifestations

During the infection with the Covid-19 virus, saliva is implicated as a source of virus transmission and salivary glands as possible reservoirs. However, few oral manifestations have been reported such as dysgeusia, dryness, aphthous-like lesions, anosmia, and vesiculobullous lesions [30,31]. Other manifestations including fissured or depapillated tongue, ulcer, bulla, vesicle, erosion, macule, whitish plaque, necrosis, erythema, hemorrhagic crust, and spontaneous bleeding have also been noted. The tongue was most commonly involved, whereas labial mucosa and palate were also involved in many cases [32]. Further, the oral lesions were observed to be symptomatic in most of the population. However, there wasn't much difference in manifestations according to gender. Patients who suffer from a high severity case of Covid-19 infection or belong to old age showed severe oral manifestations in the majority of cases.

The most common predisposing factor leading to oral manifestations onset during covid-19 is immunosuppression. Oral hygiene and stress also play a key role in the development of oral lesions. Some patients observed cases of burning sensation, unilateral commissural fissures, dry mouth, pseudomembranous candidiasis, and angular cheilitis. Treatments include ointments like neomy-

cin, maintaining proper oral hygiene, proper rinsing agents, and salivary gels. Prescribed usage helps in the improvement of the situation and sometimes cures it all together. Chloroquine has been used in Covid-19 treatment, therefore as a result oral pigmentation can also be expected. A proper intraoral examination must be performed for early diagnosis of the disease, however, the risk of spread is also high [33].

5. COVID-19 Ocular Impacts

The immuno-histochemical evaluation found ocular surface cells inclusive of the conjunctiva are liable to contamination through SARS-CoV-2 [34]. The epithelial cells of the conjunctiva, its fibroblast, and cornea can bind to the spike proteins of SARS COV-2 as ACE2 receptors are expressed in these cells and their epithelium [35]. Therefore, consequently functioning as an entry point and reservoir for virus transmission. The presence of ACE2 receptors in the ciliary and vitreous bodies along with the retina of the eye has also been reported [35, 36].

The infection may not be limited to the tear film. In corneal transplant of COVID-19 affected cornea, there is a potential danger of ocular transmission by the presence of SARS COV-2 in the conjunctiva and tear film [37, 34]. According to studies infection by SARS-CoV-2 can cause inflammation of the conjunctiva, leading to itching and redness in the eyes. Moreover, viral particles were found in conjunctival secretions of COVID infected patients and can be one of the modes of transmission of infection [38].

Increased risk of ocular transmission and infection by SARS COV-2 is associated with unprotected eyes and exposed mucous membrane [39]. SARS-CoV-2 might be the reason for conjunctivitis, either as an early signal of contamination or at the stage of hospitalization. Coronavirus can be transmitted to the conjunctiva either through direct hand-eye contact or by liquid droplets [40]. The statistics suggest SARS-CoV-2 conjunctivitis can be related to the severity of the disease, and highlight the requirement of eye protection for those, who have the potential of being infected [41]. Numerous studies hypothesized that the exposure of the ocular surface to SARS-CoV-2 can be a cause of infection to the respiratory system because of the drainage of the viral particles through the nasolacrimal duct to the nasal cavity and into the respiratory tract [42, 43]. However, till now no clear evidence of spread from eyes to the brain via corneal nerves is found [43].

6. Damage to Respiratory System by SARS COV-2

A novel strain of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) disease (COVID-19) affects the respiratory system of humans. It enters the airway and lung epithelia via binding to ACE2 receptors by viral Spike(S) glycoprotein [44, 45]. Mechanisms for the interaction of host/viral cells are central for replication and cell infection that in turn lead to local damage and disease onset. SARS-CoV-2 infected ciliated, mucus-secreting, and club cells of the bronchial epithelium and type 1 pneumocyte in the lung.46 SARS-CoV-2 can be transmitted via inhalation or direct contact with droplets from infected people. In most cases the infection is mild, but in elderly patients of age 50 or more and those with respiratory or cardiac disorders, it may lead to acute respiratory distress syndrome, pneumonia, and multi-organ failure [47].

7. Cardiovascular System and Hypertensive Condition in COVID-19

As mentioned previously, the clinical manifestation of COVID-19 has been definitively associated with respiratory symptoms [48,49]. Despite so, on several occasions, some COVID-19 patients were identified with cardiovascular diseases that in some cases, may even increase their risk of death.48Several reviews have discussed the underlying mechanism on how cardiovascular complications may occur, with more emphasis being put on the roles of ACE2 receptors, which play a pivotal role in heart function and regulation of blood pressure via the RAAS system [48-51]. Other potential mechanisms that may cause further cardiovascular injuries include (a) systemic inflammation, in which greater production of interleukins and cytokines with an inflammatory response may lead to multiple organ damage. (b) An alteration in myocardial demand due to oxygen supply cut-off accompanied with respiratory symptoms found in COVID-19. (c) Coronary endothelial rupture and thrombus formation may also occur due to the great amount of stress systemic inflammation applied to the coronary vessels. 49 Based on the three mechanisms, the most common heart disease manifested was acute cardiac injury (12%) which is commonly defined as an elevation of cardiac troponin I (cTn I) above the 99th percentile upper reference limit, followed by heart arrhythmias and chronic cardiovascular damage [48, 49].

Regarding patients with pre-existing cardiovascular diseases, a positive feedback relationship was found in which patients with comorbidities, such as heart disease, hypertension, and diabetes, are more likely to be infected with COVID-19 [49, 50]. Moreover, patients comorbid with cardiovascular disease are more at risk for severe symptoms of COVID-19, thus explaining the linear relationship between the two in regards to mortality [49,51]. This phenomenon was observed in the poor prognosis of patients with acute cardiac injury infected by COVID-19 due to cardiac insufficiency and sudden deterioration of the myocardium [48]. On patients with hypertension, there was no causative relationship identified that increases their risk of infection towards COVID-19 [50, 51]. some studies implied careful safety considerations in using antihypertensives (especially ACE inhibitors) due to potentially exposing more ACE2 receptors for the spike proteins found on the SARS-CoV-2 envelope to bind with. 51 Despite being logically possible, this relationship was disproven following repeated use of ACE inhibitors and angiotensin receptor blockers (ARB) on hypertensive COVID-19 patients which surprisingly revealed better survivability in comparison to the administration of other hypertensives.

7.1. Thrombus enhancing action of SARS COV-2

Blood Platelets expresses ACE2, a host cell receptor for SARS-CoV-2, which enhances the platelet activation directly by its spike protein to cause platelet aggregation and may lead to thrombus formation and inflammatory responses in patients of COVID-19.52 High rate of thrombotic complications have been noticed in COVID-19 patients by the use of multiple drugs and is a cause of increased mortality by thrombolytic action. But no direct relation of these drugs with ACE2 receptors have been observed till now.

8. Renal Damage by SARS COV-2

A study showed that the development of acute renal failure among patients with COVID-19 getting new admission in hospitals is on the rise due to which the mortality rate has increased. Thus clinicians should have accurate information regarding kidney diseases in patients with COVID-19 [53]. Most common cause of death in Individuals suffering from renal failure undergoing dialysis is infection. The reason is a compromised immune system along with chronic malnutrition. Patients undergoing immunosuppressive therapy are more susceptible to damage [54]. Kidneys show high expression of ACE2 receptors, found commonly in the tubular epithelial cells but less commonly in the renal vasculature and glomerular epithelial cells. The activity of ACE is shown to be compromised in patients suffering from hypertensive renal disease and diabetic kidney disease [55]. ACE2 is also expressed in the proximal tubules of kidneys where it colocalizes with angiotensin receptors and ACE. Subtotal nephrectomy and kidney disease are linked with reduced ACE2 count, as a result causing damage to progressively failing kidneys.

53 Patients being treated in COVID-19 Intensive care unit suffered from renal damages and had to undergo dialysis since the SARS-CoV-2 uses ACE2 receptors to enter the cells that are largely localized in the kidney [56]. TMPRSS proteases and angiotensin 2 conversion receptors (ACE 2) mediates several pathophysiological mechanisms including decreased renal perfusion associated with mechanical ventilation, cytokines release, and sepsis along with the direct effect of virus toxicity in podocytes and proximal tubular cells of the kidney [57].

9. Gastrointestinal Impact of COVID-19

Human epithelial cells of the gastrointestinal tract have ACE2 receptors which again are the main SARS COV-2 receptors [58, 59]. According to a study the potential relationship between the gastrointestinal system and COVID-19 infection following multiple reports of diarrhea, nausea, and vomiting is found among patients in China [58]. Moreover, several studies reported on the detection of the SARS-COV strain in the fecal matter of infected patients. Viral strains are also identified in various gastrointestinal locations via biopsies taken during endoscopy. Regardless of this seemingly definitive relationship, the link on how COVID-19 could induce symptoms in the gastrointestinal tract is missing. A systematic review conducted by Almeida et al. on 14 studies that presented gastrointestinal outcomes in COVID-19 patients showed great variance (6.8 - 61.3%) that could imply multiple confounding and regional factors at play for gastrointestinal etiology [60]. A review by Ma et al. perpetuated the role of ACE2 receptors in gastrointestinal pathogenesis due to its higher expression in the endothelial linings of the ileum and colon in comparison to the lungs, with some receptors also found in the stratified cells of the esophageal lining [61,62]. Moreover, the presence of ACE 2 receptors also correlates with the prevalence of systemic inflammation resulting in multiple and targeted organ damage. Additionally, SARS-CoV-2 could potentially hinder tryptophan absorption, due to the involvement of ACE2 receptors in the regulations of amino acid transporters. 63 However, whether the gastrointestinal symptoms are a result of direct infection or rather a manifestation of systemic inflammatory responses is debatable.

10. Extensive Musculoskeletal Manifestations in COVID-19

Patients who had moderate to severe respiratory infections have indicated a considerable musculoskeletal burden, skeletal muscle, neurological, bone, and joint disorders from Covid-19 infection. Extended ventilator times induce unhealthy conditions causing muscle and bone fragility [64].

Muscle pain is one of the most common signs in people who are admitted after contracting SARS-CoV-2 within the first three days of infection. Following fever and cough, myalgia/fatigue is the third most common symptom in people with symptomatic SARS-CoV-2 infection. Researchers believe that muscle weakness in COVID-19 patients is caused by a complex set of interconnected causes like disease severity, malnutrition, physical inactivity during hospital stays, and prolonged mechanical ventilation [65].

Excessive cytokines, seen in cytokine storms, are the potential culprits responsible for the widespread manifestations, including skeletal muscles, which are known to undergo degenerative changes and shrinkage. Hormones responsible for maintaining muscular integrity, such as testosterone, are also affected. Since skeletal muscles express ACE2 and TMPRSS2, a protease that aids virus-cell fusion, it has been hypothesized that SARS-CoV-2 may infiltrate skeletal muscle through adjoining ACE2-expressing cells. Sarcopenic muscle and adipose tissue develop myokines and adipokines, which promote inflammation and oxidative stress, resulting in a hyper-catabolic state, particularly in individuals with advanced age and metabolic disorders. Through its ability to modulate molecules outside of the RAS, ACE2 is known to protect against age-related muscle wasting [66].

COVID-19 has been linked to many short and long-term musculoskeletal symptoms. These normally appear early on in the disease's progression. The majority of these effects are mild but incapacitating, manifesting as nausea, myalgia, or transient arthralgia.

It's more widespread in females and tends to be linked to disease behavior.

The word "long COVID" refers to the long-term symptoms of COVID-19 in individuals who have been diagnosed with the virus. There are found in a population of individuals who have recovered from the disease but are still exhibiting COVID-19 symptoms much longer than the disease pattern would suggest. Fatigue, dyspnoea, knee pain, and chest pain are the most frequently recorded conditions among these patients [67].

11. Neuronal Manifestation in COVID-19

Several neurological complications have been observed in COVID-19 patients ranging from mild to serious symptoms with involvement of the peripheral as well as the central nervous system. Patients who have mild COVID-19 might show neurological symptoms like headache, dizziness with loss of smell and taste sensation. While serious neurological conditions, like altered mental status (confusion, anxiety, disorientation) known as encephalopathy, have been observed in patients with severe covid-19 infection [68] (Figure 1 and 2).

Anosmia, olfactory function loss, myalgia, muscle fatigue, and Guillain Barre Syndrome are all symptoms of COVID-19, showing its effect on the nervous and musculoskeletal systems. Scientists are working on the disease mechanism, including pathogenicity, viral replication, and epidemiology. However, no evidence of the same is reported yet. Nonetheless, physicians must take the neural effects into account when diagnosing the disease to avoid any future complications such as acute cerebrovascular disorder can cause complications of a stroke, seizure, and headache, which can lead to long-term impairment and recovery (Table 1).

Since the virus is thought to be neurotrophic, patients may experience neurological symptoms or complications, particularly in the long run. Respiratory failure can cause symptoms such as headaches and loss of consciousness. The virus might enter the central nervous system through the bloodstream and invade endothelial cells or leukocytes, or it could infect peripheral nerves through retrograde neuronal paths. Second, the virus causes pneumonia, which can lead to systemic hypoxia, which can damage the brain and other nerve cells over time. Peripheral vasodilation, hypercarbia, hypoxia, and anaerobic metabolism are some of the mechanisms that cause injury, resulting in neuronal swelling and brain edema. Neuronal injury can also be caused by cytokine storms, which are characterized by elevated levels of inflammatory cytokines and actions of T lymphocytes, macrophages, and endothelial cells. The release of interleukin-6, in particular, results in vascular leakage and the activation of complement and coagulation cascades [69].

A typical cytokine storm causes significant physiological alterations as well as multiple organ failures. Ischemic or hemorrhagic stroke may be associated with severe coagulopathies. SARS-CoV-2 virus encephalitis, as well as symptoms such as acute disseminated encephalomyelitis and acute necrotizing encephalopathy, have been identified in some rare cases. A headache that isn't specific is a typical neurological symptom [70].

The number of SARS-CoV-2 infections-related neurologic manifestations is growing exponentially. Possible causes for this include the virus-induced hyper inflammatory and hypercoagulable states, noticeable effects of penetration of the central nervous system (CNS), and post infectious immune-mediated processes [71]. Anosmia, or partial deprivation of odor, is the most common symptom in COVID19 cases, according to clinical trials, indicating that olfactory deficiency and the preliminary ultra- rapid immune responses may be a prognostic factor [72].

In one of the study, the expression of ACE2 receptors in neurons derived from pluripotent stem cells has been found by the use of immunocytochemistry. So in human neurons ACE2 expression highlights the SARS COV-2 potential to infect human neurons that could affect respiratory function and patient's ability to breath. This indicates COVID-19 severe respiratory disorder might be treated from CNS [73].

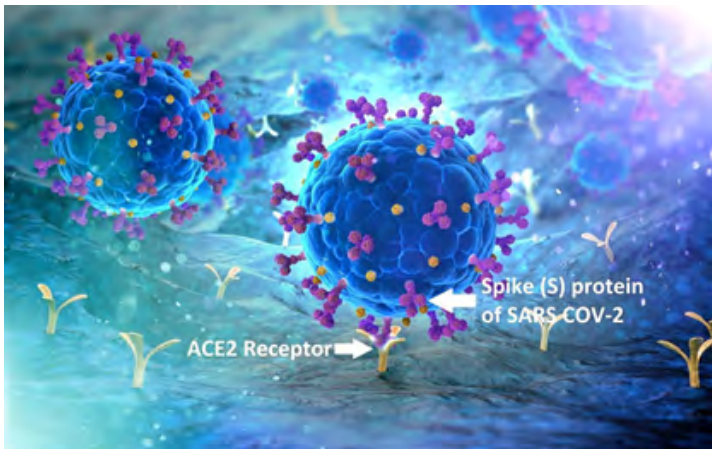

Figure 1: Attachment of ACE2 Receptor from a body organ surface with the spike protein of SARS COV-2 viral particle.

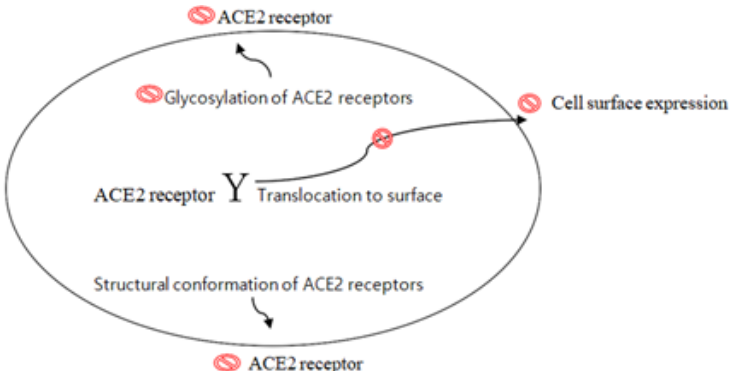

Figure 2: Major Mechanisms for ACE2 expression control on cell surface.

Table 1: A summary table of major human body systems with ACE2 receptor involvement and pathological mechanism of infection by COVID-19.

Body Systems	Pathological mechanism	Risk Factors	Clinical manifestations	ACE2 receptor involvement
Sensory (Ocular)	Contamination of ocular surface cells via binding of conjunctiva, fibroblast, and the cornea epithelial cells	Corneal transplant, unprotected eyes, exposed mucous membrane	Inflammation of the conjunctiva, redness, conjunctivitis,	ACE2 Receptors are expressed in the epithelial cells and ciliary bodies along the retina
Respiratory	Replication within host cells (ciliated, mucus-secreting, club, and type 1 pneumocyte cells) leading to local damage and disease onset	Exposure to droplets	Acute respiratory distress syndrome (ARDS), pneumonia, multi-organ failure	ACE2 receptors are expressed in the lung epithelia
Cardiovascular (with hypertension)	Systemic inflammation, alteration of myocardial oxygen demand, coronary endothelial rupture with thrombus formation	History of heart disease, hypertension, diabetes	Acute cardiac injury, heart arrhythmias, chronic cardiovascular damage	ACE2 receptors plays a role in the RAAS system in regulating blood pressure
Renal	Compromised immune system such as: decreased renal perfusion, cytokine release, and sepsis	Patients undergoing dialysis and immunosuppressive therapy,	Acute kidney failure	ACE2 receptors are highly expressed in the tubular epithelial cells
Gastrointestinal	Immunosuppression and systemic inflammation (highly influenced with multiple confounding factors)	Oral hygiene maintenance and stress, direct contact with infected person's fecal matter	Dysgeusia, Dryness, Aphthous-like lesions, Fissured tongue, diarrhea, nausea, vomiting	ACE2 receptors are expressed in gastrointestinal epithelial cells with higher expression in the endothelial lining of ileum and colon
Musculoskeletal	Cytokine storms, systemic inflammation, oxidative stress as the virus infiltrates the skeletal muscles	Malnutrition, physical inactivity, prolonged mechanical ventilation	Musculoskeletal burden, muscle and joint pain, myalgia/fatigue, and dyspnoea	ACE2 receptors are expressed in skeletal muscle
Nervous	Entry via the central nervous system through the bloodstream in invade endothelial cells and peripheral nerves via retrograde neuronal paths.	Pneumonia, history of neuronal injury	Headache, dizziness, altered mental status (confusion, anxiety, disorientation), encephalopathy, anosmia with olfactory function loss, encephalitis	ACE2 receptors are expressed in pluripotent stem cells (PSC)-derived mixed neurons

12. Conclusion

COVID-19 is a multi-systemic infectious disease that generates a body-wide inflammatory response. SARS COV-2 is recognized by the ACE2 receptor, a gateway for viral entry, which is present in many body cells and tissues, in different proportions, allowing the virus to infect the cell and in turn the tissue or organ. The amount of damage to the tissue by SARS COV-2 depends on the number of ACE2 receptors present in the infected tissue.

Researchers should look for ways to prevent the docking of SARS COV-2 with ACE-2 receptors by drugs to prevent Spike protein attachment, creating structural conformation in ACE2 receptors and inhibiting the glycosylation of ACE2 receptors to restrict its translocation on the surface and in turn prevent viral pathogenesis. This can facilitate the development of coronavirus therapy and pose a strong link for future therapeutic developments.

The ACE2 receptors expression can might of different proportions in different regional populations. That can be a cause of high positivity rate in one region but low in other regions. So Different proportions of ACE2 expression in populations can be studied. Similarly proportions of ACE2 receptors in different systems of body can be brought under consideration. Also the role of TMPRSS2 with ACE2 receptors needs to be observed in populations. As TMPRSS2 is one of the leading factor with ACE2 receptors to control the multi-systems viral damage by priming and binding with surface cells respectively. This raises a question that TMPRSS2 expression is equally important as that of ACE2 receptors or they both can work independently in spread of COVID-19 infection.

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17. Ethical Statement: Not applicable.

18. Data Availability: The data included in this study is used in the manuscript.

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