

Multi-organ system involvement in coronavirus disease 2019 (COVID-19): A mega review

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ABSTRACT

Since the pandemic of the coronavirus disease 2019 (COVID-19) infection, many people have been affected in different ways. The majority of infected people experience mild to moderate symptoms and recover without the need for hospitalization. However, in some affected people, it may lead to catastrophic disease. The severity of COVID-19 infection is widely influenced by co-morbidities, immune system functions, and extra-pulmonary organ injuries. Since the emergence of COVID-19, multi-organ involvement has been documented. In order to implement preventative and protective measures, full attention to potential organ injuries is required. Most existing articles and review papers are focused on a specific organ system, and their numbers are growing. In this review paper, attempts were made to collect review papers and articles published on seven organ system involvements in COVID-19 infection published till 15 July and highlight conclusions and managements of all affected organs. We tried to add to the medical knowledge on COVID-19, pointing out its multi-organ system impact. Finally, we tried to facilitate access to organized information and optimum conclusion by representing review tables for each organ system. Besides, this review article can clarify and magnify the empty research space easily for future investigations.

Keywords: COVID-19, mega review, multi-organ

Introduction

Coronavirus disease 2019 (COVID-19) is a significant health threat worldwide. It is produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was initially discovered in China in December 2019.^[1,2] COVID-19 is a health emergency, and the situation is evolving daily. Since the outbreak of COVID-19 globally, considerable verities of information from

basic research and expert opinions to clinical observations have been published. These data have enriched our insight into better prevention, diagnostic, and treatment strategies. Although most infected cases either are asymptomatic or showed mild symptoms, it may lead to catastrophic disease in some affected people. In severe cases, growing numbers of evidence have shown that multi-organ system involvements are the cause of essential organ failure and death.^[3] Therapeutic management is mostly based on the clinical manifestations in the beginning and other symptoms observed during the patients' follow-up.

Surly, primary care played a vital role and continues to do so in the pandemic situation. Reports from many countries described the role of multi-professional primary care teams that played as

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the first point for evaluating patients with COVID-19 infection. It is now well documented that strong primary care is essential if we plan to strengthen health systems with equalities.

One of the first signs and symptoms of the infection appears in the respiratory system that led to research on the immune system's involvement. Then, attention was drawn to renal, cardiovascular (CV), and central nervous system (CNS) engagements. Some other organs that have been reported later following COVID-19 infection are the skin, eyes, reproductive system, oral mucosa, and olfactory tract. In fact, no organ system is safe from the virus, and because of unclear reasons, people might show different clinical manifestations. This disease has shown a large number of clinical manifestations, including asymptomatic or paucisymptomatic forms, severe viral pneumonia with respiratory failure, multi-organ infection, or death.^[4,5] So far, there have been few papers that review the whole organ involvements one-by-one to clarify the strength or weakness of the fields and show the free research spaces left for more attention. In this review, attempts were made to collect review papers and articles published about main organ involvements in COVID-19 infection and study conclusions, highlights, and management of all affected organs. Finally, we tried to facilitate access to organized information and optimum conclusion by representing review tables for each organ.

Search for the Literature

An extensive review search was performed on PubMed, SCOPUS, Embase, Google Scholar, and several scientific websites to identify “review articles” or “systematic reviews” that discussed the coronavirus, COVID-19, and involvement of different organ systems of the human body. Keywords used were mainly ‘COVID’, ‘SARS-CoV-2’, and ‘COVID-19’ plus an organ's name [respiratory (lung), CV (heart), gastro intestine (stomach, intestine), immune system, CNS, olfactory bulb, oral mucosa]. If there was not any review, then articles were searched and chosen. In the case of search results related to organs such as the respiratory, CV, gastro-intestinal (GI), immune, and central nervous systems and the olfactory system, review articles were found. However, in the case of organs such as the oral mucosa, no review article was found, and consequently, articles have been searched and reported. All the relevant articles were identified and screened by two co-authors till mid-July and then finalized by the corresponding author; their conclusions are briefly described and highlighted in each related section, followed by summarized tables. Each table includes the last name of the first author, the month and year of publication/acceptance, conclusions/highlights, type of article, and a number of references used.

Organ System Involvement during COVID -19 Infections

1. Cardiovascular system

CV complications are reported in patients with COVID-19, and such patients are at a higher risk of morbidity and mortality.^[6] However,

whether the presence of CV conditions is an independent risk or mediated by other factors is not clear. Six review articles are presented in Table 1 with their remarks. More than a quarter of critical cases have been identified to have a myocardial injury, which can take two forms: 1) acute myocardial injury and dysfunction at the time of diagnosis and 2) myocardial injury that occurs as the severity of the illness increases. Regarding the function of angiotensin-converting enzyme 2 (ACE2) in COVID-19 infection, clinically indicated angiotensin-converting enzyme (ACEi) and angiotensin-receptor blocker (ARB) medications should be continued at all times based on the available evidence. A variety of promising therapies are being studied, but their effectiveness has yet to be demonstrated in a clinical setting. CV diseases are generally occurring non-communicable diseases worldwide. On the other hand, viral infections, such as COVID-19, and their relationship with these diseases represent a major concern. Previous studies reported that the renin-angiotensin system plays an important role in maintaining normal CV functions and contributes to a wide spectrum of CV diseases.^[7] ACE is an ectoenzyme that is found in many cell types, tissues, and organs. ACE plays a pivotal role in catalyzing the decapeptide Ang II extra-cellular conversion, which in turn generates angiotensin II (Ang II).^[8] ACE2, as a new homolog of the enzyme, can convert Ang II to Ang^[9] or convert Ang I to Ang ACE2 and has been shown to play a critical role in CV disease.^[10-13] It has also been suggested that it may be a functional coronavirus receptor that attaches directly to the viral spike protein [including severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as 2019-nCoV].^[14,15] Furthermore, it plays a role in acute lung injury induced by influenza viruses. A recent study showed a role for ACE2 in involvement in vascular protective actions; they reported that the risk of the coronavirus or influenza virus infection partly because of high ACE2 expression in this population is high among the CV disease-susceptible people.^[7] They also stated that this result needs to be confirmed in future studies. Based on their findings, it is recommended that more protection should be employed for patients with CV disease. On the other hand, coronavirus vaccine usage in high CV risk people could potentially prevent CV disease and coronavirus virus infections. Several reports have shown that patients with CV and metabolic co-morbidities are more vulnerable to COVID-19 infection and that the infection is worsened by these conditions.^[16] Although CV was a common co-morbidity in COVID-19 predecessors, SARS and Middle East respiratory syndrome (MERS) patients, these associations' mechanism is unknown. CVD is more common in patients with an advanced age, a functionally compromised immune system, or elevated levels of ACE2 or patients with CV having a predisposition to COVID-19, according to some researchers.^[17] According to Li *et al.*, people with CV conditions may be at a higher risk of developing a serious condition. Co-morbidities can also influence the development of COVID-19. COVID-19, on the other hand, can exacerbate heart damage.^[18]

2. Central Nervous System

The impact of the coronavirus and the host immune response to infection on the human CNS and associated neuropsychiatric

Table 1: Summarized review articles related to COVID -19 and CV system involvement

Author (s)/Year	Title	Highlights	Type/Ref.
Chen L. and Hao G. ^[7] (April 2020)	The role of angiotensin-converting enzyme 2 in coronaviruses/influenza viruses and cardiovascular disease	Focused on the findings to indicate the role of ACE2 in the relationship of coronaviruses and influenza viruses to CV disease. Coronavirus and influenza virus vaccine usage in high CV risk populations could be a potential strategy to prevent both CV disease and coronavirus/influenza virus infections.	Review
Clerkin K. J. <i>et al.</i> ^[17] (May 2020)	Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease	Despite ACE2 serving as the portal for infection, the role of ACE inhibitors or angiotensin receptor blockers requires further investigation. COVID-19 poses a challenge for heart transplantation, impacting donor selection, immunosuppression, and post-transplant management.	Review
Danser A.H Jan <i>et al.</i> ^[9] (May 2020)	Renin-Angiotensin System Blockers and the COVID-19 Pandemic; At Present, There Is No Evidence to Abandon Renin-Angiotensin System Blockers	Animal data support elevated ACE2 expression as conferring potential protective pulmonary and CV effects. Based on the currently available evidence, treatment with renin-angiotensin system blockers should not be discontinued because of concerns with coronavirus infection.	Review
Azevedo RB <i>et al.</i> ^[6] (2021)	COVID-19 and the Cardiovascular System, A comprehensive review	Patients with previous CV, metabolic diseases may face a greater risk of developing into a severe condition, and the co-morbidities can also greatly affect the prognosis of the COVID-19. On the other hand, COVID-19 can, in turn, aggravate the damage to the heart.	Review
Madjid M. <i>et al.</i> ^[10] (March 2020)	Potential Effects of Coronaviruses on the Cardiovascular System, A Review	Coronavirus disease 2019 is associated with a high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias. Meanwhile, cardiovascular risk factors and conditions should be judiciously controlled per evidence-based guidelines.	Review
Xiong T. <i>et al.</i> ^[18] (May 2020)	Coronaviruses and the cardiovascular system: acute and long-term implications	Acute and chronic CV complications of pneumonia are common and result from various mechanisms, including relative ischemia, systemic inflammation, and pathogen-mediated damage.	Review
Mokhtari T <i>et al.</i> ^[19] (sep, 2020)	COVID-19 and multi-organ failure, a narrative review on potential mechanisms	Elevation of cardiac biomarkers can cause myocardial injury and myocarditis. Severe symptoms indicate serious complications mostly in old ages, CV risk factors, and pneumonia	Review

outcomes is discussed. Potential mechanisms by which neuropsychiatric symptoms can evolve,^[20] especially in the context of immune responses to a viral infection, are also discussed. In Table 2, six review articles related to CNS involvement are summarized. Different ranges of neuropsychiatric symptoms may appear and progress during viral infection,^[21] such as encephalopathy, mood changes, psychosis, neuromuscular dysfunction, or de-myelinating processes, which may continue for weeks, months, or longer in recovered patients.^[22] The COVID-19 virus has recently been discovered to invade cells through the ACE2 receptor. As a result, more emphasis has been placed on ACE2 expression in neurological tissues and evaluating the potential contribution of COVID-19-induced neurological damage.^[23] Moreover, it has been proposed that the COVID-19 pandemic is a unique opportunity to advance the understanding of the association of neurotropic respiratory viruses with mood disorders and suicide. Anti-inflammatory interventions can be beneficial, but they are still an under-studied treatment option.^[24] Infection with a virus has a negative effect on neurological functions and may also result in serious neurological damage. Although the coronavirus is mainly a respiratory virus, it also has neuro-invasive capabilities and can spread from the respiratory tract to the CNS. The coronavirus has neurotrophic properties and has the potential to cause neurological disorders.^[25] The coronavirus has been detected in the brain and cerebrospinal fluid, according to reports. It has been established that coronavirus infection is linked to neurological symptoms.^[26] Coronaviruses

have been shown to have neuroinvasive capabilities in humans. The coronavirus reaches the CNS via nasal infection and the olfactory bulb, causing inflammation and de-myelination. As a result, human coronaviruses are not only limited to the respiratory tract; they can even infect the CNS. SARS-CoV-2 affects the respiratory tract and invades the CNS, according to Kotfis *et al.*,^[27] resulting in an extremely high-risk situation. Delirium is a symptom of overt CNS invasion in patients with COVID-19. The burden of long-term post-SARS-CoV-2 delirium may be important, particularly for elderly patients who are more susceptible to post-infectious neurocognitive complications,^[28] according to emerging evidence of hyper-cytokemia in hospitalized COVID-19 patients.^[29] It is crucial to figure out how much the nervous system is involved in COVID-19 and which neural circuits, if any, are affected by SARS-CoV-2. People who have been infected with the coronavirus should be checked for neurological symptoms as soon as possible. To help critically ill patients, early examination of the cerebrospinal fluid is needed, as is knowledge of and treatment of infection-related neurological complications.

3. Respiratory system

The clinical representation of respiratory system involvement in COVID-19 shows mild to severe symptoms, including acute respiratory distress syndrome (ARDS). Importantly, critically ill patients with COVID-19 are more likely to develop ARDS

Table 2: Summarized review articles related to COVID -19 and CNS involvement

Author (s)/Year	Title	Highlights	Type/Ref.
Asadi-Pooya A.A and Simani L. ^[30] (April 2020)	Central nervous system manifestations of COVID-19: A systematic review	Precise and targeted documentation of neurological symptoms, detailed clinical, neurological, and electrophysiological investigations of the patients, attempts to isolate SARS-CoV-2 from the cerebrospinal fluid, and autopsies of the COVID-19 victims may clarify the role played by this virus in causing neurological manifestations.	Systematic review
Dossantos M.F. <i>et al.</i> ^[31] (June 2020)	Neuromechanisms of SARS-CoV-2: A Review	Some studies have demonstrated that synapse-connected routes may enable coronaviruses to access the CNS. However, evidence related to the presence of SARS-CoV-2 in the CNS, its direct impact on the CNS, and the contribution to symptoms suffered remain sparse.	Review
Kotfis K. <i>et al.</i> ^[27] (April 2020)	COVID-19: ICU delirium management during the SARS-CoV-2 pandemic	Patients with COVID-19 are at an accelerated risk for delirium because of at least seven factors, including (1) direct CNS invasion, (2) induction of CNS inflammatory mediators, (3) secondary effect of failure of other organ systems, (4) effect of sedative strategies, (5) prolonged mechanical ventilation time, (6) immobilization, and (7) other needed but unfortunate environmental factors including social isolation and quarantine without the family.	Review
Troyer E.A. <i>et al.</i> ^[28] (April 2020)	Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms	Acute and delayed neuropsychiatric sequelae have been associated with past viral pandemics. A psychoneuroimmunology perspective will aid in promoting post-pandemic public mental health.	Review
Wu Y. <i>et al.</i> ^[32] (March 2020)	Nervous system involvement after infection with COVID-19 and other coronaviruses	Coronaviruses not only affect the respiratory system but also have deleterious effects on the CNS. Most neurological diseases could be caused by coronavirus invasion.	Review
Yan Z. <i>et al.</i> ^[33] (August 2021)	Long COVID-19 syndrome, a comprehensive review of its effect on various organ systems and recommendation and rehabilitation plans	Long-term effects of COVID-19 on CNS are known as mood changes, cognitive difficulties, memory loss, and headache. The possible mechanisms are blood vessel damage or impaired oxygen supply	Review

regarding cytokine cascade activation over a short period. Therefore, the most common complication is ARDS, which is seen in the COVID-19 patients with high mortality rates.^[34] Different drug regimens have been used according to patients' conditions. Three review articles have been found, and their highlights are described in Table 3. Both influenza viruses and coronaviruses are infectious viruses that cause respiratory infections. COVID-19, which is caused by the coronavirus that causes the extreme acute respiratory syndrome, causes respiratory and intestinal infections in both animals and humans.^[35] The spread and incidence of severe acute respiratory infections have been regarded as one of the most significant challenges to global health over the past 2 decades. COVID-19 patients have a higher risk of developing serious respiratory diseases in general, particularly because they may be treated with immune-suppressive or immune-stimulating medications.^[36] Coughing and sneezing spread the virus primarily by respiratory droplets. The pathological results revealed ARDS with multiple organ involvement.^[37] The coronavirus is divided into four genera based on genome characteristics: α -CoV, β -CoV, γ -CoV, and δ -CoV.^[38] The coronavirus may be isolated from lower respiratory tract samples of a patient with COVID-19, according to genome sequencing.^[39] Usually, in the second week of the illness, some patients may develop to breath shortness, which might be accompanied by hypoxemia.^[40,41] As a result, serious pneumonia should be taken into account. ARDS, characterized as the partial pressure of oxygen to fraction of inspired oxygen

ratio less than 300 mmHg, as well as non-cardiogenic pulmonary edema and mechanical ventilation, will eventually develop in 10% to 20% of serious patients within the first 8–14 days of their illness. The most common cause of respiratory failure, ARDS, is linked to a high morbidity and mortality rate. Older age and underlying co-morbidities, such as hypertension, diabetes, CV disease, and cerebrovascular disease, are also risk factors for developing into serious or critical cases.^[41,42]

4. Immune system

Three reviews explain how the immune system can protect us from COVID-19. They show the immune system's process, function, and mechanism to fight the virus.^[43] Their summaries are mentioned in Table 4. Besides, Taghizadeh-Hesari and Akbari, in an article that is not included in the table, have provided a new theory on how an increase in cellular adenosine triphosphate (c-ATP) can potentially boost the performance of innate and adaptive immune systems in preventing or fight with COVID-19. The immune system, by producing an antibody, protects the body from viruses and diseases. Because there is no registered medicine, the immune system is the best defense against COVID-19. When our body is affected, skin and inflammatory responses begin.^[44] On the other hand, the immune system is unable to function properly when our bodies are exposed to viruses for the first time.^[45] The immune response to COVID-19 has been shown to include all immune system components that tend to be responsible for viral removal when taken together.^[46]

Table 3: Summarized review articles related to COVID-19 and the respiratory system

Author/Year	Title	Highlights	Type/Ref.
Russell B. <i>et al.</i> ^[56] (March 2020)	Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence	Low-dose prednisolone and tacrolimus may have beneficial impacts on COVID-19. There is no definitive evidence that specific cytotoxic drugs, low-dose methotrexate for auto-immune disease, NSAIDs, JAK kinase inhibitors, or anti-TNF α agents are contraindicated.	Systematic review
Zhou M <i>et al.</i> ^[2] (March 2020)	Coronavirus disease 2019 (COVID-19): a clinical update	Pathological findings showed representative features of acute respiratory distress syndrome and the involvement of multiple organs. The efficacy of some promising anti-virals, convalescent plasma transfusion, and tocilizumab needs to be investigated by ongoing clinical trials.	Review

Table 4: Summarized review articles related to COVID-19 and immune system involvement

Author (s)/Year	Title	Highlights	Type/Ref.
Asaduzzaman Chowdhury <i>et al.</i> ^[44] (July 2020)	Immune Response in COVID-19: A Review	Various types of potential challenges are discussed for the immune system. Some foods have been suggested, and some are discouraged. Physical exercise is also encouraged.	Review
Garcia L.F. ^[46] (June 2020)	Immune Response, Inflammation, and the Clinical Spectrum of COVID-19	Describes the general aspects of both COVID-19 and its etiological agent SARS-CoV-2, stressing the similarities with other severe coronavirus infections, such as SARS and MERS, but more importantly pointing toward the evidence supporting the hypothesis that the clinical spectrum of COVID-19 is a consequence of the corresponding variable spectrum of the immune responses to the virus.	Review
Li X. <i>et al.</i> ^[55] (March 2020)	Molecular immune pathogenesis and diagnosis of COVID-19	The individual's immune system factors include genetics (such as HLA genes), age, gender, nutritional status, neuroendocrine-immune regulation, and physical status. These factors all contribute to whether an individual is infected with the virus, the duration and severity of the disease, and the re-infection.	Review

SARS-CoV and SARS-CoV-2, according to Chu *et al.*,^[47] can both infect type I and type II pneumocytes as well as alveolar macrophages. At the same time, SARS-CoV-2 had a greater ability to replicate in pulmonary tissues.^[33] Although SARS-CoV induced the expression of IFN-I, IFN-II, and IFN-III, SARS-CoV-2 did not induce either of these immune mediators and was also less infectious.^[48] Previous research has shown that SARS-CoV-2 causes a signature of decreased IFN-I and IFN-III responses as well as substantial induction of multiple proinflammatory chemokines, including IL-1B, IL-6, TNF, and IL1RA.^[49] The increased levels of these molecules in COVID-19 patients backed up these findings. SARS-CoV-2 appears to be distinct from other coronaviruses based on these observations in terms of its ability to replicate inside pulmonary tissue, evade IFN-I and IFN-III anti-viral effects, activate innate responses, and produce the cytokines necessary to recruit adaptive immunity cells.^[46] The transition between innate and adaptive immune responses is crucial for COVID-19 infection to advance clinically. Immune regulatory events will result in either a defensive immune response or an inflammatory response that is amplified.^[50,51] On the other hand, several pieces of evidence show that the humoral response,^[52] main antibodies against the S protein, blocks virus attachment to susceptible ACE2⁺ cells.^[53] Finally, boosting up the immune system is a good resource for the treatment of COVID-19 patients. The immune system's process and mechanism may be a potential source of understanding for developing the immune system.^[54]

5. Gastro-intestinal tract

In most cases, the presence of SARS-CoV-2 in GI tissues suggests extreme symptoms. The importance of GI symptoms

in clinical practice should not be overlooked. Individual GI system vulnerability to SARS-CoV-2 would be better understood, allowing for more tailored COVID-19 therapy.^[56] In Table 5, six review articles are presented with their highlights and conclusions. Although the most common effects of COVID-19 are fever and respiratory symptoms,^[57] GI symptoms, such as diarrhea, vomiting, and abdominal pain, have also been reported in some studies.^[58,59] When compared to the MERS coronavirus and the extreme acute respiratory syndrome coronavirus (SARS-CoV), the literature indicates that GI involvement in COVID-19 is relatively uncommon.^[60] As a result, 5.6% of the 1602 patients had diarrhea, and 4.49% had nausea or vomiting symptoms.^[57,61] As a result, GI symptoms can be overlooked, especially in critics. Although GI symptoms may not appear to be conspicuous, it should be considered that detecting these symptoms may aid in early detection and prevention of the disease's spread.^[62] ACE2 is highly expressed in absorptive intestinal epithelial cells in the ileum, colon, and lung cells, as well as esophageal upper and stratified epithelial cells, according to findings from a study examining four datasets with single-cell transcriptomes of the lung, esophagus, stomach, ileum, and colon.^[63] According to current data, ACE2 expression is higher in the epithelial cells of the colon of patients with adenomas or colorectal cancer than in healthy adults, which may indicate a higher risk of infection with SARS-CoV-2.^[64] Furthermore, after studying single-cell RNA sequencing data from patients with colitis or inflammatory bowel disease, it was discovered that ACE2 played a dual role in mediating SARS-CoV-2 infection in the colon.^[65] These results suggest that ACE2 expression is linked to a viral infection. In a systematic review and meta-analysis titled “gastrointestinal

Table 5: Summarized review articles related to COVID-19 and GI system involvement

Author (s)/Year	Title	Highlights	Type/Ref.
Li L.Y. <i>et al.</i> ^[57] (Accepted 2020)	Digestive system involvement of novel coronavirus infection	A timely understanding of the relationship between the disease and the digestive system and implementing effective preventive measures are of great significance for a favorable outcome of the disease and help mitigate further transmission by appropriate measures.	Review/(39)
Mao R. <i>et al.</i> ^[68] (July 2020)	Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis	The pooled prevalence of digestive symptoms was 15%, with nausea or vomiting, diarrhea, and loss of appetite being the three most common symptoms. Pediatric patients with COVID-19 had a similar prevalence of GI symptoms to those of adult patients. 10% of patients presented with GI symptoms alone without respiratory features.	systematic review and meta-analysis
Rokkas T. ^[62] (June 2020)	Gastrointestinal involvement in COVID-19: a systematic review and meta-analysis	A percentage of patients with COVID-19 will manifest symptoms from the digestive system. The GI tract may be a target organ and potential transmission route of SARS-CoV-2, with important implications for disease management and transmission.	Systematic review and meta-analysis/
Tian Y. <i>et al.</i> ^[69] (March 2020)	Gastrointestinal features in COVID-19 and the possibility of faecal transmission	SARS-CoV-2 enters GI epithelial cells, and the feces of COVID-19 patients are potentially infectious. ACE2 and virus nucleocapsid protein were detected in GI epithelial cells, and infectious virus particles were isolated from feces.	Review
Wong S.H. <i>et al.</i> ^[66] (March 2020)	COVID-19 and the digestive system	Although patients typically present with fever and a respiratory illness, some patients also report GI symptoms such as diarrhea, vomiting, and abdominal pain. Studies have identified the SARS-CoV-2 RNA in stool specimens of infected patients, and its viral receptor ACE2 was found to be highly expressed in GI epithelial cells.	Review
Zheng Ki, <i>et al.</i> ^[70] (2020)	Extra-pulmonary complication of COVID-19, a multi-system disease	Most of the patients had diarrhea as the first GI symptom; according to the invasion and transmission of COVID-19 from the GI route, negative fecal nucleic acid testings for hospital discharge in COVID-19 are suggested	Review

involvement in COVID-19," Rokkas T.^[62] found that a proportion of patients with COVID-19 would experience digestive symptoms. The GI tract may be a target organ and a possible transmission route for SARS-CoV-2, which could have serious consequences for disease control and transmission. SARS-CoV-2 can actively infect and replicate in the GI tract, according to a review by Wong *et al.*^[66] This is crucial for disease management, transmission, and infection prevention. Overall, it is important to note that SARS-CoV-2 can infect the digestive system and evolve into an alternative source of infection.^[67]

6. Oral Mucosa

Because the oral mucosa can be the first site of SARS-CoV-2 infection, it is possible that oral mucosa lesions may be the first COVID-19 signs to appear if they are to be considered COVID-19 signs.^[71] If studies back up this theory, dental professionals will first recognize SARS-CoV-2-positive patients and refer them to be checked and treated accordingly. One review article was the result of our search that is reported in Table 6. In a report, Xu *et al.*^[72] looked into the possible routes of 2019-nCoV infection on the oral mucosa. They discovered that ACE2 was expressed in the oral cavity and was particularly abundant in epithelial cells. Furthermore, ACE2 expression was higher in the tongue than in gingival tissues and the buccal mucosa. Their findings suggest that the mucosa of the oral cavity may be a high-risk route for 2019-nCoV infection.^[73] They also discovered that ACE2 was expressed in lymphocytes within the oral mucosa and similar results in various digestive organs and

the lungs. These findings are consistent with other studies.^[67] As a result, the ACE2-expressing cells in the tongue's epithelial cells may provide possible entry routes for the 2019-nCoV. Many studies' preliminary results revealed the basic mechanism of oral activity and highlighted that the oral cavity is a potential risk carrier for nCoV infection.^[74]

7. Olfactory

Patients with COVID-19 face several problems when it comes to smell and taste disorders.^[75] In addition to anosmia, evidence of ageusia and dysgeusia (parageusia) was found in patients with COVID-19,^[76] according to a study of recent studies. One review article was found in this regard and is summarized in Table 7.^[76] According to some studies, SARS-CoV-2 infection is linked to olfactory and gustatory dysfunction. Infection with the human alpha coronavirus disrupts the nasal ciliary epithelium, according to previous reports.^[77] The CoV-2 receptor, also known as ACE2, is expressed by olfactory epithelial cells.^[78] CoV-2 infiltration of higher-order structures within the CNS, or cranial nerves, involved in chemosensory processing, can underpin olfactory and taste perception dysfunction. It is currently unclear whether acute anosmia during the early stages of infection, as recorded in COVID-19, is also linked to post-viral olfactory disorders.^[79] Taste and olfactory changes are a useful and simple screening tool for identifying people with COVID-19 and limiting viral spread because they appear early.^[75] Possibly the mechanisms for the changes in taste and olfactory during COVID-19 are linked to the role of the ACE2

Table 6: Summarized articles related to COVID-19 and oral mucosa involvement

Author (s)/Year	Title	Highlights	Type/Ref.
Xu H. <i>et al.</i> ^[72] (February 2020)	High expression of the ACE2 receptor of 2019-nCoV on the epithelial cells of the oral mucosa	ACE2 is expressed on the mucosa of the oral cavity. This receptor was highly enriched in epithelial cells of the tongue. The oral cavity is a potentially high risk for 2019-nCoV infectious susceptibility and provided a piece of evidence for the future prevention strategy.	Original article/(49)

Table 7: Summarized review articles related to COVID-19 and olfactory system involvement

Author (s)/Year	Title	Highlights	Type/Ref.
Mehraeen E. <i>et al.</i> ^[70] (June 2020)	Olfactory and gustatory dysfunctions because of the coronavirus disease (COVID-19): a review of current evidence	SARS-CoV-2 may infect oral and nasal tissues and cause olfactory and gustatory dysfunctions. These findings may aid future research on the diagnosis, prevention, and treatment of COVID-19 consequences.	Review article/(51)

receptor.^[80] It has been shown that SARS-CoV-2 uses this receptor to bind and penetrate cells. The widespread expression of the ACE2 receptor in epithelial cells of the oral and nasal mucosa indicates that SARS-CoV-2-related damage in these areas is connected to the virus's.^[70]

Conclusion

The rapid sharing of scientific results is astonishing since the outbreak and fast transmission of COVID-19 starting in December 2019. Fortunately, published papers and reviews are increasing every day, which enriched our knowledge to better management of the disease. By now, the catastrophic pulmonary effects of COVID-19 are well documented. However, the coronavirus can also damage many other organs. It affects the blood and immune system in certain people, which can lead to heart, renal, or multiple organ failure, which can lead to death. A series of complications, particularly in critically ill patients admitted to the intensive care unit, are common, including shock, sepsis, acute cardiac injury, acute kidney injury, and even multi-organ dysfunction. Alterations in the mental state, low oxygen saturation, decreased urine production, slow heartbeat, cold extremities, low blood pressure, and a mottled skin are all possible symptoms. Furthermore, tachycardia or bradycardia will be present in patients with an acute cardiac injury. When we looked at the diversity of organs that were affected by the virus directly and at the same time searching for the common sites that the virus can enter the cells and use them as a receptor, we came across ACE2. In most tissues, ACE2 is bound to the cell membrane of type II alveolar cells in the lungs, enterocytes in the small intestine, arterial and venous endothelial cells, and arterial smooth muscle cells. The cerebral cortex, striatum, hypothalamus, and brainstem all have ACE2 mRNA expression. The presence of ACE2 in cortical neurons and glia makes them vulnerable to a SARS-CoV-2 infection, which could explain anosmia and neurological defects observed in COVID-19. Therefore, apart from attempts to introduce the vaccine, control inflammation, and potentiate the immune system, the strong hypothesis is still focusing on ACE2 and the medications that can affect its expression and function to prevent organ system involvement.

Key points: Symptoms of COVID-19 are very variable, ranging from mild to severe signs. Common symptoms include those happening in common cold. Because of involvement of different organs in severe cases in some people, health care professionals play important roles in managing illness. The proposed role of ACE2 in different organs during COVID infection leads health professionals to be more vigilant, encountering any strange symptoms in any organ to monitor patients more carefully.

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Conflicts of interest

There are no conflicts of interest.

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